

REVIEW

Noncovalent interactions: A brief account of a long history

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Funding information

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Abstract

The history of noncovalent interactions is outlined, starting with early interpretations of the symmetry of crystals, then with the fast development of coordination chemistry, and of fundamental analyses in the last century. An attempt is made to provide for the practicing scientists who use noncovalent interactions a historical background of the field, paying credit to often forgotten predecessors. A separate section shows that only in the 20th century instrumentation provided a firm basis for the exploration of noncovalent interactions. Selected examples illustrate the early and rather accurate calculations of some noncovalent energies. With the advent of supramolecular chemistry, noncovalent interactions became a mainstream field of science; this allowed further insight into the nature and strength of these seemingly weak forces. Intermolecular interactions in biological systems have also received early attention. As far as possible, exact references are given for the original publications.

KEYWORDS

history, instrumentation, intermolecular interactions, noncovalent interactions, supramolecular complexes

1 | INTRODUCTION

Many names are used for noncovalent interactions, a term actually mentioned for the first time only in 1974.^[1] The term “intermolecular interactions” is actually more common and appeared in the literature already in 1954.^[2] The first book with the title *Zwischenmolekulare Kräfte* by Briegleb appeared in 1937.^[3] Another common name is cohesive interactions, the history of which until around 1870 has been recently been treated in admirable depth in a recent monograph by Rowlinson.^[4] The history of intermolecular interactions has also been treated in more general terms, starting from ancient Greek ideas on forces, including gravity, attraction, and repulsion.^[5] Van der Waals forces^[6] or interactions are sometimes

also taken as synonym for intermolecular interactions, but do not include, for example, hydrogen bonds or ion pairs. In general chemistry textbooks, such interactions were in the past treated with little detail. Walter Hückels *Theoretische Grundlagen der organischen Chemie* devoted already in 1936 a whole chapter with over 50 pages to intermolecular interactions.^[7] It was the advent of supramolecular chemistry^[8] which brought the field to a large blossom, also by many new applications; measurements with supramolecular complexes enabled to identify and quantify all kind of noncovalent interactions.^[9] Modern computational technology helped to develop after World War II sophisticated tools for the theoretical analysis of intermolecular interactions. The present account aims to provide for practicing scientists using noncovalent

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interactions a historical background of the field, paying credit to often forgotten predecessors.

2 | CRYSTALS

The most obvious manifestation of noncovalent interactions, as we see it today, is the formation of crystals. The German Johannes Kepler wondered about the origin of perfect symmetry in snowflakes, and wrote 1611 in his *Strena Seu de Nive Sexangula* that the arrangement of particles “will be the tightest possible, so that in no other arrangement could more spheres be stuffed into the same container”, as visible in his drawings (Figure 1A).

In the following centuries, the principle of tight packing and corresponding symmetries in crystals were explored by many scientists, as by the Dutch Christiaan Huyghens with his *Traité de la Lumière* of 1690, in France G. F. Rouelle around 1745, P. J. Macquer with his *Dictionnaire de chymie* of 1766, Romé de l'Isle with his *Essai de cristallographie* of 1772, R. J. Haüy with his *Traité de Minéralogie* (1801), William Barlow in England, and L.A. Seeber in Germany around 1820. More than 400 years after Kepler's assumption of tight packing the Russian chemist A. I. Kitaigorodsky derived for the first time rules for then known crystal structures based on minimizing intermolecular repulsions between molecules.^[11]

The nature of the particles anticipated by Kepler and the later proponents, and even more that of their interaction, remained obscure until Dalton developed in 1803 the atomic theory, based inter alia on the law of mass conservation by Lavoisier and others. The distance dependence of the interaction between particles was, however, considered already at the end of the 17th century by Newton, who spoke of attraction of small particles of bodies, and forces decreasing in any ratio of distances; he noticed also that crystallization of a salt

from “a liquor suggests a regularity in the forces between the particles of the salt”.^[4]

3 | INSTRUMENTATION

Magnifying glasses and simple microscopes appeared around 1600, mainly in the Netherlands, and helped in the study of crystals. Other important instruments became available much later and played a significant role for the characterization of noncovalent interactions. Electron microscopes arrived in the early 1940s and helped, for example, in the characterization of self-aggregates such as micelles. After World War I, X-ray crystallography became the most important tool for structure determination (see Section 4 below). Infrared, or “Ultrarot” instruments were built 1938 in the German BASF, and in the 1940s in the United States. Before, the Indian C.V. Raman developed the method that bears his name and won him the [Nobel Prize in Physics](#) in 1930. The results regarding molecular complexes are already discussed in 1937 in Briegleb's book^[3]; on the basis of hundreds publications such data allowed distinction for example between dispersive, dipole–dipole, and induced dipole effects. Infrared spectroscopy became a standard method, in particular for the investigation of hydrogen bonds. NMR spectroscopy was practically accessible after the 1950s, and rapidly became a major method not only for structural analysis of supramolecular complexes, but provided much insight for example into electron density distribution, or solvation effects. Calorimetry instruments, allowing measurements of interactions free enthalpies, were built first by Joseph Black (1728–1799) and brought already to some perfection in the 1790s by A. L. Lavoisier and P. S. Laplace; differential scanning calorimetry could determine [transition temperatures](#) and [enthalpies](#) also with crystals.^[12] Methods for the analysis of supramolecular complexes in the gas phase, such as

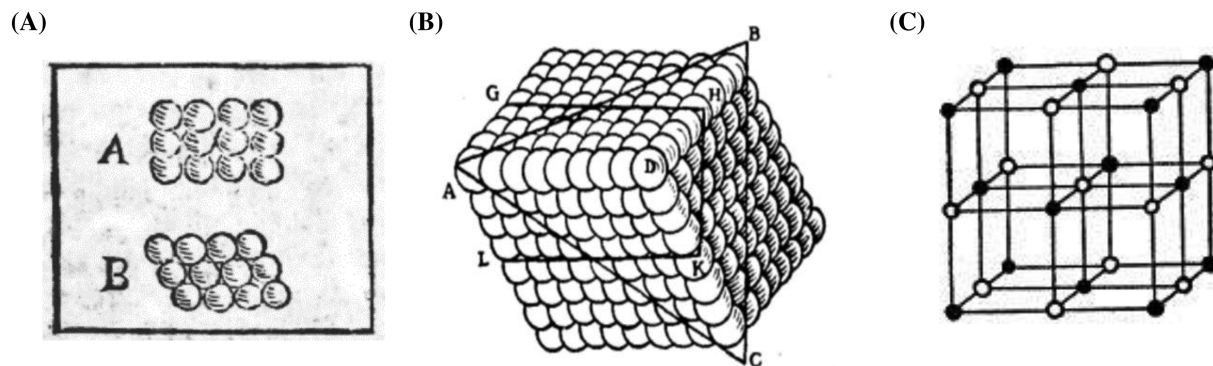


FIGURE 1 Drawings from Johannes Kepler (A) and Christiaan Huyghens (B) illustrating the consequences of tight particles packing; (C) the first X-ray-derived crystal structure (NaCl) by Bragg^[10]

electrospray ionization mass spectrometry (ESI-MS) arrived only in the 1970s.^[13] In the 1960s, the Quartz sensor balance^[14] became a significant method also for following complex formation. The advent of techniques such as matrix isolation and supersonic expansion of gases permitted spectroscopic studies of the noncovalent adducts of halogens and interhalogens with Lewis bases in effective isolation. After 1945, methods such as rotational and microwave spectroscopy which help, for example, the investigation of van der Waals clusters became available, as did fluorescence spectroscopy for the identification of supramolecular complexes in the excited state, such as excimers and exciplexes. Application of special techniques that are increasingly used in the last decades, mainly for the structural characterization of molecular complexes in the gas phase, such as mass-resolved ZEKE, resonance-enhanced multiphoton ionization (REMPI), or microwave and terahertz spectroscopy, is described in several reviews.^[15] The advent of computers brought an enormous progress not only for theoretical approaches to noncovalent interactions (see Section 12) but also for data processing.

4 | CRYSTAL STRUCTURE/ COORDINATION CHEMISTRY

The geometry and properties of metal coordination complexes, and the at that time new concept of coordination bond was elucidated in the 1890s by the Swiss Alfred Werner. Before the Swedish Christian Wilhelm Blomstrand and the Danish Sophus Mads Jørgensen proposed around 1870 the so-called chain theory, where, for example, NH_3 was linked to a metal by coordination bond. Werner developed starting 1890 in his seminal publications the spatial arrangement of ligands around metal centers.^[16] In a paper of 1893, Werner distinguished for the first time Hauptvalenz and Nebenvalenz, equivalent to oxidation state and coordination number.^[17] In his Noble prize^[18] lecture, Werner admitted, however, that he was “not yet able to characterise precisely the difference that exists between the two types of valence”. The distinction was clarified in 1923 by the American Gilbert Lewis, a pioneer of the electronic theory of valency, which then was further developed by Irving Langmuir, Nevil Sidgwick, Linus Pauling, and others. The concept of *electron-pair acceptor* as Lewis acid and *electron-pair donor* as Lewis base provided the first explanation of coordination complex structure and stability.^[19] Crystal field theory (CFT) theory has been introduced for [transition metal coordination complexes](#) by Hans Bethe^[20] and van Vleck^[21] in the 1930s, describing mostly optical spectra,

later extended to the MO-based [ligand field theory](#) (LFT), which provides insight into [chemical bonding](#) in transition metal complexes.^[22]

The decisive steps for investigation of crystal structures were the discovery of X-ray diffraction with crystals by Friedrich et al in 1912^[23] and the application for structure elucidation by Bragg in 1913,^[10] and these achievements finally verified the lattice theory of crystals. The unbeatable precision of the X-ray method, their applicability to large complex structures, and the rapid development of automatized techniques started to lead already in the 1950s to accumulation of big structural databases, which became an essential tool for the characterization of noncovalent interactions.

Crystal engineering, a term coined 1971 by Schmidt,^[24] is based on the knowledge of noncovalent interactions and has led to the design of many new materials.^[25] The use of metal coordination complexes for catalysis started in 1938 with Calvin's publication on the copper-catalyzed reduction of quinoline by molecular hydrogen^[26]; it became also the industrially most used applications of coordination complexes on the basis of noncovalent interactions. Other early developed complexes were those for catalytic hydrogenation, and in the 1950s by Ziegler and Natta for the polymerization of 1-alkenes, who both got 1963 the Nobel price. Later, many coordination cages have been introduced with noncovalent binding of guests and catalytic function.^[27]

Clathrates as naturally occurring crystalline compounds, which by noncovalent interaction bind guest molecules were first identified by Powell et al in 1948,^[28] and the responsible binding forces were first calculated on basis of the London equations (see Section 6) by Van der Waals in 1959.^[29] Nanoporous materials were in the form of zeolites discovered already by Cronstedt in 1765,^[30] but their ability to entrap reversibly, for example, water molecules were described first in the 1930s.^[31]

5 | STABILITY CONSTANTS/ION INTERACTIONS

The measurement of stability constants was introduced rather late, first by Paul Job using spectroscopic titrations in 1928,^[32] with potentiometric titrations by Jannik Bjerrum in 1941.^[33] These titrations provided soon an enormous amount of data on interaction energies for all kind of complexes, and allowed to construct empirically general binding factors for noncovalent interactions. The Gibbs–Helmholtz equation allowed to distinguish free enthalpy and entropic driving contributions and goes

back to papers by Gibbs in 1873^[34] and by Helmholtz in 1882.^[35] Stabilities of metal coordination complexes could be evaluated and predicted on the basis of correlations with Lewis acid/base parameters, those of complexes between organic compounds with empirical factors developed first by Drago et al.^[36]

Calculation of electrostatic interactions started already 1785 with the Coulomb-equation.^[37] In contrast to many present day quantum chemical computations, which are often restricted to gas-phase equilibria, early workers compared their calculations with experimental data and found surprisingly good agreements (see also Section 6 and Table 2). In 1918, Max Born and Alfred Landé proposed that the lattice energy could be derived from the electrostatic potential of the ionic lattice and a repulsive potential energy term, and arrived at an excellent agreement (Table 1).^[39]

Calculations of ion interactions *in solution* started in 1923 with the Debye-Hückel theory of activity coefficients^[40] and were extended by the theory of ion pairing of Bjerrum in 1926.^[41] The Fuoss equation, following Bjerrum's footsteps, was published in 1958 and is applicable also for solvent-separated pairs and for loose solvated complexes^[42]; Figure 2 shows a surprisingly good correlation with ions of very different shape and polarizability^[9a]; the slope (or sensitivity) of the correlation is with $m = 0.57$ close to the one predicted by the Fuoss equation. The salt effect on ion pair association constants is also predicted surprisingly accurate for different organic ions^[43] on the basis of the Debye-Hückel equation, with a sensitivity of, for example, $m = 4 \pm 0.6$ for a 2 + 2 combination of dianion + dication, close to the theoretically expected value, although the Debye-Hückel equation is based on the assumption of spherical ions.

TABLE 1 First calculations of lattice energies, of alkali halide crystals (in kcal/mol^[39])

	ΔG_{Exp}	ΔG_{Calc}		ΔG_{Exp}	ΔG_{Calc}
NaCl	182	182	KCl	165	162
NaBr	170	171	KBr	154	155
NaI	159	158	KI	144	144

TABLE 2 First calculations of sublimation heats of hydrogen halide crystals (ΔH , kcal/mol)^[58]

	Exp. at m. p.	Exp. extrapolated at 0°C	Calculated
HCl	4.34	5.05	4.04
HBr	4.79	5.52	4.53
HJ	5.41	6.21	6.50

6 | CAPILLARY ACTION, VAN DER WAALS DESCRIPTION, AND DISPERSIVE INTERACTIONS

Capillary action is another obvious manifestation of noncovalent interactions and has received attention quite early. The first observation of such cohesive effects is attributed to Leonardo da Vinci. The Irish chemist Robert Boyle carried out early quantitative measurements of the capillary effect,^[44] followed by several scientists in the 17th, such as Jacob Bernoulli, Honoré Fabri, Isaac Vossius, and Giovanni Borelli, and in the 18th century among others Louis Carré, Josia Weitbrecht, and in particular Francis Hauksbee.^[45] The first equation describing the capillary action was put forward by the British Thomas Young^[46] and the French Pierre-Simon Laplace.^[47] Other experimentally observable macroscopic properties such as vaporization heats, surface tensions, viscosity, and sublimation heats originate in intermolecular interactions and also have received quite early attention. Apart from hydrogen bonds (see Section 7), most of them turned out to have their origin in van der Waals, in particular in dispersive effects.

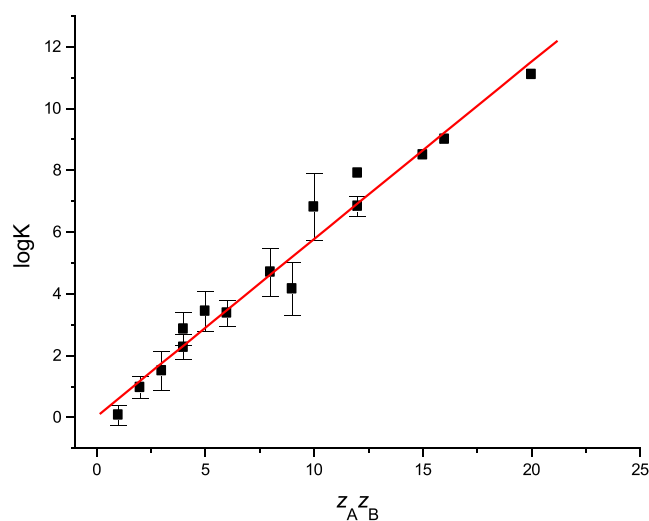


FIGURE 2 Experimentally measured stability constants of ion pairs calculated with the Fuoss equation for 203 inorganic and organic ion pairs at zero ionic strength as function of charge product.^[9a]

The decisive rationalization goes back to van der Waals, who in 1873 observed the deviation of gases from the ideal gas law and derived an **equation of state** assuming that molecules occupy a finite volume.^[48] Several force-distance potentials were proposed in the early 20th century, starting with Gustav Mie,^[49] then with the now most often used potentials of John Lennard-Jones^[50] and R. A. Buckingham.^[51] Einstein also wrote early a paper on the interaction potential between molecules.^[52] Keesom^[53] and Debye^[54] were the first to describe cohesion forces on the basis of electrostatic interactions, including induced dipoles and quadrupoles with transient dipole moments, and their dependence on polarizability. Already at the end of the 19th century, the Russian physicist, P. N. Lebedev, developed a description of intermolecular forces on the basis of the Faraday–Maxwell theory, considering electromagnetic interactions between molecules, which he regarded as resonators.^[55] His experiments and equations lead to energy versus interatom distance curves quite close to those derived later.^[56] Thirty years later, F. London used a QM approach for the description of dispersive interactions, based on perturbation theory, leading to the well-known r^{-6} dependence of interaction energy versus distance.^[38] In 1932, Henry Eyring included dispersion his kinetic transition state theory.^[57] London and Eisenschitz calculated sublimation heats of crystalline hydrogen halides already with remarkable small deviations (Table 2).^[58]

7 | HYDROGEN BONDS

The definition of hydrogen bonds appeared surprisingly late, in view of long known observations such as boiling point differences, for example, between dimethyl ether and ethanol, both having the same molecular weight, but a boiling point difference of 102°C. Intramolecular hydrogen bonding was occasionally mentioned already after 1900, for example, in azo compounds,^[59] or by the interaction between a hydroxyl hydrogen and a carbonyl oxygen.^[60] In 1920 hydrogen bonding were described on the basis of Lewis valence theory.^[61] In 1939, Linus Pauling put in his *The Nature of the Chemical Bond* book the description on firm grounds, based electrostatic and quantum chemical arguments, with covalent contributions. Coulson distinguished 1959 the hydrogen bond attraction energy by four factors: electrostatic, covalent, repulsive, and dispersion contributions.^[62] Correlation of hydrogen bond with acidity were evaluated experimentally in aqueous solution first by Taft et al.^[63] An empirical description of hydrogen bond energies in all kind of aggregations followed in the 1990s, with a general correlation with donor and acceptor scales, which themselves

are measures of basicity and acidity factors.^[64] Weak hydrogen bonds such as those with C–H as donor^[65] could be detected first in the solid state, later also in supramolecular complexes in solution.^[9b]

8 | ELECTRON DONOR ACCEPTOR

Electron donor acceptor (EDA) complexes were known in the form of chinhydron already before 1900, and were in the following years the subject of many discussions, often favoring Thiele's Partialvalenzen (partial valences) hypothesis.^[66] In 1949, Brackman described them as a kind of intermolecular mesorism^[67]; in 1951, Mulliken developed the quantum chemical description of EDA complexation.^[68] The first comprehensive book on EDA complexes was published by Briegleb in 1961.^[69]

9 | HYDROPHOBIC EFFECTS

According to Franks,^[70] the foundations of hydrophobic effects go back to Hartley who attributed the formation of micelles in aqueous surfactant solutions to an increase in the entropy of the solution.^[71] In their 1945 paper, Frank and Evans^[72] contributed the effect to enthalpy–entropy compensation and the peculiar nature of water as an associated solvent, which solvates chemically inert species by spatial and orientational rearrangements. The liberation of water molecules from lipophilic surfaces upon association of particles results in an entropic advantage, and an enthalpic gain can result from more hydrogen bonds in the bulk phase after association of lipophilic particles. Kauzmann identified alkyl group interactions as major driving force for hydrophobic bonds in globular proteins.^[73] Nemethy and Scheraga described the effect quantitatively with ice-like clusters of water molecules in equilibrium with non-hydrogen-bonded liquid and arrived at results which agreed with the radial distribution curve derived from x-ray diffraction.^[74] The tetrahedral arrangement of hydrogen bonds in ice was described already in 1933 by Bernal and Fowler.^[75] The first monograph on hydrophobic effects by Tanford summarized the observations essentially as result of entropic contributions.^[76] The Hildebrand solubility parameter from 1949 relates to the hydrophobic effect as the association of nonpolar solutes depends on cohesive energy density.^[77] The nature of the hydrophobic effect has always been a subject of controversy, such as already in the late 1960s between Hildebrand and Shinoda at one side, and Nemethy, Scheraga, Kaufmann, and others at the other side.^[78] The Sinanoglu equation^[79] quantified the hydrophobic force by multiplication of the water–air surface

tension with the microscopic difference in surface between the interacting particles before and after association.

10 | NONCOVALENT INTERACTIONS IN BIOPOLYMERS

A well-known historical landmark is Emil Fischer's lock-and-key principle, which he proposed for the action between glucosides and enzymes.^[80] Few years later, Paul Ehrlich extended the lock-and-key concept to immunology, based on the notation that cell surfaces bear specific side chains interacting with toxins.^[81] Emil Fischer, although the father of the designation of optical isomerism, did not really care about three dimensions of molecules, which was at his time still a matter of debate, and cared even less about interactions between key and lock. Geometric fitting without noncovalent interactions can indeed be sufficient for the formation of inclusion complexes: This became clear decades later, after Cram and others synthesized molecular containers,^[82] and Collet demonstrated that both absence and presence of noncovalent interactions are visible in experimentally derived packing coefficients in related complexes.^[83] The decisive role of noncovalent interactions for the formation of functional 3-D structures of biopolymers became clear much later. The formation of extended peptide β -pleated sheet and also hairpin structures by hydrogen bonding between distant amino acid parts was demonstrated by Astbury et al in 1941.^[84] In 1950, Pauling showed how peptides form spiral alpha helices, with about 3.7 amino acids residues and hydrogen bonds to the third residue from it in each direction.^[85] The role of mostly dispersive interactions of less polar parts in biopolymers became apparent later, in the most spectacular way for nucleic acids; these EDA were believed to play a large role in the nucleobase stacking, although such interactions are energetically notoriously weaker than dispersive ones between strongly polarizable parts. A most important step for the understanding of enzyme action was the model of a pretransition complex, formulated first by Wurtz and Hebd in 1880,^[86] improved mainly by Henri and Hebd,^[87] and led to the well-known equation of Michaelis and Menten.^[88] This opened the

way to the evaluation of enzyme binding processes and action and in particular to inhibitors and to drug finding, a field which started in the 1960s.^[89] That enzymes are responsible also for asymmetric syntheses became clear in the early 1900s.^[90]

11 | ORGANIC SYSTEMS FOR THE QUANTIFICATION OF NONCOVALENT INTERACTIONS

How noncovalent interactions can be evaluated with covalently bound switchable organic molecules is been shown with the examples in Figure 3; such molecular balances^[91] have found widespread use as double mutant cycles, first for interaction energy quantification in proteins.^[92]

The systematic investigation of host-guest interactions opened a new access for the evaluation of noncovalent interactions. The oldest host compounds known to bind different guest molecules were the cyclodextrins, isolated first by Villiers,^[93] then obtained in crystalline form by Franz Schardinger, who also noted the uptake of iodine,^[94] Freudenberg then characterized them as cyclic oligosaccharides with a hydrocarbon-like interior.^[95] It was Freudenberg's student Friedrich Cramer (1923–2003) who, starting 1953,^[96] published 24 papers on the inclusion properties of CD's and explored for the first time their use for separations, including enantiomers, and their enzyme-like association kinetics and catalytic capacities.^[97] Long before this became common, Cramer used for example competition titration with dye inclusion for determination of stability constants^[98] and derived models for the catalysis of, for example, decarboxylation by CD, involving several hydrogen bonds (Figure 4A).^[99] The extensive use of supramolecular chemistry to the elucidation of noncovalent interactions and their application started with crown-ether type of ionophores, the strength of which rely on the number of the involved electrostatic interactions or hydrogen bonds.^[8,9b] Figure 4B illustrates a 1983 example of binding and catalytic cleavage of ATP with an azacrown ether.^[100]

With the advent of supramolecular chemistry in the late 20th century, many new synthetic host compounds,

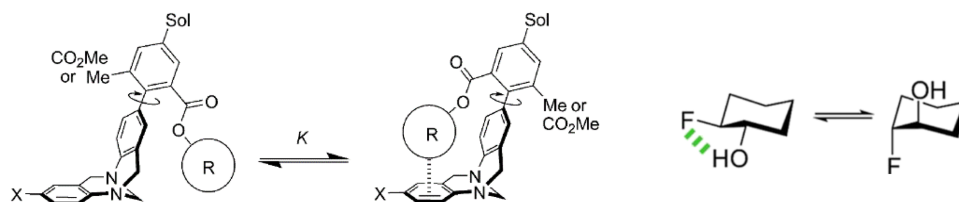


FIGURE 3 Evaluation of noncovalent interactions with molecular balances

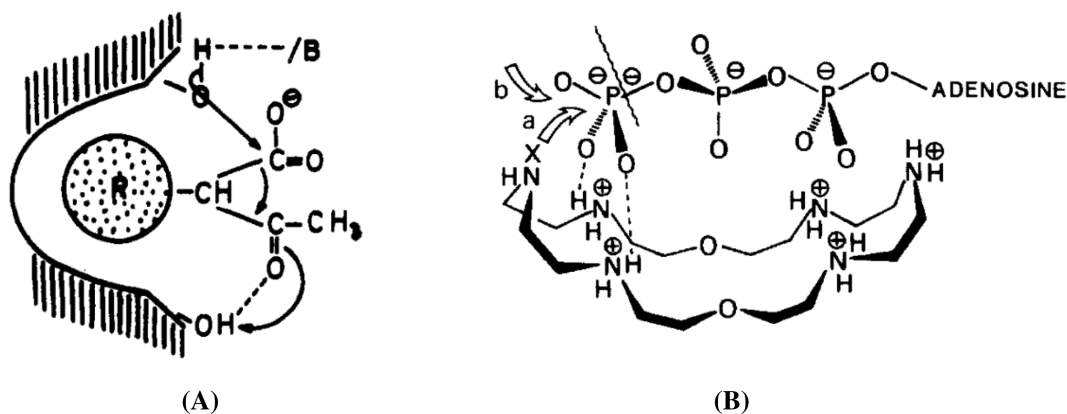


FIGURE 4 (A) Bifunctional catalysis of decarboxylation by cyclodextrin with hydrogen bonds,^[98] (B) catalysis of ATP cleavage with an azacrown ether, attack by a nucleophilic X and binding by several hydrogen bonds^[100]

FIGURE 5 (A) Cyclophane complex showing cation- π interactions^[105b]; (B) a calixarene complex with hydrogen bonds and anion- π interactions.^[106]

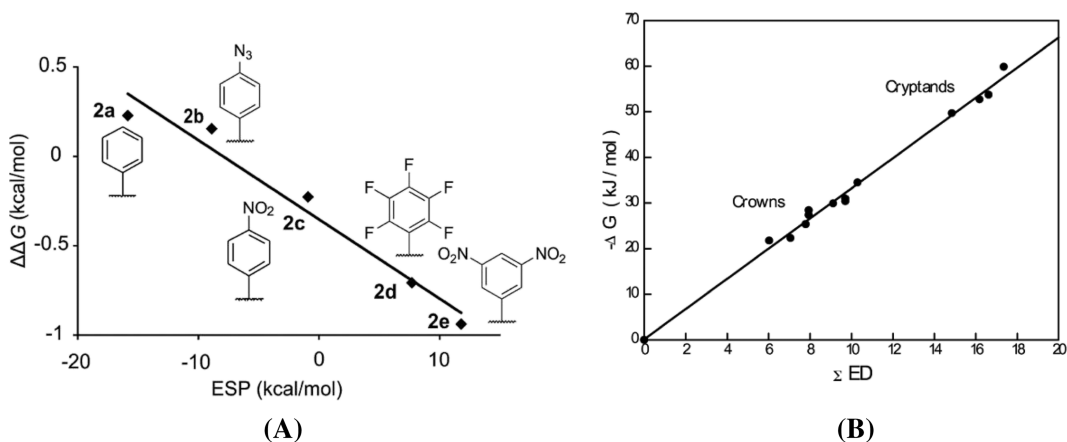
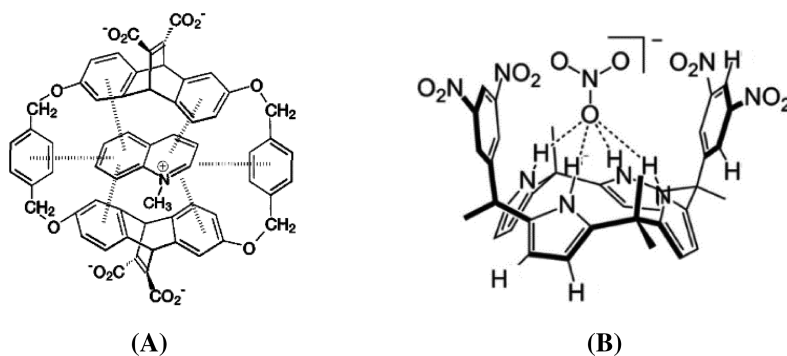


FIGURE 6 (A) Correlation of anion binding energies with electron donor parameters in substituted calixarenes.^[108] (B) Binding affinities ΔG (in methanol) for crown ether and cryptand potassium K^+ complexes with the sum of group electron donor parameters^[109]

such as cyclophanes,^[101] calixarenes,^[102] and cavitands,^[103] were synthesized, designed for many applications and also the identification of noncovalent interactions, providing numbers for their quantification. Several new interactions were identified for the first time in solution with the help of supramolecular host-guest complexes.

Cation- π interactions, which had been investigated already before in the gas phase by Kebarle et al,^[104] were independently by three groups quantified in solution with several cyclophanes interacting with cationic guest molecules^[105] (example in Figure 5A). Anion- π interaction were identified in a related way,^[107] in particular with electron deficient arenes. The calixarene complex in

Figure 5B shows a typical use of a supramolecular complex: It is stabilized by hydrogen bonds with the nitrate, and introduction of nitro substituents increases the partial positive charge in the benzene rings and allows to measure an anion- π contribution of 16 kJ/mol.^[106]

The electrostatic nature of anion- π interactions were confirmed by a Hammett-like correlation between binding energies and calculated electrostatic surface potential ESP of such calixarene complexes (Figure 6A).^[108] Such linear free energy correlations began in the 1990s to play a major role for the identification and quantification of noncovalent interactions in supramolecular complexes^[110]; Figure 6B illustrates how interactions of metal ions such as K^+ with oxygen atoms in crown ether or cryptands can be ascribed to electrostatic donor capacities ED derived from hydrogen bond measurements.^[109]

Halogen bonds, interactions between halogen atoms, acting as Lewis acids, and neutral or anionic acceptors (or Lewis bases) have been evaluated more recently, in the gas phase already in 1970,^[111] then in particular in solid state,^[112] and with a variety of organic receptors for anion or ion pairs in solution.^[113]

Investigation of host-guest complexes with cavities of different shape and volume brought rather late experimental evidence for a nonclassical^[114] hydrophobic effect. In cavities like those in cucurbiturils (Figure 7A), there are high energy water molecules with an insufficient number of interhydrogen bonds; occupation by a guest leads to release of these and formation of up to four

hydrogen bonds in bulk water with a significant enthalpy gain.^[115] A similar, although weaker high energy water effect holds for cyclodextrins, a neutron diffraction study showed already in 1984 the presence of six water molecules inside the β -CD cavity, which involve much less than four hydrogen bonds that are possible in bulk water.^[116]

12 | COMPUTATIONAL APPROACHES

It was the advent of modern computers which made extensive theoretical analyses of molecular complexes to a widely used application. The development of computational methods also with respect to noncovalent interactions led to an enormous amount of publications and can be found in several books and reviews^[117]; here only some of the early important contributions will be mentioned. Fritz London was the first to use quantum chemical methods for the description of dispersive forces (see Section 6).^[38,118] Other early papers on quantum chemistry, making use of pseudopotentials, are due to H. Hellmann.^[119] The application of wave function theory needs very large basis set calculations.^[113] For the calculation of electron-pair correlation, or dispersive effects, Møller and Plesset described in 1934 how the Hartree-Fock method can be used on the basis of second-order perturbation theory (MP2).^[120] Over

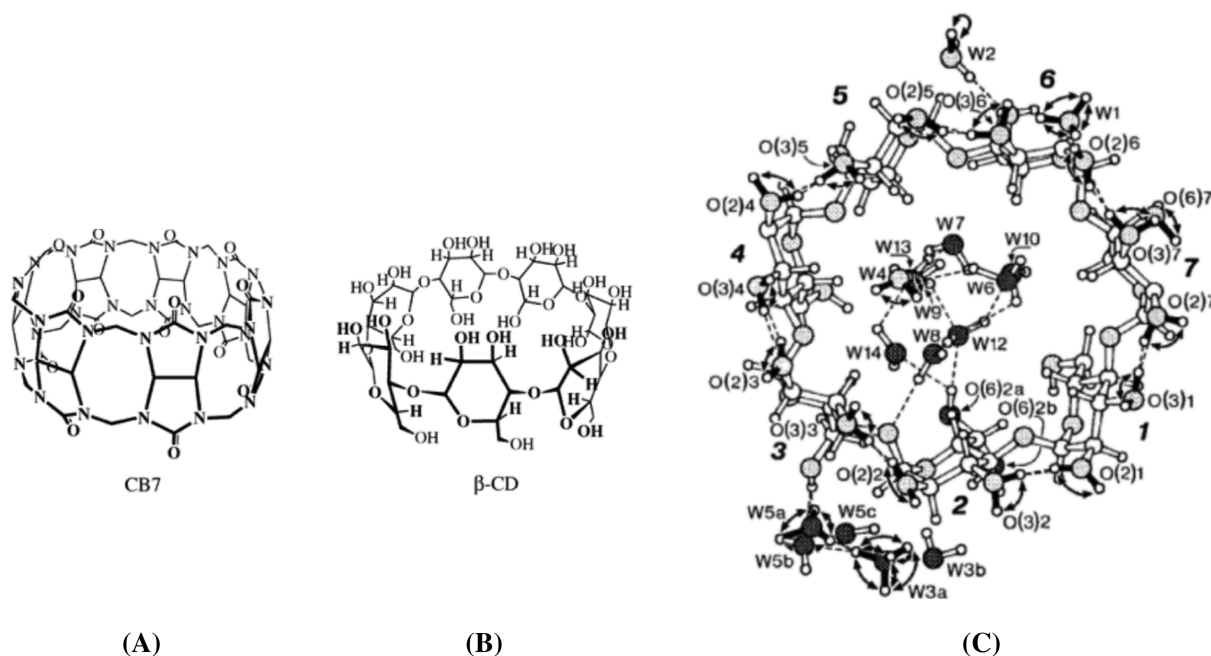


FIGURE 7 Guest molecules that contain high energy water (A) a cucurbituril, (B) β -cyclodextrin, and (C) neutron diffraction of β -cyclodextrin with six water molecules inside^[116]

40 years later, Morokuma et al developed their ab initio SCF theory description, decomposing the interaction energy into electrostatic, polarization, exchange repulsion, charge transfer, and coupling components.^[121] The widely used density functional theory (DFT) requires significantly less computing power and is applicable also to large molecules, and it goes back to the original paper by Kohn and Sham in 1966.^[122] Some 200 different non-empirical and semi-empirical density functionals have been developed since then,^[123] one of the most popular stems from 2010.^[124] Force fields with terms for non-bonded interactions on the basis of Lennard-Jones potentials^[48] (see Section 6) allow fast simulations of large assemblies, and were introduced in the late 1960s,^[125] later with more explicit functions.^[126]

13 | CONCLUSIONS

For centuries, the seemingly weak interaction between molecules has been a subject of curiosity, mainly between specialists, and was often more a matter of speculation. As often, the scientific development did not always follow logical steps, as seen in the rather late appearance of papers on hydrogen bonds. From the end of the 19th century, modern instruments allowed exact structure determinations and measurements, which soon led theoretically interested scientists to promising fundamental analyses of noncovalent interactions. Interest in the related forces increased significantly with the importance of biological interaction mechanisms and with the countless applications of supramolecular complexes, including new materials. The development of related studies is characterized by an enormous increase of related publications, which will be more difficult to summarize in a single review or book.

ACKNOWLEDGEMENT

The author acknowledges the help of Professor Anatoly Yatsimirsky and of a reviewer who both provided helpful suggestions. Open Access funding enabled and organized by Projekt DEAL.

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How to cite this article: H.-J. Schneider, *J Phys Org Chem* **2022**, *35*(7), e4340. <https://doi.org/10.1002/poc.4340>