

1 Introduction

Parts of this chapter previously appeared as

Activation Strain Model & Molecular Orbital Theory

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The Many Faces of Halogen Bonding: A Review of Theoretical Models and Methods

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1.1 Theoretical Chemistry

Chemistry is, roughly speaking, the branch of the natural sciences investigating the properties, composition and transformation of matter. Within theoretical chemistry, this is done not by observation, but by a mathematical description of the physical system of interest. The field is also referred to as ‘quantum chemistry’ or ‘computational chemistry’, because often the descriptions are derived from quantum mechanics, and a large amount of computer power is required to solve the complicated equations. The constant improvement in the quality of mathematical descriptions, combined with the enormous advancement of computer technology in the past decades, has allowed the field of theoretical chemistry to advance as well. Nowadays, it is feasible to computationally study a large variety of molecular systems and chemical processes with, for many purposes, sufficient accuracy.

Although some of the romance of doing practical experiments is lost, theoretical chemistry opens up a whole new world of research by eliminating many practical limitations. Theoreticians can, for example, safely study explosives, recklessly experiment on expensive materials, investigate processes on timescales too short to be measured, or too long

to be observed, or obtain insight into interstellar processes from a comfortable office chair. Theoretical models can also be helpful to gain insight into a synthetically useful chemical reaction that, however, does not occur, and therefore cannot be studied experimentally. Such a process can be studied *in silico* to reveal the reasons why it is not viable, and what can be done to change this situation for the better.

Moreover, one can achieve a fundamental understanding of a certain chemical aspect based on the theoretical description itself. Whereas many experimental studies are only descriptive of a phenomenon, theoretical sciences can go one step further and often provide an explanation, and thereby understanding, of the phenomenon. Within this thesis, such an understanding is sought for several aspects of the oxidative addition reaction, as well as for the mechanism of halogen bonding interactions. Both phenomena involve the stretching, and eventually breaking, of a chemical bond, and involve charge transfer from one molecular moiety to another.

1.2 Oxidative Addition

Catalysis is typically described as increasing the rate of a chemical reaction due to the participation of an additional substance, without changing its outcome. The additional substance then acts as a catalyst, and must not be consumed in the process. The increased rate of the chemical reaction is achieved by lowering its activation energy: the minimum energy needed for a chemical reaction to occur. Thus, catalysis can lead to significant energy savings. Besides, when the rate of the desired reaction is enhanced compared to that of an unwanted side reaction, catalysis can lead to significant waste reduction. In an era of growing human energy demands and environmental concern, the importance of catalysis is therefore evident.

An important class of chemical reactions involving catalysis is that of coupling reactions.^[1-22] These reactions are carried out to form carbon-carbon bonds, which are the basis of organic molecules, and thereby the very basis of the chemistry of life itself. In these reactions, often a homogeneous catalyst is used, meaning that the catalyst is codissolved in a solvent with the reactants. Figure 1.1 shows a schematic representation of a generic catalytic cycle for a coupling reaction catalyzed by a transition metal complex ML_n . More specifically, the scheme features an example of a cross-coupling reaction, since the coupling partners in this case are not identical.

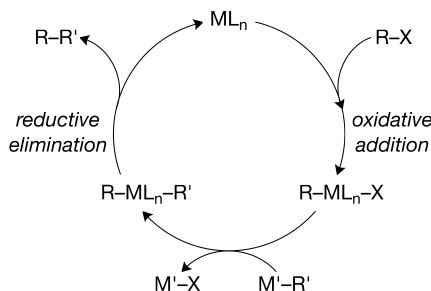


Figure 1.1 General catalytic cycle for a metal-catalyzed cross coupling.

The first step in many coupling reactions is the oxidative addition of a substrate RX to the metal center of a catalyst, thereby breaking the $R-X$ bond, while simultaneously forming new $M-R$ and $M-X$ bonds. In subsequent steps X is replaced by R' , and by reductive elimination, which is the reverse reaction of oxidative addition, the product RR' is obtained, and the catalyst ML_n recovered.

The oxidative addition step is of crucial importance for both the efficiency and selectivity of the process, and also plays a role in, for example, hydroformylations, hydrogenations and $[2+2+2]$ cyclotrimerizations.^[2] This reaction step has therefore been studied extensively using experimental,^[9,13,23-31] as well as theoretical techniques.^[7,8,32-35] The catalysts used in practice are typically based on a late transition metal, such as palladium, to which ligands are attached. The activity of the catalyst complex depends on the electronic nature of the metal center, which is affected by the number and type of ligands, as well as the structural properties of the catalytic complex.^[36-48] Of these structural parameters, the bite angle, that is, the ligand-metal-ligand angle, is probably the most notable parameter that is adjusted in attempts to achieve the desired reactivity.^[49-56]

Besides these examples, there are several other parameters that influence the characteristics of a catalytic complex. Therefore, the reactivity of a catalyst is, unfortunately, difficult to predict, and selecting a catalyst is still too often a process of trial-and-error. Theoretical chemistry can play an important role in facilitating this selection process, because it allows systematic variation of one parameter at a time, under strictly controlled conditions and without any experimental limitation. Simultaneously, the added benefit of available analysis tools allows for an explanation of the observed effects and eventually their interplay. A significant part of this thesis is therefore dedicated to the oxidative addition reaction and the role of the catalyst. It is part of an extensive research line, which aims at

achieving a fundamental understanding of the reactivity of catalyst complexes in the activation of different target bonds. This strategy of gradually building up insight into catalytic activity, starting from detailed studies on the effect of one variation in small model systems and eventually proceeding towards combinations of several effects in more realistic, larger systems, has been termed ‘Fragment-oriented Design of Catalysts’.^[57-60] Its aim is to allow chemists in the future to rationally design catalysts with the desired selectivity and optimized efficiency.

The purpose of several of the following chapters is to explain how reaction barriers and reaction energies change when certain aspects of the catalysts are modified in a systematic manner. To explain the observed effects, the bonding mechanism between molecular fragments had to be further elucidated, in order to obtain a better understanding of the intrinsic structural properties of the catalyst complex. Thus, in chapter 3, the geometries of a number of dicoordinated d^{10} - ML_2 complexes are investigated. The metal center M is varied along the metals from group 9, 10 and 11 from the first three transition metal rows of the periodic table, that is, Co^- , Rh^- , Ir^- , Ni , Pd , Pt , Cu^+ , Ag^+ and Au^+ . The ligands are varied along NH_3 (a strong σ donor), PH_3 (a σ donor and π acceptor) and CO (a strong π acceptor). Although such d^{10} - ML_2 complexes are generally assumed to have linear ligand-metal-ligand angles, this chapter describes a variety of ML_2 complexes with significantly smaller angles, and, by careful studies on the bonding mechanism of the metal-ligand bonds, the origin of this nonlinearity is uncovered. It is shown that steric effects favor a linear ligand-metal-ligand angle, but that π -backbonding interactions favor nonlinear geometries. When the latter are sufficiently strong, d^{10} - ML_2 complexes can become bent. Chapters 4 and 5 elaborate on these findings by including more bulky ligands, namely the series PH_3 , PMe_3 , $PiPr_3$, $PtBu_3$, PCy_3 and PPh_3 , and the series along PF_3 , PCl_3 , PBr_3 and PI_3 . These chapters provide insights into how to achieve a nonlinear ligand-metal-ligand angle and how to adjust this bite angle via both electronic, as well as steric mechanisms. These chapters also include a brief discussion on the consequences of this nonlinearity for the reactivity of the catalyst complexes in oxidative addition reactions.

Chapter 6 then discusses how the reaction barrier for oxidative addition of the methane C–H bond is affected by the nature of the metal center and the presence of different types of ligands. To this end, a large and consistent set of 72 model reactions is studied. Based on the results, combined with those of the preceding chapters, new light is shed on the nature of the bite angle in oxidative addition reactions. Interestingly, it is not the value of the bite angle itself that is important, but rather the flexibility of the catalyst towards

assuming a nonlinear ligand-metal-ligand angle during the bond activation process. Furthermore, the results show that the choice of metal and ligands not only determines the bite-angle flexibility, but also the catalyst's binding capability towards the substrate. The concepts of the d regime and the s regime of catalysts are introduced. In the former, the primary mode of catalyst-substrate interaction is electron donation from the catalyst's d hybrid orbitals to the σ^* acceptor orbital of the substrate, whereas in the latter the catalyst's s hybrid orbital acts as an acceptor for electrons donated from the σ orbital of the substrate. The results indicate that ligands affect the electronic nature of the catalyst similarly within each regime. Importantly, however, since the catalyst takes opposite roles in the dominating donor-acceptor interactions present in these regimes, the effect of ligands on the reaction barrier can be reversed when switching between d-regime and s-regime catalysts. Altogether, the results reveal causal relationships between oxidative addition reaction barriers and the orbital-electronic and structural properties of the catalyst complex.

In chapter 7 the oxidative addition of the ethane C-H and C-C bonds is studied, using the same large and consistent set of catalyst complexes. The concepts introduced in chapter 6 are validated, but, more importantly, also subtle differences are revealed between the ethane C-H and C-C bond, as well as between the methane and ethane C-H bonds. Based on a careful understanding of the differences between these bonds and by applying the previously introduced design principles, catalyst complexes are devised that allow selective activation of each of these bonds.

Although there are several important new insights discussed in these chapters, additional studies will be required for the actual optimization of a catalyst for a specific process. This is only in part because there are still many more possible combinations of metal centers and ligands that can be included, as well as a plethora of variations of the substrate, and also the effects of different reaction conditions and possible side reactions. Note, however, that one should not only consider the reaction step in which the overall reaction barrier occurs, but also take into account the stability of intermediate species that occur during the catalytic cycle. For kinetic assessments of catalytic cycles, which is not pursued in this thesis, the energetic span model has been developed.^[44,61-63]

1.3 Hydrogen Bonds and Halogen Bonds

Hydrogen bonds are one of the most important intermolecular interactions known.^[64,65] Being responsible for unique features of water, as well as playing a key role in the structure

of DNA and its replication, the importance of hydrogen bonds for human life can hardly be overestimated. A hydrogen bond, $DH\cdots A$, is a bonding interaction that typically occurs between a hydrogen, H, bound to an electronegative atom D, such as nitrogen, oxygen, or a halogen atom, and a second electronegative atom A. Of course, D and A can be part of a larger molecular structure, as for example in the Watson-Crick base pairs in DNA. In a hydrogen-bonded molecular moiety, some of the electron density around hydrogen will be shifted towards the electronegative atom D, leading to a partial positive charge δ^+ located on the hydrogen atom. Based on this feature, hydrogen bonds are often considered to arise due to the electrostatic attraction that occurs between this partial positive charge on the hydrogen, and the partial negative charge δ^- on the electronegative atom A (see Figure 1.2a). It should be noted, however, that although the electrostatic component of the bonding interaction is important, it has been shown that a description based on merely Coulomb attraction is incomplete.^[66]

In analogy to the hydrogen bond in $DH\cdots A$, a halogen bond can occur in $DX\cdots A$, where the hydrogen atom H is replaced by a halogen atom X. Halogen bonds are known for already more than 150 years,^[67] and nowadays receive interest from chemists working in various fields,^[68,69] such as supramolecular chemistry,^[70-77] and biochemistry.^[78-83] Often it is found that halogen bonds can, both in terms of practical applications and bond strength, compete with hydrogen bonds.^[84-92] This has led to a comparison of the nature of their bonding mechanism, but applying a similar explanation based on electrostatics to halogen bonds makes little sense, as a partial positive charge would then be assigned to the central halogen X. This directly opposes chemical intuition, since halogens are well known to be electronegative elements.

However, experimental studies^[85,93-95] on intermolecular interactions involving halogen atoms suggest that the electron density around a covalently bound halogen is not isotropic, but, in fact, oblate: it is slightly flattened along the extension of the D–X bond. Around the halogen atom X, the electrostatic potential therefore often shows a region of positive sign at this flattened area, meaning that a negative point charge at that location would experience net Coulomb attraction in the direction of the nuclei of the X atom.^[96] Based on this finding, the region of positive electrostatic potential, termed the σ -hole,^[97] has been put forward as an explanation of the halogen bond, similar to the hydrogen bond, in electrostatic terms, as shown schematically in Figure 1.2.

Interestingly, there is indeed often a correlation between the magnitude of the σ -hole and the strength of the halogen bond, as well as between the location of the σ -hole and the

directionality of the halogen bond. Carefully conducted numerical control experiments, however, demonstrated a number of failures of the σ -hole description. It has been shown that, when the $D-X\cdots A$ angle in the halogen-bonded compound is bent around the central X, the electrostatic attraction often increases in strength, despite the fact that the electro-negative A is no longer facing the σ -hole. Thus, the directionality of the halogen bond is a result of minimizing repulsive interactions, and is not related to the electrostatic interactions with the σ -hole.^[98-100] Furthermore, there are documented examples of series of halogen-bonded compounds with increasingly strong interaction energies and electrostatic attraction, even though the maximum potential at the position of the σ -hole becomes less positive.^[101] Taking into account a polarization-induced strengthening of the σ -hole^[102] does not resolve the discrepancy.

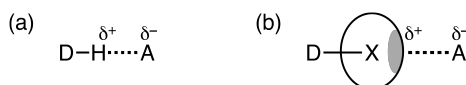


Figure 1.2 Schematic depiction of (a) a hydrogen bond $DH\cdots A$ with partial charges indicated, and (b) an analogous halogen bond $DX\cdots A$ showing the anisotropic charge density around the halogen atom X which gives rise to a region of positive electrostatic potential, indicated by the shaded area.

The σ -hole description fails primarily because the molecular electrostatic potential on an isodensity surface of the DX fragment reveals the Coulomb interaction with a point charge, while, on the scale of atoms, the properties of fragment A are significantly different from those of a point charge: it has a three dimensional, diffuse electron density extending in all directions in space. The shortcomings of a description in which both fragments are perceived as point charges (Coulomb attraction between partial atomic charges) can not be completely resolved by treating one fragment as a three dimensional structure, while still treating the other one as a point charge, as is done in the σ -hole model. Ironically, however, the erroneous conceptual reduction of atoms to point charges is sometimes presented as an argument in favor of a description based on the molecular electrostatic potential!^[103] Furthermore, descriptions using the molecular electrostatic potential neglect the overlap of the wavefunctions of the interacting fragments. The interactions are not only electrostatic in nature: quantum mechanical effects and properties have to be considered as well.

Proponents of the σ -hole hypothesis have argued in favor of a simplified description of the bonding mechanism, limited to mainly electrostatics (with some contributions from

polarization and dispersion^[104]), and to omit the contribution of charge transfer, because it is hard to make a physical distinction between charge transfer and polarization. Also, it has been argued that, ultimately, the two are the same, because they can both be described by overlapping an occupied orbital with an unoccupied one.^[105] The two arguments are not particularly strong. Indeed, it is true that the boundary between charge transfer and polarization is not easy to define, but this might also be perceived as an argument to abandon this dichotomous view, and to consider the terms as describing two parts of a continuous spectrum. Furthermore, within a fragment-based description, which is not an unreasonable starting point to describe the bonding between molecular moieties, these terms refer to two effects that can be separated conceptually: polarization can be regarded as the reorganization of the density of one fragment due to the electric field induced by the presence of the other fragment, whereas charge transfer is used to indicate a net depletion of density on one fragment, because part of its density is transferred to the other fragment. Still, this does not mean that the two effects can be rigorously separated and their individual importance can be uniquely quantified (which is therefore also not attempted in many energy decomposition schemes, such as the EDA method applied throughout this thesis and discussed in section 2.6). However, this also does not constitute a valid reason to leave charge transfer out of the description of the bonding mechanism, and most certainly not when the purpose of this omission is to reduce the description to one that is based on misleading, and conceptually flawed molecular electrostatic potential plots.

In a number of instances, also the principle of Occam's razor (also known as Ockham's razor, or *lex parsimoniae* in Latin) has been inferred as an argument to limit the description of halogen bonds to mainly electrostatics.^[105] Sometimes, this argument is accompanied by an appeal to authority, quoting J. W. Gibbs: "*One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity*".^[104,105] However, to state that Occam's razor dictates that the most simple explanation should be preferred, is a misrepresentation of this important principle. Modern-day science philosophers more commonly interpret the principle as stating that, out of several competing possible explanations, the one that introduces the fewest new assumptions should be preferred. But, most importantly, this principle only applies after the first selection procedure, which is the assessment of (i) the agreement between the description and empirical data, and (ii) the quality of the predictions that are made using the model. Therefore, it seems unlikely that Gibbs would have advocated a literal interpretation of his cited quote. A more suitable, but of course equally fallacious

appeal to authority, would be “*Everything should be kept as simple as possible, but no simpler*”, which is commonly attributed to Albert Einstein, although its origin has never been verified.

Although the mechanism of halogen bonds (and probably many other chemical interactions) cannot be accurately described by molecular electrostatic potential plots, investigating these plots has nevertheless led to the improvement of force fields to describe halogen bonding interactions with classical molecular mechanics (MM) methods.^[106-109] These methods are unable to account for the quantum chemical effects that play such an important role in halogen bonds. By adding a virtual particle with a partial positive charge within the Van der Waals region of the halogen atom to mimic the σ -hole, some of the stabilization due to quantum chemical effects (charge transfer) can be recovered by the induced additional electrostatic interactions.

To obtain not only a truly satisfying level of understanding for these interactions, but also to consolidate the physical description with results obtained by studies on other subjects in chemistry, many studies have been performed to unravel the nature of hydrogen bonds,^[110-117] and halogen bonds.^[84,86,99-101,118-127] A number of studies directly compared the two interactions.^[85,90-92,128-131] In chapter 8 a detailed comparison of the bonding mechanisms of both halogen bonds and hydrogen bonds is presented in terms of molecular orbital theory. To this end, a range of strongly halogen-bonded trihalides $\text{DX}\cdots\text{A}^-$ and analogous strongly hydrogen-bonded hydrogen bihalides $\text{DH}\cdots\text{A}^-$ (with D, X and A being one of the halogens F, Cl, Br or I) is subjected to extensive computational analyses. Through a variety of analysis tools, it is shown that both bonding interactions can be explained at a satisfactory level with molecular orbital theory: both types of bonds arise because of significant donor-acceptor orbital interactions, which occur on top of electrostatic interactions.

Chapter 9 demonstrates the similarities between hydrogen bonds and halogen bonds even further. Earlier work already provided a detailed description of the hydrogen bonds in Watson-Crick base pairs in terms of molecular orbital theory.^[114,132,133] More recently, also the cooperative effect observed in guanine quartets has been elegantly explained.^[115] Guanine quartets consist of four essentially coplanar guanine bases that interact via hydrogen bonds in a circular pattern. These quartets occur in the telomeric part of the chromosome and play a crucial role in protecting the genetic code. It is known that the total bonding energy of such guanine quartets is more strongly stabilizing than four times the hydrogen bond energy of one pair of guanine bases. Within this chapter, it is investigated whether these characteristics are retained when the hydrogen bonds in the naturally occurring hy-

drogen-bonded base pairs and quartets are replaced by halogen bonds. The resulting halogen-bonded *N*-halo-base pairs and *N*-halo-guanine quartets are found to indeed possess the same characteristics, again indicating that hydrogen bonds and halogen bonds are similar in nature. Moreover, these results provide evidence that the physical description given in chapter 8 is equally valid for more realistic, and more weakly interacting complexes, and that a description in purely electrostatic terms is insufficient.

