Monitoring of

Chemistry under Non-Classical Conditions

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Summary

The rapid development of the analytical methods available to the scientific community forces a cycle of learning, using, and replacing with every new iteration. While Electrospray Mass Spectrometry is relatively young compared to other methods, it has already gained wide acceptance and a broad number of applications, including mechanistic studies of organometallic reactions, the main topic of the present work. To extend its applicability to the realm of chemistry under high-pressure and non-classical conditions a special setup was envisioned, built, tested and challenged in real-world problems like the mechanistic study of palladium catalyzed hydrogen transfer and rhodium catalyzed hydroformylation reactions. The first one of these two topics was carried to the point were a reproducible proof-of-concept was achieved. The second one was carried out beyond that point because a more detailed picture of the mechanism as well as the role of the ligands involved could be obtained.

Our new setup, designed for the purpose of on-line monitoring and analysis of reaction mixtures proved invaluable for the production of species that have not been spotted in solution and to determine some of their reactive pathways. While a 1:1 translation of gas-phase chemistry to solution cannot be made at this point, the results obtained allow for a better, more focused study of processes that occur in solution.

Zusammenfassung

Die schnelle Entwicklung der für die chemische Forschung zur Verfügung stehenden analytischen Methoden erfordert einen stetigen Zyklus von Erlernen, Anwenden und Ersetzen mit jedem neuen Schritt der Entwicklung. Obwohl die ESI Massenspektrometrie im Vergleich zu anderen analytischen Methoden relativ jung ist, hat sie bereits heute weitgehende Akzeptanz und eine große Zahl an Anwendungsmöglichkeiten erlangt. Zu diesen Anwendungen gehören auch mechanistische Studien bezüglich organometallischer Reaktionen, die die Hauptthematik der momentanen Arbeit bilden.

Um die Anwendbarkeit der Massenspektrometrie auf das Gebiet der Chemie unter Hochdruckbedingungen und der Chemie unter nicht-klassischen Reaktionsbedingungen auszudehnen, wurde ein spezieller Messaufbau konzipiert, aufgebaut, getestet und mit realen, chemischen Problemstellungen konfrontiert. Beispielsweise wurden mechanistische Studien zu palladiumkatalysierten Wasserstofftransferreaktionen und rhodiumkatalysierten Hydroformylierungsreaktionen durchgeführt.

Das erstgenannte Projekt konnte soweit vorangetrieben werden, als daß es als proof-ofprinciple für das Gesamtkonzept angesehen werden konnte.

Das zweite Projekt konnte zu einem noch weiterführenden Punkt entwickelt werden, da es gelang, sowohl den Reaktionsmechanismus aufzuklären als auch die Rolle der einzelnen, involvierten Liganden durch massenspektrometrische Beobachtungen zu erklären. Der neuartige Messaufbau, mit der Absicht konzipiert, Reaktionsabläufe direkt zu verfolgen und die Analyse von Reaktionsmischungen zu ermöglichen, hat sich inbesondere bei der Erzeugung und Detektion von labilen Spezies bewährt, die bislang mittels "konventioneller" Analyseverfahren wie NMR, IR usw. nicht untersucht werden konnten. Ebenso konnten einige Reaktionswege dieser Spezies aufgeklärt werden. Obwohl an diesem Punkt keine 1:1-Gleichsetzung von Gasphasenchemie und Chemie in Lösung getätigt werden soll und kann, erlauben die erhaltenen Ergebnisse detaillierte und somit auch tiefere Einsichten über die in Lösung ablaufenden Prozesse.

1. Introduction

1.1 The quest

It is well known from the literature that thermochemical data, kinetic studies and thus mechanistic information are lacking for many of the common organometallic reactions in use nowadays. In quest for better yields and selectivity, many chemists forget that the lack of insight in the reaction hide the real path to these goals, reducing their efforts to a repetitive and wasteful trial-and-error method also disguised as combinatorial approach.[1] For more than a decade our group has been making steady inroads in the field of mechanistic studies.[2] Cited work deal with specially crafted reactions and compounds, i.e. the reactants were modified or the conditions were adjusted in a way that allowed unencumbered analysis using a tandem mass spectrometer. Nowadays our group can take advantage of a new approach to obtain insight into organometallic reactions; the combined use of several new techniques, known as Non-Classical Conditions, coupled with the powerful analytical tool that is a tandem mass spectrometer. The following paragraphs describe in detail the features and advantages of these non-classical conditions together with a description of the usefulness of mass spectrometry in such studies.

1.2 Non-Classical Conditions

Under the name of non-classical conditions several methods and conditions to perform chemical reactions are known, namely supercritical fluids, gas-expanded liquids, ultrasound and microwave irradiation.[3]

1.2.1 Supercritical fluids

A fluid becomes supercritical in the zone of $Tr \sim 1-1.1$ and $Pr \sim 1-2$ (Tr and Pr are reduced temperature and pressure: Tr = T/Tc, Tc: critical temperature, T working temperature, Pr = P/Pc, Pc: critical pressure, P working pressure), where densities are a fraction of the liquid density, existing as a single phase. This new fluid possesses characteristics of both liquids and gases. Mass transfer is one of the most affected properties, due to the lower than liquid density and viscosity.[4-7] Solubility is also greatly affected compared to the gas.

Compatible solutes can become much more soluble due to the higher density and diffusivity. The useful properties of some supercritical fluids (SF) do not correlate to the better mass transport. Due to the fact that at room temperature and pressure some of them are gases, separation of reactants and products can become as easy as uncompressing the reactors' content. One important advantage is the ability to tune the solvent. Mixing small amounts (few percent) of alcohols or acids change the polarity of the media, increasing or decreasing solubility as needed, giving more control over the reaction.[8] Successful application of SF unique properties has been made for extraction and purification, like coffee extraction, [4, 5] but their usefulness does not stop there, and applications to organic synthesis, specially in catalysis are also abundant. [9-11] Among other properties, SF tend to be more benign to the environment than organic solvents, so its use and applications are growing steadily. [12]

1.2.1.1 Catalysis under supercritical conditions

Since their introduction many years ago, SFs have gained notable attention and multiple application to catalytic processes. Hydroformylation, a very useful and widely used industrial method of extending the carbon chain and introducing versatile functionalization, [13], was successfully implemented using continuous reactors and supercritical CO₂. Poliakoff and co-workers reported very good linear to branched ratios and around 14 % yield of aldehydes when an immobilized rhodium catalyst was used together with terminal olefins. [14] The advantages of continuos flow reactors combined with SFs are enhanced due to the very nature of supercritical conditions. In this case separation of products and reactants occurs during expansion of CO₂.

Alkylation of alkanes for the petrochemical industry yields high-priced products for the petrochemical industry, like naphtha. Mineral acids are used as catalysts with the drawback of corrosion of reactors and environmental impact. This kind of alkylation can be performed under supercritical conditions using CO₂ and Y-type zeolites to produce octanes starting from butene and isobutane, as reported by Santana and Akgerman. [15] Separation of liquid products from gaseous reactants is again achieved through simple expansion after reaction. This process was also carried out using a continuous flow reactor with great success.

Friedel-Crafts alkylation of arenes requires a Brønsted-type acid in equimolar amounts to the reactants.[16] A number of alternatives have emerged in the literature lately. [17-24]

Solid reusable catalysts have emerged providing a more environmentally friendly alternative to a traditionally wasteful reaction. Several commercial sources for these catalysts exist nowadays, from companies like DuPont and Degussa. To assess their effectiveness under supercritical conditions, Poliakoff and coworkers tested the alkylation of anisole with n-propanol successfully. Very good yields and selectivity were obtained. [25]

All these findings demonstrate clearly the potential of SF in industrially important synthesis.

1.3 Ultrasound irradiation

Ultrasonic waves produce cavitation, i.e. formation of gas or vapor bubbles and clouds of bubbles in liquids. This interaction of the sonic waves with matter does not affect vibrational or electronic levels of atoms and molecules. [26] Cavitation can be generated by acoustic means: a vibrating element inside the medium will produce waves, and dissolved gas or evaporation of liquid will give rise to cavitation; or via hydrodynamic forces: a propeller that rotates inside the medium will produce similar effects when rotating fast enough (normally around tens of thousands of revolutions per minute).[27] Two theories exist to describe the chemical effects of cavitation. An older model, called the hotspot theory by Noltingk and Neppiras, [28] and a more modern theory in better accordance with experimental results proposed by Margulis.[29] From his theory it is derived that cavitation is directly influenced by frequency. At low frequencies bubbles last few cycles and grab small amounts of volatile compounds. At higher frequencies, they last many more cycles and collect larger amounts of volatiles from the medium.[30] At the end of its life, the bubble collapses, producing temperatures as high as 5000 K and pressures on the order of tens of MP. [26] These extreme conditions produce highly reactive radicals that, if carefully managed, can afford useful products.[31, 32]

Synthetic application of ultrasound can be found for a range of frequencies that go from 20 kHz to about 2 MHz.[33] Between 20 to 100 kHz commercial equipment up to several kW exist, but in the upper range of 100 kHz to 2 MHz output power is limited to around 100 W. Experiments show that acoustically useful power is not always dependent on electrical power at the output, for example hydroxyl radical production is several times higher at 520 kHz than it is at 20 kHz at the same output power.[34]

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The first applications of ultrasound in organic synthesis were viewed as a convenient mixing technique, [35] but further work proved that other, beneficial advantages existed, such as improved yields, shorter reaction times and milder conditions when compared to more classical approaches. [26, 36-40]

Nowadays it is accepted that other effects exist. Ando et al. were the first to report that the path of the reaction can be influenced. They found that a reaction that under normal conditions gives Friedel-Crafts alkylation, under ultrasound irradiation undergoes substitution at benzylic position.[41]

Two ways of ultrasonic irradiation (also known as sonication) exist nowadays. A direct approach where the ultrasonic probe is submerged in the reaction medium, thus transferring the maximum energy. And a milder, indirect method where the ultrasonic transducers are at the walls of a bath that contains the reaction vessel. This latter approach is often used when only mixing is desired.

1.4 Electrospray Mass Spectrometry

Electrospray mass spectrometry (ESMS) is a technique that allows ions present in solution to be transferred to the gas phase with minimal fragmentation, followed by conventional ion-molecule techniques and eventual mass-spectrometric characterization. Three features of electrospray set it apart from other mass-spectrometric ionization techniques. The first is the truly unique ability to produce extensively multiply charged ions. This attribute allows the creation of highly charged forms of very large molecular-weight compounds which may be analyzed on virtually all types of mass spectrometers. A second distinguishing feature of ESI is that samples under analysis must be introduced in solution. A third unique feature is the extreme softness of the electrospray process which permits the preservation in the gas phase of weakly binding interactions between molecules which existed in solution. ESMS has been widely used for the measurement of molecular masses of non-volatile and thermally unstable compounds.[42] Characterized by soft ionization, ESMS in the beginning had its most spectacular successes in the area of mass spectrometry of large biomolecules. Strangely, despite the enormous impact of electrospray on the mass spectrometric characterization of biomolecules, applications to inorganic and organometallic chemistry had been lagging somewhat behind. With hindsight, there is no reason why ESMS should have been restricted to large protonated molecules such as proteins and, in principle, any cation or anion that is present in solution

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and more or less stable in the solution environment can in principle be transferred to the gas phase by electrospray. Thus, all ionic inorganic coordination and organometallic compounds, together with neutral compounds that can be chemically converted to a closely related ion, are potential candidates for ESMS studies. There are a number of practical advantages in ESMS with inorganic/organometallic compounds as compared to biochemical samples. Charges on most inorganic cations are small, and often only singly charged ions are observed in the ES mass spectrum, because multiply charged ions frequently form ion-pair adducts with either the counter ion in the solution or other anions available. Hence, the characteristic isotopic patterns of metal ions are readily resolved even by quadrupole mass analyzers, and unambiguous identification of metal-containing species is thus possible. Straightforward analytical applications of ESMS to organometallic and transition-metal coordination chemistry have become more or less standard nowadays. Because of the ease and speed of transferring all solution-phase ions to the gas phase, ESMS has become increasingly popular as a mechanistic tool for studying short-lived reactive intermediates in organometallic catalytic cycles. More recently, the potential of ESMS for mechanistic studies of ion-molecule reactions by electrosprayed organometallic ions has started to be exploited.

What might one hope to learn from gas-phase ion studies of organometallic compounds? After all, it is extremely unlikely that any chemistry in a gas-phase ion system will translate into a commercial reaction or catalyst operating in the gas phase. Condensed-phase chemistry dominates organometallic studies and processes, but it is possible to refine the understanding of such reactivity through the study of analogous gas-phase chemistry. The next several paragraphs summarize some of the main issues that can be addressed, in principle, through the study of gas-phase ion chemistry.

Solvent effects and intrinsic reactivity: In the case of ions, in particular, the role of solvation in determining the chemical properties of molecules cannot be overlooked, and gas-phase studies offer the promise of eliminating such effects and revealing the underlying intrinsic reactivity of organometallic molecules. Often chemists tabulate and rationalize chemical reactivity based on the molecular and electronic structures of the species, ignoring the contributions of solvation to thermochemical trends, rates of reactions, etc. The impact of removing solvent on basic chemical properties, as investigated in gas phase chemistry, has led to some reevaluations of this "molecular centered" view of chemistry. For example, one of the major revolutions of understanding in acid-base chemistry arose from classic gas-phase ion studies done over 35 years ago. It was shown that the order of gas-phase

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acidity and basicity for series of acids and bases can be quite different in the gas phase, revealing that the strength of an acid or base in solution is strongly influenced by solvation, even to the point of reversing trends due to changes in substituents.[43-50] More recently it was shown that alkyl substituents effects in the electrode potentials of nickelocenes and transition metal β -diketonate complexes could be reversed when going from polar solvents to the gas phase.[51] In addition to thermochemical changes, solvation has profound kinetic consequences. For example, approximately 20 years ago it was shown that polar solvents reduced the rate constants of organometallic ion-molecule electron transfer reactions (e.g., MCp²⁺/0 self exchange) from the gas-phase rate constants by a factor of ~10⁴, in general agreement with theories that had been accepted but not directly tested until then.[52]

Ancillary ligand effects: The extraordinary reactivity of bare metal ions (M⁺) compared to their ligated counterparts (ML_n⁺) shows how dramatically bound ligands can alter the reactivity of metal ions. Such observations clearly demonstrate the role of electronic structure in determining reactivity. For example, the cobaltocenium ion (CoCp₂⁺) is a rather unreactive 18-electron gas- phase ion,[53] but Co⁺(g) reacts rapidly with strong C-H bonds in alkanes. Gas-phase ion-molecule studies can also reveal more subtle effects of ancillary ligand changes on reactivity, again without the potentially confusing interference of solvent. For example, variations in the ligand (L) environment of $L_2ZrCH_3^+(g)$ will alter the intrinsic electrophilicity of the metal center as revealed by the kinetics of reactions with a variety of substrates such as H₂ and C₂H₄,[54] and such results are useful in interpreting experimental and computational data for condensed-phase Zr polymerization catalysts.[55]

Aggregation and ion-pairing: In the study of ionic condensed-phase organometallic catalysts and reagents, it is often found that ion-pairing and/or aggregation phenomena can greatly complicate mechanistic understanding of their reactions. One clear advantage of gas-phase studies is that ions can be readily isolated from other ions and neutrals, thereby allowing one to observe intrinsic reactivity of the ion. Any pairing or aggregation that does occur is generally easy to quantify since exact mass spectrometric methods are used. For example, the $L_2ZrCH_3^+(g)$ species reacts in an ion trap as the cation without the perturbing influence of ion pairing, which controls the solution reactivity to a large degree. [55, 56]

The transition from metal clusters to surface chemistry: The study of metal cluster ions (e.g., Mn⁺) can lead to insights concerning the properties of bulk solids and surfaces, particularly in the area of catalysis.[57] Of particular interest has been the point at which the chemistry of a gas-phase cluster begins to approach that of a solid.[58]

Thermochemical determinations: The use of various gas-phase methods for determining reaction energies is clearly an advantage moving out of the condensed phase. The thermochemistry data for M-C bond dissociation energies and related quantities from gas-phase experiments are truly impressive.[59] There has also been a reasonable amount of data produced on ionization energies and electron affinities for gas-phase organometallic compounds using mass spectrometric techniques.[60] The role of so-called thermochemical "ladders" based on ion- molecule reactions has been significant in much of this work.[61]

Direct observation of key reactive intermediates: Transient, metal-centered intermediates variously appear and disappear via the typical elementary steps of organometallic chemistry, such as oxidative addition, insertion, metallocyclization, etc. However, due to their highly reactive nature, which is invariably linked to their role in catalytic cycles, organometallic intermediates are rarely observed. They usually exist only in infinitesimal concentration in steady-state and catalytic sequences. In solution, coordinatively unsaturated species interact significantly with virtually all solvents, even with alkane C-H bonds. Consequently, a detailed study of these intermediates and their reactivity towards solvent or substrates is beyond the reach of even the fastest spectroscopic methods. Gas-phase approaches to the problem of chemical transients do not suffer from this limitation. Hence, direct transfer of the relevant solution-phase intermediates or of suitable precursors circumvents all the problems related to solution-phase sensitivities. Thus, it does not come as surprise that applications of electrospray ionization mass spectrometry (ESI-MS) for the study of organometallic species have become increasingly popular. It is possible to analyze highly diluted solutions when using electrospray as an ionization method and the mild conditions for the ionization process and for the transfer of charged species from solution to the gas phase. Neutralization-reionization MS is very useful for the characterization of transient neutral species in ion molecule reactions.[62]

Identification of solution species (speciation): The precise identities and structures of organometallic catalysts and reactive ions are often unknown since traditional methods

such as NMR or X-ray crystallography may be less than informative or even impossible to use. There have been many attempts to do speciation analysis by mass spectrometry, especially using the soft ionization methods such as electrospray ionization (ESI).[61] The relationship of the observed ions to the true solution composition is sometimes tenuous, but in favorable cases there is certainly a strong confirmed relationship. Thus, techniques such as ESI-Mass spectrometry have many potential analytical applications in organometallic chemistry. Using this and other appropriate methods, even very large organometallic clusters can be characterized.[64] It has also found its use in high-throughput screening of homogeneous catalysts.[65]

Assessing the adequacy of quantum theoretical models: Experimental work in gas-phase ion chemistry produces data that are amenable to theoretical modeling, especially in recent years as computational power has increased and DFT methods have developed into quantitative tools for handling large, metal-containing systems.[66] The attractiveness of experimental gas-phase data for theoreticians arises from the absence of solvent, which remains an extremely difficult challenge to thermochemically accurate quantum theory. In this way, the underlying competency of theoretical models for many-electron, metalcontaining systems can be assessed for a variety of reaction types. Once calibrated for accuracy, the modeling of condensed-phase systems becomes more believable, although still computationally difficult.

Only during the last 10 years has the potential of ESI-MS for organometallic research been fully recognized.[2, 64] Published studies of electrospray ionization applied to inorganic and organometallic molecules have been reviewed through 1995.[42, 67, 68] A few major traits of organometallic reactions and catalysis are challenging for conventional analytical techniques. Reactions at a transition metal center include a vast number of reaction channels that a substrate may undergo. This means a great number of intermediates, transition states, and reaction steps are involved in each possible reaction coordinate. In addition these steps sometimes proceed on a millisecond time scale. The development of new reactions or the improvement of known reactions strongly depends on the knowledge of these factors. Electrospray ionization mass spectrometry is a tool for mechanistic research with widespread but not unlimited possibilities. The ESI process does not always transfer intact sample ions to the gas phase, and each experimental result must be interpreted with caution if one is draw conclusions about solution chemistry.

ESI works well in the concentration range 0.001-10 mM, which also corresponds to the concentration of many catalysts under realistic conditions. Therefore, by direct sampling from a running catalysis a number of intermediates that are present in solution in small concentrations and with short life times can be isolated and identified. Isolated, intact catalyst ions or ions of any other species present in solution in the gas phase provide the opportunity to investigate these compounds in the absence of unwanted ligand exchange reactions or solvent influence. Ion-molecule reactions can be performed by addition of a reagent gas in the ion-guide regions of the mass spectrometer to determine for instance the intrinsic reactivity towards different substrates, or the relative stabilities of a metal ligand bonds. If successive reactions are performed in the gas phase, intramolecular reactions can be investigated by the analysis of the products of the second reaction, often collision-induced dissociation (CID).

1.5 Coupling of reactors to mass spectrometers, Off-line and On-line monitoring

The previous chapter showed the possibilities that mass spectrometry brings to mechanistic studies in general. But nothing was said about how these results can be practically obtained. In many cases, complete studies can be done with a sample from a reactor's contents. In other cases the reaction fully occurs inside the boundaries of the mass spectrometer. Now, if a reactor is directly coupled to the mass spectrometer, so actual reaction samples can be fed, a new world of analytical possibilities is opened.

Off-line monitoring occurs when individual samples of a reaction medium are collected and then analyzed in two separated stages. A simple example is the sample collection, subsequent freezing of the samples with or without quenching agents, and the final analysis which can be delayed by hours or days.

On-line monitoring occurs when samples are taken from the reaction medium and analyzed immediately, with as little delay as possible. This process is also known as realtime analysis.

A handy method to do on-line monitoring with an ESI-MS is with a mixing tee. A simple polyetheretherketone (PEEK) tee, normally used in HPLC, can provide an extremely simple small-volume continuos-flow reactor. The center tap is fed to the mass

spectrometer and both ends of the tee are free to receive reactants, substrates or solvents from common syringe pumps. A schematic can be seen in Fig. 1.1.[69-71] The reaction time is the time from the moment the reactant and the substrate mix till they reach the electrospray tip. This time can be as short as 1 s, depending on the length of the capillary between the center tap of the tee and the electrospray head and the flow.

Another method employs a syringe, syringe needle and a capillary to form a reactor. The syringe contains one reactant and the capillary contains the substrate and the syringe needle. At the tip of the needle, both liquids mix. Retracting the needle provides variable reaction times, so spectra can be collected at specific intervals and positions allowing to acquire successive data points. Fig. 1.2 shows this approach.

Traditional reactors can also be directly interfaced. A fishing tube is used to collect sample, either by capillarity or by applied pressure. Our method corresponds to this kind, where a reactor with all the necessary accessories: i.e. heating, stirring or ultrasonication, and high pressure capabilities is interfaced with a tandem mass spectrometer equipped with electrospray ionization source. This kind of setup provides a wide spectrum of possibilities for mechanistic studies. A schematic view of this equipment can be seen in Fig. 1.3.

1.6 Research

Several techniques were combined, supercritical or high-density fluids, gas-expanded liquids, ultrasonic irradiation and mass spectrometry to investigate a handful of reactions beyond the concept proof described previously.[72] Following sections detail the experimental setups used, many of them developed in our group, and how all of them fit and work together as a single tool.[73]



Fig 1.1: a) Cross section of a Tee used as reactor, b) PEEK Tee with fittings..



Fig 1.2, Schematic view of a syringe reactor.



Fig 1.3, Schematic view of the reactor linked to the mass spectromer.

2. Experimental Setup

Reactions under described conditions need specially designed reactors. The following paragraphs detail their construction, workings and the modifications they underwent to perform at specification.

2.1 Variable-volume High Pressure Reactor

The variable volume reactor, (between 30 and 60 ml) capable of withstanding 70 MPa at 473 K is made of a steel cylinder with windowed closings at both ends. The far end window is movable, to modify the inner volume of the reactor, via a hydraulic piston. This piston is actuated via a second, pneumatic and electronically-controlled, piston, see Fig. 2.1 shows a photorealistic render (ray-traced with PovRay) of the reactor. The windows are made of tempered sapphire and the body is made of stainless steel 1.4571, especially suited for chemical reactors due to its resistance against corrosion. The front window is kept in place with 8 M5 screws and seals due to a rubber paraffin-resistant o-ring, see Fig. 2.2a. The rear window has a more complex sealing: two concentrical o-rings, copper-made the inner and rubber-made the outermost conform the seal, due to its mechanism of axial movement (Fig. 2.2b). The hydraulic piston assembly is attached to the reactor body using again 8 M5 screws. The pneumatic piston is a separated assembly connected to the hydraulic piston through a ruggedized rubber pipe.

Stirring is provided by a magnetically coupled high-pressure resistant motor stirrer as shown in Fig. 2.3. This sealed stirrer is able to withstand continuous operation at full pressure and temperature. The stirrer assembly consists of a direct current (DC) motor *a*, a magnetically coupled axle *b*, a propeller *c*, and a housing *d*. An external adjustable power supply allows to regulate the stirring power. The housing is screwed at the top of the reactor and sealed via an o-ring.





Fig 2.2a - Cross-section of the variable-volume reactor.





Fig 2.2b: Cross-section along the longitudinal axis of the rear of the reactor. **a** rear of the reactor body, **b** saphire window with seals, **c** hydraulic piston assembly.

Alternatively, an ultrasonic probe assembly can be used (instead of the stirrer). This probe, depicted in fig 2.4, consists of an ultrasonic piezo-electric transducer *a*, a titanium booster *b*, a titanium probe *c*, and a housing *d*. The housing is screwed to the booster at the zero amplitude point. Two o-rings seal this junction. The other end of the housing is screwed at the top of the reactor and sealed by an o-ring. An external ultrasound generator is used to power the transducer. This generator is described in detail in Appendix A. The optimal working frequency of the sonotrode surrounds 20 kHz at normal pressure, but the working frequency was experimentally determined to be 19730 Hz for this reactor at pressures in the range 2 to 6 MPa.

Heating is provided by two heating elements buried in the walls of the reactor. An integrative controller is used to drive the heating elements and keep the temperature constant during reactions. A type K thermocouple is used to sense temperature.

Finally, a manometer is used to keep track of the pressure.

A wheeled bench completes the set and allows transporting the reactor and its supporting components: power supply, pneumatic piston, compressor and CO₂ pump.

Several holes in the reactors' body exist diametrically positioned. They serve as in- and out-lets. Sampling is performed through a capillary that ends inside the reactor. This capillary forms part of the reactor-spectrometer link, see Fig. 2.5.

2.2 Small-Volume High Pressure Reactor

The small-volume reactor, capable of withstand 15 MPa at 473 K is made of two pieces of 1.4571 stainless steel. Fig. 2.6. The two halves are kept together with a clamp. This reactor has an inner volume of 5 ml with the small container and 40 ml with the bigger one. Stirring and ultrasound irradiation are provided by the same equipment mentioned in previous section.





Fig 2.4: Ultrasonic probe assembly, **a** piezo-electric transducer (housed), **b** titanium booster, **c** titanium probe, **d** housing A heating element buried into the lower half of the reactor, together with a type K thermocouple and an integrative controller allow temperature control. The bigger container has no place for a buried heater element and uses an aluminum jacket with a pair of buried elements.

Sample extraction is achieved with a fishing capillary that ends just over the surface of the bottom of the reactor. An external needle valve can be used to control the output flow.

2.3 Reactor to mass spectrometer link

In order to screen reactions in real time a link from the reactor to the mass spectrometer was developed. A 75 μ m inner diameter polyetheretherketone (PEEK) capillary fishes into the reaction media and through a series of pressure reducing valves reaches the electrospray head (Fig 2.5). A first unsuccessful attempt to control the flow through the capillary was made with a needle valve. The piston of the valve was set to press the capillary and strangulate it. The natural property of PEEK, i.e. its lack of softness, made adjusting the flow all but impossible. Thus a method with one or more needle-valves was envisioned. A pair of split valves, normally used for HPLC, proved excellent flow shapers.

To mix the liquid solvent used for electrospray and the reaction medium different approaches can be used according to the composition of the last. When a low content of gas is present, i.e. reactions at lower pressure of around 2 MPa with gases that dissolve poorly in the solvent, the medium can be used directly. When another reactant has to be mixed, a PEEK tee can be used before the electrospray head. When this mixing element proved unsuccessful, because bubbles of gas formed in the stream of liquid stopping the electrospray process (this can only occur with liquids), another approach was developed. The sheath gas inlet in the electrospray head was used to provide the reaction media, and the mixing tee was skipped altogether. Fig 2.7, details how the electrospray head is composed. The inner capillary a, carries the liquid for the electrospray process. coaxially to this capillary, a second capillary carries the sheath gas: in this case, the raw reaction mixture from the rector. Sheath gas and liquid solvent mix at the exit of the inner capillary. This method proved to be excellent for the analysis of CO₂ containing reactors.



Fig 2.5: Reactor link to he electrospray head. **a** reactor, **b** stirrer, **c** thermocouple, **d** split valve, **e** second split valve, **f** electrospray solvet inlet, **g** sheath gas inlet, **h** electrospray head.



Fig 2.6: Cross-section of the Small volume high-presuure reactor.



Fig 2.7: Cross-section of the electrospray tip, the arrows show the flowpath

2.4 Tandem Mass Spectrometer

The apparatus used in our experiments is shown schematically in Fig. 2.8. In a typical experiment, a 1 μ M to 1 mM solution of the analyte in a polar organic solvent (preferentially acetonitrile or dichloromethane) is pressed through a capillary at a flow rate of 1 – 15 μ l/min and electrosprayed at a potential of 3 – 5 kV using N₂ sheath gas or raw .

The ions are then passed through a heated capillary (typically at 423 – 473 K) where they are de-clustered and the remaining solvent molecules evaporate. The extent of desolvation and collisional activation can further be controlled by a tube lens potential in the electrospray source which typically ranges from 35 to 75 V. The first octopole (O1) acts as an ion guide to separate the ions from neutral molecules, which are pumped off by a turbomolecular pump located underneath the octopole. O1 is fitted with an open cylindrical sheath around the rods into which, depending on the setup, a collision gas can be bled for thermalization or reaction at pressures up to ~13 Pa. The ions then enter the actual mass spectrometer, which is at ~1 Pa and 343 K manifold temperature during operation [Fig. 2.8 (b)]. The configuration is guadrupole/octopole/guadrupole (Q1/O2/Q2), with the two quadrupoles as mass selection stages and the second octopole operating as a CID cell. Spectra are recorded in three different modes. In the normal ESMS mode, only one quadrupole is operated (either Q1 or Q2), and a mass spectrum of the electrosprayed ions is recorded. This mode serves primarily to characterize the ions produced by a given set of conditions. In the daughter-ion mode, Q1 is used to mass-select ions of a single mass-tocharge ratio from among all of the ions produced in O1, which are then collided or reacted with a target gas in O2, and finally mass analyzed by Q2. This mode is used to obtain structural information (by analysis of the fragments) or the specific reactivity of a species of a given mass. The third mode of operation, the RFD mode (radio frequency daughter mode), is used to record CID thresholds for quantitative thermochemical measurements. lons produced in O1 are mass selected, with Q1 acting as a high-pass filter. The selected ions are then collided with a target gas in O2, and mass analyzed in Q2. In the RFD mode, the reaction of ions in a particular mass range are isolated by setting the mass cutoffs above and below the desired range and then subtracting the latter from the former spectra.





Fig 2.8: Schematic view of the Finnigan TSQ 7000 tandem mass spectrometer, **A** atmospheric pressure electrospray ionization chamber, **B** manifold

This first octopole can be exchanged with some modifications for a larger 24-pole. A larger multipole provides two main advantages, firstly it confines the ions to a narrower path due to a more homogeneous field,[74] and secondly because the physical length is larger than the standard octopole, the ions are allowed more time to react with the added collision

gas. A suitable oscillator to drive this multipole has been developed and is described in Appendix II.

2.5. On-line monitoring under high-pressure

The set-up described in this section was used for a series of studies, firstly to assess its usefulness and then in real-world scenarios. These assessing experiments consisted in the mass spectrometric identification of the substances streamed from the reactor. Two sets of experiments were carried out: firstly a series of known substances were live-streamed from the reactor into the mass spectrometer; secondly a few reactions were carried out in the reactor and the reaction mixture was live-streamed and mass analyzed. [72]

The first set of experiments consisted in charging the reactor with either a methanolic solution of analyte and then the reactor would be pressurized with CO₂, or the analyte was injected into the reactor directly and then the reactor would be pressurized. The substances used provided a broad spectrum of possible analytes: quaternary ammonium salts, amines, esters, ketones and ethers. Neutrals were conveniently treated with methanolic solutions of alkali metals which complex to the oxygen atom while amines bind protons. All these substances gave encouraging feedback about the versatility of the method because we were able to detect them all.

The second set of experiments consisted of a few reactions under high pressure that were to be monitored on-line via mass spectrometry. Again a mixture of ionic and neutral analytes were employed to show the broad applicability of the method. The first reaction tested was the addition of a Grignard compound to CO₂ to produce an acid, propionic acid in this case. The Grignard compound ethylmagnesiumbromide, dissolved in ethylether, was injected into the reactor and then it was pressurized with CO₂ and the reaction mixture was live-streamed into the mass spectrometer and analyzed in negative ion mode where the propionate ion was detected. The second reaction was the palladium catalyzed hydrogen transfer from 1,4-cyclohexadiene to 5-norbornene-2-carbonitrile. This reaction was carried out in the smaller reactor described in section 2.2. The reactor was firstly charged with Pd over charcoal, freed from air, charged with the substrate and the donor and finally pressurized with CO₂. The live stream was then mixed with a methanolic /water

solution of silver ions and injected into the mass spectrometer. As silver has a great affinity for the nitrile function, silver complexes of both the substrate and the product, norbornane-2-carbonitrile could be detected and thus the course of the reaction tracked. The third reaction consisted on the ultrasonically promoted dehydration of hydroxenine monoacetate (HMA). When irradiated with ultrasonic waves in alcohol:carbon tetrachloride mixtures, this compound affords vitamin A acetate via loss of water and isomerization, or incorporates an alcoholate to form an ether, among other by-products, depending on the reaction's temperature. As the temperature could not be controlled, no vitamin A acetate was produced but the corresponding ethers. The reaction mixture was not live-streamed into the mass spectrometer as in the previous cases, it was collected in vials to be analyzed off-line. The analysis of these samples, together with a calibration curve allowed to track, albeit off-line, the course of the reaction. Mass spectrometric analysis of these samples allowed for direct analysis without further separation steps, reducing the time needed for results.

With these sets of experiments showing the advantages of the method over other more conventional approaches we went ahead to fully utilize the method and to analyze on-line the dehydration of HMA.

2.5.1 The isomerization of polyenes

From the many natural occurring polyenes, the ones that belong to the carotenoid group are widely used as food supplements and in the cosmetic industry. Their chemistry is widely known, and a thriving industry exists behind them.[75] The synthesis of vitamin A presents several challenges due to the multiple stereoelements of the molecule and to its sensitivity to light. In the final stages of one of the commercial synthesis, hydroxenin monoactetate (HMA) is dehydrated with subsequent isomerization to yield vitamin A acetate as seen in Fig. 2.9. This crucial step produces a mixture of isomers, with all-*E* vitamin A acetate being the most active compound. This step requires an acid that protonates the hydroxyl moiety affording -after the loss of water- a carbocation, that undergoes proton loss under concomitant isomerization. Bonrath and coworkers demonstrated in 2001 that this crucial step could be carried out under ultrasound irradiation, because in a mixture of an aliphatic alcohol and a chlorinated hydrocarbon, hydrochloric acid is produced in small quantities due to radical cleavage.[31]



Fig. 2.9: Reaction of HMA with CCl₄/Alcohol under ultrasound irradiation.

Working from this point on, Bonrath *et al.* determined the temperature and alcohol dependance of this reaction under pulsing ultrasound irradiation. Vitamin A acetate and some by-products were finally isolated and characterized using several analytical techniques. This allowed them to identify new by-products and deducing important insight regarding the thermochemical characteristics of this reaction.[32]

While this work provided unprecedented detail of the process, the sample treatment as well as the low yield prompted re-evaluation of the whole approach. It was decided that if we could take advantage of the autoclave-to-mass-spectrometer-link to follow the course of the reaction, better, faster and simpler access to results could be obtained. The dehydration of HMA was performed under high-pressure with gas-expanded solvents. Sampling was performed at regular intervals but the samples were analyzed off-line. A protocol for analysis of these samples was not available and thus one was developed.[72] After this goal was reached, the next step was to use on-line monitoring to reproduce the off-line results.

For these experiments, the small fixed-volume high-pressure reactor described in section 2.2 was fitted with an ultrasound probe and on-line monitoring was used to analyze samples in real-time. Most of the species involved, except for the carbocations, do not bear a charge. As was explained before, neutral species should be paired with an ion. In this particular case, the carbonyl moiety can complex alkali ions already present in the electrospray solvent, forming monomeric and dimeric species. This is one of those cases where a post-treatment of the sample is needed, though a trivial one, which was performed in real-time without introducing any delay in the sample analysis. Closer inspection together with CID experiments revealed that the samples contained oxides. The

peak at m/z 385 is formed by two isobaric species. The sodium complex of oxidized HMA plus the potassium complex of HMA, as the spectrum in Fig 2.10 shows. This is due to the oxidizing effect of electrospray and the ability of vitamin-A and related compounds to act as anti-oxidant agents.[76-77] The dimeric complex at m/z 729 show also the addition of an O atom as well as the loss of H₂ on the one molecule that gained one oxygen, depicted in Fig. 2.11. While such a loss is normal for the action of tocopherols and has been spotted in the ESI-MS analysis of γ -tocopherol,[72] its significance as well as its true nature has not been explored further.

Mass spectrometric analysis of samples produced in silent conditions, i.e. without application of ultrasound, revealed only unreacted starting material.

The reaction was carried out at room temperature where it is known that ethers of the alcohol used as solvent are the main and in this particular case the sole products. Although no vitamin A acetate was detected, the set-up worked as expected producing useful data that allowed us to track live progress of the reaction.



Fig. 2.10: Spectrum of the CID experiment of m/z 385.



Fig. 2.11: Spectrum of the CID experiment of m/z 729

2.5.2 Experimental

All experiments were carried out in the reactor described in section 2.2, fitted with the ultrasonic probe with a 10 mm tip and connected to a CO₂ cylinder (purity 3.5). HMA (99.5 %) was kindly provided by Dr. W. Bonrath (DSM Nutritional Products Ltd., Basel, Switzerland).

In the reactor, HMA with 10 ml of alcohol in 10 ml of CCl₄ were let to react at room temperature under ultrasound irradiation in pulsed mode. Sampling was performed through the capillary that forms the reactor to mass spectrometer link described in section 2.3, at regular intervals, and mixed with methanol before entering the mass spectrometer. A calibration curve was done to quantify products and all samples were mass spectrometrically analyzed with the same settings in one run, flow rate 1 μ l/min, ESI potential 3.2 kV, scan time 2 min, tube lens potential was 67.8 V. Fig. 2.12, shows the evolution of products vs time and the spectrum of one of the by-products (HMA-O-Et]⁺) in a live-streamed sample.

To help identify the products of this reaction methanol instead of ethanol was used in a separate control experiment, and methoxylated products were produced instead.



Fig. 2.12: (I) Evolution of products vs time. (r) Spectrum of live sample. A+ [HMA+Na]+, B+ [HMA+K]+/[HMA+(O)+Na]+, C+, [HMA-O-Et+Na]+.

3. Insight into the mechanism of the Pd-catalyzed H-transfer

While investigating the possibility of using ultrasound irradiation to improve the yields of hydrogenation over a small plate (25x25 mm²) of metallic palladium, [72] the substrate, cyclohexene, underwent partial hydrogenation under a H₂/CO₂ atmosphere regardless of the presence of ultrasonic waves. But, an unexpected side-effect caught our attention: when doing a control experiment, without hydrogen, a fairly large amount of cyclohexane was produced. But this was not the only product: benzene was also present. At this point the source of benzene was not very clear, because successive experiments gave varying amounts of benzene. Thus a series of experiments with cyclohexene. 1.3-cyclohexadiene (1,3-CHD) or 1,4-cyclohexadiene (1,4-CHD) as substrate, under different conditions of ultrasound irradiation, pressure, temperature and reaction time, were carried out. The products of them, benzene, cyclohexene (in case of the dienes) and cyclohexane, and an unidentified residue led us to the conclusion that disproportionation was the reason for the presence of the mentioned products. One of the interesting results was that with so little palladium surface one could afford a good yield in such a transformation. A blank experiment, without palladium was also carried out resulting in unreacted starting material, after 12 h. These reactions and their products are shown in Fig. 3.1.



Fig. 3.1: Disproportionation of of cyclohexene, 1-3-cyclohexadiene and 1-4-cyclohexadiene over Pd foil under high-pressure.

These preliminary experiments led us to consider the disproportionation, and in more general terms, the catalytic H-transfer as a serious alternative process for the synthesis of useful building blocks from cheaper commercial sources. While this reaction has been covered in the literature and some industrial processes exist, [78-80] our focus is the production of pyridinic and phenolic derivatives as well as the mechanism involved.

The H-transfer reaction involves donor and acceptor molecules in which the donor will in the end give pairs of H atoms to an acceptor molecule. Disproportionation occurs when the donor and the acceptor are the same substance. Isomerization occurs when the donor and the acceptor are the same molecule.

3.1 Disproportionation and isomerization

As mentioned before, disproportionation was the starting point and it proved to be very useful. When searching for suitable compounds, disproportionation was used as the benchmark for the ability of a compound to donate pairs of H atoms. One of the first ones to be tested was 2-cyclohexen-1-one, shown in Fig. 3.2. This compound affords phenol:cyclohexanone in a 1:1 proportion. This reaction proved easy for analysis because all compounds can be unequivocally identified via ¹H NMR or GC-MS, so it could be used to test different catalysts, but only worked when using Pd on charcoal (Pd/C) or on CaCO₃ (Pd/CaCO₃), failing to react over the small piece of Pd foil used previously even under pressure and higher temperature.



Fig. 3.2: Disproportionation of 2-cyclohexen-1-one over Pd/C or Pd/caCO₃.

Similar compounds, i.e. with cyclohexenic or cyclohexenonic skeletons are available commercially. γ -Terpinene, carvone and limonene are some of them. Under similar conditions, i.e. with Pd foil under pressure they fail to react. On the other hand, when let to react under pressure with Pd/C or Pd/CaCO₃ they afford disproportionation products with varying yields.

 γ -Terpinene, for instance, reacts completely under pressure over Pd/CaCO₃ to afford 2 eq. of *p*-cymene and 1 of *p*-menthane, as seen in Fig. 3.3.

Because the reactor was washed with ethanol, small amounts of the alcohol were present during some of the reactions. In some cases others product not related to to the olefines were formed, diethylether and ethylphenylether. These products could come from simple condensation of two alcohol molecules.


Fig. 3.3: Disproportionation of γ -terpinene under pressure.

Under normal pressure, on the other hand, γ-terpinene reacts slower towards disproportionation than 1,4-cyclohexadiene (1,4-CHD).

Under the same conditions, both (S)-(+)-carvone and (R)-(-)-carvone afford only 40 % of the aromatic isomer carvacrol, and a few percent of another and still unidentified isomer. Such an isomerization would involve two pairs of H-transfers with the tautomerization from the keto to the phenol as a final driving factor. The reaction is shown in Fig. 3.4. Increasing the reaction time does not afford more conversion.



Fig. 3.4: Isomerization of (*R*)-(-)-carvone to carvacrol.

Another related terpenoid, namely (R)-(+)-pulegone proved even less reactive than carvone. After 12 h some disproportionation products are formed, less than 3 % of thymol and around 10 % of another still unidentified isomer for a total of 13 % of conversion. The reaction is depicted in Fig. 3.5.

From the tested compounds, there were some that did not produce any detectable products. Among them, α -pinene and 5-norbornene-2-carbonitrile were chosen because they cannot give aromatic products without ring cleavage. For these, isomerizations would be possible, but they were not detected.



Fig. 3.5: Disproportionation of (*R*)-(+)-pulegone to thymol.

3.2 H-donors

Synthetically more useful than disproportionation, where only a fraction of the desired product is formed, is the H transfer from a donor to an acceptor because it could afford up to quantitative yield of product. From the compounds tested, 1,4-CHD seems like the best candidate because its conversion to benzene should be an important driving factor. The commercially available isomer, 1,3-CHD, behaves in a similar way, but its high price makes it as un-attractive as a H-source as 1,4-CHD for larger than lab-scale applications. Terpenes with similar skeletons are widely available and come from renewable sources at much more affordable prices, so our attention went in that direction. Among them, γ -terpinene was closely studied while limonene only briefly because it proved to be very poor as donor, reacting very slowly.

While γ-terpinene reacts slower than 1,4-CHD during disproportionation, it reacts faster as H-donor when 2-cyclohexen-1-one is used as acceptor, after 4:17 h only traces of 2-cyclohexen-1-one were detected but 35 % of starting material remained unreacted when 1,4-CHD was used instead.

The hydrogenation of 5-norbornene-2-carbonitrile with 1,4-CHD as donor proceeds almost to completion but a small amount of disproportionation products (around 3 %) are formed. 5-Norbornene-2-carboxylic acid reacts in a similar fashion. These two compounds do not undergo disproportionation nor isomerization under these conditions.

3.3 The role of the catalyst

Initially the catalyst used was a small piece of palladium metal but numerous other maybe more convenient forms can be used. A suitable catalyst has to be readily available, have a good endurance, be easy to recover, and be able to withstand varying conditions. Tested catalysts were Pd over charcoal (10% Pd w/w), Pd over CaCO₃ (poisoned with Pb (CH₃COO)₂, also known as Lindar's catalyst, 5% w/w), Pd(AcO)₂ and PdCl₂. 2-

Cyclohexen-1-one was used as benchmark due to its facile disproportionation into phenol and cyclohexanone.

The foil has some advantages over finely dispersed powder in that it is easier to recover. But it has a small area compared to a few mg of any of the other catalysts thus its usability was limited to pressurized reactions of very reactive compounds as seen before.

Pd/C and Pd/CaCO₃ were equally tested for endurance and rate of conversion using equivalent amounts of Pd, as summarized in Table 3.1.

Catalyst	Cycle	Conversion after 1 h
Pd/C (10% Pd)	1	97% ⁽¹
	2	85% ⁽¹
	3	81% ⁽¹
	4	97% ⁽²
	5	83% ⁽²
Pd/CaCO ₃ (5% Pd)	1	50% ⁽¹
	2	50% ⁽¹

Table 3.1: Endurance of Pd/C and Pd/CaCO₃ in cycles with 2-cyclohexen-1-one. 0.038 mmol Pd, 115 °C (oil bad), ¹⁾ 50 mmol substrate, ²⁾ 32.5 mmol substrate. The catalyst was washed and dried before each use. Analysis was done using ¹H NMR.

From this table it is clear that Pd over charcoal has reasonable endurance and affords higher rates of conversion. Other palladium sources like Pd(PPh₃)₄, Pd(AcO)₂ and PdCl₂ work as well with the acetate more active than the chloride and as active as Pd(PPh₃)₄. All tested catalysts, being Pd²⁺ or Pd⁰ based, seem to give the same reaction with the same products but vary in their activity. As Pd²⁺ is partially reduced to Pd⁰ during the reaction, it is not clear if the activity is due to the latter more than to the former.

3.4 Unreactive compounds and catalyst poisoning

From all the compounds tested, there is a small group of unreactive compounds. They are pyridine, 2-methyl-2-pyrroline, 2-methyl-2-oxazoline, cyclohex-1-enecarbonitrile, 3-nitrocyclohex-1-ene (mixture with 4-nitrocyclohex-1-ene). These compounds do not

undergo disproportionation or hydrogenation with either 1,4-CHD or γ -terpinene, but they inhibit in most cases the disproportionation of the donor. To see if catalyst poisoning could be a reason for this lack of reactivity, a thiol, butanethiol or 2-mercaptoethanol, was added to a series of H-transfer reactions that work without the thiols. Complete inhibition of the reaction took place. It could be then postulated that the thiols form strongly-bound chelates rendering the catalyst inactive, but this still do not explain why the other compounds do not react.

When using pyridine- d_5 as an acceptor and either γ -terpinene or 1,4-CHD as donors, only disproportionation products were detected and a small amount of a H/D exchange product at position 2 occurred, around 5 % after 5 h.

3.5 Mass spectrometric investigations of Pd promoted C-H activation

The solution-phase investigations described previously point to similar catalytic activity for both Pd⁰ as well as for Pd²⁺, but do not give any hints about the mechanism, albeit they provide a set of reactive compounds. To properly perform a mechanistic study a higher level of detail had to be obtained. To this end, gas-phase chemistry inside the mass spectrometer was performed. Due to the paucity of studies of palladium catalyzed C-H activation using MS, it was decided that a thorough approach, starting from the very beginning would be necessary if real knowledge was to be gained.[81] With that in mind a selection of a suitable, at least initially, palladium precursor was the first step. Pd⁰ would be a good candidate if complexed with a charged ligand. Pd²⁺ needs a simpler approach because it is already charged. A suitable counter-ion can already be available in solution. Another possibility of getting a look at the species of interest which allows to track the formation of product and concomitant disappearance of reactant exists. This method was recently successfully applied in the hydrogenation of 2-norbornadiene-5-carbonitrile. Aq+ ions were mixed with live-stream and the resulting mixture was then analyzed via ESI-MS. [73] This approach allows for uncomplicated real-time analysis of reaction progress. While the possibility of detecting Pd complexes exits, and will depend on the palladium precursor used, none were detected in this case.

Our efforts were then concentrated on the Pd²⁺ cation using PPh₃ as ligand in MeOH:CH₂Cl₂:CF₃CH₂OH solutions. The choice of Pd source, and triphenylphosphane as a ligand are due to their availability at the time in our laboratories and the fact that the phosphane complexes readily to Pd. The mixture of solvents was chosen after several

tests with a handful of commonly used solvents, water, MeOH, EtOH, THF, CH₃CN, and CH₂Cl₂. The mixture 1:1 MeOH:CH₂Cl₂ provides a stable signal at low electrospray voltages when in the presence of small quantities, in the order of 5 % v/v, of CF₃CH₂OH. When solutions of Pd(CH₃COO)₂ in the mentioned solvents are electrosprayed into the machine described in section 2.4, a series of singly charged ion-groups containing one Pd atom can be identified, as seen in Fig. 3.6. These groups are going to be referred to by their ¹⁰⁶Pd-containing ions because it is the most abundant isotope (otherwise noted).



Fig. 3.6: Spectrum of Pd(CH₃COO)₂ in MeOH:CH₂Cl₂:CF₃CH₂OH.

Assignment was performed using CID techniques: an ion is chosen in *daughter mode* and collided with an inert gas to yield a fragmentation spectrum: a spectrum were only the products of fragmentation are present. The term *fragmentation* is used to indicate decomposition of a parent ion in its constituent parts due to intramolecular reactions, normally unimolecular, that yields one or more neutrals and an ion. Using another isotopologue from the group of signals, +2 m/z for Pd for instance, it can be proved whether the ions still contain the metal or not and if they follow the same fragmentation pattern. The mass difference between the parent and the daughter accounts for the losses, normally neutral molecules. From these pieces of information a model of the connectivity can be built, but it must be noted that isobaric species complicate this scheme because they are different species and thus have different fragmentation patterns.

Unimolecular reactions giving rise to cleavage and formation of covalent bonds can also take place because the energy gained during the collision cannot always be transformed in vibrational or translational energy without bond scission, a process normally more pronounced with smaller than with bigger ions. For these reasons CID experiments are normally a group of experiments carried out using several collision energies; the use of different and increasingly energetic conditions help to pin-point such processes in most cases. These reactions, when carefully crafted, can provide valuable additional structural information, as it will be described in the following paragraphs. All these methods are implied when assignments of ions, groups of ions, are described.

The first ion subjected to CID experiments was m/z 629, which corresponds to a $Pd(PPh_3)$ (PPh₃-H)⁺ species. One of the ligands lost a proton, most probably during electrospray, to reduce the ion's charge. The spectrum can be seen in Fig. 3.7.



Fig. 3.7: CID experiment of m/z 629 with Ar at -50 V (lab scale).

When collided with Ar, this ion fragments losing one intact phosphane ligand to give rise to m/z 367 as main product, and several other products of intramolecular reactions: m/z 183, 261, m/z 289, m/z 337, m/z 339, m/z 397, m/z 446, m/z 475 and m/z 552. The ions with m/z 289, 397, 475, 552 contain palladium. Besides the ion with m/z 339 that should

correspond to the tetraphenylphosphonium ion, the rest of the ions remain unassigned at this point.

Collision of this ion, m/z 629, with either ethene or cyclohexene yields only the products mentioned. When this ion is let to collide with D_2O or toluene- d_8 no new species are formed, nor are any of the detected products mass-shifted due to H/D exchange.

When the ion beam is let to react with ethene at low collision energies in the first octopole, only one new species is detected, namely m/z 657. When this ion is mass selected and collided with Ar a loss of m/z 28 takes place indicating the cleavage of the weak Pd-olefine bond, as seen in Fig. 3.8. Other important products include m/z 553, where a benzene ring is lost and m/z 367, already discussed. The product with m/z 553 is quite interesting because it is not formed when m/z 629 is collided with ethene directly; it hints to a double C-H activation of ethene and transfer of two H to a phenyl ring that is lost to give benzene after the insertion of Pd into the C-P bond. The rest of the products are the same as for m/z 629. There exists in the literature some precedence for the C-H activation of ethene, albeit not under these conditions.[82, 83]



Fig. 3.8: CID experiment of ion m/z 657 with Ar at -50 V (lab scale).

Using cyclohexene instead of ethene in the first octopole, a product with m/z 713 (¹⁰⁸Pd) is formed. Upon collision with Ar, this ion loses 82 mass units to give m/z 629, but it also

loses 158 m/z to give 555 (¹⁰⁸Pd). Such a loss accounts for a similar pair of products as in the case of ethene, namely benzene and probably a cyclohexadiene.

When 2-cyclohexen-1-one is mixed in solution with $Pd(AcO)_2$ and triphenylphosphane, a new complex, namely m/z 725 is formed. This complex loses the ketone upon collision with Ar to give again m/z 629 and the tetraphenylphosphonium ion at m/z 339 upon collision with Ar as seen in the spectrum of Fig. 3.9. No products with m/z 553 or similar were detected.



Fig. 3.9: CID experiment of m/z 725 with Ar at -50 V (lab scale).

The ion at m/z 661 corresponds to either $[Pd(PPh_3)_2(CH_3O)]^+$ or $[Pd(PPh_3-H)(PPh_3)$ $(CH_3OH)]^+$. After simple inspection it is not clear if here a methanol molecule is bound to Pd which itself in σ -bound to a phenyl ring or if the phenyls are intact and a methoxy moiety is present. CID experiments reveal the loss of 32 mass units upon collision with Ar or an olefine to give m/z 629; the isotopologue m/z 663 (¹⁰⁸Pd) behaves in a similar manner losing 32 mass units, too. DFT calculations at the B3LYP/6-311G(d,p) level of theory, and using the LANL2DZ basis set for Pd, show that the energy difference is only 18.4 kcal/mol favoring the complex with the Pd-C bond, the one on the right of Fig. 3.10.



 $[Pd(PPh_3)_2(CH_3O)]^+: +18.4 \text{ kcal/mol} \qquad [Pd(PPH_3-H)(PPh_3)(CH_3OH)]^+: 0 \text{ kcal/mol}$

Fig. 3.10: Optimized structures of the two possible ions of m/z 661.

Interesting are the methylated product ions with m/z 277, 383 and 645. The first one does not contain Pd and should correspond to the methyl-triphenylphosphonium ion. Their formation hints to a C-O activation with subsequent loss of water, see Fig. 3.11.



Fig. 3.11: CID experiment of ion m/z 661 with Ar at -40 V (lab scale).

The use of methanol- d_4 proves quite revealing. For CID, the isotopologue with m/z 667 (¹⁰⁸Pd) was selected because it was less contaminated with the isobaric but lighter

isotopologue of ¹⁰⁶Pd than m/z 665. This ion loses 35 mass units pointing to the loss of CD₃OH; The remaining daughter ion of m/z 632 has one extra mass unit that would correspond to the incorporation of one deuterium to a ligand, as the spectrum in Fig 3.12 shows.



Fig. 3.12: CID experiment of ion m/z 667 with ethene at -40 V (lab scale).

For the ion with m/z 689 two possible structures are [Pd(PPh₃)₂(CH₃COO)]⁺ and [Pd(PPh₃-H)(PPh₃)(CH₃COOH)]⁺. Using DFT and optimizing the structures at the B3LYP level using 6-31G(d,p) and LANL2DZ basis sets for P, O, C, H and Pd respectively, both structures have an energy difference of only 2.2 kcal/mol, much smaller than that of the ion with m/z 661. The structures are shown in Fig. 3.13. Upon CID with Ar, the ion loses one CH₃COOH molecule to give again m/z 629, and probably loses CO to give m/z 661, but the structure of this ion is not clear at this moment. Methylated products like m/z 277 and m/z 383 are also formed suggesting the activation of the C-C and C-O bonds of the acetic acid molecule. The spectrum is depicted in Fig. 3.14.

The presence of a product of m/z 553 or maybe m/z 552 could not be ruled out because a very weak signal in this range is present but further experiments may be necessary to prove its real existence. A very weak signal for the ion with m/z 427 is present, this ion corresponds to the parent ion less a phosphane ligand.



Fig. 3.13: Optimized structures for the ion with m/z 689.



Fig 3.14: CID experiment of ion m/z 689 with Ar as collision gas at -50 V (lab scale).

The experiment with methanol- d_4 shows that H/D exchanges with C-H activated bonds are possible and thus we went a step further and tried to force H/D exchange using other substrates like toluene- d_8 and D₂O. We expected the incorporation of one or two D atoms into the ligands.

When all the ions electrosprayed from the Pd^{2+}/PPh_3 solution are let to collide at low energy, in the first octopole, with toluene- d_8 a new complex with m/z 729 is formed. This toluene- d_8 adduct fragments upon collision with Ar at 50 eV (lab scale) to yield mostly m/z 629, but also some of the products already seen for m/z 629. No mass shifted products could be detected indicating the failure of the substrate to undergo H/D exchange. When D₂O was used instead of toluene- d_8 , neither new complexes were formed nor deuterated species were detected.

3.6 Discussion and Mechanism

Several mechanistic proposals for the C-H activation of olefines have been put forward. While many examples with metals other than Pd exist and fewer with it, the experiments carried out show that such a process indeed takes place. One suggested mechanism, albeit using a zirconium complex as catalyst, involves an oxidative insertion into one of the sp³ C-H bonds of 1,4-CHD with subsequent 1,4-elimination to produce benzene and a hydrido complex that will transfer this H atom to an acceptor molecule.[84] This mechanism needs a suitable complex that is pre-bound to a suitable acceptor, in this case a CH₃ group, to start the cycle, as depicted in Fig. 3.15 for a palladium complex. If we assume that a similar mechanism takes place, this initial acceptor has to be generated *insitu* from the starting 1,4-CHD. And as our solution experiments show that H-transfer takes place we can assume the existence of such a starting complex. All solution experiments show that pairs of H atoms are transferred together at least up to the detection limit of the analytical methods used.



Flg. 3.15: Proposed mechanism for the disproportionation of 1,4-CHD.

The gas-phase reactions show clearly that such starting points can be generated quite readily. Methylated products are formed in high yields when either palladium acetate (m/z 689) or its methanolic form (m/z 661) are activated energetically. But that explains not how such a precursor is formed when the heterogeneous catalyst Pd/C is used.

To obtain cyclohexane from the mechanism shown above, the acceptor will be cyclohexene and again a Pd-H will be added to the double bond as before. Such a process could be inferred from the gas-phase experiments carried out. When the ion with m/z 657, the one containing ethene, collides with Ar the loss of 78+26 mass units occurs. When the ion with m/z 713 (isotopologue with ¹⁰⁸Pd), the one which contains cyclohexene collides with Ar, a loss of 80+78 is accounted for. We would like to propose two possible mechanistic pathways. The first one involves a sequence of oxidative additions and subsequent reductive eliminations. A double C-H activation of the substrate, ethene or cyclohexene, takes place and two H atoms are thus transferred from it to the phenyl ring bonded between Pd and P. Such a mechanism would be in agreement with the previously discussed mechanism. For ethene, this first pathway is depicted in Fig. 3.16 and for cyclohexene in Fig. 3.17.



Fig. 3.16: Proposed mechanistic pathway to explain the loss of 78+26 mass units when ion with m/z 657 yields m/z 553 upon collision with Ar.



Fig. 3.17: Proposed mechanistic pathway to explain the loss of 158 mass units when ion with m/z 713 yields m/z 553 upon collision with Ar.

The second pathway involves the formation of benzyne due to scission of the Pd-C and P-C bonds of the phenyl ring, as shown in Fig. 3.18. The involvement of the substrate, which does not undergo C-H activation, is clear when the bond energy of the benzyne is taken into account. Using phosphane to model the ligands and DFT for the calculations, the bare complex, m/z 629, has a bonding energy of 44.5 kcal/mol while the energy in the ethene complex, m/z 657, is only 33.9 kcal/mol. The methanolic complex, m/z 661, has a bonding energy of 49.44 kcal/mol for the model and 44.3 kcal/mol for the real ion, also higher than the ethene complex. These higher energies could explain why this reaction only takes place in the case of the olefinic complexes.



Fig. 3.18: Alternative mechanism to explain the loss of 158 mass units from m/z 713.

While the labeled compounds did not produce significant results, especially when used for CID, and except for methanol- d_4 , a number of unexplored avenues remain. Heavy water should exchange the hydrogen atoms at the *ortho* position of the phenyl groups but failed

to do so. Toluene- d_8 also did not react as expected, there was no H/D exchange with the ligands' phenyl rings.

The complexes studied demonstrated a strong C-H activity but the ligand used interacted too much with Pd limiting the scope of application. A ligand less prone to C-H activation, like the pyridine based phenantroline, could broaden the field and allow more control over the course of the reaction.

3.7 Experimental

Experiments in solution were done either in the small pressurized reactor described in section 2.2 using CO₂ or in glass flasks heated by an oil bath. Sampling was performed using syringes and the raw reaction mixture analyzed via ¹H NMR or GC-MS after filtration and preparation of the corresponding samples.

Gas-phase experiments were carried out using the mass spectrometer described in section 2.4. The external gas inlets for CID and reagent gas were employed. Gas cylinders for ethene, argon and xenon were used while the liquid reactants were either mixed into the solution to electrospray or injected into the machine via the mentioned inlets using small glass bottles specially designed for such an end. Palladium acetate solutions were prepared dissolving the $Pd(AcO)_2$ salt in water and then adding dichloromethane to finally obtain a single-phase system by addition of methanol. A solution of PPh_3 in dichloromethane was then added in a 1:4 proportion. Best results were obtained when the concentration of Pd was in the 0.1 mM range.

4. Towards a mechanism for the hydroformylation of olefins using selfassembling Rh-catalysts

Hydroformylation is the addition of an aldehyde function to a double bond, typically using synthesis gas (a CO:H₂ 1:1 mixture). Extensive research has been conducted since its introduction to try to establish a mechanism. [85] and the most accepted mechanism is still that of Wilkinson and Heck, shown below in Fig. 4.1.[86, 87]



Fig. 4.1: Proposed catalytic cycle for the hydroformylation of olefins using a Rh catalyst.

A thorough understanding of the course and mechanism of these chemical reactions is of profound importance for improving catalysts and catalytic transformations by identifying reactivity- and selectivity-controlling interactions, intermediates and transition states. However, due to the often unstable and short-lived nature of those species of interest, detection can be a tedious and time-consuming endeavor, applying e.g. isotope labeling-experiments. Thus, on-line methods that enable the direct observation of an ongoing

reaction like IR- and NMR-techniques are commonly used nowadays. Commercial processes use normally triphenylphosphane as the ligand of choice because it is cheap and easily recoverable. To improve the good yields and selectivity afforded by these catalysts several routes have been explored, one of them uses self-assembled monodentate ligands that resemble DNA base pairing using two H-bonds. While the catalysts so formed provide in some cases better yields and/or selectivity, their mechanism is still unknown. It was found during the course of these work that at least one of the H atoms involved in the H bonds would play a role in the catalytic cycle.

4.1 Self-assembled ligands

A ligand that assembles itself from smaller parts provides a flexibility degree not available from common bidentate ligands. Nature has shown that structures using H bonds can be stable under wide range of conditions and can assembled with little extra energy used. The model ligand used is known as 6-DPPon and is depicted in Fig. 4.2 together with the other ligands used throughout this work.



Fig. 4.2: Phosphane ligands: **1** 6-diphenylphosphanyl-2(*1H*)-pyridinone (6-DPPon), **2** (ESI-6-DPPon), **3** 3-diphenylphosphanyl-1(*2H*)-isoquinolinone (DPPICon), **4** *N*-(6- (diphenylphosphanyl)pyridin-2-yl)pivalamide (DPPAP), **5** 4-(6-(diphenylphosphanyl)pyridin-2-ylamino)-*N*,*N*,*N*-trimethyl-4-oxobutan-1-ammonium (ESI-DPPAP), **6** *N*-(2- (diphenylphosphanyl)thiazol-4-yl)pivalamide (DPPAT), **7** tri-phenylphosphane, **8** XANTPHOS.

A multistep synthesis has been developed in the Breit group for this molecule. The electrospray technique used demands a permanent charge on the species of interest, so a

charged ligand, denominated ESI-6-DPPon, has been also synthesized using a similar procedure to 6-DPPon by Ch. Beierlein, shown in Fig. 4.3 and Fig. 4.4. [88]



conditions: i.) POBr₃, 140 °C, 16h, 86%; ii.) NaBH₄, BF₃·OEt₂, THF, 0 °C RT, 99%; iii.) DHP, PPTS, CH₂Cl₂, RT, 16 h, 96%; iv.) NaH, HOCH₂CH₂SIMe₃, THF, RT, 16 h, 81%; v.) *n*-BuLi, Ph₂PCI, THF, -100 °C, 83%; vi.) MM K10, MeOH/THF, 55 °C, 91%





Fig. 4.4: Final steps of the synthesis of [2]+ (ESI-6-DPPon).

This charged ligand [2]⁺ has a permanent positive charge away from the pyridone ring as to not affect it electronically. But DFT calculations seem to indicate that lower charge

density is placed at the oxygen atom when compared to 6-DPPon.[89] The exact influence of this finding has not yet been assed nor has it been done with a high level of theory. [2]+ forms the same Pt complexes as 6-DPPon does as ¹H-NMR shows, and produces similar yields and selectivity when used as catalyst instead of 6-DPPon, under the same conditions. [88]

4.2 ESI-MS investigations of the 1/2 system

To shed some light on the mechanism of the hydroformylation reaction several steps were examined. Firstly, only the solution resulting from simply mixing the ligand and Rh-precursor [Rh(COD)₂]BF₄ was electrosprayed to assess the complexity of the ion mixture; afterwards on-line monitoring of the reaction mixture under hydroformylation conditions (both with and without substrate) was performed.

Hence, a CH₃CN-solution of the catalyst using **2** and the Rh-precursor $[Rh(NBD)_2]BF_4$ in a 4:1 ratio was investigated by ESI-MS, revealing a much more complex mixture of ions than expected as can be seen in the spectra of Fig. 4.5 and Fig. 4.6.



Fig. 4.5: ESI-MS spectrum of 2 and [Rh(NBD)₂]BF₄ in CH₃CN (m/z 400-1200).



Fig. 4.6: ESI-MS spectrum of 2 and [Rh(NBD)₂]BF₄ in CH₃CN (m/z 1000-1500).

Most of these ions have not been detected by other methods before. IR and ¹H-NMR experiments normally only show a single complex that is thought to be a resting state containing three ligands. ESI-MS experiments show, among other ions, a complex consisting of Rh⁺ and two ligands to be the predominant species. The rest of the ion population includes multiple charged species, species containing counter-ions, singly charged species due to deprotonation as well as free uncoordinated ligand. This mixture is partially the result of the processes that take place during droplet shrinkage right after electrospray. Due to the difference in environment provided by the droplet and the gas-phase, multiply charged ions present in the droplets engage in energetically favorable processes that lead to net charge reduction: intra- and intercluster H⁺ transfers, the transfer of a proton between two ions, and binding of a counter ion.[90] This unavoidable processes complicates the acquired spectra.

To reduce this complexity several mixtures of charged ligand **2** and uncharged ligand **1** were studied. After extensive experiments it was concluded that a mixture of **2** and 6-DPPon in a 1:1 ratio (1.1. eq) with 1 eq. of Rh-precursor provided less complex spectra while in the hydroformylation reaction maintained high catalytic activity.

A closer look into these spectra shows no obvious candidates for some of the species postulated in the Wilkinson cycle, as expected, thus prompting further experiments under hydroformylation conditions.

4.2.1 Live Streaming

The next logical step was to live-stream reaction media into the mass spectrometer using the techniques developed for that end. The upper mentioned mixture was put under a CO/ H_2 atmosphere (20 bar) in a stainless steel autoclave equipped with a capillary connected directly to the ESI-MS as described previously.

Under these conditions several new complexes are anticipated to be present corresponding to the intermediates **A**, **A**['] and **B** in the commonly accepted catalytic cycle proposed by WILKINSON,[86] HECK and BRESLOW,[87] Fig. 4.7.



Fig. 4.7: Catalytic cycle for the Rh-cat. hydroformylation of alkenes with masses of expected complexes.

Without substrate present in the reaction mixture, several ions containing CO and H₂ could be detected, m/z 848, m/z 876, depicted in the spectrum of Fig. 4.8, and the "resting state" m/z 1127, depicted in Fig 4.9. In addition, the corresponding complexes derived from two charged ligands are also present (m/z 503 and m/z 517). The assignment of the molecular structures is based on CID experiments, i.e. collision of the parent ion with an inert gas at different collision energies and monitoring of the resulting fragments (daughter ions).



Fig. 4.8: ESI-MS spectrum of 2/1/[Rh(CO)₂acac]-mixture under CO/H₂ atmosphere.



Fig 4.9: ESI-MS spectrum of the proposed resting state A'.

The structure of the resting state (m/z 1127), which has been described with 6-DPPon before and affirmed by X-ray analysis,[91] was probed in CID experiments. Using argon as collision gas this ion yields several fragments, an ion with m/z 848 resulting from the loss of one 6-DPPon ligand, and m/z 437 which corresponds to **2**, thus suggesting the assumed structure **A**' as the spectrum in Fig. 4.10 shows.

To our surprise a very prominent ion of m/z 818 which corresponds to [Rh(6DPPon) (ESI6DPPon)(-H)]+ is always present. This ion has not been previously spotted using other techniques. A complex that might be comparable in structure has been prepared recently starting from 6-DPPon and [Rh(COD)acac].[88] X-ray analysis revealed the structure depicted in Fig. 4.11.



Fig. 4.10: CID-experiment of m/z 1127.



Fig. 4.11: Xray-structure of Rh(COD)(6-DPPon)(6-DPPon-H).

One of the amide groups has lost a proton resulting in a strong P,N,P-coordination motif. Such a coordination could also be present in the detected ion at m/z 818 making it more sterically compromised or even occupying all coordination sites rendering it unreactive. In addition to the analytical detection of some of the solution-phase species, ESI-MS provided information about the structure and reactivity of some of these intermediates because gas-phase ion-molecule reactions of them where conducted as described below. When reacting the ion at m/z 818 with Ar, D₂, CO, olefins or aldehydes in the gas-phase at different collision energies and pressures, no additional signals could be detected to the fragments already mentioned.

Furthermore, the ion at m/z 848 (**B**) which represents the anacrusis of the catalytic cycle and is normally not detectable in solution was of special interest and investigated further by means of CID experiments in the gas-phase.

Upon CID this ion loses 30 mass units to produce an ion of m/z 818 or loses 511 m/z units to produce an ion of m/z 437 that corresponds to **2**, as shown in Fig. 4.12.



Fig. 4.12: CID-experiment with m/z 848.

Assignment of this species (the hydridocarbonyl complex) is confirmed by an experiment using D₂ instead of H₂. The mass shift of the corresponding species \mathbf{B} - d_1 is +1 as the spectrum of Fig. 4.13 shows. Consequently the fragmentation pathway leading to the loss of CO and H₂ becomes the loss of CO and HD by CID of \mathbf{B} - d_1 . It must be pointed out that the ion at m/z 849 is a mixture of three isobaric species. The first one, the expected \mathbf{B} - d_1 with a deuterium attached to rhodium, gives m/z 818 upon loss of CO/HD as expected. The second one is the naturally occurring \mathbf{B} with a deuterium atom instead of a hydrogen somewhere in one of the ligands. And finally, the third one is the also naturally occurring \mathbf{B}

with a ¹³C. These last two species lose CO/H₂ to give the ion at m/z 819. The mechanistic interpretation of this fragmentation is discussed in detail below.



Fig. 4.13: CID-experiment with m/z 849 under CO/D2.

By those observations we concluded that the structure of the ion at m/z 848 is indeed **B** in the cycle above, Fig 4.7. To get more information about the true nature of the complex, it was reacted with CO as collision gas, producing an ion at m/z 876 in very low yield and only at low collision energies (0 to 6 eV (lab scale)) that is also spotted when synthesis gas is present and represents **A** (*vide supra*). No further fragments are created at higher energies. Upon reaction with olefins no adducts are detected and fragmentation seems to be the only pathway, as the spectrum in Fig. 4.14 shows.



Fig. 4.14: CID-experiment with m/z 848 and CO as collision gas.

As the unsaturated complex **B** should have a square-planar geometry with free coordination sites, this lack of reactivity seems unlikely. Bearing the observed loss of H₂ in mind, one could envision a modified structure of **B** that results from an oxidative addition of the N-H-part of the hydrogen bond framework. This indeed could be the case here, as some preliminary DFT-calculations of the parent systems complex [HRh(CO)(6-DPPon)₂] indicate that the OH-O-bond is much stronger than the NH-N-bond, the latter opening up to a great extent in the course of the catalytic cycle thus making it accessible for the proposed oxidative addition, Fig 4.15.[89]



Fig. 4.15: Alternative structure for B (right side).

In solution, as depicted on the left side of Fig 4.15, the species **B** would react immediately either with additional ligand or a CO-molecule, forming the saturated species m/z 876. However, this pathway is not accessible in the gas phase, as no uncharged reaction partners are present. The assumed structure **B**[']</sup> indeed could explain the observed lack in reactivity when using olefins as collision gas, as no free coordination sites are present. *Syn*-eliminiation of H₂ would be feasible from **B**['], followed by loss of CO (or the other way around), giving the complex with m/z 818, which is observed regardless of the kind of collision gas used.

4.2.2 Reactions with substrate in the mixture

After the successful identification of crucial intermediates of the catalytic cycle (A, A', B), the next logical step was to analyze a mixture under bona fide hydroformylation conditions, i.e. in the presence of an olefinic substrate. We decided to use 1-hexene as it reacts quite readily under the applied conditions. The use of a charged olefine, *N*,*N*,*N*-triethylhex-5-en-1-ammonium as substrate was also closely examined. It was expected that, when

paired with the uncharged ligand 6-DPPon, some of the species in the catalytic cycle would be detectable. It was found during these experiments that no olefine complexes could be detected, but the progress of the reaction could be easily traced because the product is also a positive ion. A similar experiment but using the charged ligand ESI-6-DPPon did not provide more information than the pairing with the uncharged **1**.

In first experiments, we applied standard hydroformylation conditions ([Rh]:L1:L2:1-hexene = 1:1.1:1.1:100, CO/H₂ = 1:1, 20 bar, CH₃CN, c(1-hexene) = 0.36 M). However, no new ions could be detected. Hence, either the steps in the catalytic cycle are faster than our time-frame or the concentrations of the species of interest lie below the detection limit of the method. Indeed, when increasing the amount of substrate to a concentration of 50 Vol.-% of 1-hexene, a possible acyl complex at m/z 960 (**E** or **F**) could be detected and further investigated. Additionally, an ion of m/z 932 (**C** or **D**) was present too, but the low intensity of the signal made CID experiments impossible.

Upon CID with Ar or D₂, the ion at m/z 960 yields several interesting fragments, namely m/z 848 that could be **B** in the catalytic cycle and m/z 818. No ions like m/z 932 (**C** or **D**), where one CO is lost, or m/z 876 (**A**) where only the unreacted olefine is lost were detected.



Fig. 4.16: CID with m/z 960.

An equivalent ion to m/z 960 but at m/z 980 is present when an excess of styrene is used

instead of 1-hexene but its signal proved too weak for further CID experiments. Styrene is thought to form a stable acyl complex with Rh under hydroformylation conditions, as proved by NMR-studies.[92]

The complex of m/z 960 that should correspond to **E** or **F** should react with D₂ to regenerate **A** + 1 m/z unit. However, it failed to do so in our experiments. Furthermore, it reacts in the same manner giving m/z 848 with Ar as collision gas where only fragmentation would be expected. One logical conclusion for this unexpected reactivity is that the structure of m/z 960 resembles neither the proposed complexes **E** nor **F**. Instead, one could think of the olefine complex **E**' resulting from β -hydride-elimination as the Fig. 4.17 suggests.



Fig. 4.17: Possible complex and fragmentation pattern of m/z 960.

Colliding **E**['] with any collision gas would result in the loss of the weakly bound olefine ligand giving m/z 876, which is **A** in Fig. 4.17. As shown before (Fig 4.14) this complex is only stable under very low collision energies, instantaneously losing the second CO molecule giving m/z 848. Alternatively, a direct β -hydride-elimination from **F**, liberating a ketene, would result directly in the complex m/z 848 (Fig. 4.17, left side). Although a reaction like this seems unlikely and has not been reported for Rh-complexes, there is evidence for the elimination of a ketene for comparable Ru-complexes [Ru(COMe)(CO)₂ (triphos)]Cl.[93]

4.2.3 D₂-incorporation experiments

Using D_2/CO as synthesis gas gave some more insight into the nature of the ion at m/z 848 and the catalytic cycle itself. When no substrate is present, only one deuterium atom is incorporated to **B** shifting its mass up in one m/z unit. Upon collision, 31 or 30 m/z mass units were lost, as shown previously in Fig 4.13. Incorporation of deuterium was not complete and thus only a part of the ion population at m/z 849 had a deuterium atom bound to the Rh-center. The ion corresponding to **2** was detected at m/z 437 and 438, as seen in Fig 4.18.

Adding a substrate proved revealing. While the main mass shift for **B** was 2 mass units and upon collision the same behavior as before was seen, the free ligand was detected as a mixture of ions with m/z 437 and 438, shown in the spectrum of Fig. 4.19.



Fig. 4.18: ESI-MS spectra under CO/D₂-atmosphere and with substrate in solution (highlighted areas are shown in Fig. 4.19 and Fig. 4.20).



Fig. 4.19: ESI-MS spectra under CO/D₂-atmosphere and with substrate in solution (m/z 750 to 860).



Fig. 4.20: ESI-MS spectra under CO/D₂-atmosphere and with substrate in solution (m/z 430 to 450) after 20 min (left) and 2 h (right) reaction time.

This finding clearly points to the involvement of the H-atoms of the hydrogen bond framework in the catalytic cycle, as turnover seems to be crucial for the observed incorporation of deuterium into the ligand. This incorporation is progressive as the right spectrum in Fig. 4.20 was taken two hours after the start of the reaction, reaching approx. a 2:1 ratio for heavy vs. normal isotopolog.

To explain the observed deuteration, two different pathways seem to be reasonable, the first one being more closely related to the commonly accepted catalytic cycle, this

proposed mechanism is depicted below in Fig. 4.21.



Fig. 4.21: Proposed pathway for the D₂-incorporation in 2.

After loss of CO and H₂ a complex with P,N,P- or even double P,N-coordination results that partially resembles the structure being identified by X-ray and shown in Fig 4.11. The close and stable P,N-coordination might be the reason for the lack of reactivity in our gas-phase investigations. In solution, on the other hand, due to the presence of a variety of competing coordinating agents (CO, solvent molecules, abundant ligand) one might envision a weaker bonding of the ligands. Activation of deuterium or hydrogen can take place over a thermodynamically preferred 6-membered transition state, resulting in the incorporation of deuterium into the ligands, as observed. CO-coordination regenerates in the last step the now deuterated complex **14**.

The second pathway that appears reasonable is based on the above mentioned *oxidative addition* step thinkable for complex **B**, giving rise to a new mechanism depicted in Fig. 4.22.



Fig. 4.22: Proposed new hydroformylation mechanism for self-assembling ligands.

The intermediate **F** could undergo an oxidative addition yielding the Rh(III)-complex **F**', followed by reductive elimination to liberate the product aldehyde. The resulting complex **15** can be seen as structurally related to **13** in Fig. 4.21 holding one more CO ligand. H_2/D_2 -activation can proceed also over a 6-membered transition state (**16**), regenerating the now deuterated complex **14** that enters a new catalytic cycle. This unprecedented catalytic cycle would not only explain the observed incorporation of deuterium into the free ligand, but explain why we never detected a complex **G** that would be the result of oxidative addition of hydrogen: if the hydroformylation reaction applying our self-assembling ligands could indeed proceed in the above depicted way, a complex **G** with m/z 962 simply would not occur.

Nonetheless, at this point we cannot comment on the possibility of these mechanistic pathways being by any means part of the catalytic cycle of the hydroformylation itself in solution and not only an orthogonal equilibrium phenomena. The unique nature of the self assembling ligand systems and the highly dynamic tautomeric behavior of the applied 6-DPPon ligand could be the basis for this unprecedented reactivity. These findings seem to be in accordance with literature examples where a similar involvement of two net H

atoms, one at the metal center, and another at the heteroatom occur.[94, 95]

4.3 Other bidentate self-assembled ligands

From the available self-assembled ligands at our disposal, some representative members, namely DPPIcon **3**, DPPAP **4**, ESI-DPPAP **5** and finally DPPAT **6** where briefly examined to try and draw some parallels with the behavior observed for the **1**/**2** pair.

The pair DPPICon/DPPAP (3/4) with Rh(NBD)₂⁺ as precursor, electrosprayed from CH₃CN solutions shows the expected pairing of **3** and **4**, and the homoleptic pairs **3**/**3** and **4**/**4**, the last one being the most abundant of the trio, shown in Fig. 4.23. Ligand exchange occurs partially, as the peak at m/z 557 contains a NBD molecule as revealed by CID experiments.



Fig. 4.23: Spectrum of the mixture of 3, 4, and Rh(NBD)₂₊.

The peak at m/z 792 corresponds, according to CID experiments, to a $[Rh(3)(4-2H)]^+$ complex, one molecule of **3** is lost upon collision with Ar to give marginal yields of m/z 463. CID of m/z 794 with Ar, on the other hand, produces a low yield of m/z 465.

When this sample was let to react in the first reaction chamber with ethene at low energy (3 eV, lab scale), it did not produce any detectable products.

When live-streamed from the high-pressure autoclave under a synthesis-gas atmosphere, a new crop of species is present, mainly containing a CO molecule. No H_2 containing species (just as +2 m/z, when z = 1) were detected as the spectrum in Fig. 4.24 shows. Reaction with ethene at low energies did not produce any new species.

The peak at m/z 493 represents a departure from the behavior of the **1**/2 system, only one of the two ligands is present together with one CO molecule. The loss of a ligand in low energy conditions, as well as the homoleptic pairing, suggest that the H-bond framework is weaker than that of the **1**/2 system.



Fig. 4.24: Spectrum of a live-stream of **3**, **4**, and $Rh(NBD)_{2^+}$ under a CO/H₂ atmosphere, only new peaks are labeled.

Further experiments with a slightly modified and charged version of **4**, namely **5**, provide some more clues about the weakness of the H-bond framework and its reactivity in the catalytic cycle of hydroformylation.

A live-stream of the mixture 3/5 with Rh(CO)₂(acac) as precursor under a CO/H₂ atmosphere affords again complex spectra that under close scrutiny show several similarities with the 3/4 system: homoleptic pairs and species where one base is missing, and also one of the characteristics of the 1/2 system, the expulsion of a proton to form a singly charged ion, m/z 837. Drawing a parallel between the 1/2 system and 3/5 the ion m/z 818 corresponds to 837 in the second and m/z 848 corresponds to m/z 867, as seen in the spectrum of Fig 4.25.


Fig. 4.25: Spectrum of a live-stream of 3/5 under CO/H₂ atmosphere.

From the visible ions and the assignments done, it is easy to see that the system is every bit as complex as the 6-DPPon one: singly charged complexes m/z 761, the homoleptic pair **3/3**, m/z 837 with **3/5**, and with just one base like m/z 536 and doubly charged ones like m/z 419, also with **3/5**. From these assignments it is clear that proton expulsion resulted in the formation of m/z 837 and also m/z 536, where only **5** and a CO molecule are present.

CID experiments of m/z 837 show an unexpected behavior. The ion loses 59 m/z units to give a new ion at m/z 778, probably the same ion that is also present in the unreacted spectrum. 59 m/z units would correspond to the loss of NMe₃ due to a nucleophilic attack from the amid N to the terminal-C to furnish a γ -lactam. This should be possible because the negatively charged pyridinic nitrogen, as shown in Fig. 4.26. An alternative route where the O attacks seems less plausible.

The ion with m/z 778, when collided with Ar, readily loses m/z 329, which corresponds to $\mathbf{3}$, to give m/z 449, which matches the bicyclic ligand coordinated to Rh⁺.



Fig. 4.26: Possible reaction pathway for the loss of 59 mass units when ion m/z 837 is collided with Ar (50 eV, lab scale).

The ion at m/z 867 was also examined closely. When collided with ethene in the range 0 to 40 eV (lab scale) it yields no ethene adducts but it fragments producing several daughters. The first one at m/z 839 accounts for the loss of 28 m/z, i.e. one CO. The one at m/z 837 accounts for the loss of 30 m/z, i.e. simultaneous loss of H₂ and CO. The others are m/z 778, 538, 536 and 406, some of them were explained before. The spectrum can be seen in Fig. 4.27.



Fig. 4.27: CID experiment of m/z 867.

The ion with m/z 867 has a similar behavior as m/z 848 (1/2 pair), but compared to that one the ligands seem to be more weakly bound and CO is lost before H₂ upon collision, something that was not apparent from the 1/2 system. The pair of ions at m/z 536 and 538 represent the loss of one ligand **3**. The difference among them being one H₂ molecule, but both still contain CO. This finding hints to one hydride at the rhodium center and one proton at, more likely, the amide nitrogen as the members of the lost H₂ pair, through a similar mechanism as the one depicted for m/z 848 in Fig. 4.15. Upon addition of 1-butene in the gas-phase (low energy, 3 eV) no new species could be detected. Selected ions were also reacted at different energy levels (0 to 40 eV, lab scale) with ethene producing fragmentation only. These experiments could hint towards fully coordinated or sterically compromised rhodium centers like in the case of **1/2**, but extensive experiments with several olefines in the search for an acyl cation, similar to m/z 960, are still needed.

Another complementary ligand of **3**, namely DPPAT, **6**, was studied under similar conditions as **4**. This uncharged ligand pairs in a similar fashion as **4** and has a similar mass. When electrosprayed from Rh(NBD)₂⁺ solutions the ligands displace the olefine but only partially. Homoleptic pairing takes also place here, with the **6**/**6** pair as abundant as the more natural **3**/**6**, at least qualitatively. When reacted with 1-butene in the gas-phase no new species could be detected, even at the high pressure of 600 mTorr, as shown in Fig. 4.28.

CID of m/z 800 yields several fragments, the most abundant represents the loss of **3**, the rest are loss of the substituted thiazole moiety and the loss of a benzene ring. This behavior is consistent with the other ligands, where C-H activation occurred and fragments of the ligands were lost, predominantly a benzene ring.

The use of Rh(CO)₂(acac) as precursor gives CO complexes but even these fail to react when collided with 1-butene in the gas-phase.



Fig. 4.28: Spectrum of the 3/6 with Rh(NBD)₂⁺ as precursor.

4.4 Investigation of ligands without a H-bond framework

For sake of completeness a comparison with ligands that do not form a H-bonded framework has been carried out. The first example is the widely used triphenylphosphane, **7**. Using Rh(NBD)₂⁺ as precursor, rhodium binds up to three molecules of PPh₃, and up to two without displacing the NBD molecule. Complexes with the solvent, CH₃CN, are also present and quite abundant, too.

When reacted in the gas-phase with a $H_2/CO/1$ -hexene mixture only the Rh(NBD)(CO) (PPh₃)⁺ ion is produced resulting from the displacement of either one PPh₃, one CH₃CN or direct addition to the abundant Rh(NBD)(PPh₃)⁺, as seen in Fig. 4.29. The olefine is not exchanged under this low energy conditions (3 eV, lab scale).



Fig. 4.29: Spectrum of a $Rh(NBD)_2^+/PPh_3$ in CH_3CN solution with $CO/H_2/1$ -hexene as reaction gas. Only a CO adduct can be detected.

Binding of CO in the gas-phase suggest that triphenylphosphane forms a much weaker ligand sphere than 6-DPPon and its charged counterpart do. Under hydroformylation conditions, using the charged olefine, no new species could be detected besides the charged olefine and the hydroformylation product.

Another commercially used ligand, **8**, known as XANTPHOS, is a wide-bite-angle (111.7°) bidentate ligand with a xanthene framework.[96] This ligand has two phosphorus atoms, at positions 4 and 5, able to coordinate to Rh. Using Rh(CO)₂(acac) as precursor and 1.1 eq. XANTPHOS in CH₃CN some differences with previous ligands can already be seen. Rhodium complexes bind to one or two XANTPHOS molecules but the only CO complexes detected were of the kind Rh(XANTH)(CO)⁺. When reacted with olefines in the gas-phase coordination of an olefine molecule occurs (ethene, 1-butene) at the expense of the CO molecule, as shown in Fig. 4.30. Such a complex loses the olefine when collided with another molecule. The bis-XANTPHOS-Rh complex does not bind a CO molecule nor it reacts with the olefine.

Under hydroformylation conditions using the charged olefine *N*,*N*,*N*-triethyl-hex-5-en-1ammonium, no hydride containing ions could be detected; this is in accordance with the proposed mechanism but no olefine complexes could be detected either.



Fig. 4.30: Spectrum of the ion-molecule reaction between Rh/XANTPHOS and 1-butene.

4.5 Discussion and conclusion

Bidentate self-assembled ligands provide greater flexibility than normal bidentate ones because both parts can be independently functionalized to better suit the study's requirement like this work shows. While the ligands performed well in hydroformylation in solution, we cannot say the same regarding their performance in our mass-spectrometric study. Hydroformylation was not achieved in the gas-phase in the sense of selecting the Rh-hydrido complex and reacting it with an olefine will lead to a charged complex the daughter ion of which should indicate the presence of an olefine adduct. Many ions corresponding to the ones proposed in the catalytic cycle were detected and a wealth of information and their inner workings was obtained. The lack of formation of olefine adducts, strongly points towards fully coordinated or very sterically compromised rhodium centers. All these evidence, together with the fact that the "acyl complex" does not react as expected, and the involvement of the H-bond framework in the catalytic cycle suggest that the mechanism followed by the 6-DPPon system is not in accordance with the proposed mechanism of Breslow and Heck. The other self-assembled ligands seem to follow a similar pattern. Simpler ligands, like the ones that do not form a H-bond framework (7 and 8), show that the methods used should afford olefine complexes if were not for the lack of reactivity of the paired species.

The study described here shows how the whole set-up built for this very end had performed exceptionally and up-to par with our expectations. While the reaction presented a tremendous challenge, extensive tuning of parameters, allowed by its very nature, meet such demands.

4.6 Experimental

Experiments were carried out in the rector described in section 2.2 or directly in the mass spectrometer described in section 2.4.

The reactor was was always flushed with CO₂ and then with CO, H₂ or D₂ according to the experiment's requirements. Once flushed, the catalyst solution was injected under a counter-current of CO₂ or CO. Then pressurized with the CO/H₂, heated if necessary and vigorously stirred using magnetically-coupled stirrer. Heating was provided with an oil bad or with an aluminum heating jacket.

Live-streaming was achieved using PEEK tubing as previously described. In selected cases a liquid was mixed with this stream using a tee and a syringe actuated via a syringe pump.

Reactions inside the mass spectrometer were done using the collision-cell built around an octopole, variable-energy range, low pressure as well as the 24-pole, higher pressure lower energy (usually around 3 eV). Due to the low pressures involved, low boiling point liquids can be used as well as room-temperature gases.

In the cases where the reactor was used as gas reservoir, it was flushed as explained before and then just filled with the appropriate mixture of components and connected to either the 24-pole inlet or the octopole inlet using stainless steel tubing.

5. Determination of bond energies via threshold CID

The determination of bond energies can be accomplished by a number of experimental methods like photoionization and photodetachment, electron ionization, direct photodissociation, unimolecular dissociation, bimolecular ion-molecule reactions and electron-molecule reactions. Most of these methods apply a statistical rate theory of unimolecular dissociation to extract the bonding energy from the experimental data. In this theory, known as the Rice-Rampsberger-Kassel-Marcus (RRKM) or quasi-equilibrium theory (QET),[97-99] the rate of dissociation only depends on the energy and angular momentum of the activated species and not on the activation method. This theory is based in the Rice-Rampsberger-Kassel (RRK) theory in which the system is modeled as a series of harmonic oscillators. Then, the rate coefficient is determined by the formula shown below.

$$k(E) = v \left(\begin{array}{c} \frac{E - E_0^{\ddagger}}{E} \end{array} \right)^{S-1}$$

where k(E) is the rate coefficient for a microcanonical ensemble of isolated molecules, each with internal energy *E*, *v* is the frequency of the harmonic oscillator, and E_0^{\ddagger} is the minimum energy required to dissociate the molecule. Because this classical theory underestimates rates, the number of oscillators is reduced by a factor of 2 to 5.[98, 100] The classical RRK model captures the essentials of statistical rate theory and thus it is applicable to the quantitative analysis of energy-dependent rates but inadequate for its application to the modeling of the experiments carried out in this work.[100, 101] For this reason, the more modern RRKM theory, which better models experiments based on isolated ions whose internal energy is fixed, is used instead. The basic equation has the form shown below.

$$k(E, J) = s \left(\frac{W^{\ddagger}(E - E_0^{\ddagger}, J)}{hp(E, J)} \right)$$

where $W^{\ddagger}(E-E_0^{\ddagger}, J)$ is the number of rovibrational energy states of the transition-state configuration at total energy *E*, total angular momentum *J*, and with a minimum potential energy barrier E_0^{\ddagger} . p(E, J) is the density of rovibrational states of the energized molecule; *s* is the reaction degeneracy and h is the Plank's constant.

The nature of the transition state has significant influence in the determination of the rate constant. While several models of transition states exist, two of them are of special interest because they are suitable for the treatment of data obtained with the methods under discussion: a *tight* transition state has the same number of vibrational modes as the energized molecule less the one treated as reaction coordinate, and it is normally located at a potential energy barrier. A *loose* transition state is useful to model ion-molecule reactions where no barrier exists, like TCID, and consists of a state more similar to the products.

Threshold energy measurements are an important means of obtaining thermochemical information from the different methods. But measurement of this energy presents its difficulties because the signal will have very low signal to noise ratio in the vicinity of the threshold, masking it. A number of models to extrapolate this threshold behavior have been developed, being the power law shown below one of the simplest and the one used throughout this work.

$$s(E)=s_0 \quad \frac{(E-E_0)^n}{E^m}$$

In this equation the cross section, s(E), which is proportional to ionization, dissociation or reaction probability, is a function of the energy; s_0 is a scaling factor that depends on the intrinsic transition strength or reaction probability, E_0 is the state-to-state threshold energy; m and n are treated as adjustable parameters and depend on the process being considered. In the case of TCID, m and n are usually 1, *E* is the relative collision energy in the center-of-mass frame and E_0 is the dissociation energy. But its applicability to TCID experiments is limited and only provides an approximation because it does not take in account the spread of the ion energy and the thermal motion of the target gas.[102, 103] Mass spectrometric measurements incur normally in a kinetic shift due to the time-window imposed by the moving ions. Fast ions dissociate normally after mass analysis takes place, then a thorough thermalization step that narrows the energy distribution contributes to lower the influence of this source of error.

In photoelectron spectroscopy, the photon energy is fixed at a value higher than the IE or EA and the kinetic energies of the ejected photoelectrons are measured upon photoionization or photodetachment. The electron binding energy is the difference between the photon energy and the electron kinetic energy. The spectrum of photoelectron energies yields information about the structure of the upper charge state. For thermochemical use, the IEs and EAs should represent adiabatic values, i.e., the energy difference between the ground states of the neutral and ion.

Threshold photoelectron spectroscopy, developed in the late 1960s, are the observation of near-threshold photoionization processes via detection of low-energy photoelectrons.[104, 105]. Coincidence techniques for simultaneous detection of the photoions to provide information in fragment ions were developed in the 1970s. These techniques essentially yield the derivative of the photoionization efficiency curve at resolutions fixed by the energy selection of slow photoelectrons. In threshold photoelectron photoion coincidence spectroscopy, the threshold photoelectron and the photoion are detected simultaneously by time-of-flight.[105-109] By energy balance, the internal energy of the initial photoion in excess of the ionization energy is known from the excitation wavelength. If the detected ion is a fragment, then unimolecular dissociation rate coefficients can be determined as a function of energy, k(E). The rate-energy curve is modeled by RRKM/QET statistical theory.

In electron impact ionization threshold measurements, ionization is achieved by the interaction of a neutral species with an energetic electron. Near-linear threshold behavior of the cross section vs electron energy, E_e , is found in high-resolution experiments on atoms and small molecules.[110] For polyatomics, the transition intensities are governed by the Franck-Condon principle.[110, 111] Because the threshold onset in near-linear, compared with a step function for photoionization, identifying individual state-to-state thresholds is difficult.[112] Modern electron ionization experiments use an electron monochromator to narrow the electron beam energy distribution, and the energy scale is calibrated by measurement of a known ionization energy.[113, 114, 115]

Photodissociation of ions occurs when a parent ion absorbs energy at the appropriate wavelength and that the resulting exited ion fragments promptly. When performed in a mass spectrometer, the parent ion is mass selected, irradiated and the products mass analyzed. A wide number of systems have been analyzed using photodissociation, including metal-containing ions.[116-122]

The basic idea behind unimolecular dissociation methods for measuring thermochemical values is that the rate of dissociation of a molecule or ion with a given internal energy content is strongly dependent upon the energy barrier for dissociation, as given by the RKKM/QET theory described above. The dissociation rates may be measured directly in

time-resolved experiments; otherwise statistical theory is used to correct for kinetic and competitive shifts in threshold energy measurements.

In the threshold collision-induced-dissociation (TCID) method, a tandem mass spectrometer is used to isolate the parent ion by mass, accelerate or decelerate the ions to a controlled kinetic energy, collide them with an inert target gas under single-collision conditions, and then mass analyze the fragment ions. An example reaction process is given below.

Ag(ethene)₂⁺
$$\xrightarrow{\text{Ar, Xe}}$$
 [Ag(ethene)₂⁺]^{*} \longrightarrow Ag(ethene)⁺ + ethene

The xenon gas is preferred as target gas because it is heavy and polarizable, promoting efficient energy transfer,[123] but other inert gases like argon work as well. In TCID the apparent cross section for formation of the fragment ion Ag(ethene)+ is measured as a function of the relative ion/target collision energy in the center-of-mass frame. The threshold energy for dissociation, E_0 , is equal to the 0 K reaction endothermicity of the dissociation, in the absence of reverse activation energies and when the translational and internal energy distributions and kinetic shifts are accounted for. TCID measurements have been carried out in a number of different mass spectrometer types, [76, 124-129] the experiments described here have been carried out in a triple-quadrupole system. The cross section in this kind of mass spectrometer may exhibit a tail in the threshold region, [130, 131] because of the energy and angular distribution of the ions emerging from the first mass filter or from collision with the gas present in the areas between quadrupoles.

Obtaining accurate dissociation energies from TCID requires corrections for kinetic shifts using RRKM theory and convolutions over the internal and translational energy distributions, as mentioned before. As with other thermokinetic methods, it is crucial that the reactant ions be prepared with a known internal energy content or temperature, for this reason a thermalization gas, also called buffer gas, that ensures a narrow energy distribution is used.[126-128] In our case the bathing gas employed was N₂ at pressures of 10 mTorr, affording around 30000 collisions/s.

Finally, the experimental data is fed into the CRUNCH program provided by Prof. Armentrout and after fitting of the data, the binding energy is calculated.[132] This energy was then compared to the binding energy calculated for the optimized structures of the complexes at the B3LYP level of theory using the 6-311G(d,p) basis set for light atoms and the LANL2DZ basis set for silver using the gaussian03 set of programs.[133] The counterpoise correction has also been performed according to literature procedures,[134] but the corrections while calculated are small, as explained by Schwarz.[135]

5.1 Silver olefine complexes

The silver cation is known to form a number of complexes with olefines both in solution [136] and in the gas-phase [135, 137] Experimental information about the binding energy remains limited mostly to Ag(ethene)⁺ and Ag(ethyne)_n⁺ (n = 3, 4) and to the mentioned publications. These same works account also for a theoretical approach to the determination of the bonding energies. Krossing and coworkers used traditional solutionphase methods to yield the mentioned complexes using bulky non-coordinating anions. When these solutions are cooled to -20 °C the complexes crystalize giving crystals suitable for structure determination via X-ray crystallography.[136] Of particular experimental interest is the setup employed by Castleman and coworkers,[137] where silver ions produced by heating a filament coated with AgNO₃ were let to react with ethene in a high pressure mass spectrometer at different temperatures. The complexes thus formed were then mass analyzed; and the equilibrium constant for the association, determined. From this constant the thermodynamic properties were calculated. Schwarz and coworkers made a thorough theoretical analysis of the problem. Comparing several computational as well as theoretical models they concluded that the hybrid method B3LYP produces acceptable values well in the range of the experimental results to date. A bond decomposition analysis showed that the Ag-C bond is both partially electrostatic and partially covalent in nature and that back-bonding from the d orbitals into the free π^* of the ethene molecule contributes to 20 % of the total covalent contributions. While they argue that perturbation theory should provide also comparable results, it fails to do so by a seizable amount. It must be also noted that they neglect the contribution of the BSSE in their calculations citing the little influence that it has when either DFT or MP2 methods are used, something that our own calculations also show.

Due to the unique nature of this kind of complexes and the proven ability of our equipment to allow to determine bonding energies, [2] we decided to focus on a small subset of the spectrum, namely ethene, 1-butene and finally corannulene, as a more real-world application of this ability.

5.1.1 The complexes of ethene and Ag+

The Ag⁺ cation has been proven to complex up to 2 ethene molecules in the gas-phase and up to 4 ethyne molecules in solution. Using the mass spectrometer described in section 2.4, fitted with the 24-pole, Ag⁺ ions were let to react at 500 mTorr with ethene to yield Ag(ethene)_n⁺ were n=1-3, as shown in the spectrum of Fig. 5.1. While Ag(ethene)₄⁺ has been predicted by theoretical calculations, its detection under these conditions has not been successful. While the goal of these experiments was the determination of the bond energy using the TCID method, the intensities afforded were not good enough. The use of the unmodified mass spectrometer, octopole instead of 24-pole, provided even less signal, as expected. Another approach tested consisted in the use of the small pressurized reactor of section 2.2 as a live-stream source of the silver complex using ethene as pressurizing gas. This approach gave even lower yields than the previous attempts.



Fig. 5.1: Spectrum of the three detected silver-ethene complexes.

DFT calculations show that the bis-ethene complex should have a staggered configuration, as depicted in Fig. 5.2 The binding energy for the second ethene molecule has been calculated as 28.48 kcal/mol, a value significantly lower than the one obtained experimentally by Castleman. The Møller-Pesset results are not much better, but the small basis set used, for comparison reasons, should account for the differences. The binding

energy for the third molecule was then calculated as 11.78 kcal/mol. This tris-ethene complex is shown on the right of Fig. 5.2.



Fig. 5.2: Optimized structures for the Ag(ethene)_n⁺ complexes, left n=2, right n=3.

Structure	Calculation (B3LYP)	Energy [a.u.]
Ag(ethene) ₂ +	Counterpoise correction (BSSE)	0.001667300949
Ag(ethene) ₂ +	Full optimization	-302.800501401
Ag(ethene)+	Single point (cplx coords)	-224.1410734
Ag(ethene)+	Full optimization	-224.141124
ethene	Single point (cplx coords)	-78.6121879
ethene	Full optimization	-78.6139781
	Bond energy [kcal/mol]	28.48

Table 5.1: Results of the calculation using DFT.

Structure	Calculation (MP2)	Energy [a.u.]
Ag(ethene) ₂ +	Counterpoise correction (BSSE)	0.008520755234
Ag(ethene) ₂ +	Full optimization	-301.4920688
Ag(ethene)+	Single point (cplx coords)	-223.10455838
Ag(ethene)+	Full optimization	-223.10484797
ethene	Single point (cplx coords)	-78.34296563
ethene	Full optimization	-78.34429139
	Bond energy [kcal/mol]	26.93

 Table 5.2: Results of the calculation using perturbation theory.

5.1.2 The complexes of 1-butene and Ag+

While 1-butene seems at first glance a much bigger molecule than ethene it forms at least theoretically, the same three complexes as ethene with similar structures, shown in Fig. 5.4 and 5.5. But experimentally things are a bit different. Injecting a high amount of 1-butene, around 500 mTorr, into both the 24-pole assembly as well as the 8-pole, affords only the Ag(1-butene)_n⁺ with n=1-2 complexes. Calculations show that the binding energy for the second 1-butene molecule should be 30.64 kcal/mol and 17.41 for the third, detailed in Tables 5.3 and 5.4 respectively. Due to the fact that only the bis-butene complex was found in acceptable yields it was the one used as the target in our TCID experiments. From the experimental data an energy of 22 kcal/mol (0.98 eV) was obtained. This value is notoriously lower than the value obtained via DFT calculations.



Fig. 5.3: Optimized structures for the $Ag(1-butene)_{n^+}$ complexes, left n=2, right n=3.

Structure	Calculation (B3LYP)	Energy [a.u.]
Ag(1-butene) ₂ +	Counterpoise correction (BSSE)	0.000399210268
Ag(1-butene) ₂ +	Full optimization	-460.1201571
Ag(1-butene)+	Single point (cplx coords)	-302.803006
Ag(1-butene)+	Full optimization	-302.8032364
1-butene	Single point (cplx coords)	-157.2650467
1-butene	Full optimization	-157.2680836
	Bond energy [kcal/mol]	30.64

Table 5.3: Results of the calculation using DFT for $Ag(1-butene)_{2^+}$.

Structure	Calculation (B3LYP)	Energy [a.u.]
Ag(1-butene)₃+	Counterpoise correction (BSSE)	0.000426140651
Ag(1-butene) ₃ +	Full optimization	-617.4039294
Ag(1-butene) ₂ +	Single point (cplx coords)	-460.1097915
Ag(1-butene) ₂ +	Full optimization	-460.1201571
1-butene	Single point (cplx coords)	-157.2663839
1-butene	Full optimization	-157.2680836
	Bond energy [kcal/mol]	17.41

Table 5.2: Results of the calculation using DFT for Ag(1-butene)₃+.

5.1.3 Corannulene complexes of Ag+

Corannulene is a bowl-shaped molecule rich in double bonds. This strained molecule is the building block of many nano-sized structures like closed nanotubes and fullerenes. The five-membered ring gives the structure its curved form as seen in Figure 5.6. Due to the unique properties that its shape confers, it has been the subject of intense research, not only synthetically but also physically.[138]. The sample used throughout this work has been kindly provided by Siegel's group (University of Zurich, Switzerland). Many synthetic pathways are available nowadays for the obtention of corannulene, while older methods are based on pyrolysis from compounds of the like of benzo[c]phenanthrene which afford very poor yields, in the 5 % range, solution phase methods also exist, [138, 139] which afford much better yields. A method developed in the Siegel group provides simplicity and versatility: being able to afford also many different substituted derivatives.[139, 140] Starting from 2,7-dimethylnaphthalene, and treating it with formaldehyde and HCl in acetic acid, methylation at position 1 occurs. The chlorine is replaced by cyanide, then hydrolyzed to the carboxylic acid and cyclized by way of the acid chloride in the steps to yield 3,8-dimethyl-1-acenaphthenone. This ketone is oxidized with SeO₂ in dioxane/water to yield the diketone. The cyclopentadienone precursor is then formed when the diketone is condensed with 3-pentenone in methanolic KOH solution. The cylopentadienone is then produced in acetic anhydride and trapped by Diels-Alder reaction with norbornadiene. A cascade of retrocycloadditions follows to release cyclopentadiene and CO and affords fluoranthene. After bromination of the fluoranthene 1,6,7,10-tetrakis(dibromomethyl)

fluoranthene is formed. Final cyclization is afforded when the fluoranthene is reacted with TiCl₄ and Zn/Cu in dimethoxyethane, as shown in Fig. 5.7.



Fig. 5.7: Synthesis of corannulene developed at the Siegel group.

When investigated using the same DFT parameters as before two possible structures emerge for the Ag(corannulene)₂+ complex, either convex-convex or concave-convex. As it can be seen from the structures the silver ions do not sit in the center but over the rim of one molecule and at the far end of the spoke of the other one, as depicted in Fig 5.8. The energy difference is only 3.24 kcal/mol favoring the convex/convex complex (left in Fig. 5.8). Using the TCID method described previously with Argon as target gas, an energy of 0.83 eV (19.1 kcal/mol) is obtained, quite lower than the calculated value of 30.17 kcal/mol via DFT. The difference arises most probably due to the inefficiency of the standard octopole in thermalizing the ions as well as the use of Argon instead of Xenon as discussed in the following section.



Fig. 5.8: Optimized structures for the two possible $Ag(corannulene)_{2^+}$ cations.

Structure	Calculation	Energy [a.u.]
Ag(corannulene) ₂ +	Counterpoise correction (BSSE)	0.002580104563
Ag(corannulene)2+	Full optimization	-1682.2282894
Ag(corannulene)+	Single point (cplx coords)	-913.8646113
Ag(corannulene)+	Full optimization	-913.8650476
corannulene	Single point (cplx coords)	-768.3134152
corannulene	Full optimization	-768.3151498
	Bond energy [kcal/mol]	30.17

Table 5.4: Results of the calculation using DFT for $Ag(corannulene)_{2^+}$.

5.2 Discussion

Our TCID experiments yielded bonding energies notoriously lower than the calculated values. There are a number of factors affecting both the calculations and the experimental procedures. Density functional theory, the one used in our calculations, is used normally as a fit-for-all method. When only covalent bonds are treated the results obtained are good enough compared to more expensive methods like CCSD, but when polarized bonds like the ones in the ions described here are involved, the results start to deviate too much from the ones obtained via more comprehensive methods. For this reason a number of semiempirical corrections have arisen lately but are yet to be applied to this particular problem.[141] A richer basis set than the one used, one that includes more polarization functions for example, can also provide a better description of the bonds in the silverolefine complexes. A rigorous treatment of all these factors means a work in itself and deviates from the purpose of giving a guideline for comparison with the experimental data. Another source of error when calculating bonding energies are the basis set incompleteness error (BSIE) and the basis set superposition error (BSSE), both arise because a limited number of gaussian functions are used to approximate the atomic environment and thus describe atomic and molecular orbitals. Here is where a richer basis set provides a better description of the orbitals. In the cases described here the BSSE accounts for 0.24 and 1.56 kcal/mol for the butene and corannulene complexes respectively. While Schwarz argued that these corrections where of not great importance because they are small for the silver(ethene) complex, they are nonetheless a source of error to be accounted for.

On the experimental side the possible sources of errors are also multiple. If we look at the values obtained, 30 % lower than the calculated, then we arrive to the conclusion that the ions seem to be "hot", they posses too much internal energy. The thermalization process that occurs in the first octopole should narrow the energy distribution of the ions and bring them to a ground state. Incomplete thermalization will widen the energy distribution skewing the threshold curve. Another source of energy is the use of the first quadrupole as a mass selector instead of a pass-through. This mass selection was necessary because we measured bis-butene and bis-corannulene complexes and the mono-olefinic complexes where present in the recorded data. One method to remove them is to use a mass filter. Either *daughter* or *rfd* modes can be used, being the second one the one that gives the ions the less energy. In our case the less favorable method, *daughter* was used.

In this mode the quadrupole works as a band-pass filter with a narrow window, usually one mass unit. After the data has been collected it has to be processed. For this aim the program CRUNCH developed in the Armentrout group has been used. This program implements the RRKM theory and has been written based on empirical feedback, meaning that there are many corrections and manipulations that can be performed to the data. It basically needs two sets of data as inputs, on one side the experimental data collected from TCID experiments, on the other a set of vibrational frequencies for the products, reactants and the transition state. These set of vibrational frequencies has to be calculated with for instance DFT methods, as described before. If these sets of frequencies corresponds to partially described species, then the results obtained may not be realistic. The experimental data has to be fitted to an equation that models the threshold behavior, this fitting is critical because it strongly affects the results. In our case the fittings where good and further optimizations did not provide better results.

6. Experimental

6.1 Materials and analytical methods

6.1.1 Solvents

Methanol used for electrospray was dried over molecular sieve (3 Å) and distilled. Diethylether used for Grignard reactions was dried over sodium and distilled. Other solvents and reagents were used as received. Ethanol was +99 %. HMA (99.5 %) was obtained from Dr. W. Bonrath, DSM Nutritional Products Ltd., Basel Switzerland. Gases were used as received in steel cylinders, purity was H₂, CO, CO₂ 3.5, ethene, 1-butene, 2-butene, Ar 5.0, Xe 4.0.

6.1.2 Working conditions

Light sensitive substances were handled in protective containers and reactions were carried out in darkness. Moisture-sensitive and oxygen-sensitive reactions were carried out under dry conditions using standard techniques for these cases using a dry nitrogen or argon atmosphere and dried glass-ware.

6.1.3 Analytics

Mass spectrometric measurements were performed in a Thermo Finnigan TSQ7000 tandem mass spectrometer. Particular measurement conditions are given in each case. As a general rule, scan mode was Q3MS, positive ion mode (otherwise indicated), tube lens potential was optimized in each case or for a series of measurements that required equal conditions, a time span of 1 minute was used to collect spectra and average them, in some cases 2 minutes where used as indicated.

CID experiments are recorded using Q3 as mass analyzer and Q1 as mass selector (daughter mode). A reactant or collision gas like Ar, Xe, olefines, etc. is introduced in O2 at constant pressure (~1 mTorr) and a spectrum is recorded. The collision offset can be varied from -196 to 196 V. Usual values are in the 0 to -100 V range for positively charged ions.

Ion-molecule experiments are carried out in a similar fashion to CID with the exception that the reactant is introduced into O1 at constant pressure (up to 600 mTorr) and a low voltage offset is used, usually -2 to -3 V for positively charged ions.

Nuclear magnetic resonance measurements were performed in a Varian Mercury VX (300 MHz for hydrogen), displacements (δ) are given in parts per million (ppm), CHCl₃ (7.26 ppm) was used as solvent and as internal standard. Coupling constants, *J*, are given in Hertz. Multiplicity is indicated as: w (wide peaks or groups), s (singlet), d (duplet), t (triplet), q (quartet), m (multiplicity greater than 4).

GC-MS analysis were done in a Varian GC connected to a Finnigan TSQ700 MS using EI at 70 eV. The column used is a fused-silica capillary column: Optima-5. A nonpolar 5% phenyl – 95% dimethylpolysiloxane, length 30 m, ID 0.25 mm column. An internal standard was normally used, unless stated otherwise.

Elementary analysis (C, H, N and S) was done on a VarioEL (Elementaranalysensysteme GmbH).

6.2 Dehydration of HMA



Fig. 6.1: Dehydration of HMA under ultrasound irradiation and high pressure.

In the reactor described in section 2.1, 0.1 g of HMA in 15 ml of ethanol (99.5%) with 15 ml of CCl4 and enough CO2 to pressurize it to 3.8 MPa at 294 K, were let to react under ultrasound irradiation (19730 Hz) for 6 h. During the reaction the pressure increased to 4 MPa and the temperature rose to 299 K. Sampling was performed through the capillary that forms the reactor to mass spectrometer link (described in section 2.3). At regular

intervals (1 h) sampling and measurement were performed in real-time. Calibration curve: In separated vials, appropriate amounts of HMA were dissolved in methanol to produce dilutions with concentrations 100 nM, 300 nM, 1 μ M, 3 μ M, 10 μ M, 30 μ M, 100 μ M, 300 μ M and 1 mM. These samples were measured to obtain a calibration curve used to normalize and to calculate the concentration of species of interest in the samples taken in the previous step from the reaction mixture. All samples were mass spectrometrically analyzed on the same day with the same set of conditions: flow-rate 1 μ I/min, ESI potential 3.2 kV, scan time 2 min and a tube lens potential of 67.8 V.

Mass spectrum: [HMA-O-Et+Na]⁺ 397.50 m/z, [HMA-O-Et+K]⁺ 413.50 m/z, [HMA+Na]⁺ 369.23 m/z, [HMA+K]⁺ 385.25 m/z. Vitamin A acetate complexes were not detected, but they are known to undergo substitution to form HMA-O-Et under these conditions.[32] Other unidentified peaks are also present.

Control experiment: Methanol instead of ethanol was used and the rest of the conditions were the same as described above.

Mass spectrum: [HMA-O-Me+Na]⁺ 383.40 m/z, [HMA-O-Me+K]⁺ 399.20 m/z, [HMA+Na]⁺ 369.23 m/z, [HMA+K]⁺ 385.25 m/z. Vitamin A acetate complexes were not detected, but they are known to undergo substitution to form HMA-O-Me in these conditions.[32] Other unidentified peaks are also present.

6.3 Disproportionation of olefines



Fig. 6.2: Disproportionation of cyclohexene, 1-3-cyclohexadiene and 1-4-cyclohexadiene over a 25x25 mm² piece of Pd foil.

General procedure:

The reactor described in section 2.2, was cleaned with ethanol (99.5 %) and degassed with CO_2 and then charged with the substrate and pressurized with CO_2 . The olefine (~1 mL) was let to react over a 25x25 mm² piece of Pd foil for a specific amount of time. Temperature and pressure measurements were performed with a thermocouple and a electronic pressure meter. Heating was realized using a buried heating element connected to an integrative controller. The reactor was cleaned with ethanol (99.5 %) and degassed with CO_2 . before the reaction. Ultrasonic irradiation (19730 Hz) was provided with the described setup using a titanium probe.

Variant 1: In the reactor cyclohexene (1 mL, 9.86 mmol) was pressurized with CO_2 (40 bar, 20 °C), heated up to 120 °C and let to react with the Pd foil under ultrasound irradiation for 6:50 h. The pressure inside the reactor rose to 55 bar at 120 °C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]: mixture of cyclohexane δ = 1.42 (s, 12 H). benzene δ = 7.39 (s, 6 H).

Variant 2: In the reactor 1,3-cyclohexadiene (1 mL, 9.86 mmol) was pressurized with CO₂ (40 bar, 20 °C), heated up to 120 °C and let to react with the Pd foil under ultrasound irradiation for 11 h. The pressure inside the reactor rose to 55 bar at 120 °C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]: cyclohexane δ = 1.42 (s, 12 H), benzene δ = 7.39 (s, 6 H).

Variant 3: In the reactor 1,4-cyclohadiexene (1 mL, 9.86 mmol) was pressurized with CO₂ (40 bar, 20 °C), heated up to 120 °C and let to react with the Pd foil for 12 h. The pressure inside the reactor rose to 60 bar at 150 °C. The products were analyzed via ¹H-NMR.

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<sup>1</sup>H NMR [300.13 MHz, CDCl<sub>3</sub>]: cyclohexane \delta= 1.42 (s, 12 H), benzene \delta= 7.39 (s, 6 H).
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Variant 4: In the reactor 1,4-cyclohadiexene (1 mL, 9.86 mmol) was pressurized with CO₂ (40 bar, 20 °C), heated up to 120 °C and let to react without the Pd foil for 12 h. The

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pressure inside the reactor rose to 60 bar at 150 °C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]: 1,4-cyclohadiexene, δ = 2.67 (s, 4 H), δ = 5.69 (s, 4 H) (unreacted starting material).

6.4 Disproportionation of olefins over Pd/C or Pd/CaCO₃



Fig. 6.2: Disproportionation of 2-cyclohexen-1-one over Pd/CaCO₃



Fig. 6.3: Disproportionation of γ-terpinene over Pd/CaCO₃

General procedure:

The reactor described in section 2.2, was cleaned with ethanol (99.5 %) and degassed with CO_2 and then charged with the substrate and pressurized with CO_2 . The olefine (~1 mL) was let to react over Pd/CaCO₃ a specific amount of time. Temperature and pressure measurements were performed with a thermocouple and a electronic pressure meter. Heating was realized using a buried heating element connected to an integrative controller. The reactor was cleaned with ethanol (99.5 %) and degassed with CO_2 . before the reaction.

Variant 1: In the reactor 2-cyclohexen-1-one (1 mL, 9.86 mmol) was pressurized with CO_2 (40 bar, 20 °C), heated up to 150 °C and let to react over Pd/CaCO₃ (21.5 mg) for 12 h. The pressure inside the reactor rose to 60 bar at 150 °C. The products were analyzed via ¹H-NMR.

Variant 2: In the reactor 2-cyclohexen-1-one (1 mL, 9.86 mmol) was pressurized with CO_2 (40 bar, 20 °C), heated up to 150 °C and let to react over Pd/CaCO₃ (20.0 mg) for 12 h. The pressure inside the reactor rose to 60 bar at 150 °C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]:

Variant 3: In the reactor 2-cyclohexen-1-one (1 mL, 9.86 mmol) was pressurized with CO₂ (40 bar, 20 °C), heated up to 150 °C and let to react over Pd/CaCO₃ (20.0 mg) for 12 h. The pressure inside the reactor rose to 60 bar at 150 °C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]:

6.5 Isomerization of (S)-(-)-carvone



Fig. 6.4: Isomerization of (S)-(-)-carvone.

The reactor described in section 2.2, was cleaned with ethanol (99.5 %) and degassed with CO_2 and then charged with the substrate and pressurized with CO_2 . The olefine (~1 mL) was let to react over Pd/CaCO₃ a specific amount of time. Temperature and pressure measurements were performed with a thermocouple and a electronic pressure meter. Heating was realized using a buried heating element connected to an integrative controller. The reactor was cleaned with ethanol (99.5 %) and degassed with CO_2 . before the reaction.

Variant 1: In the reactor 2-cyclohexen-1-one (1 mL, 9.86 mmol) was pressurized with CO_2 (40 bar, 20 °C), heated up to 120 °C and let to react over Pd/CaCO₃ or 12 h. The pressure inside the reactor rose to 55 bar at 120 °C. The products were analyzed via ¹H-NMR.

6.6 Disproportionation of (R)-(+)-pulegone



Fig. 6.5: Dispropotionation of (R)-(+)-pulegone to thymol and menthone.

The reactor described in section 2.2, was cleaned with ethanol (99.5 %) and degassed with CO_2 and then charged with the substrate and pressurized with CO_2 . The olefine (~1 mL) was let to react over Pd/CaCO₃ a specific amount of time. Temperature and pressure measurements were performed with a thermocouple and a electronic pressure meter. Heating was realized using a buried heating element connected to an integrative controller. The reactor was cleaned with ethanol (99.5 %) and degassed with CO_2 . before the reaction.

In the reactor (*R*)-(+)-pulegone (1 mL, 9.86 mmol) was pressurized with CO₂ (40 bar, 20 $^{\circ}$ C), heated up to 120 $^{\circ}$ C and let to react over Pd/CaCO₃ or 12 h. The pressure inside the reactor rose to 55 bar at 120 $^{\circ}$ C. The products were analyzed via ¹H-NMR.

¹H NMR [300.13 MHz, CDCl₃]:

6.7 Synthesis of 3-nitrocyclohex-1-ene



Fig. 6.6: Nitration of cyclohexene.

In a 1 L round-bottomed flask equipped with an argon bubbler, acetic anhydride (400 mL, 4.23 mol) was mixed with nitric acid (δ = 1.4, 54 g, 0.857 mol) and the flask was chilled to

-20 °C. To this mixture, cyclohexene (30.4 mL, 0.300 mol) was added, and then the mixture was let to warm to 1 °C were it turned yellowish in color and then cooled again to -20 °C. Finally the mixture was given to water (d, 1.5 L) and separated in two fractions for better work-up. The organic product was extracted with ether (200 ml), washed with water (3x400 ml) and dried over MgSO₄. The raw extract was then freed from ether and vacuum distilled. Fractions 2 and 3 (0.77 mbar, 48.5 to 57 °C) were collected and analyzed via ¹H NMR and elemental analysis. A mixture of 62 % 3-nitrocyclohex-1-ene and 38 % 4-nitrocyclohex-1-ene was obtained in 30 % yield.

¹H NMR: nitrocyclohex-2-ene: $\delta = 6.15$ (m, 1H), $\delta = 5.9$ (m, 1H), $\delta = 4.95$ (m, 1H). 4nitrohex-1-ene: $\delta = 5.75$ (m, 1H), $\delta = 5.65$ (m, 1H), $\delta = 4.65$ (m, 1H), $\delta = 2.65$ (m, 2H). Elemental analysis, fraction 2: found 55.28 % C, 7.04 % H, 10.58 % N, calculated 56.68 % C, 7.13 % H, 11.2 % N.

Elemental analysis, fraction 3: found 54.82 % C, 6.94 % H, 10.60 % N, calculated 56.68 % C, 7.13 % H, 11.2 % N.

6.8 Systhesis of cyclohex-1-enecarbonitrile



Fig. 6.7: Two step synthesis of cyclohex-1-enecarbonitrile

In a 250 ml round-bottomed flask equipped with a gas outlet, NaCN (10.0 g, 204 mmol) was dissolved in water (30 mL) and to this solution cyclohexanone (24.55 g, 250 mmol) was added under stirring while cooling to 0 °C. Then, more water (15 mL) and finally H₂SO₄ (43.5 mL) drop-wise during a period 1 h were added caring that the mixture remained below 15 °C. After the addition was complete the reaction was let to warm to RT and stirred for another 20 min, and then TBME (30 mL) was added. The phases were then separated and the inorganic phase was washed with TBME (3x15 mL) and the combined organic portions were distilled under reduced pressure. The fractions that between 80 and 83 °C boiled were combined, and redistilled under reduced pressure using a vigreux column. The higher boiling fraction containing 1-hydroxycyclohexanecarbonitrile was kept and analyzed via ¹H NMR.

In a 250 ml round-bottomed flask, 1-hydroxycyclohexanecarbonitrile (15.3548 g, 122.6 mmol) was dissolved in toluene (122.6 ml) and let to react with SOCl₂ (21.8786 g, 183.9mmol) under reflux for 3 h. The raw reaction mixture was then poured into ice-water (400 ml) and the phases separated. The inorganic phase was then extracted with toluene (2x120 mL), the org. phases combined, washed with NaHCO₃ sol. (5 %, 100 mL), water (100 mL), dried with Na₂SO₄, and finally freed from the solvent. The product, cyclohex-1-carbonitrile was the obtained via column chromatography using cyclohexane:ethylacetate (9:1) as mobile phase.

¹H NMR: cyclohex-1-enecarbonitrile: δ = 6.60 (m, 1H), δ = 2.18 (m, 4H), δ = 1.65 (m, 4H).

6.9 Synthesis of 1-cyclohexenylpiperidine



Fig. 6.8: Catalyzed synthesis of 1-cyclohexenylpiperidine

In a 250 ml round-bottomed flask equipped with a water separation funnel, a reflux condenser and an argon bubbler, cyclohexanone (19.6 g, 200 mmol), freshly distilled piperidine (21.3 g, 250 mmol), p-toluenesulfonic acid (0.5g, 2.6 mmol) were heated to reflux till around 3.6 mL water were recovered (5 h). The raw reaction mixture was washed with sat. sol. of NaHCO₃ (20 mL), and the solvent removed in vacuo. The product (19.8 g) was obtained after distillation under reduced pressure (3 to 6 mbar, 75 °C) and analyzed via ¹H NMR.

¹H NMR: 1-cyclohexenylpiperidine: δ = 4.66, (t, 1H), δ = 2.75 (t, 4H), 2.07 (m, 4H), 1.57 (m, 10 H).

6.10 Catalyst endurance experiments



Fig. 6.9: Disproportionation of 2-cyclohexen-1-one.

A series of experiments where the disproportionation of 2-cyclohexen-1-one was used to asses the catalyst endurance were carried out. The same portion of catalyst, either Pd/C or Pd/CaCO₃ is used multiple times. After each reaction the catalyst was washed with cyclohexane (10 mL) and dried in vacuo and weighted again. Analysis was done via ¹H NMR, ratios of reagent and products were determined via integration.

General procedure

In a 50 mL round-bottomed flask fitted with a reflux cooler and an argon bubbler, 2cyclohexen-1-one (4.8985 g, 50.96 mmol) was let to react with Pd/C (40.8 mg, 0.038 mmol Pd) for 1h at 115 °C (oil bad temp). The raw reaction mixture was then analyzed via ¹H NMR. The reaction with a fresh portion of cyclohexanone was repeated 5 times.

In a 50 mL round-bottomed flask fitted with a reflux cooler and an argon bubbler, 2cyclohexen-1-one (4.9413 g, 51.40 mmol) was let to react with Pd/CaCO₃ (76.4 mg, 0.038 mmol Pd) for 1h at 115 °C (oil bad temp). The raw reaction mixture was then analyzed via ¹H NMR. The reaction with a fresh portion of cyclohexanone was repeated 2 times.

¹H NMR [300.13 MHz, CDCl₃]: cyclohexanone δ = 1.42 (s, 12 H), benzene δ = 7.39 (s, 6 H).

6.11 Kinetic of the disproportionation over Pd/C



Fig. 6.10: Disproportionation of 2-cyclohexen-1-one.

6.11.1 Analysis via NMR

A series of experiments where the disproportionation of 2-cyclohexen-1-one was used to determine the rate of product evolution for Pd/C and Pd/CaCO₃ under normal pressure. Sampling was performed at regular intervals extracting a small amount of reaction medium. Analysis was done via ¹H NMR, ratios of reagent and products were determined via integration.

6.11.1.1 General

In a 50 mL two-necked-round-bottomed flask fitted with a reflux cooler and an argon bubbler, 2-cyclohexen-1-one (4.8985 g, 50.96 mmol) was let to react with Pd/C (40.8 mg, 0.038 mmol Pd) for 1h at 115 °C (oil bad temp). The flask was submerged into the bad when it reached 115 °C. Sampling was performed every 15 min with a syringe, the sample was then filtered over glass wool and transferred to a NMR probe tube and mixed with CDCl₃.

6.11.2 Analysis via GC-MS

A series of experiments where the disproportionation of 2-cyclohexen-1-one was used to determine the rate of product evolution for Pd/C under normal pressure. Sampling was performed at regular intervals extracting a small amount of reaction medium. Analysis was done via GC-MS.

A calibration curve with 3 points was used to determine the concentration of analytes in the samples. For every substance a reference solution was realized dissolving 500 mg of substance in 100 mL of cyclohexane in a volumetric flask. Every point was then done

mixing in a 10 mL volumetric flask a 1 mL aliquot of internal standard, and aliquots of 1, 0.2 and 0.1 mL of the other solutions and then filling up to 10 mL with cyclohexane. From these solutions 1 ml aliquots were used to prepare the GC-MS samples together with the reaction's medium.

Cyclohexanol was used as internal standard, and phenol, 2-cyclohexen-1-one and cyclohexanone were used as references for the curve.

In a 50 mL two-necked-round-bottomed flask fitted with a reflux cooler and an argon bubbler, 2-cyclohexen-1-one (2.4483 g, 25.5 mmol) was let to react with Pd/C (10.8 mg, 0.0103 mmol Pd) for 1h at 110 °C (oil bad temp). The flask was submerged into the bad when it reached 110 °C. Sampling was performed every 10 min, at 2, 12, 22, 32, 42, 52, 62 min, with a syringe, the sample was then filtered and mixed with the internal standard solution to a total concentration of 0.5 mg/mL.

6.12 Disproportionation and hydrogenation of heterocycles

Variant 1: In the small reactor described in section 2.4, 2-methyl-2-oxazoline (11.6 mmol, 1 ml), and Pd over CaCO₃ (0.012 mmol Pd, 21.3 mg) were pressurized with CO₂ to 41 bar at 23 °C, heated up to 150 °C and let react for 12 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Unreacted starting material and an unknown polymeric residue were recovered.

Variant 2: In the small reactor described in section 2.4, 2-methyl-2-oxazoline (11.6 mmol, 1 ml), and Pd over charcoal (0.018 mmol Pd, 19.0 mg) were pressurized with CO₂ to 21 bar at 23 °C, heated up to 85 °C and let react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was recovered.

Variant 3: In the small reactor described in section 2.4, 2-methyl-2-pyrroline (11.6 mmol, 1 ml), and Pd over CaCO₃ (0.021 mmol Pd, 22.8 mg) were pressurized with CO₂ to 40 bar at 22 °C, heated up to 150 °C and let react for 2 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR and ESI-MS. Only unreacted starting material was detected.

Variant 4: In a 25 ml round-bottomed flask fitted with a reflux condenser, pyridine (24.7 mmol, 2 ml) and Pd over CaCO3 (0.024 mmol Pd, 26.5 mg) were heated to reflux and let to react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was detected.

Variant 5: In a 50 ml round-bottomed flask fitted with a reflux condenser, pyridine (24.7 mmol, 2 ml), 2-cyclohexen-1-one (20.8 mmol, 2 ml) and Pd over CaCO3 (0.048 mmol Pd, 50.4 mg) were heated to 140 °C (oil bath) and let to react for 2 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Unreacted pyridine and the products of disproportionation of 2-cyclohexen-1-one, phenol and cyclohexanone were detected.

Variant 6: In a 10 ml round-bottomed flask fitted with a reflux condenser, 3-nitrocyclohex-1ene (7.87 mmol, 1 g) and Pd over CaCO₃ (0.02 mmol Pd, 21.7 mg) were heated to 160 °C (oil bath) and let to react for 2 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was recovered.

Variant 7: In the small reactor described in section 2.4, α -pinene (11.6 mmol, 1 ml), and Pd over CaCO₃ (0.020 mmol Pd, 21.7 mg) were pressurized with CO₂ to 38 bar at 23 °C, heated up to 150 °C and let react for 12 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was detected.

Variant 8: In the small reactor described in section 2.4, α -pinene (5.35 mmol, 0.9 ml), 1,4cyclohexadiene (5.35 mmol, 0.5ml) and Pd over CaCO₃ (0.020 mmol Pd, 21.0 mg) were pressurized with CO₂ to 40 bar at 23 °C, heated up to 150 °C and let react for 12 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only the disproportionation products of 1,4-cyclohexadiene, benzene and cyclohexane were detected.

6.13 Catalyst poisoning experiments

Variant 1: In a 25 ml round-bottomed flask fitted with a reflux condenser, 5-norbornene-2carboxylic acid (8 mmol, 1.1054 g), 1,4-cyclohexadiene (8 mmol, 0.6410 g), 2mercaptoethanol (4 mmol, 0.3125 g) and Pd over charcoal (0.016 mmol Pd, 20.4 mg) were heated to 80 °C (oil bath) and let to react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was recovered.

Variant 2: In a 25 ml round-bottomed flask fitted with a reflux condenser, 5-norbornene-2carboxylic acid (8 mmol, 1.1062 g), 1,4-cyclohexadiene (8 mmol, 0.6775 g), abuthylmercaptane (4 mmol, 0.3607 g) and Pd over charcoal (0.016 mmol Pd, 20.4 mg) were heated to 80 °C (oil bath) and let to react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. Only unreacted starting material was recovered.

6.14 H/D exchange of pyridine-d₅

Variant 1: In a 25 ml round bottomed-flask fitted with a reflux condenser pyridine- d_5 (6 mmol, 0.5048 g), 1,4-cyclohexadiene (6 mmol, 0.4808 g) and Pd over charcoal (0.012 mmol Pd, 12.8 mg) were heated to reflux and let react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. ¹H NMR (300 MHz, CDCl₃): δ = 8.62 (s, 2 H) pyridine- d_3 , δ = 7.36 (s, 6 H) benzene, δ = 5.67 (s, 2H) cyclohexene, δ = 1.97 (m, 4H), δ = 1.59 (m, 4H), δ = 1.42 (s, 12 H) cyclohexane.

Variant 2: In a 25 ml round bottomed-flask fitted with a reflux condenser pyridine- d_5 (6.63 mmol, 0.5577 g), γ -terpinene (6.09 mmol, 0.5295 g) and Pd over charcoal (0.018 mmol Pd, 18.9 mg) were heated to reflux and let react for 5 h. The raw reaction mixture was filtered over glass-cotton and then analyzed via ¹H NMR. ¹H NMR (300 MHz, CDCl₃): δ = 8.62 (s, 2 H) pyridine- d_3 , δ = 7.11 (s, 4 H) p-cymene, δ = 2.86 (hept, 1H, *J*=6.95 Hz) p-cymene, δ = 2.31 (a, 3H) p-cymene, δ = 1.24 (d, 6H) p-cymene. An unidentified compound is present in the mixture, probably a p-menthene

6.12 ESI-MS investigation of the Pd-catalyzed H-transfer

All experiments were carried out electrospraying a $Pd(AcO)_2$ solution prepared as follows: In a small vial $Pd(AcO)_2$ (3 µmol, 0.62 mg) was dissolved in 1 mL of MeOH. This solution was further diluted to furnish the stock Pd solution by adding 0.1 mL of CH_2Cl_2 . An aliquout (0.1 mL) of the stock solution was mixed with a solution of PPh₃ in CH_2Cl_2 (0.023 mM, 0.1 mL) and diluted with CH_2Cl_2 (1 mL), CF_3CH_2OH (0.05 mL) to furnish the analysis solution. Note: the solution degrades quickly and thus a freshly prepared solution was used every day.

6.12.1 ESI-MS analysis of the Pd²⁺/PPh₃ solution

The analysis solution was electrosprayed into the mass spectrometer. Ion-molecule experiments were carried out using the reagent gas inlet in the mass spectrometer to inject a reagent gas, cyclohexene, D₂O, toluene- d_8 , or ethene into the first octopole at low collision energies (2 to 3 eV, lab scale). Pressures varied with the reagent used but were normally in the 500 mTorr range. CID experiments were carried out using the collision gas inlet of the mass spectrometer to inject a variety of gases Ar, Xe, ethene, cyclohexene, D₂O, toluene- d_8 , or diethylether into the collision cell. Pressures were kept in the 1 mTorr range.

6.12.2 ESI-MS analysis of the Pd²⁺/PPh₃/cyclohexenone solution

To the analysis solution a small amount of 2-cyclohex-1-one (0.05 mL) was added and this mixture was then electrosprayed into the mass spectrometer. Ion-molecule experiments were carried out using the reagent gas inlet in the mass spectrometer to inject a reagent gas, cyclohexene, D_2O , toluene- d_8 , or ethene into the first octopole at low collision energies (2 to 3 eV, lab scale). Pressures varied with the reagent used but were normally in the 500 mTorr range. CID experiments were carried out using the collision gas inlet of the mass spectrometer to inject a variety of gases Ar, Xe, ethene, cyclohexene, D_2O , toluene- d_8 , or diethylether into the collision cell. Pressures were kept in the 1 mTorr range.
6.12.3 ESI-MS analysis of the Pd²⁺/PPh₃/CD₃OD solution

All experiments were carried out electrospraying a $Pd(AcO)_2$ solution prepared as follows: In a small vial $Pd(AcO)_2$ (3 µmol, 0.62 mg) was dissolved in 1 mL of CD₃OD. This solution was further diluted to furnish the stock Pd solution by adding 0.1 mL of CH₂Cl₂ and 0.1 mL of D₂O. An aliquout (0.1 mL) of the stock solution was mixed with a solution of PPh₃ in CH₂Cl₂ (0.023 mM, 0.1 mL) and diluted with CH₂Cl₂ (1 mL), CF₃CH₂OH (0.05 mL) to furnish the analysis solution.

The mass spectrometer was cleaned with CD₃OD to avoid contamination of the sample, and the analysis solution was electrosprayed into the mass spectrometer. Ion-molecule experiments were carried out using the reagent gas inlet in the mass spectrometer to inject a reagent gas, cyclohexene, D₂O, toluene- d_8 , or ethene into the first octopole at low collision energies (2 to 3 eV, lab scale). Pressures varied with the reagent used but were normally in the 500 mTorr range. CID experiments were carried out using the collision gas inlet of the mass spectrometer to inject a variety of gases Ar, Xe, ethene, cyclohexene, D₂O, toluene- d_8 , or diethylether into the collision cell. Pressures were kept in the 1 mTorr range.

6.13 ESI-MS investigation of the self-assembling ligands 1 (6-DPPon) and 2 (ESI-6-DPPon)



Fig. 6.X: Hydroformylation of olefines using self-assembling ligands

6.13.1 ESI-MS analysis of the self-assembling ligands in solution

The ligands **1** and **2** (synthesized by C. Beierlein, [88] (3.6 mM or 7.2 mM) were dissolved in either CH_3CN or CH_2Cl_2 (10 mL) to give 0.36 or 0.72 mM solutions. This solution was mixed with a rhodium precursor, either $Rh(CO)_2(acac)$ or $Rh(NBD)_2BF_4$ (3.6 mmol or 7.2 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, 1-hexene, cyclohexene, propanal, pentanal, D_2 (one at a time) in daughter mode. Ion-molecule reactions at low energy levels were done in the first octopole (or 24-pole) using the same gases or a H_2 :CO (1:1) mixture at pressures up to 1 Torr.

6.13.2 ESI-MS analysis of the live-streamed reaction mixture without substrate

In the small reactor, described in section 2.2, cleaned and purged from air with H_2 and CO, the catalyst solution (20 mL), prepared from the ligands and precursors mentioned before to a final concentration of 3.6 or 7.2 mM was injected into the reactor at counter-flow of CO. Then the reactor was pressurized with H_2 and CO to the desired pressure of either 20 or 14 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, 1-hexene, cyclohexene, propanal, pentanal, D_2 , one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using the same gases or a H_2 :CO (1:1) mixture at pressures up to 1 Torr.

6.13.3 ESI-MS analysis of the live-streamed reaction mixture with substrate

In the small reactor, described in section 2.2, cleaned and purged from air with H_2 and CO, the catalyst solution (20 mL), prepared from the ligands and precursors mentioned before to a final concentration of 3.6 or 7.2 mM was injected into the reactor at counter-flow of CO. The substrate either cyclohexene, 1-hexene, styrene or norbornene were either mixed into the catalyst solution (wen the amounts were in the 1 mL range) or added afterwards. Then the reactor was pressurized with H_2 and CO to the desired pressure of either 20 or 14 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, 1-hexene, cyclohexene, propanal, pentanal, D₂, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using the same gases or a H_2 :CO (1:1) mixture at pressures up to 1 Torr.

6.13.4 ESI-MS analysis of the live-streamed reaction mixture without substrate under D₂:CO

In the small reactor, described in section 2.2, cleaned and purged from air with H_2 and then with CO, the catalyst solution (20 mL), prepared from the ligands and precursors mentioned before to a final concentration of 3.6 or 7.2 mM was injected into the reactor at counter-flow of CO. The reactor was then pressurized with D_2 and CO to the desired pressure of 20 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, 1-hexene, cyclohexene, propanal, pentanal, D_2 , one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using the same gases at pressures up to 1 Torr.

6.13.5 ESI-MS analysis of the live-streamed reaction mixture with substrate

In the small reactor, described in section 2.2, cleaned and purged from air with H_2 and CO, the catalyst solution (20 mL), prepared from the ligands and precursors mentioned before to a final concentration of 3.6 or 7.2 mM was injected into the reactor at counter-flow of CO. The substrate either cyclohexene, 1-hexene, styrene or norbornene were either mixed with the catalyst solution (wen the amounts were in the 1 mL range) or added afterwards. Then the reactor was pressurized with H_2 and CO to the desired pressure of either 20 or 14 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, 1-hexene, cyclohexene, propanal, pentanal, D₂, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using the same gases or a H₂:CO (1:1) mixture at pressures up to 1 Torr.

6.14 ESI-MS investigations of the self-assembling ligands 3 (DPPICon) and 4 (DPPAP)

6.14.1 ESI-MS analysis of the self-assembling ligands in solution

The ligands **3** and **4** (3.6 mM) were dissolved in CH_3CN (10 mL) to give a 0.36 mM solution. This was mixed with the rhodium precursor $Rh(NBD)_2BF_4$ (3.6 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 1 Torr.

6.14.2 ESI-MS analysis of the live-streamed reaction mixture without substrate

In the small reactor, described in section 2.2, cleaned and purged from air with H₂ and CO, the catalyst solution (20 mL), prepared from the ligands and precursors mentioned before to a final concentration of 3.6 mM was injected into the reactor at counter-flow of CO. Then the reactor was pressurized with H₂ and CO to the desired pressure of 14 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 1 Torr.

6.15 ESI-MS investigations of the self-assembling ligands 3 (DPPICon) and 5 (ESI-DPPAP)

Firstly the ligands **3** and **4** (3.6 mM) were dissolved in CH₃CN (10 mL) to give a 0.36 mM solution (20 mL). This was then mixed with the rhodium precursor $Rh(NBD)_2BF_4$ (3.6 mmol) to form the final catalyst solution.

In the small reactor, described in section 2.2, cleaned and purged from air with H_2 and CO, the catalyst solution (20 mL), prepared as mentioned before was injected into the reactor at counter-flow of CO. Then the reactor was pressurized with H_2 and CO to the desired pressure of 14 bar. Then the reactor was connected to the API of the mass spectrometer

using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 1 Torr.

6.16 ESI-MS investigations of the self-assembling ligands 3 (DPPICon) and 6 (DPPAT)

The ligands **3** and **6** (3.6 mM) were dissolved in CH_3CN (10 mL) to give a 0.36 mM solution. This was mixed with the rhodium precursor $Rh(NBD)_2BF_4$ (3.6 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 600 mTorr.

The ligands **3** and **6** (3.6 mM) were dissolved in CH_3CN (10 mL) to give a 0.36 mM solution. This was mixed with the rhodium precursor $Rh(CO)_2(acac)$ (3.6 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 600 mTorr.

6.17 ESI-MS investigations of the neutral ligands PPh₃ and XANTHPHOS

6.17.1 ESI-MS analysis of Rh/PPh₃ in solution

The ligand PPh₃ (7.2 mM) was dissolved in CH₃CN (10 mL) to give a 0.72 mM solution. This was mixed with the rhodium precursor Rh(NBD)₂BF₄ (3.6 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 600 mTorr.

6.17.2 ESI-MS analysis of Rh/XANTHPHOS in solution

The ligand XANTHPHOS (3.6 mM) was dissolved in CH_3CN (10 mL) to give a 0.36 mM solution. This was mixed with the rhodium precursor $Rh(NBD)_2BF_4$ (3.6 mmol) and analyzed via ESI-MS. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene at pressures up to 600 mTorr.

6.17.3 ESI-MS analysis of the live-streamed reaction mixture Rh/XANTHPHOS without substrate

In the small reactor, described in section 2.2, cleaned and purged from air with H₂ and CO, the catalyst solution (20 mL), prepared as mentioned before was injected into the reactor at counter-flow of CO. Then the reactor was pressurized with H₂ and CO to the desired pressure of 20 bar. Then the reactor was connected to the API of the mass spectrometer using the link described in section 2.3. The live sample provided via this link was then analyzed and further reacted in the mass spectrometer. CID experiments were carried out using a variety of gases Ar, ethene, 1-butene, one at a time in daughter mode. Association experiments were done in the first octopole (or 24-pole) using ethene or 1-butene at pressures up to 1 Torr.

6.18 Determination of the bonding energy of silver-olefine complexes

The silver solution for analysis is prepared from an $AgNO_3$ solution (0.014 M) in $H_2O:CH_3OH:CH_3CH_2OH:CH_2Cl_2$ (3:11:2:4) and then further diluted to 0.0007 M in $CH_3OH:CH_3CH_2OH:CH_2Cl_2$ (0.95:0.1:0.95).

The mass spectrometer was fitted with the appropriate collision and reagent (used to thermalize or to form the Ag complex) gases and the collision pressure was set to 1, 2 and 4 10^{-4} mbar (approx. but stable to +/- 5%) for three series of experiments. The thermalization gas was kept at 10 mTorr and the reagent gas, when Ag complexes were built in the gas-phase, to 500 mTorr.

Threshold CID measurements were carried out in *rfd*-only mode or *daughter* mode depending on the complex.

6.18.1 Silver ethene complexes

Using ethene as reagent gas, three series of experiments with collision potentials between 5 and -30 V in steps of 0.5 V were recorded. The collision gas used was Ar.

6.18.2 Silver 1-butene complexes

Using 1-butene as reagent gas, three series of experiments with collision potentials between 5 and -30 V in steps of 0.5 V were recorded. The collision gas used was Ar.

6.18.2 Silver corannulene complexes

The silver solution was slightly modified adding corannulene (4 equivalents) before methanol was added to reach a one phase system. Using N₂ as reagent gas (10 mTorr), three series of experiments with collision potentials between 0 and -40 V in steps of 0.5 V were recorded. The collision gas used was Ar.

6.19 Determination of the bonding energy of Na+/18-crown-6 complexes

A solution of NaI 100 μ M in MeOH:CH₂Cl₂ (1:100) was mixed with a 20 μ M solution of 18crown-6 in MeOH:CH₂Cl₂ (1:100) to a final concentration of 10 μ M in crown ether and 50 μ M in Na⁺. Using N₂ as reagent gas (10 mTorr), three series of experiments with collision potentials between 0 and -40 V in steps of 0.5 V were recorded when the collision gas used was Xe or from 0 to -80 V when the collision gas used was Ar.

Appendix I. Design of a ultrasound generator for piezoelectric transducers

I.1 Introduction

Among the methods available to the chemist the use of ultrasound to influence the course of a reaction has become more and more popular. However, the specific interaction between sound waves and matter is still not very well understood. The pioneering work of Luche in the 80s resulted in many applications of ultrasound to solve chemical problems. The use of ultrasound can afford higher yields, faster reactions, easier work-up or general simplicity of the process.[26] Ultrasound produces cavitation in liquids, i.e. the formation of gas or vapor bubbles and clouds of bubbles in liquids. The interaction of sonic waves with matter does not affect vibrational or electronic levels of atoms and molecules.[26] Cavitation can be generated by acoustic means: a vibrating element inside the medium will produce waves; dissolved gas or evaporated liquid will then give rise to cavitation. Alternatively, cavitation can be triggered via hydrodynamic forces: e.g. a propeller that rotates inside the medium will produce similar effects when rotating fast enough.[27] In order to explain the effects of cavitation on chemical reactions several theories were put forward. Of these, Margulis' theory seems to be in best agreement with experimental data. [29] From this account it is concluded that cavitation is directly influenced by frequency. At low frequencies, in the tens of thousand of Hertz range, bubbles are stable for a couple of frequency cycles and collect small amounts of volatile compounds. At higher frequencies they can last many more cycles and thus collect much more volatiles. At the end of the cycle the bubbles collapse producing temperatures as high as 5000 °C and pressures approaching 1000 bar. These extreme conditions produce radicals that due to their highly reactive nature can afford useful products, destroy organic matter in sewage, etc.[31, 32] While mass spectrometry is guite well understood and developed at the commercial level, ultrasound generation and delivery is not. Conventional commercial equipment is generally not well suited for chemical purposes. Commercial instruments were designed mostly to destroy cells under normal pressure. They lack frequency stability, do not provide a way of setting the frequency and, even worse, they have no means to analyze the output signal. Some of these problems are aggravated when the reactor employed is under pressure. Most of the energy will be transferred when the system operates under resonance, but the resonance has proved to be pressure-dependent. In addition, ultrasound irradiation suffers from an unusual problem: the geometry of the reactor influences how well energy is transferred to the medium.[142] This problem is difficult to overcome but critical considering scale-up issues. To better understand and control the effects of ultrasound, defined and stable conditions are needed, and to this aim the generator described here was developed.

I.2 Design and specifications

A useful ultrasound generator would need the following minimum specifications

- * Ability to drive a piezo-electric transducer. Output voltage > 500 Vpp when loaded.
- * Stable and tunable output frequency. Crystal-based oscillators or references. Either by direct digital synthesis or by nanosecond-resolution timers.
- * Harmonics analysis. Digitizing of output and reference waveforms and real-time FFT analysis with Hz resolution. It should be a stand-alone design preferably. With graphic output display.
- * Options: timer, frequency sweep, pulsed and continuous modes.

Based on this specifications the generator comprises several distinct functional blocks as seen in Fig. A.I.1: main control and display, oscillators, modulator, power amplifier and power supply. The output signal is generated by a sine-wave oscillator based on a direct digital synthesizer (DDS). This signal is converted to a pulse-width-modulated (PWM) signal, amplified by a class D power amplifier and finally delivered to the piezo resonator through a low pass filter. This approach provides very low (1 mHz) frequency granularity, ample frequency range, lower power dissipation due to the class D power stage and requires no tunable parts.



Fig. A.I.1: Block diagram of the proposed generator.

I.2.1 Oscillators

In order to drive a class D amplifier a PWM signal is needed. There are two basic ways to generate such a signal, using a reference triangle signal and a comparator, or digitally. For the second method a nanosecond-resolution timer, only available in some high-end DSPs, is needed if the output signal has to have 1 Hz granularity in the ultrasound (20 kHz in this case) range as was desired here. The first method does not require such a timer circuit, only a fast comparator and two signals. To produce the frame signal, i.e. the high frequency modulated signal, an AD9834 DDS (Analog Devices) is used. With few external components this integrated circuit (IC) is able to produce a triangle wave of 384 kHz (a sine signal can also be output but is not needed in this case) of the desired frequency. To synthesize such a signal a higher frequency clock is used together with a phase accumulator. The resolution of this signal can be as good as 1 part in 2x10⁸. The sine wave oscillator is based on an AD9835 (Analog Devices). This DDS uses the same principle as the AD9834 but utilizes the cosine table and a 10-bit DAC to output a sine wave instead. The resolution of this oscillator is as good as 1 part in 4x10⁹. Both oscillators are clocked by the same 50 MHz 50 ppm oscillator. Frequency programming is performed using a 3-wire serial protocol. Both signals are amplified by fast low-noise operational amplifiers with variable gain adjusted by multi-turn potentiometers, R1 and R2 in Fig. A.I.2. This amplitude adjustment, the only calibration step, is important to ensure a good modulation ratio (at least 95%) and thus maximum output amplitude.



Fig. A.I.2: Schematic diagram of the modulator board.

I.2.2 Modulator

The modulator consists of a fast comparator AD8611 (Analog Devices) that generates the PWM signal as a pair of complementary signals needed in the power stage. The comparator produces the pulse-modulated signal using the two input signals generated by the oscillators. By comparing the amplitude of the sine wave to that of the triangle wave a signal with the same frequency (called frame frequency) as the triangle-shaped wave but with a pulse width proportional to the amplitude of the sine at the comparison time is produced, as seen in the oscillograms in Fig. A.I.3.



Fig. A.I.3: Left oscillogram represents the output of both oscillators, right oscillogram represents the generated PWM signal (blue).

I.2.3 Class D amplifier

The class D amplifier is based around an IC built specifically for this purpose. The TAS5261 (Texas Instruments) can provide up to 300 W of output power over a 4 ohm load when powered from a 50 V rail. The inputs come directly from the modulator as complementary signals. The output circuitry has been modified to suit the needs of the piezo resonator. The output drives a transformer and goes then to the piezo after a LC low pass filter. This amplifier has a low part count, low dissipation, easy driving and built-in over-temperature and short-circuit protections. A reset input allows for easy shutdown and is utilized within this circuit to implement the pulsed and off modes. Two extra outputs indicate normal operation or one of the failure modes like over temperature or short-circuit condition. A 50 VDC power supply implemented as a linear regulator in a separated board

powers the circuit. Fig. A.I.4 shows a schematic diagram of the TAS 5261 class D amplifier as described. The signal after the transformer is shown in Fig. A.I.5. The output transformer was winded over a ferrite N87 EDT 49 core (Epcos) using the fitting coil former B66368 (Epcos). The primary consists of a tetrafilar 12 turns winding using 0.5 mm (24 AWG or similar) copper wire and the secondary are 120 turns of the same wire. Depending on the piezo-resonator used a different number of secondary turns may be necessary. The importance of a good core for maximum energy transfer and lowest no-load loses cannot be stressed enough. The low pass filter's coil has been winded on an Amidon T184-2 toroidal core (Amidon) using 100 turns of the same wire (around 240 μ H). Such a filter produces a clean sinusoidal output signal. While Amidon cores are useful in this frequency range as RF chokes they are not at all good transformer cores. The piezo resonator is connected after the low pass filter.



Fig. I.4: Class D amplifier.



Fig. A.I.5: Oscillogram of the signal after the transformer.

I.2.4 Feedback

The transducer not only works as an energy source to the reaction but can also work as an input device. Tapping into the output signal with an analog-to-digital converter (ADC) provides the feedback circuit with a digitized version of this signal. An AD581 12 bit ADC (Analog Devices) at 100 to 200 ksps fulfills this role. This signal is then frequency-domain analyzed. The feedback circuitry consists of a second Propeller microcontroller (Parallax) to calculate the Fourier transformation on the acquired data and display it on either an attached VGA monitor or on the built-in graphic LCD. Fig. A.I.6 shows the schematic diagram of the proposed feedback circuitry.



Fig. A.I.6: Feedback controller

I.2.5 Main control

Control of all parts and operation is achieved by a Propeller microcontroller (Parallax). These microcontrollers contain 8 independent processors capable of 20 MIPS @ 80 MHz each. Hardware interface, keyboard input, graphic LCD control, inter-processor communications, debug interface, PS/2 controller and user interface reside in this controller. Most of the firmware has been written in assembler and in-house developed. The user interface consists of a graphic LCD, six buttons and a rotary encoder. These controls allow to program the desired values for all parameters, view the current status, realtime output signal and spectral analysis. For better resolution a VGA monitor can be connected to the feedback propeller. The schematic diagram of the proposed main control circuitry is shown in Fig. A.I.7.

I.3 Software

The software has been written around the propeller architecture. Eight cores, each core is called a cog, with limited program memory share a bigger 32 kbytes memory space. The cores execute up to 20 MIPS @ 80 MHz each.



Fig. A.I.7: Main controller

The feedback propeller presents the simplest software due to its limited functionality. From the 8 cores available one is used for reading of the 2 12 bit ADCs and to calculate either a 1024 or 4096 points FFT. Calculations are performed with 16 bit arguments in fixed point notation. A second core is used to display the calculated data taking the output of core 0 as input. Zooming is also done here. A third core is used to refresh the VGA display regardless of this output being used or not. A fourth core is used for inter-propeller communication for commands and data. A 4 bit synchronous protocol is used with 2 start bits for synchronization per 32 bit word. The control propeller sends the setup commands, FFT length and ADC sampling frequency and receives processed FFT results as a 64 point array. A fifth core is used for debug purposes using a CMOS compatible asynchronous serial link. The sixth core is used to read a PS/2 keyboard that together with the VGA display allow for better display of data. The other 2 remaining cores are not used and thus powered down. All software except for the debug interface have been programmed in assembler. Few modules with a MIT License from obex.parallax.com have been used, asynchronous serial communications module, VGA refresh and PS/2 keyboard interface. The FFT part was specifically written for this purpose. While a 8192 point FFT

could be calculated, he data cannot be displayed by the same propeller because of lack of free memory for a frame buffer. A 4096-point FFT is used instead providing a resolution of approx. 25 Hz.

The control propeller is more complicated because it contains the user interface, oscillators and power stage control and monitoring. The user interface has been coded in assembler using long memory model (LMM) techniques due to the need of fast routines and length of the program. The propeller cogs, have very limited program memory: only 496 instructions fit in the 2048 bytes of program memory. LMM helps to extend this memory space using the shared memory (HUB memory) and a small kernel that fetches each instruction and executes it. The cogs are used as follows:

COG 0: Debug interface

If needed, a simple debug interface that allow to peek the shared memory can be enabled. It uses a serial bus and can be connected to a terminal at 115200 8N1.

COG 1: Display refresh

The display is a 240x64 monochrome LCD with a T6963 (Toshiba) controller. This controller keeps the LCD refreshed with a bitmap stored in a dedicated memory. This COG copies the bitmap contained in HUB memory to the T6369's memory once every 20 ms. It uses an 8 bit parallel interface with several control lines. One PWM output, generated using one of the timers, is used to produce the required negative bias supply (-6.5VDC).

COG 2: User interface

All user interface is performed in this COG. The program is realized using LMM techniques, for this avail a small LMM kernel is used extending the available program memory.

COG 3: Keyboard interface

The small keyboard, 4 push-buttons and an rotary encoder communicate with this COG via a serial synchronous bus. This COG waits till a key is pressed and stores the value in HUB memory to be consumed by the user interface.

COG 4: Inter-propeller communication.

Both propellers share a bidirectional synchronous 4 bit BUS. It consists of 2 bits of synchronism one low-to high transition and one high-to-low transition. Then 8 4-bit words follow forming a 32 bit word. This cog sends commands to the feedback propeller and requests FFT data to be displayed.

COG 5: Oscillator daughterboard control

This COG keeps the DDS updated with the current frequency settings.

COG 6: Output Control

This COG handles the RESET input to the output stage (TAS5261) and reads the two status signals that indicate its status as normal operation, over temperature or undervoltage on the gate drivers. It also reads two temperature sensors, DS18S20 (Maxim) that are mounted in the TAS5261 heat sink and in the power supply transistors' heat sink. These thermometers use a 1-Wire (Dallas Semiconductors/Maxim) bus.

Calculation of frequency words for the DDS is done in BCD using a packed BCD representation. Only addition, subtraction and multiplication are needed and thus implemented.

I.4 Build

The different building blocks were assembled into separated printed circuit boards (PCBs) for faster prototyping. The modulator and power stages require surface mounted parts, so two separate PCBs were designed and manufactured. For the remaining blocks prototyping boards (breadboards) were used because they contain less-critical parts and no surface mounted integrated circuits. An aluminum housing was used to hold all the parts together converting it in a laboratory-ready apparatus. Low-power boards were mounted on the top of a middle plate and power parts on the other side. A small fan provides forced-air cooling needed for the power supply and output stage. The front panel sports a graphical LCD for easy configuration and information display, several buttons, a rotary encoder and the on-off switch. Fig. A.I.8 shows the frequency related configuration menu as seen on the LCD. On the back side the fuse receptacle, the power and the output sockets are located. For safety reasons the housing is grounded and a line fuse is used. On the inside two debug ports, one for a VGA monitor and one for a PS/2 keyboard are

available. These provide convenient access to higher resolution graphics and better input handling. An extra CMOS level RS-232 port is also available for debugging purposes.



Fig. A.I.8: Frequency setting menu.

I.5 Discussion and conclusions

There are several points where more than one choice was available starting with the oscillators. High-end DSPs, or FPGAs could have been used instead but this only adds complexity without much gain beyond maybe less part count. In the control module an ARM based control unit was built but later discarded for similar reasons. The output stage uses a low-voltage class-D amplifier with a power transformer. A mains voltage class-D output stage could also be used but the driver circuit becomes more critical. Such an approach presents less parts, no low-voltage power supply but turns the output stage in a more dangerous business, as it will mean a mains power circuit.

A higher resolution display could have also been used as was planned but the lack of a suitable cabinet decided in favor of a smaller one that is enough for day-to-day use. A higher resolution display using a VGA monitor is provided anyways, thus aiding in the tuning of a reaction.

The different parts of the generator were tested before assembly to assure functionality and to perform the calibration step. The generator was tested with a piezo-resonator UW-2200 (Bandelin) under normal pressure. From an electronics point of view the goals set were achieved.

Compared to other equipment found commonly in laboratories this design innovates in every area for this specific application :

Oscillator			
Our design	 The base frequency is generated using direct digital synthesis based on a 50 MHz crystal source. Advantages: reproducibility, programmability and accuracy in 1 Hz steps, ensuring that the end frequency does not depend on supply voltage 		
Commercial	 RC oscillators with discreet components. Disadvantages: the tolerances in the components alone are 1% or more. Advantages: cheaper, and simpler 		

Power stage			
Our design	 The output stage has been developed using a monolithic class D amplifier with a PWM signal discreetly produced based on two of the oscillators above mentioned. Advantages : high output power, sinusoidal-shaped output signal and constant output amplitude. 		
Commercial	 Commonly used output stages are based around a power transformer driven by MOSFETs or IGBTs fed directly form a 20 kHz square signal. A low pass filter then removes part of the harmonic content. Advantages: simpler and cheaper design. Disadvantages: The output signal has nothing to do with a sinusoid due to the high harmonic content, even after the filter. Output amplitude varies with varying mains voltage. 		

Power supply			
Our design	 Constant-voltage with series transistors. Advantages : keeps the output stage in working voltage range and reduces the possibility of output signal distortion due to changes in the voltage line. 		
Commercial	 No regulation provided. Simple rectifier bridge plus electrolytic capacitor. Advantages: simpler and cheaper design. Disadvantages: Output amplitude follows the changes in the line voltage. 		

Frequency control and tuning			
Our design	 The output frequency can be set at will and is displayed continuously. The feedback system allows the operator to tune the experiments for the desired parameter. Advantages : Ensures reproducibility of experiments. 		
Commercial	 No control over the frequency nor it is know at which precise frequency it is working. No tuning or feedback possible. Some machines have an automatic frequency correction system that works sampling the current consumed by the output stage but does not provide any information whatsoever to the operator and cannot be disabled. Advantages: none. Disadvantages: No reproducibility. 		

From the literature some examples of machines similar in purpose but different in application can be extracted.

Ricci and coworkers developed a Field Programmable Gate Array (FPGA) arbitrary waveform generator for medical ultrasound applications.[143] A high-end Stratix II (Altera) device is used but the signal generation method is somewhat similar because the waveform is read from a memory and then converted to an analog signal. While this method surely provide many simultaneous signals, 32 in the described case, it presents a more complicated approach and it is better suited for higher frequency, in the MHz range, domain of application. In this range the use of top-of-the-line DDS would be required and one per channel.

Xu and coworkers describe also a high frequency generator using a crystal as frequency source but to produce only trains of pulses through a pair of MOSFETs.[144] This device is also specific to the use of ultrasound in imaging applications.

Gammel *et al.*[145] describe an output stage suitable for ultrasound applications similar to the one supplied in commercial equipment. It is based on the discharge of a capacitor through an IGBT. While it can provide enough output power it suffers from the same drawbacks. When coupled to a properly constructed differential PWM signal some of these drawbacks could be avoided like constant amplitude and signal shape, but that would require a circuit different to the one proposed here.

Steines and coworkers described another ultrasound generator for imaging applications. [146] Their design is also based on an AD9834 DDS (Analog Devices) but operated in a much higher frequency range required by the application. The output of this DDS is directly fed into an pre- and amplifier with an AB output stage. While this machine is the closest to the one described it is still considerably different in construction, features and purpose to the one described here.

Appendix II. RF generator for high order multipoles

A digital solid state radio frequency (RF) generator was developed to drive the 24-pole inside the tandem mass spectrometer TSQ 7000. Complete digital control of frequency, offset voltage and amplitude were the main driving goals resulting in a compact, lower power, and higher frequency range device compared to other generally available vacuum-tube based designs.

II.1 Introduction

The tandem mass spectrometer Finnigan MAT 7000 (depicted in Fig. 2.8) have two reaction chambers both octopole based. The second one is normally used for collision induced dissociation experiments while the first is available for thermalization and more general gas-phase ion-molecule reactions where a higher pressure is needed (around 100 mTorr).[2] Gerlich investigated extensively multipoles as ion transmitters as well as ion traps, constructed high order multi-poles and determined that they provided better performance: ion beam confinement and ion transmission than lower order ones.[147] Following this line of thought we decided to improve the first reaction chamber's performance with the use of a 24-pole of own design. To accommodate the resulting longer assembly a housing with an extra turbo-molecular pump was also installed. To drive this new 24-pole a vacuum tube based oscillator similar to the one described by Anderson et al., [148] was firstly employed. This oscillator provided a small frequency range but otherwise stable operation in the mass range of 100 to 1000 m/z. No ions with m/z lower than around 100 were ever spotted with this setup, for comparison the factory octopole has no problems with masses down to few m/z. For this reason we decided to use another kind of oscillator less prone to narrow frequency range, solid-state based and with digital control.

II.2 Design and requirements

To drive the 24-pole the generator has to produce a sinusoidal signal that has stable and reproducible frequency in the 1 to 10 MHz range, an output amplitude of around 300 Vpp and voltage offset to ground from -10 to 10 VDC. From the broad spectrum of possible oscillators available we went firstly with an analog design based around a voltage

controlled oscillator (VCO), a SN74LS624 (Texas Instruments). While this first stage performed well, the following stage, a discrete level shifter had problems because the transistors available behaved like their transition frequency was well below its nominal value, i.e. they behaved as if they had a big, in the nanofarad range, base-emitter capacity. The use of several different transistors proved to give the same results. These findings combined with the fact that no readout of frequency was possible, unless a pulse counter was incorporated to the circuit make us decide to use a more up-to-date design. Monolithic programmable oscillators like the LT6904 (Linear Technologies) provide a simple, low part count approach to frequency synthesis. This particular part works from a single 5 VDC power supply and does not need any external parts except for decoupling capacitors. It is programmed using a simple two wire interface and can produce a square wave signal in the range of 1 kHz to 68 MHz. While on paper it seemed like a useful device, it was found during the test phase that this part has some problems: programming works unreliably, leaving the part unchanged or in an unprogrammable state till power is cycled. Such a behavior was unacceptable and a third and final solution was found in the way of a simpler design based around a crystal oscillator and a frequency divider. While such a circuit does not produce as many frequency steps as the previous methods, it has the great advantage of *working reliably*. A 50 MHz crystal based oscillator with 50 ppm accuracy and a counter and comparator programmed in a small Complex Programmable Logic Device (CPLD) of type XC9572 (Xilinx) comprise the programmable oscillator. A simple two wire interface is used to transmit the programming word, the end of count value. The kind of CPLD used is not at all critic, because most small CPLDs with at least 64 macrocells, from the different manufacturers can perform at the required frequency. The only requirement is that the counters work at 50 MHz. The counter and comparator form an integer frequency divider giving from 1 to 10 MHz for dividers in the 100 to 10 range. A schematic of the built generator can be seen in Fig. A.II.1.

Six simultaneous outputs can be used, each driving the gate of one N-channel MOSFET, totaling three parallel double MOSFETs of type IRF7103 (International Rectifier). This MOSFET has small gate capacitance, fast on/off times and can be driven with a 5V signal. The MOSFET drives an air transformer that raises the voltage to the required output level. The schematic can be seen in Fig. A.II.2. The output waveform together with a spectral analysis at 1 and 5.000 MHz can be seen in Fig. A.II.3.



Fig. A.II.1: Schematic diagram of the built HF oscillator.

The programmable divider is based around the following piece of Verilog code:

```
always @(posedge in_clk)
if (r_cnt == r_reg)
begin
    r_cnt <= 0;
    r_out <= ~r_out;
    end
else
    r_cnt <= r_cnt + 1;</pre>
```

where the rising edge of the input clock signal in_clk is counted as many times as r_reg specifies to invert the level of the output signal, r_out . The input clock is thus effectively divided by the number loaded to r_reg times two. After the comparison the counter register r_cnt is reset.



Fig. A.II.2: Circuit diagram of the CPLD-based oscillator and power stage.



Fig. A.II.3: Controller board.

Output amplitude control was realized with a digital-to-analog converter (DAC), an operational amplifier and a series power transistor to supply the output MOSFETs. A second DAC and one operational amplifier generate the offset voltage that is applied between ground and the center tap of output transformer through two pi filters to block the RF. The DAC used, while a bit dated, contain precision 10 V references and operate directly from symmetric 15 VDC supplies and can output +/- 10VDC directly. Oscillograms and spectral plots for two different output frequencies can be seen in Fig. A.II.4.



Fig. A.II.4: Oscillograms and spectral analysis of the output signal with a heavy load (500 pF), left 1 MHz, right 5 MHz.

A.II.2 Construction and operation

The microcontroller (ATMega32, ATMEL) has been programmed to realize all operations needed to control the DACs, the programmable oscillator, read the button and rotary encoder and output to a text LCD. The firmware was written using a mixture of C for user interface and assembler for LCD and oscillator interface.

The power supply is divided into two modules each with its own transformer. The control board is supplied with 2x15 VAC from one transformer and produces internally regulated +/-15 VDC. The oscillator and output board is powered by the second transformer and receives regulated 5 VDC and unregulated 17 VDC. All regulators are 3-terminal regulators LM7815, LM7915 and LM7805, available from a number of manufacturers.

The electronics are housed in a grounded aluminum case- The front panel consists of a small 4 lines text LCD and a rotary encoder/button combo. The back panel contains the mains inlet, fuse and output connectors.

A simple and straightforward menu allows to change offset voltage, frequency and output voltage. To set any of these parameters the cursor, denoted by a greater-than symbol (>) in the corresponding line, has to be positioned appropriately and the button pressed. The cursor then changes to an arrow (\rightarrow) and the rotary encoder is then used to adjust the value. A new press of the button sets the new value. A schematic of this procedure is shown in Fig. A.II.5.

| ** HF Oscillator ** |
|---------------------|---------------------|---------------------|---------------------|
| Vofs (VDC) 0.00 | Vofs (VDC) 0.00 | Vofs (VDC) 0.00 | Vofs (VDC) 0.00 |
| Freq (MHz) > 1.000 | Freq (MHz) → 1.000 | Freq (MHz) → 2.500 | Freq (MHz) > 2.500 |
| Vout (Vpp) 100. | Vout (Vpp) 100. | Vout (Vpp) 100. | Vout (Vpp) 100. |
| a | b | С | d |

Fig. A.II.5: Example of configuration. a) normal operation, b) after pressing the button, the cursor changes to indicate that the current value can be changed, c) set of a new value using the rotary encoder and d) set of the new value by pressing the button again.

A few potentiometers have to be set for correct feedback of offset voltage as well as output voltage readout, but they are not critical for the operation of the generator. R3 has to be set to read 1/2 of the DAC's output voltage at the test point TP1. R4 has to be set to read 5V (full scale) when the output offset is -10 VDC. R10 has to be set to have a readout of 5 V when the output voltage is 300 Vpp. R18 has to be set to output 15 VDC at X3-1 when the output of the DAC U\$1 is 10 VDC, measured at pin 10.

II.3 Discussion and conclusions

From all the designs built and tested: vacuum tube based and solid state, this design provided the most complete set of working features. While the simplicity of the tube design is appealing, the inherent nature of the tubes, i.e. fragility and short life span make them a weak factor. When combined with the small frequency range, then its usefulness decreases considerably. A manual adjust of the coil's taps in a experiment-per-experiment basis makes it not appropriate for our needs. The VCO based solution proved easy to implement but the need for a new level shifter questioned the whole approach of signal generation leading us to consider an all CMOS approach, avoiding numerous stages. The current design is conceptually very simple but has its own set of points that have to be taken in consideration. A small half pi filter at the output is one of the main concerns. The filter has to provide an output signal with low harmonic content. The capacity of the driven multipole can be used as the capacitive component of the filter.

The present design is low cost and not particularly difficult to build. The most cumbersome part could be the programming of the CPLD that needs a special (albeit low cost) programmer.

Appendix III: Example data files

Binding energy of the Ag(2-butene)₂+ complex was calculated after optimization of the structure with the following data file.

%chk=a05-001-008-005.chk %nproc=4 %mem=2GB # b3lyp/GenECP counterpoise=2 Ag/2x1-Butene cplx, coords from -002.log, cc 1 1 1 1 0 1 0.00001500 -0.00013900 -0.17963800 1 Ag С -2.41194100 -0.55737600 0.40884300 1 -0.80844300 Н -2.30681100 1.46451800 1 С -1.87077000 -1.40757400-0.50671800 1 -2.34170700 Н -1.41177400-0.19658400 1 Η -2.06913200 -1.28333400 -1.56812200 1 0.60909000 0.09486200 1 С -3.30120300 Η -2.96253600 1.49209100 0.64704900 1 Η -3.25492800 0.84589800 -0.97166700 1 С -4.75697900 0.30202000 0.50695800 1 -5.38891600 1.16527400 0.29245300 1 Η -0.55461400 -0.04440000 1 Η -5.14933500 -4.83303400 0.08736600 1.57542400 1 Η С 1.87062000 1.40751600 -0.50698900 2 Η 1.41148400 2.34163500 -0.19702000 2 Η 2.06901500 1.28312400 -1.56836800 2 С 2.41187200 0.55752900 0.40872200 2 Η 2.30668900 0.80875200 1.46435500 2 С 3.30129000 -0.60887500 0.09494500 2 2.96271800 -1.49183400 0.64725700 2 Η Н 3.25507200 -0.84585300 -0.97154900 2 С 4.75701700 -0.30156000 0.50703100 2

5.38906800

5.14928000

4.83301600

-1.16476800

-0.08672800

0.55503600

0.29268000 2

1.57546500 2

-0.04445100 2

С Н О 6-311G(d,p)

**** Aq 0 LANL2DZ ****

Ag LANL2DZ

Η

Η

Η

The input for the CRUNCH program consists of two files, the asc file containing raw experimental data and the rkm file containing vibration frequencies.

0.000000E+00	0.000000E+00	1.2793304E-01	2.3215140E-01	4.0415700E-01
5.0000000E-01	7.8244275E-02	9.7146605E-02	2.1516729E-01	3.5548930E-01
1.0000000E+00	1.5648855E-01	9.3767041E-02	1.7756740E-01	2.8126903E-01
1.5000000E+00	2.3473282E-01	7.3081228E-02	1.2970602E-01	2.2860913E-01
2.0000000E+00	3.1297710E-01	5.0715640E-02	1.1940048E-01	2.1190660E-01
2.5000000E+00	3.9122137E-01	5.7724315E-02	1.0385009E-01	1.9949476E-01
3.0000000E+00	4.6946565E-01	5.6922628E-02	1.0894461E-01	1.9023424E-01
3.5000000E+00	5.4770992E-01	5.1546841E-02	1.2396138E-01	2.0060620E-01
4.0000000E+00	6.2595420E-01	7.5352566E-02	1.7364391E-01	2.3353612E-01
4.5000000E+00	7.0419847E-01	8.4602069E-02	1.9495840E-01	2.7177040E-01
5.0000000E+00	7.8244275E-01	1.1700429E-01	2.5784673E-01	3.3670189E-01
5.5000000E+00	8.6068702E-01	1.1882791E-01	3.3772648E-01	4.4013981E-01
6.000000E+00	9.3893130E-01	1.7875870E-01	4.6066582E-01	6.1569917E-01
6.5000000E+00	1.0171756E+00	2.3226478E-01	6.2547716E-01	8.4564308E-01
7.0000000E+00	1.0954198E+00	3.0574841E-01	7.9684886E-01	1.2377330E+00
7.5000000E+00	1.1736641E+00	3.7254234E-01	1.0307529E+00	1.7560733E+00
8.000000E+00	1.2519084E+00	4.2615579E-01	1.3956200E+00	2.5976317E+00
8.5000000E+00	1.3301527E+00	5.6787844E-01	1.7290693E+00	3.8612522E+00
9.0000000E+00	1.4083969E+00	6.8372318E-01	2.1212313E+00	5.2905291E+00
9.5000000E+00	1.4866412E+00	6.8372318E-01	2.4083789E+00	7.4829994E+00
1.0000000E+01	1.5648855E+00	8.7313784E-01	2.8961782E+00	1.0328243E+01
1.0500000E+01	1.6431298E+00	9.0279893E-01	3.5325050E+00	1.1285697E+01
1.1000000E+01	1.7213740E+00	1.0544345E+00	3.6469836E+00	1.7812660E+01
1.1500000E+01	1.7996183E+00	1.3670027E+00	4.0823735E+00	2.3167772E+01
1.2000000E+01	1.8778626E+00	1.4856542E+00	5.8987296E+00	1.6983218E+01
1.2500000E+01	1.9561069E+00	1.5548677E+00	7.1391354E+00	3.7972714E+01
1.300000E+01	2.0343511E+00	1.7392827E+00	7.8393101E+00	3.9224717E+01
1.3500000E+01	2.1125954E+00	1.6498072E+00	7.8986304E+00	3.3316751E+01
1.4000000E+01	2.1908397E+00	1.6619477E+00	7.3069125E+00	5.3441730E+01
1.4500000E+01	2.2690840E+00	2.0759175E+00	9.0831030E+00	4.8316634E+01
1.5000000E+01	2.3473282E+00	2.1252510E+00	8.6840804E+00	5.5009541E+01
1.5500000E+01	2.4255725E+00	2.1251988E+00	1.0241853E+01	6.8870506E+01
1.6000000E+01	2.5038168E+00	2.2570250E+00	8.5750455E+00	6.8134762E+01
1.6500000E+01	2.5820611E+00	2.1455592E+00	7.6159480E+00	1.0167473E+02
1.7000000E+01	2.6603053E+00	2.2123326E+00	9.7806972E+00	7.0424819E+01
1.7500000E+01	2.7385496E+00	2.0497906E+00	1.0150975E+01	5.3243944E+01
1.8000000E+01	2.8167939E+00	2.1741671E+00	8.0245470E+00	5.1504296E+01
1.8500000E+01	2.8950382E+00	2.2834807E+00	9.0399250E+00	6.2717217E+01
1.9000000E+01	2.9732824E+00	2.3420947E+00	7.6255810E+00	8.9100599E+01
1.9500000E+01	3.0515267E+00	2.5218407E+00	9.9268109E+00	7.1542912E+01
2.000000E+01	3.1297710E+00	2.1069836E+00	8.3694239E+00	6.4566845E+01
2.050000E+01	3.2080153E+00	2.6975259E-01	6.2277580E-01	1.0874261E+00
2.100000E+01	3.2862595E+00	2.7638327E-01	6.6550429E-01	8.7023551E-01
2.1500000E+01	3.3645038E+00	2.4825265E-01	4.8894767E-01	8.2808653E-01
2.200000E+01	3.4427481E+00	2.1019108E-01	4.9956236E-01	7.8033829E-01
2.2500000E+01	3.5209924E+00	2.0070305E-01	3.8247897E-01	8.3312110E-01
2.300000E+01	3.5992366E+00	2.5520280E-01	3.4945081E-01	7.2434542E-01
2.3500000E+01	3.6774809E+00	2.0655336E-01	3.6821391E-01	6.5569963E-01
2.400000E+01	3.7557252E+00	2.7043843E-01	2.6521399E-01	6.9366037E-01
2.4500000E+01	3.8339695E+00	1.8705335E-01	2.4737309E-01	5.7352302E-01
2.5000000E+01	3.9122137E+00	1.3684325E-01	2.5290422E-01	4.8178113E-01

0.000000E+00 0.000000E+00 2.4430000E 1.000000E+00 1.000000E+00 1.000000E 2.190000E+02 0.000000E+00 1.6300000E 4.000000E+01 0.000000E+00 5.6000000E	E+01 E+00 E+01 E+01 E-03 E-02
1.0000000E+00 1.000000E+00 1.000000E 2.1900000E+02 0.0000000E+00 1.6300000E 4.000000E+01 0.000000E+00 5.6000000E	E+00 E+01 E+01 E-03 E-02
2.1900000E+02 0.000000E+00 1.630000E 4.000000E+01 0.000000E+00 5.600000E	E+01 E+01 E-03 E-02
4.0000000E+01 0.0000000E+00 5.6000000E	E+01 E-03 E-02
	E-03 E-02
5.5780000E-03 5.5780000E-03 5.4200000E	E-02
1.0868000E-02 1.0868000E-02 -1.0552000E	
0.000000E+00 0.000000E+00 1.0552000E	E-02
2.8601700E+01 2.8601700E+01 7.4489400E	C+01
5.0142700E+01 5.0142700E+01 8.6344700E	C+01
6.7239300E+01 6.7239300E+01 1.6034980E	S+02
7.4820100E+01 7.4820100E+01 2.2128860E	S+02
8.8343700E+01 8.8343700E+01 2.7546270E	S+02
9.3524400E+01 9.3524400E+01 3.9468420E	S+02
1.5909950E+02 1.5909950E+02 4.2294760E	S+02
1.7017190E+02 1.7017190E+02 7.4444110E	S+02
2.2096480E+02 2.2096480E+02 8.1105660E	S+02
2.5080540E+02 2.5080540E+02 8.6385460E	C+02
2.8133560E+02 2.8133560E+02 9.7504210E	C+02
3.8965790E+02 3.8965790E+02 9.8974970E	S+02
4.2457980E+02 4.2457980E+02 1.0097612E	C+03
7.3015880E+02 7.3015880E+02 1.0552064E	5+03
8.0890780E+02 8.0890780E+02 1.0856531E	5+03
8.6028060E+02 8.6028060E+02 1.2060325E	C+03
9.7987580E+02 9.7987580E+02 1.2786620E	5+03
9.8638760E+02 9.8638760E+02 1.3115646E	C+03
1.0054301E+03 1.0054301E+03 1.3278382E	5+03
1.0072326E+03 1.0072326E+03 1.4120214E	C+03
1.0609093E+03 1.0609093E+03 1.4482725E	5+03
1.0624757E+03 1.0624757E+03 1.4888542E	5+03
1.0896125E+03 1.0896125E+03 1.4959673E	5+03
1.2046495E+03 1.2046495E+03 1.5076873E	5+03
1.2867875E+03 1.2867875E+03 1.5898220E	5+03
1.3139273E+03 1.3139273E+03 3.0348755E	5+03
1.3359626E+03 1.3359626E+03 3.0459408E	5+03
1.4140129E+03 1.4140129E+03 3.0796384E	5+03
1.4495458E+03 1.4495458E+03 3.1113826E	5+03
1.4975884E+03 1.4975884E+03 3.1184624E	5+03
1.5079924E+03 1.5079924E+03 3.1257667E	5+03
1.6167248E+03 1.6167248E+03 3.1268469E	5+03
3.0303862E+03 3.0303862E+03 3.2070767F	5+03
3.0432547E+03 3.0432547E+03 0.0000000F	5+00
3.0730732E+03 3.0730732E+03 0.0000000	5+00
3.1246407E+03 3.1246407E+03 0.0000000	2+00
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