

Kurzzusammenfassung

Hyperpolarisierung hat sich zu einer wichtigen Methode zur Signalverstärkung in Magnetresonanzmethoden wie NMR oder MRT entwickelt. Die Verwendung von Parawasserstoff als eine einfach verfügbare Quelle von Spinordnung für Hyperpolarisierung erwies sich als eine vielversprechende Technik. In SABRE (*Signal amplification by reversible exchange*, Signalverstärkung durch reversiblen Austausch) wird ein NHC-Iridium Komplex reversibel von Wasserstoff und einem geeigneten Substrat wie Pyrazin, Pyridin, Nicotinamid (Vitamin B3) oder Pyruvat koordiniert. Die Verwendung von Iridiumverbindungen und Methanol als Lösungsmittel machen Anwendungen in lebenden Zellen oder *in vivo* in medizinischen Anwendungen durch deren Toxizität unmöglich. Aktuelle Bemühungen zur Anwendung von Hyperpolarisationstechniken in solchen Bereichen basieren auf der Filtration der Katalysatoren oder der Verwendung heterogener Katalysatoren sowie der Verwendung von Wasser als Lösungsmittel. Die Entwicklung neuer heterogener Katalysatoren, zweiphasiger Systeme und wasserlöslicher Katalysatoren sind unabdingbar für neuartige Anwendungen von hyperpolarisiertem NMR.

Als Ziel dieser Arbeit sollten neuartige heterogene Katalysatoren für SABRE, basierend auf metallorganischen Gerüstverbindungen (MOFs, *metal-organic frameworks*) hergestellt werden. MOFs als poröse und kristalline Materialien sind für die Verwendung als heterogene Katalysatoren gut geeignet. Im Rahmen dieser Dissertation wurden NHC-Iridium-funktionalisierte Linker für die Herstellung NHC-Iridium-funktionalisierter MOFs entwickelt. Strukturell verschiedene Linker wurden identifiziert und Synthesevorschriften entwickelt. Erste Untersuchungen der Linkervorstufen zeigen vielversprechende Verstärkungen und die Aktivität neuartiger NHC-Iridium Komplexe konnte bestätigt werden. Einige Linker konnten erfolgreich zur Herstellung von MOF Materialien verwendet werden.

Weiterhin wurden Komplexe mit fluorierten Alkylketten modifiziert. Diese sollten in zweiphasigen Systemen aus Wasser und fluorierten Lösemitteln für die einfache Trennung von Katalysator und Substrat verwendet werden. Da bisher publizierte wasserlösliche Katalysatoren schlechte Löslichkeiten und Aktivitäten

zeigen, sollten in dieser Arbeit neue PEG-funktionalisierte Komplexe hergestellt werden. Ein neuartiger Komplex zeigte dabei eine gute Löslichkeit in Wasser und erste SABRE Experimente deuten auf sehr gute Aktivitäten hin. Ein weiterer Komplex mit freien Säuren wurde hinsichtlich der Löslichkeit in Wasser abhängig vom pH-Wert und seiner Aktivität in SABRE untersucht.

Abstract

Hyperpolarization emerged as an important method for increasing the signal strength of magnetic resonance measurements like NMR or MRI. The use of parahydrogen as an easily accessible source of spin order for hyperpolarization turned out to be a promising technique. Next to PHIP (parahydrogen induced polarization), where the spin order is transferred by hydrogenation of a compound, in SABRE (signal amplification by reversible exchange) spin order is transferred *via* a reversibly formed NHC-iridium complex of hydrogen and substrates like pyridine, pyrazine, nicotinamide (Vitamin B3) or pyruvate. The use of NHC-iridium complexes in methanol in this technique make an application *in vivo* impossible due to the toxicity of the compound and the solvent. Recent strategies to apply SABRE and PHIP in living cells or *in vivo* in medicine use the separation of the complexes by filtration or heterogeneous catalysts. The development of new heterogeneous systems, biphasic systems and the synthesis of catalysts with improved water solubility are important for the advanced applications of SABRE.

In this work, a new class of heterogeneous catalysts for SABRE NMR based on MOFs (metal-organic framework) was aimed. MOFs as porous crystalline materials were frequently used as heterogeneous catalysts in numerous reactions. As a part of this thesis, NHC-iridium-functionalized linker molecules for the synthesis of an NHC-iridium-functionalized MOF were developed. Geometrically differing linkers with imidazolium salts or NHC moieties and anchoring groups were identified and synthetic routes were established to obtain these precursors for the application in MOFs. First SABRE enhancement studies indicated promising results for the linker precursor complexes, whereby new NHCs were established in SABRE experiments. In the scope of this work, linkers were successfully used for the synthesis of MOF materials.

Additionally, NHC-iridium complexes were functionalized with fluorinated alkanes. These were aimed to be used in a biphasic system of water and fluorinated solvents for an easy separation of the catalyst and the enhanced substrate. Reported water-soluble catalysts suffer from low solubilities and activities.

Hence, novel PEG-functionalized catalysts were designed with improved solubility in water. Initial SABRE studies indicated activities exceeding the values reported to literature. An NHC-iridium complex functionalized with carboxylic acids was further examined for its solubility depending on the pH value and its activity in SABRE in the aqueous phase.

1 Introduction

The analytical methods based on nuclear spin resonance have reached enormous importance in today's society. Since its discovery in 1946, an astonishing progress based on this principle can be observed, steadily opening up new developments and improvements. Next to the application of nuclear magnetic resonance (NMR) as an analytical tool in natural sciences, magnetic resonance imaging (MRI) brought medical diagnosis to a new level since images of the anatomy and organs can be generated non-invasively. As an additional imaging procedure to X-ray computed tomography (CT), MRI works as a counterpart and helps physicians to identify diseases. The transition between nucleus spin states can be stimulated radio frequencies, making it a generally soft diagnostic method compared to CT using X-ray. Since nuclear spin resonance in general suffers from the low amount of detectable spins, strong magnets are used to generate possibly high occupation differences (see chapter 1.3.1). Also, in MRI, strong magnets are necessary to increase the signal strength and signal-to-noise ratio to obtain good-quality images, making the performance expensive and sometimes challenging.^[1-2]

Another way to increase the signal strength is to generate polarization by enlarging the difference in the occupation of the spin energy levels. Since a few years, enhanced ^{13}C MRI is used in clinical studies, while hyperpolarization is reached by dissolution dynamic nuclear polarization (dDNP). Here polarization is transferred from electron spins of a free radical in a cold environment (0.8 K) in a strong magnetic field and under microwave irradiation. The enhanced substrate (mostly pyruvate) can then be transferred to the patient. Since the signal enhancement decays over a few minutes, all has to be done in a short time.^[3-5] Another method to reach hyperpolarization is signal amplification by reversible exchange (SABRE), transferring spin orientation from *para*-hydrogen to a desired molecule. Iridium metal complexes with *N*-heterocyclic carbene (NHC) ligands typically catalyze spin order transfer. Nevertheless, the NHC-iridium complexes are toxic and therefore cannot be used for medicinal applications. Since polarization transfer can be conducted at ambient temperature in low magnetic fields, SABRE offers many practical advantages compared to dDNP. One strategy to

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make this soft hyperpolarization method applicable in *in vivo* experiments is to separate the activated substrate from the catalyst before being transferred to cells. The development of new catalyst materials based on NHC-iridium complexes is sufficient, obtaining heterogeneous catalysts based on porous materials for instance. Water-soluble catalysts can further help to analyze living organism tolerating the metal complex but not the organic solvent. Next to the new available diagnostic options, the possibility of making NMR and MRI analysis cheaper due to the usage of common magnets demonstrates the importance of such SABRE catalyst development.^[6-9] The following chapters will describe information on metal-organic frameworks (MOFs), heterogeneous SABRE catalysts and water-soluble catalysts. Details on NHCs, porous crystalline materials, and the explanation of hyperpolarized NMR will be given.

1.1 N-Heterocyclic carbenes

1.1.1 General properties of NHCs

Molecules containing an uncharged carbon with two unpaired valence electrons are called carbenes. The incomplete electron octet and the coordinative unsaturation make this class of molecules highly reactive and instable. The first stable compounds with carbenes have been known since the 1960s when FISCHER reported a tungsten carbene complex,^[10] followed by the first complexes with NHCs as ligands.^[11-12] NHCs have at least one nitrogen bond to the carbene carbon, both located in a heterocycle with optional ring size, number and class of heteroatoms.^[13-15] The first stable carbene, obtained by deprotonation of an adamantyl-substituted imidazolium salt, was reported in 1991 by ARDUENGO *et al.* and is therefore known as ARDUENGO carbenes.^[16] Outstanding is the use of NHCs as ligands in transition metal complexes, steadily increasing the number of new compounds and opening up fields for various applications.^[14] A selection of heterocyclic carbenes with varying numbers of heteroatoms, ring sizes and substitution patterns is shown in **Figure 1**.^[17]

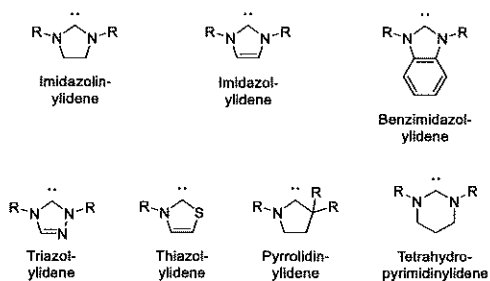


Figure 1: Examples of basic structures of *N*-heterocyclic carbenes.

The nitrogen atoms in the heterocycle can be substituted by several sterically demanding substituents, which tune the compound's stability and electronic properties, therefore influencing the resulting compound for later applications. The scope of substituents includes aromatic systems like adamantyl, mesityl, phenyl, or aliphatic substituents such as *tert*-butyl, *iso*-propyl, or methyl groups. The bulky substituents hinder a possible dimerization, which is one side reaction isolated carbenes undergo to reach the electron octet.^[14] However, electronic effects contribute more to stabilizing the carbene than the steric effects.^[17] Generally, depending on the location of the unpaired electrons and their spin orientation, singlet and triplet carbenes can be differentiated. The carbene carbon has a sp_2 -hybridized orbital and a p -orbital in which the unpaired electrons can be localized. In triplet carbenes, each of these is occupied by one electron, both having the same spin orientation. In singlet carbenes, only the sp_2 -hybridized orbital is filled with two electrons having opposite spin orientation.^[18] NHCs only form singlet carbenes, as a further stabilization is reached by the σ -withdrawing and π -donating properties of the nitrogen stabilizing the occupied sp^2 - and unoccupied p -orbital (**Figure 2**). The increased electron density at the C^2 -carbon makes NHCs nucleophilic, while in comparison most carbenes are known to be electrophilic. Furthermore, the NHC has a longer N–C bond and a smaller N–C–N angle than the azolium salt precursor.^[19]

N-Heterocyclic carbenes

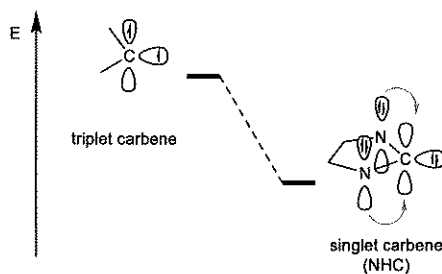
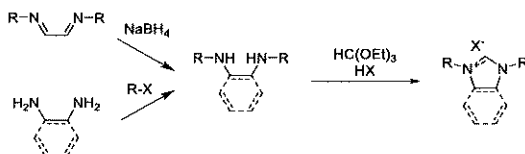


Figure 2: Electron occupation in a triplet and singlet carbene (*N*-heterocyclic carbene). Schematic representation of the electronic properties of an NHC. Indication of the energy as a molecular orbital diagram.

1.1.2 Synthesis strategies to NHCs

Imidazolium/Benzimidazolium salts. The most prominent route to NHCs is the deprotonation of a corresponding heterocyclic azolium salt, either isolated or in the presence of a metal source. Several synthetic strategies for azolium salts are reported, and with varying starting materials in these processes, a wide scope of azolium salts can be obtained. Next to imidazolium salts, imidazolinium salts are the most prominent compounds. One strategy to obtain these compounds is the formation of a suitable 1,2-diamine, followed by cyclization with triethyl orthoformate (**Scheme 1**, top).^[20-21] The diamines can be synthesized by reduction of the corresponding diimine, reductive amination,^[22] or HARTWIG-BUCHWALD amination.^[23] Benzimidazolium salts are also available *via* this synthetic route, performing first a HARTWIG-BUCHWALD amination to obtain an aromatic diamine, which is cyclized in the presence of tetrafluoroboric acid etherate to the desired benzimidazolium salt (**Scheme 1**, bottom/dashed).^[24]



Scheme 1: Possible pathways to obtain imidazolium or benzimidazolium salts by fabrication of a diamine (reduction of diimines (top), HARTWIG-BUCHWALD amination (bottom)) and subsequent cyclization with triethyl orthoformate. HX: halogen acid or tetrafluoroboric acid etherate.