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Substituent Influences on the NMR Signal Amplification of Ir Complexes with Heterocyclic Carbene Ligands

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Abstract

A number of Ir–*N*-heterocyclic carbene (Ir–NHC) complexes with asymmetric *N*-heterocyclic carbene (NHC) ligands have been prepared and examined for signal amplification by reversible exchange (SABRE). Pyridine was chosen as model compound for hyperpolarization experiments. This substrate was examined in a solvent mixture using several Ir–NHC complexes, which differ in their NHC ligands. The SABRE polarization was created at 6 mT and the ^{1}H nuclear magnetic resonance signals were detected at 7 T. We show that asymmetric NHC ligands, because of their favorable chemistry, can adapt the SABRE active complexes to different chemical scenarios.

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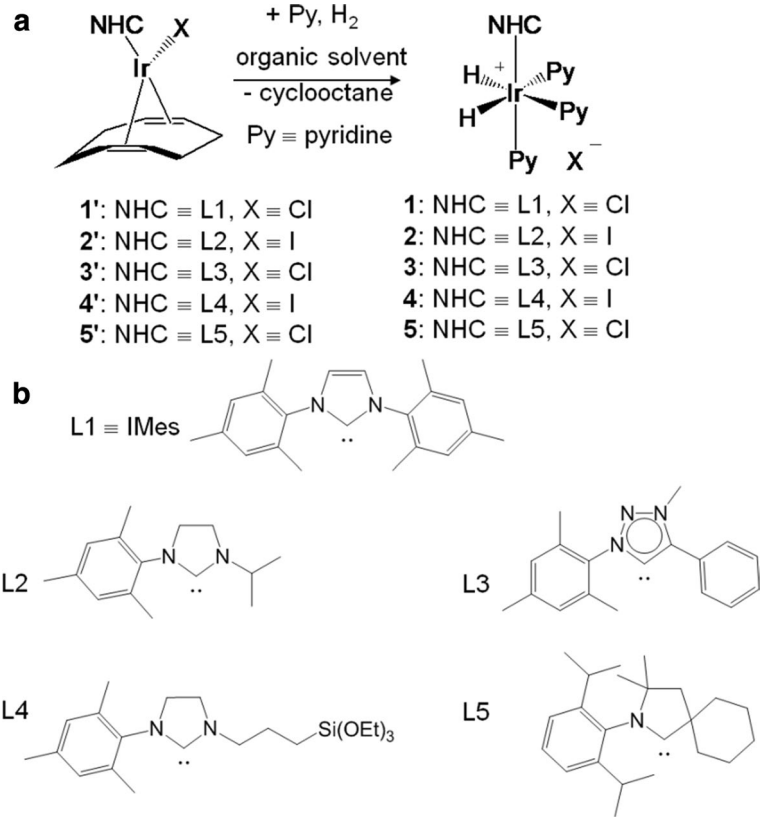
1 Introduction

In recent years, novel complexes have been synthesized containing *N*-heterocyclic carbenes (NHCs) as ligands [1–3]. The latter are strong electron-donors, are highly sterical demanding but stable and can bind to most transition metal and main group elements in different oxidation states [3]. NHC containing catalysts have been used, for example, for Heck and Suzuki couplings [4–6], hydrogenation [7, 8], and olefin metathesis [9–11]. Such complexes have also been immobilized on solid supports, facilitating their separation from the reaction products [12, 13].

Such complexes can also be used in nuclear magnetic resonance (NMR) signal enhancement by reversible exchange (SABRE) [14–17] of various heterocyclic substrates. To obtain useful complexes, the NHC ligand containing catalysts are converted into dihydrides using hydrogen and substrate molecules such as pyridine as illustrated in Scheme 1a. For example, to produce the cationic Ir complex **1** containing the



Scheme 1 **a** Conversion of NHC-containing transition metal complexes $[Ir(L)COD(Py)_3X]$, L = **L1**... **L5** to SABRE complexes $[Ir(H)_2(L)(Py)_3]^+ X^-$. **b** Structure of the symmetric NHC ligand IMes (**L1**) studied previously [15, 16] and novel asymmetric complexes **L2** to **L5** synthesized recently [5] studied in this work

symmetric NHC ligand, IMes (**L1** 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, Scheme 1b) has been used to generate **1** in organic solvents. When parahydrogen (pH_2) is added, enhanced emission signals of pyridine are observed by ^1H NMR. The enhancement factors strongly depend on the magnetic field where polarization transfer from the dihydride sites to the bound substrate occurs [14–16]. Recently, the number of substrates, which can be hyperpolarized, has been extended to other biologically active molecules such as nicotinic acid and even amino acids [18–20].

For many practical applications, SABRE has substantial advantages compared to competing hyperpolarization methods such as high-field dynamic nuclear polarization (DNP) [21–27], which necessitates very expensive technical equipment and operates only at low temperatures around 100 K or the Parahydrogen Induced Polarization (PHIP) [28–37] technique, which is produced via a chemical modification of the substrate, which afterwards cannot be used for PHIP again.

To use NHC–SABRE complexes in biological or medical applications, it is necessary to immobilize the complexes on a solid support for better separation purposes. This requires the synthesis of asymmetrically substituted NHC complexes, in which one of the ligands is chemically bound to a support. Such complexes will necessarily be asymmetric, since even a complex, which is symmetric in its unbound form, will become asymmetric, upon binding to a surface. For these reasons, we became interested in the SABRE performance of asymmetric complexes, where two different ligands are bound to the NHC ring. Ruddlesden et al. [39] have reported an asymmetric complex, which delivered an excellent 600-fold increase of the pyridine ortho-proton NMR signal at room temperature in THF. Duckett and co-workers synthesized a series of iridium complexes containing imidazol-2-ylidene based asymmetric NHC ligands, and used them for SABRE hyperpolarization of 3,4 and 3,5 lutidines [40]. In a seminal work, Shi et al.[41] developed an inhomogeneous complex in the form of a polymer microbead with an asymmetric NHC ligand, which enables SABRE enhancement. Although its performance as SABRE complex was strongly reduced as compared to **1** with enhancement factors between 2.7 and 5.2 of the pyridine protons, this still corresponds to substantial savings in experimental time on the order of ca. 10–30.

Therefore, we decided to explore how the hyperpolarization performance of a symmetric NHC complex changes upon asymmetric substitution. We focused on a series of non-symmetric NHC complexes (**2**; **3**; **4**; **5**, see Scheme 1b), which were recently synthesized by some of us. In the following, we describe the results of the SABRE experiments and show that depending on the degree of chemical changes, the SABRE performance of **1** can be either reached using asymmetric ligands or completely quenched.

2 Experimental Section

2.1 Catalyst Synthesis

All complexes employed in this work were synthesized in-house under an argon atmosphere, using Schlenk techniques. All chemicals used for the synthesis were

commercially purchased from Sigma-Aldrich, Carl ROTH GmbH and STREM Chemicals and they were used as received. The reference Ir–IMes complex **1′** was prepared in accordance with the procedure described by Vazquez-Serrano et al. [8]. The asymmetric complexes **2′**–**3′** are synthesized following the procedures described by Savka et al. [5]. The synthesis of complex **4′** was prepared in the following way: A flame-dried Schlenk flask that contained imidazolium iodide **L4**·HI (62 mg, 0.119 mmol) and [{IrCl(cod)}$_2$] (40 mg, 0.059 mmol) was evacuated and back-filled with nitrogen three times. THF (4 mL) and a solution of sodium tert-pentoxide in THF (2.5 M, 47.6 µL) were added. The mixture was stirred for 2 h at RT. Next the solvent was removed under vacuum and the residue was purified by column chromatography (silica, cyclohexane/ethyl acetate, 5:1, v/v, a yellow-orange band was collected), which afforded after drying in vacuum the desired iridium complex as yellow viscous oil (yield 76%).

The synthesis of complex **5′** was prepared in the following way: A flame-dried Schlenk flask that contained **L5**·HOTf (77.9 mg, 0.163 mmol) was evacuated and back-filled with nitrogen three times. Dry THF (5 mL) was added and suspension was cooled to − 78°C. KHDMS (35.9 mg, 0.180 mmol) was added and the mixture was stirred at − 78°C for 1 h. Next, [{IrCl(cod)}$_2$] (50 mg, 0.074 mmol) was added under nitrogen and the reaction mixture was stirred at − 78°C for 3 h. After this, the solvent was evaporated under reduced pressure and residue was purified by column chromatography (silica, cyclohexane/ethyl acetate, 10:1, v/v), which afforded after drying in vacuum the desired iridium complex **5′** as yellow solid (yield 93%).

3 SABRE Experiments

The solvents for the SABRE experiments, CD_3OD (99.8 atom% D), $CDCl_3$ (99.8 atom% D) were purchased from Eurisotop. Pyridine (anhydrous, 99.8%) was bought from Sigma-Aldrich and used without further purification.

^{1}H NMR SABRE spectra were recorded on a Bruker, WB-300, Ultrashield spectrometer with Avance III system at the Otto-von-Guericke University Magdeburg, Medical Faculty, Institute for Biometrics and Medical Informatics, Germany. Parahydrogen was produced using a hydrogen generator from Hogen GC (600 cc/min) and cooling down over charcoal in liquid nitrogen. The samples were prepared in 5 mm Pyrex® Screw Cap NMR Tubes from Rototec-Spintec GmbH, equipped with a PTFE/silicone septum from Wilmad LabGlass. After degassing the sample with argon, the sample was pressurized for 10 s with 3 bar dihydrogen gas containing 50% pH_2. Hyperpolarization was achieved by manually shaking the sample for 10 s at a polarization transfer field of about 6 mT and subsequent insertion into the detection field of 7 T corresponding to a ^{1}H Larmor frequency of 300 MHz. The field of 6 mT was chosen as it is known to yield the best SABRE enhancement for the symmetric IMes catalysts [15, 42] and we assumed that the magnetic field dependences should differ not strongly between the complexes. This assumption was probed by tests at few other polarization fields.

In all our SABRE experiments, samples of 1 mg of the complexes were dissolved in 600 µl $CDCl_3$:CD_3OD (1:1) and pyridine was employed as a substrate (for details

see Supporting Information). SABRE signal enhancement factors were determined from the integrated signal intensities as described below. The thermal spectra were measured 5–10 min after the SABRE measurement and after the sample signals had completely returned to thermal equilibrium. All spectra were measured with identical acquisition parameters.

SABRE enhancement factors were calculated in the standard way [16] as the ratio of the integrated intensity of a given signal measured under SABRE and under thermal conditions,

$$\epsilon_{\mathrm{SABRE}} = \frac{S_{\mathrm{SABRE}}}{S_{\mathrm{thermal}}}. \tag{1}$$

4 Results and Discussion

The thermal ^{1}H NMR signals of free and bound pyridine (Py) dissolved in CD_3OD:CD_3OD (v/v 1:1) in the presence of either complex **1, 2, 3**, **4** or **5** are compared in Fig. 1a with those obtained under SABRE conditions (Fig. 1b). These signals exhibit negative signal enhancements as described previously for the reaction with catalyst **1** dissolved in CD_3OD [15, 16]. The signal enhancement factors calculated according to Eq. (1) and chemical shifts are assembled in Table 1. The dominant negative signals arise from free pyridine released from the complexes and the small negative signals from pyridine molecules bound to Ir in axial and equatorial

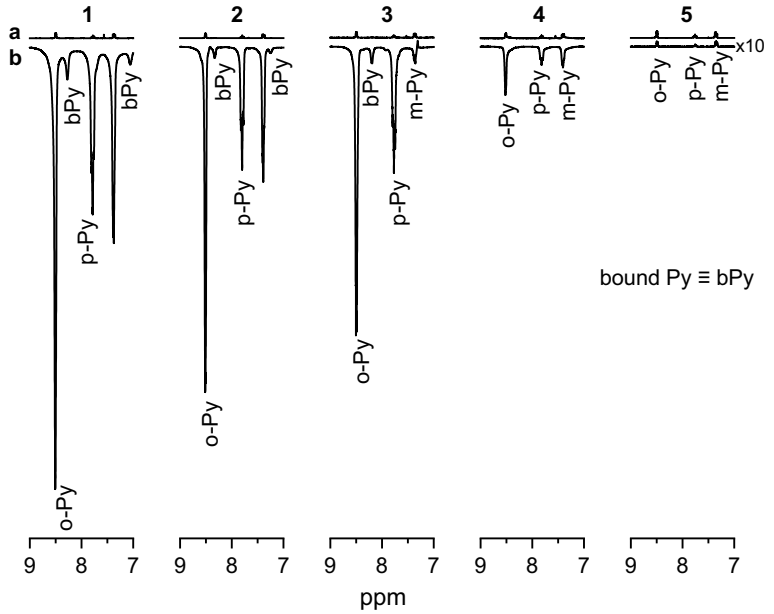


Fig. 1 Comparison of the thermal spectra (**a**) and of the SABRE spectra (**b**) of pyridine (Py) in the presence of complexes **1, 2, 3, 4** and **5** in $CDCl_3$:CD_3OD(1:1)

Table 1 SABRE-derived NMR enhancement factors of free pyridine dissolved in $CDCl_3$:CD_3OD (1:1) in the presence of different catalysts

Catalyst[a]	Ortho		Para		Meta	
	δ/ppm	ε_{SABRE}	δ/ppm	ε_{SABRE}	δ/ppm	ε_{SABRE}
1[(IMes)$IrPy_3H_2^+Cl^-$]	8.50	− 160	7.78	− 140	7.33	− 80
2[(ipr-NHC)$IrPy_3H_2^+I^-$]	8.51	− 140	7.80	− 130	7.39	− 60
3[(tzNHC)$IrPy_3H_2^+Cl^-$]	8.50	− 80	7.76	− 80	7.35	− 5
4 [(Si–NHC)$IrPy_3H_2^+I^-$]	8.50	− 15	7.81	− 15	7.39	− 10
5 (CAAC)NHC)$IrPy_3H_2^+Cl^-$]		–	–	–		–

[a]see Scheme 1. Solvent $CDCl_3/CD_3OD$ (1:1)

[b]Polarization around 6 mT, detection at 7 T

positions. The full spectra are shown in the supporting information. We did not attempt to analyze the signals of bound pyridine because of the low resolution at 7 T.

The chemical shifts found here are slightly different from those reported previously for methanol as a solvent [14, 16] because of the $CDCl_3/CD_3OD$ solvent mixture employed here.

First, we note that in view of the non-automatic way how the experiments were conducted, the enhancement factors observed are more of a qualitative rather than of a quantitative nature.

We observe SABRE-derived NMR polarization of pyridine not only in case of the symmetric IMes complex **1** which has been described previously [15, 16] but also for the asymmetric complexes **2**–**5** using a 6 mT polarization field and a 7 T detection field. As illustrated in Table 1, breaking the symmetry of the complexes reduces the absolute signal enhancements. Only a small reduction is observed in the case of complexes **2** and **3**. A significant decrease of the signal enhancement is observed for complex **4**. Particularly interesting are the results obtained for complex **5**, where the SABRE effect is so weak, that only a small decrease of the thermal signal is observed and no negative pyridine signal could be observed under SABRE conditions. Therefore, we did not list the SABRE effect on the different pyridine protons of complex **5** in (Table 1).

The very weak SABRE activity of complex **5** is most probably caused by two effects, which are not mutually exclusive, namely its molecular structure (see Scheme 1) and the different electronic structure of the NHC ring. On the one hand, the ligands of complexes **1**–**4** exhibit a molecular flexibility leading to a number of different conformations, and the ligand **L5** of complex **5** is sterically more demanding, and on the other hand, **5** is the only complex in our series where one of the carbons bound to the nitrogen with the lone pair is sp^3-hybridized.

5 Conclusions

The aim of the present study was to develop and test NHC ligand-based iridium complexes with asymmetric ligands for application in SABRE experiments. The SABRE performance of four asymmetric complexes was compared to the performance of the standard IMes complex under equivalent conditions. It was found that the achievable SABRE enhancement depend significantly on the nature of the ligands. In particular, rigid voluminous ligands might reduce the SABRE effects. Moreover, there can be also effects due to the changes of the magnetic parameters of the complex, which cause a different spin dynamics in the asymmetric complexes.

Moreover, our qualitative results show that it will be worth to try to immobilize Ir-containing NHC complexes on suitable supporting materials, which will allow one to easily separate the complexes from hyperpolarized solutions. That immobilization requires necessarily asymmetric complexes.

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