

# Synthesis of novel ligands for the coordination of titanium, scandium, yttrium, and zirconium for medical use as radiopharmaceuticals and theragnostics



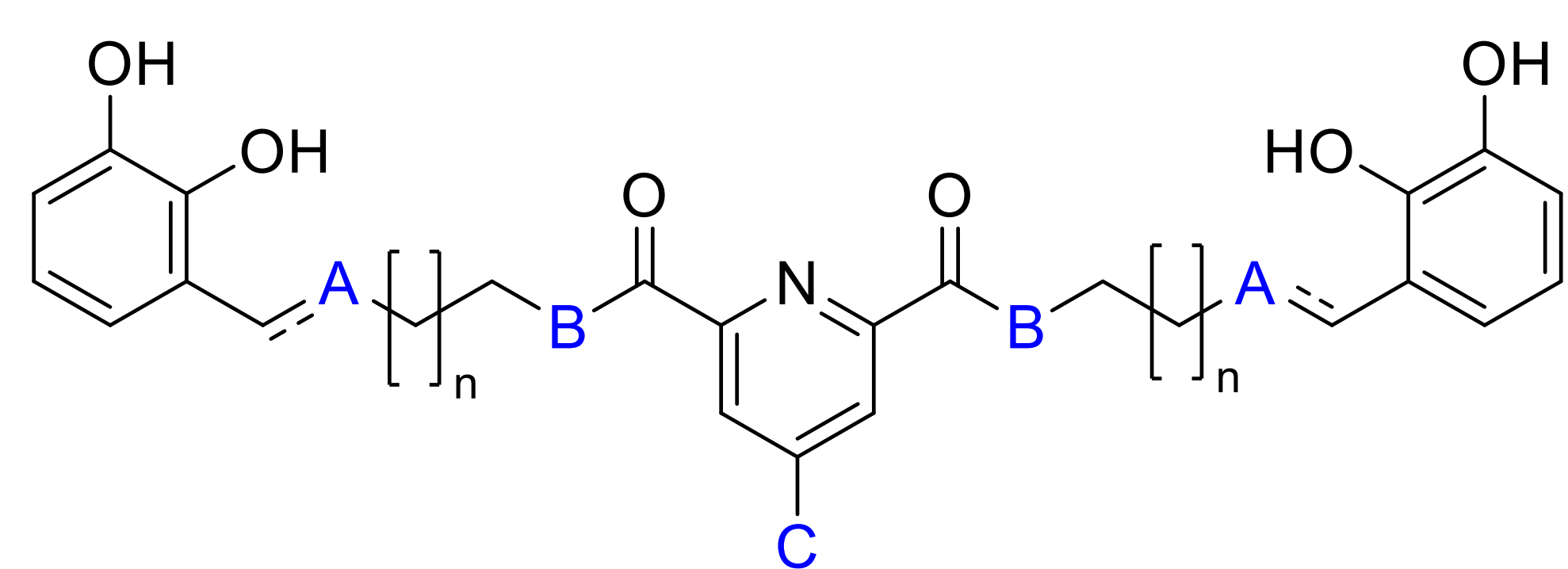
D. Sommer, R. Mittelstedt, E. Temur, N. Schmit, I. M. Oppel

Institute of Inorganic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany  
lisa.sturm@ac.rwth-aachen.de, iris.oppel@ac.rwth-aachen.de

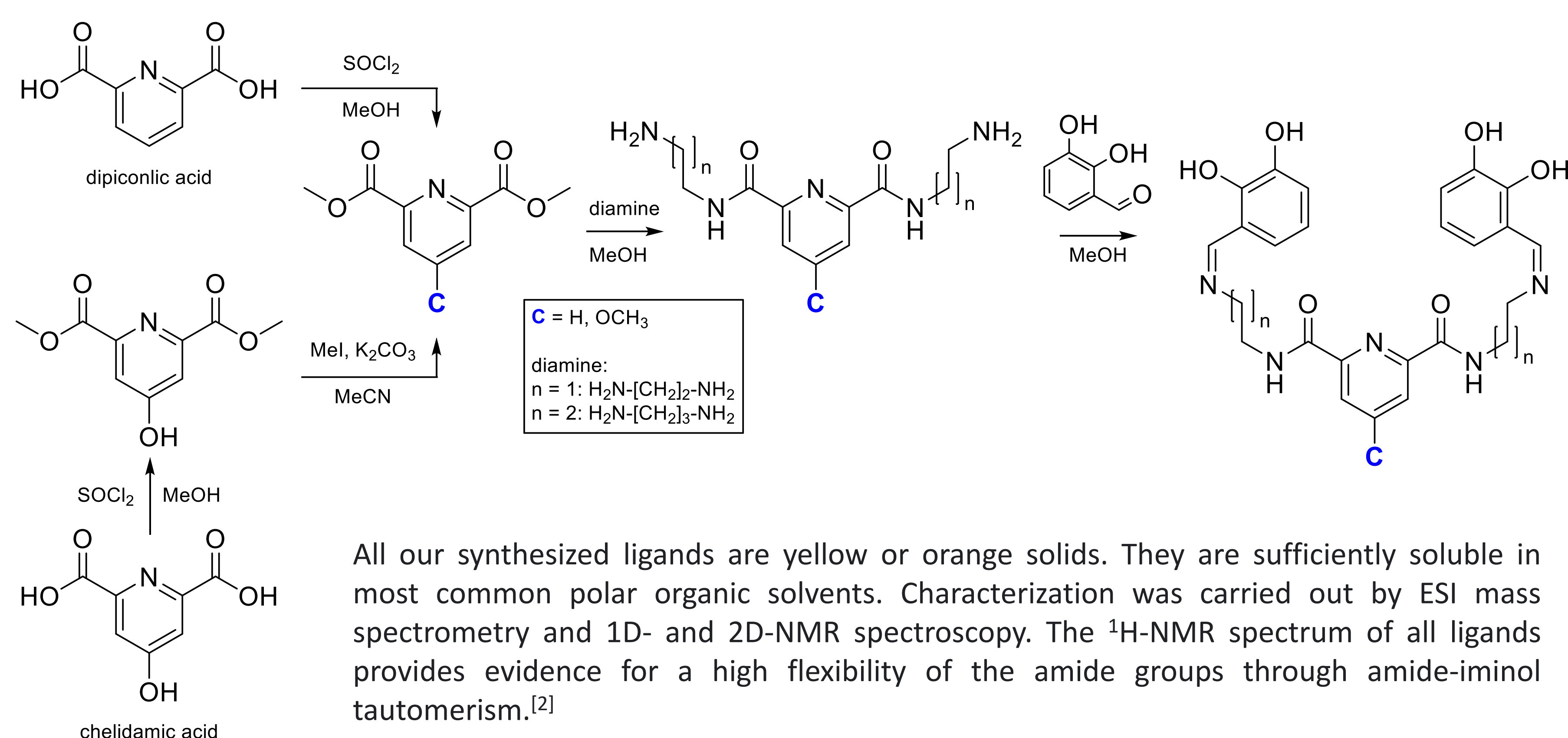
## Introduction

In addition to their anti-cancer properties, titanium complexes offer great potential in medical applications for diagnostics using positron emission tomography (PET). Due to their excellent properties in radioactive decay and a suitable half-life, tracers based on coordination compounds of the radionuclide  $^{45}\text{Ti}$  could be used to produce high-resolution images in PET. Previous tracer candidates were not reliable due to the observed non-target ligand exchange reaction in vivo testing.<sup>[1]</sup> In our work we try to establish a unimolecular coordination compound of  $^{nat}\text{Ti}$  from  $C_2$ -symmetrical ligands (Figure 1) based on catechol groups. To complete the coordination environment and to connect the catechol groups to target specific tracers via optimized linkers, we use dipicolinic acid or chelidamic acid for sufficient stability against exchange reactions, solubility and ligand volume. The ligands are also optimized regarding a comparable coordination of  $^{nat}\text{Zr}$ , since  $^{89}\text{Zr}$  is also a candidate for use in PET. On our poster we present the synthesis of the ligands and the first observed supramolecular coordination compounds.

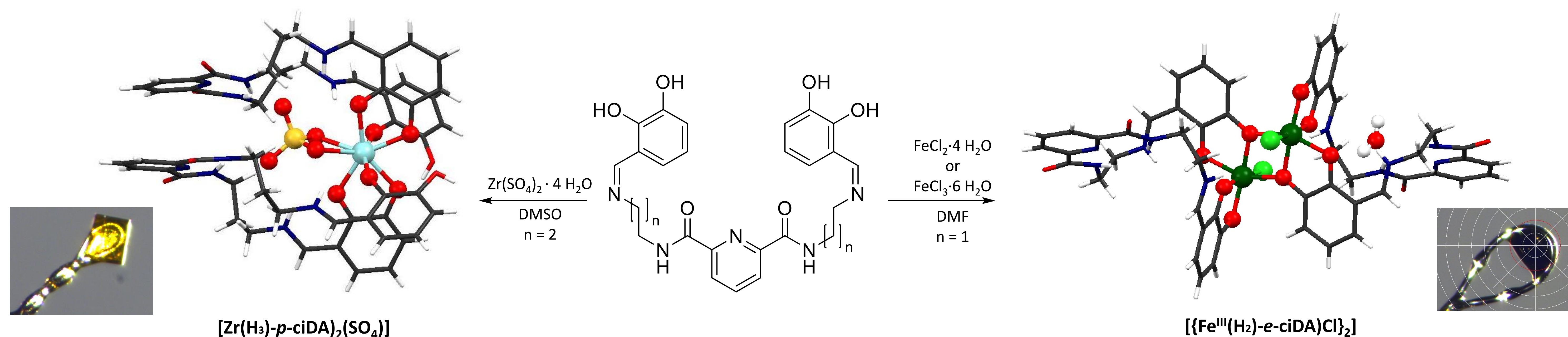
## Development of ligands optimization and synthesis of promising candidates



- Gen. 1 & 2**  $n = 1, 2$   $A = N_{\text{imin}}, N\text{CH}_3$  issues in synthesis and purification  
 $B = O$   $C = H$ :
- Gen. 3**  $n = 1, 2$   $A = N_{\text{imin}}$   $n = 2$ : **e-CIDA** (3 steps,  $Y = 91\%$ )<sup>[2]</sup>  
 $B = NH$   $C = H$ :  $n = 3$ : **p-CIDA** (3 steps,  $Y = 88\%$ )
- Gen. 4**  $n = 1, 2$   $A = N_{\text{imin}}$   $n = 2$ : **e-CICA** (4 steps,  $Y = 54\%$ )  
 $B = NH$   $C = OCH_3$ :  $n = 3$ : **p-CICA** (4 steps,  $Y = 63\%$ )
- Gen. 5 & 6**  $n = 1, 2$   $A = NH, N_{\text{amid}}$  synthesis in progress  
 $B = NH$   $C = OCH_3$



## First coordination compounds of our ligand system with Ti(IV), Zr(IV) and Fe(III)



In orientational coordination experiments black crystals of the compound  $\{[Fe^{II}(H_2-e-ciDA)Cl]_2\} \cdot 4 H_2O \cdot 4 DMF$  (**1**) were obtained after a few days in equimolar reactions of *e*-CIDA with iron chloride hydrate, regardless of the oxidation number (II, III) of the used precursor. **1** is an iron dimer in which iron cations are coordinated in a distorted octahedral manner by a chloride anion, the four oxygen atoms of the catechol groups of one ligand *e*-CIDA and bridging to the second iron atom via another oxygen atom of a second ligand. For the formation of **1**, the imino nitrogens are protonated to give a neutral crystal structure as iminium. Water is positioned in the ligand pockets between the pyridinic groups and the ligand arms via stabilizing H-bridges of the amide groups. The formation of this compound **1** could be shown not only by SCXRD but also by ESI mass spectrometry.<sup>[3]</sup>

The equimolar reaction of zirconium sulfate hydrate with *p*-CIDA leads to compound  $[Zr((H_3-p-ciDA)_2(SO_4))] \cdot 6 DMF$  (**2**). In **2** a Zr(IV) cation is coordinated eightfold by two (*H*<sub>3</sub>)-*p*-CIDA ligands and by two atoms of an additional sulfate anion. Half of the sulfate anion is inserted into each of the two ligand pockets of the two *p*-CIDA ligands by forming H-bridges with the amide groups. The coordination of the catechol groups is also asymmetrical for each ligand, because via one catechol one oxygen atom and on the other side both oxygen atoms bind to the Zr(IV). In this structure the four imine groups are protonated to achieve charge neutrality, too. In addition to XRD, this complex was characterized by ESI and 1D- and 2D- NMR spectroscopy. The NMR experiments provided a double set of signals, so we assume that the asymmetric coordination of the ligands is also present in solution. The results for the reaction of *p*-CICA with zirconium sulfate provide analogous NMR spectra and also ESI-MS signals. Therefore, the formation of  $[Zr((H_3-p-ciCA)_2(SO_4))]$  (**3**) be confirmed also with a identical constitution to that of **2** apart from the substitution on the pyridine ring. A crystal structure of **3** analogous to **2** has not yet been obtained.<sup>[4]</sup>

The reaction of other cations (Y(III), Sc(III), Ga(III)) with this ligand system led to the formation of further selective complexes in NMR experiments and by means of ESI-MS analysis, which have yet to be identified.<sup>[3]</sup>

By reacting various Ti(IV) precursors with all four ligands, the formation of air- and water-stable complexes can be shown using NMR and ESI-MS experiments. The reactions have so far not been selective. However, one-metal-one-ligand complexes can be detected by ESI-MS.<sup>[2]</sup>

## Summary and Outlook

The reactions of the four ligands obtained from our ligand system with different metal cations show the great flexibility of the system. Depending on the type of metal selected, one-metal-one-ligand complexes, dimers or one-metal-two-ligand compounds can be obtained. The incorporation of anions or solvent molecules by means of hydrogen bonds in the existing ligand pocket is possible.

The high flexibility of the ligands makes it difficult to predict reactions with other metal cations. For the selective coordination of Ti(IV) we want to switch to a  $C_3$ -symmetric ligand system. Basically, this system still allows a lot of potential for other interesting complexes.

## References

- [1] Søborg Pedersen et. al., *Molecules* 2020, 25, 1104.  
[2] Bachelorarbeit und Forschungsarbeit, Rik Mittelstedt, RWTH Aachen, 2022.  
[3] Forschungsarbeit, Eren Temur, RWTH Aachen, 2022.  
[4] Bachelorarbeit, Nathalie Schmit, RWTH Aachen, 2022.