

Review on Ing. Alexandra Tsybizova's thesis:

Direct Monitoring of Metal-Catalyzed Reactions Using Electrospray Ionization Mass Spectrometry

The investigation of reaction mechanisms is an important topic in physical organic chemistry and catalysis, since the information generated can be applied to predict new reactivity and to optimize existing reactions. Although currently most reactions are performed in condensed phase, investigations in the gas phase provide valuable information.

Ing. Tsybizova's thesis contributes to the field of metal catalysis in the gas phase, which is an emerging field. Therefore, basic previous mechanistic investigations in the gas phase are collected in the first chapter. Direct monitoring, the use of charge tags to study organometallic catalytic processes and the coupling with spectroscopic techniques are outlined. The importance of ESI-MS for studying solution-phase reactions is outlined next with an emphasis on potential problems that may arise in the interpretation of results. The aims are derived next.

Chapter 2 summarizes instrumentation and methods for investigation. ESI ionization and subsequent collision-induced dissociation (CID) of the initial ions are described. The determination of activation energies of fragmentations is illustrated. The coupling with infrared multiphoton dissociation spectroscopy (IRMPD) is outlined at the end of the chapter. The experimental part is documented in Chapter 3 of the thesis. In the beginning the instrument dependence of the results is mentioned. Subsequently the experimental setups and the HRMS investigations for speciation of ions are summarized. This adds a good level of confidence to the assignment of the detected species.

The results and discussion section starts with ESI-MS investigations of copper(II) acetate solutions in methanol and acetonitrile. The compound shows a high degree of clustering in both solvents. The cluster size is somewhat dependent on the concentration. The degradation of these clusters was studied by CID and reveals that reduction with fragmentation of the solvent and elimination of $\text{Cu}(\text{OAc})_2$ or $\text{Cu}(\text{OMe})_2$ units proceed competitively under the conditions and that the latter is more pronounced for larger clusters, whereas the former occurs in smaller clusters.

The change in the spectra of methanolic $\text{Cu}(\text{OAc})_2$ is interesting (Fig. 4.7). The author states that the increasing amounts of "impurities" in the presence of water result from their solubilization. An inspection of the spectrum shows, however, that the peak at 409, 619 or 695 seem to be copper clusters, since they show the isotopic $^{65}/^{63}$ copper isotope ratio, right? The second part concerns the mass-spectrometric investigation of the Liebeskind-Srogl reaction. All species were first individually studied and stoichiometric versions were subsequently investigated. The intermediacy of (thiol)copper complex **5** was probed. The catalytic reaction was online monitored and the change in ions is documented in table 4.2. Potential catalytic intermediates could unfortunately not be determined using the technique, but the intense peaks of sodiated complexes allowed determination of the kinetic parameters of the coupling reactions.

The third part concerns the potential of nickel-catalyzed C-H activation of isomeric phenylpyridines. The nickel complexes were studied by ESI MS and reveal differences in the regioisomeric phenylpyridine complexes. Further CID investigations aimed at deciphering the fragmentation pathways were performed and it was revealed that the ion $[\text{NiCl}(\text{2-Phpy})_2]^+$ undergoes competitive C-H insertion and pyridine ligand loss. The required energies for the two processes were determined and found to be similar. For comparison, simple mixed D_5 -pyridine complexes were also investigated. Here almost no C-H insertion was observed, but ligand loss strongly dominates for all complexes. The results are complemented by ion mobility MS studies, which showed that the most compact ions and those with higher charges

have the lowest arrival times. A second ion was found for the 2-PhPy complex, which was investigated by theoretical methods without success and which turned out to result from an isomeric purity in the starting material 2-PhPy.

The last part discusses carboxylate-assisted directed C-H activations of 2-phenylpyridine by ruthenium, copper and palladium carboxylates. At first the ruthenium complex was investigated. The results show that C-H activation proceeds as expected. On standing a complex that apparently undergoes double C-H activation is detected. For the corresponding copper acetate system, ligand elimination seems to be strongly favored over C-H insertion. The analogous palladium acetate system shows in contrast the opposite trend: C-H activation seems to be very facile and simple complexes were detected only to a minor extent.

The C-H activation study is supported by a computational investigation and IRMPD measurements, which allow closer structural characterization of the ions and conclusions, whether the observed ions are already C-H activated or not. A Hammett LFE correlation of the copper-catalyzed C-H activation using differently substituted benzoate anions concludes this part and shows that the C-H activation involves likely a cyclic transition state with little charge participation.

The present thesis is clearly written and organized. The key results are well presented and supported by sufficient experimental detail. A balanced representation of spectra allows for the mostly easy understanding of the processes that are described.

Several questions should be addressed in the defense:

- 1) In Figure 4.7, and also in Figure 4.8 several peaks show apparently the 65/63-isotopic pattern of Cu and are apparently Cu(OAc)₂-derived. Can they really be just only considered "impurities"?
- 2) In the monitoring of the reaction of thioester **1**, with the boronic acid and Cu(OAc)₂ it is stunning that the product **4** represents only a minor part in the spectrum displayed in Fig. 4.14b and that a large part of unreacted **1** remains, despite the fact that the boronic acid **2** is in excess over **1** in the solution and Cu(OAc)₂ is also present in larger amounts than in the actual catalytic experiments. How can this be explained?
- 3) In the CID of the fragmentation of the (2-phenylpyridine)nickel chloride complex it is stated that the minor fragmentation path of HCl elimination requires less energy to occur than the major 2-phenylpyridine elimination (p.63/64). This is apparently in contradiction to kinetics where the lower activation energy path (and the collision is considered to provide the activation energy!) is usually followed. What is the reason for this apparent contradiction?
- 4) It is stated that in the mixed [(3- or 4-phenylpyridine)(D₅-pyridine)nickel] chloride complexes significant DCl elimination was observed (p.65, first paragraph). Is this typical for the mixed complexes only, or does this also happen in [(D₅-pyridine)_nNiCl⁺] complexes alone? Has a blank experiment been performed?
- 5) In the CID spectrum of the ruthenium complex (Fig. 4.34a) the fragmentation of CO₂ is reported. The question that arises would be that the ion at m/z = 425 represents a methylruthenium complex, since CO₂ can only result from acetate. How would such a complex form and what would be potential mechanisms for its formation? Wouldn't that rather be in line with an oxidizing Ru(IV) intermediate?

Overall Ing. Alexandra Tsybizova fulfilled the aims of her work and provided a very good thesis, which fulfills the requirements. The results were published in four papers. Therefore, I recommend acceptance of the thesis and further proceeding to the defense.

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