Assessment of PhD. Thesis of Ing. Alexandra Tsybizova titled

Direct monitoring of metal-catalyzed reactions using electrospray ionization mass spectrometry

The Thesis was aimed in the study of reaction mechanism using modern methodology, mass spectrometry using soft ionization technique, electrospray ionization. This methodology was accompanied by other recent mass spectrometry based analytical approaches as ion mobility mass spectrometry, collision induced dissociation and infrared multiphoton dissociation spectroscopy. The results obtained were often compared and evaluated with the structures obtained by DFT calculations. The Thesis was devoted to four different subjects loosely connected by the methodology employed: study of solvation of cupric acetate, investigation of the mechanism of Liebeskind-Šrogl coupling of thiol esters with 4-tolylboronic acid, study of nickel-catalyzed C-H activation of phenylpyridines and investigation of the role of acetates in other transition-metal activation of 2-phenylpyridine.

In the first short part the author summarizes the knowledge about the methodology employed in the Thesis. It concisely summarizes the basic principles used for the research accomplished in the Thesis and introduces well the reader into the problematics studied. In the last section of the first part, the author declares individual targets of the Thesis, which normally forms short independent section of the Thesis.

The second part of the Thesis is devoted to the description of the instrumentation employed and I strongly appreciate that it gives even to the inexperienced reader very good insight into modern techniques, which are often quite exotic for common organic chemist.

The third part focuses more narrowly on the details of experimental techniques tailored specifically to the four individual targets of the Thesis.

The key fourth part describes the results obtained in the Thesis and is logically divided into four separate subparts dealing with four different problems (although the third and fourth subpart do have some connections). The first subpart studies the role of concentration and water content on the structure of cupric acetate clusters in methanol and its paramagnetic/diamagnetic properties. The second subpart was originally intended to elucidate the mechanism of catalytic version of Liebeskind-Šrogl coupling of thiol esters with 4-tolylboronic acid. Although this was not successful, on-line monitoring of the reaction mixture allowed to obtain thermochemical data of the reaction. Probably the most interesting is the third subpart dealing with different structures of ions formed from various regioisomers of phenylpyridines, which revealed that only 2-phenylpyridine can be deprotonated by nickel(II) chloride forming the C-Ni bond. Subsequent ion mobility study pointed out that this technique can be used for experimental evaluation of the stability of complexes formed. The fourth subpart was aimed in the comparison of three different transition metal complexes bearing 2-phenylpyridine and acetate ligands and their transformation to deprotonated complexes accompanied by the loss of acetic acid. Although here the comparison of the IRMPD spectra obtained experimentally with DFT computed results did not fit in all cases, it illustrated well the power of the methodology employed. Finally and beyond the original aims declared in the first part of the Thesis, the electronic effects of a series of substituted benzoates instead of acetate in the Cu-2-phenylpyridine complexes were studied both experimentally and theoretically. Hammett equation was employed and the results confirmed the expected assumption that electron-acception substituents should accelerate the deprotonation. Unfortunately, this approach could not be extended to other metals (Ru, Pd) studied.

I have some comments and questions:

Comments:

1) Page 25 row 11: The fingerprint region in IR spectroscopy is commonly described as an area between 800-1500 cm^{-1}, not up to 1800 cm^{-1}.

2) Deuterated compounds should named as e.g. (D$_3$)acetate or (^{2}H$_3$)acetate (IUPAC) or acetate-*d$_3$* (Chemical Abstracts), the names in the Thesis are neither consistent not correct.

3) Page 30: Number **1** and **2** for the compounds were already used for different compounds on page 7.

4) As is declared on page v, „the Thesis was developed independently". From this point of view, the use of plural („we decided..., we have analyzed..., we have theoretically compared..." etc. sounds inappropriately and should be substituted either by strong first singular (when the work was really done by the author) or by weaker passive voice (when cooperations could not be avoided, especially in the case of the computations.

5) Page 67 Fig. 4.29b: The results do not look linear and if linear dependence was really used (as shown), I cannot understand how R^2 = 0.95847 could be achieved. Moreover, the precision of the R^2 value should correspond to the precision of the measured data, which to my opinion is not to 5 valid numbers (and this is probably true for all correlations given).

6) The term „activated complex" is in physical chemistry used as an analogy of transition state. Hence, I do not think its use for the deprotonated species is lucky.

7) Page 85 row 1: Dispersion correction do not have a large influence on the elimination channel of AcOH, they better desribe it.

8) Page 85 Chapter 4.4.5: The choice of the substituents on the benzoates looks arbitrarily, it should be better to use a constistent set, e.g. NO$_2$ (-M), CF$_3$ (-I), halogen (-I + +M), CH$_3$ (+I) and OH or OCH$_3$ (+M), covering the basic types of substituents, preferably first in the *para*-position, and then, in the case of sufficient time, the same in the *meta*-position.

9) Page 90 row 4: To my opinion, it is not the role of the author of the Thesis to desribe her research as „fundamental findings".

10) Page 85 row 1: The abbreviation *int* is not described and listed in the List of Abbreviations.

11) Although not done by the author, the theoretical calculations are described as „done by number of methods and basis sets in order to better understand and theoretically describe...". I have to disagree with this statement as the methods employed probably reflect more the tastes of the individual cooperating theoreticians. Moreover, the use of B3LYP hybrid functional without empirical dispersion correction cannot be recommended today for weakly bonded transition metal complexes. In general, the use of pure functionals is recommended for transition metals and especially the MN12 family of functionals with non-empirical description of medium-range electron interaction deserve attention. Also, it is not described how relativistic properties of heavier transition metals (Ru, Pd) was included: using relativistic correction as ZORA, ECP potential or was it neglected? The use of different basis sets in the frame of one molecule is in general not recommended and I do not understand why DFT-tailored basis sets of the def2 family were not employed in the second part of calculations. Nevertheless, this is in principle not the question to the author...

12) There are very few typos which even do not deserve to be mentioned.

Questions:

1) Page 22 Fig. 2.6 and other calibrations: Is there some theoretical background for the calibration curves to be linear?

2) Page 50 row 19: It quite clear that Na^+ cation come from the glass capillary, but from where comes the highly abundant Ca^+ cation?

3) Page 54 row 1: What is meant by discrimination effect of ligand **4**?

4) Page 66 Fig. 4.28: From the figure it looks as the height of the second minorite species reaches around 3% of the major species. This corresponds to the concentration of the regioisomeric phenylpyridine of about 1.5%, but you found only 0.2% in the mixture. Can you please explain this?

5) Page 68 Fig. 4.7: Which energies are compared, electronic energies, ZPE-corrected energies or Gibbs free energies? If the former case was used, the role of entropy was neglected which could lead to erroneous assumptions.

6) Page 73 Fig. 4.3: Do you have some assumptions about the structure of ion formed after the loss of CO_2?

7) Is is quite interesting to compare the structures in Fig. 4.25 and 4.41 with analogous structures for Ni and Pd, where Ni does not form three-coordinated ions but for Pd it is one of the major fragments, while van der Waals ratio of the metals in nearly the same. Do you have some explanation? Also, the ions are written as $[Ni(2\text{-}PhPy)_2\text{-}H]^+$, but $[Pd(2\text{-}PhPy\text{-}H)(2\text{-}PhPy]^+$. Is there some reason for this?

8) Who made the theoretical study of the ions in Chapter 4.4.4 (again, „we have applied a number of methods…" should not be used in the Thesis when the work of other scientist is included)?

To evaluate the Thesis as a whole, it is very well written, the second part is highly informative about quite exotic techniques for common organic chemist, the third part describes briefly the neccessary details of the techniques used and finally the fourth part brings many interesting information showing that various coupled mass spectrometry techiques can be efficiently employed in the study of reaction mechanisms including transition metal complexes. The author managed to deal very well with very difficult problematics and obtained highly interesting results. The results of PhD. Thesis have been published in five papers in international peer-reviewed journals with high impact factors, two more papers deal with different problematics. The student thus unequivocally reached the targets postulated in the Thesis.

Due to abovementioned reasons, I **recommend** to accept the PhD. Thesis of Ing. Alexandra Tsybizova as the basis for defending her **Ph.D.** title.

In Prague, 11.1.2016   Prof. Ing. Jaroslav Kvíčala, CSc.