

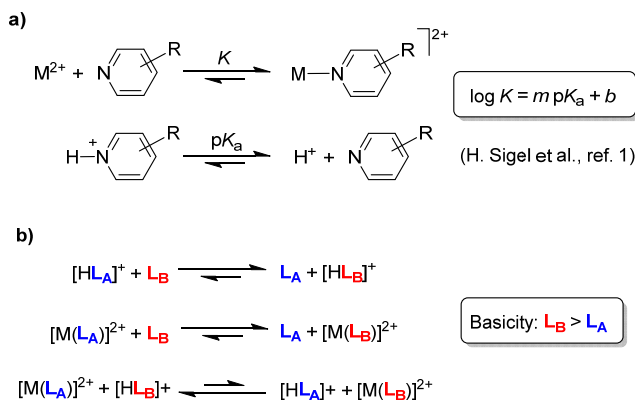
Palladium-Based Metal-Ligand Assemblies: The Contrasting Behavior Upon Addition of Pyridine or Acid

Suzanne M. Jansze and Kay Severin*

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL),
1015 Lausanne, Switzerland. E-mail: kay.severin@epfl.ch

ABSTRACT: The stability of five different $[\text{Pd}_n(\text{N-donor})_m]^{2n+}$ assemblies was examined by performing disassembly experiments with pyridine and with trifluoroacetic acid. Pyridine-induced disassembly was found to be most pronounced for Pd complexes containing N-donor ligands of low basicity. At the same time, these assemblies displayed high acid resistance. The contrasting stability in the presence of acid or pyridine can be used for the pH-controlled switching between different metallosupramolecular structures.

The relation between the basicity of a ligand and the stability of a metal complex has been investigated by Kapinos and Sigel for dicationic metal ions and a series of pyridine ligands.¹ In aqueous solution (25 °C, $I = 0.5 \text{ M NaNO}_3$), they observed that the logarithm of the association constant K is proportional to the $\text{p}K_a$ value of the protonated pyridine ligand (Scheme 1a). For 3d transition metal ions and for sterically non-demanding pyridines (no *ortho* substituents), they found that the correlation factor m varies between 0.10 (Mn^{2+}) and 0.42 (Cu^{2+}). The fact that the correlation factor m is significantly smaller than 1 has an interesting consequence: Let's consider two ligands L_A and L_B , with L_B being more basic than L_A (Scheme 1b). Ligand L_B will form a more stable complex with M^{2+} . When the two ligands compete for a limiting amount of M^{2+} , complex $[\text{M}(\text{L}_B)]^{2+}$ will be more abundant than $[\text{M}(\text{L}_A)]^{2+}$. However, in the presence of an appropriate amount of acid, ligand L_B will be protonated first, and $[\text{M}(\text{L}_A)]^{2+}$ will be the dominant metal complex in solution.



Scheme 1. Correlation between ligand basicity and complex stability.

We hypothesized that similar trends might be observed in non-aqueous solutions for more complex metallosupramolecular assemblies. If this would be the case, then one could use acid to switch

between different metal-ligand assemblies, in a similar way as it is possible to perform an acid-induced switch from $[\text{M}(\text{L}_B)]^{2+}$ to $[\text{M}(\text{L}_A)]^{2+}$ (Scheme 1b)

For our studies, we focused on supramolecular structures containing Pd^{2+} ions and polydentate N-donor ligands. These kinds of complexes have been studied extensively over the last years,² and applications in the fields of catalysis,³ medicinal chemistry,⁴ and materials science⁵ are currently being investigated.

There is evidence that the ligand basicity is an important factor for the stability of $[\text{Pd}_n(\text{N-donor})_m]^{2n+}$ assemblies. Mukherjee and co-workers have shown that a $[\text{Pd}_2\text{L}_4]^{4+}$ complex based on a ditopic pyridyl ligand can be converted into a macrocyclic $[\text{Pd}_3\text{L}'_6]^{4+}$ complex or a spherical $[\text{Pd}_6\text{L}''_8]^{12+}$ cage by addition of more basic imidazolyl ligands, which displace the pyridyl ligands.⁶ Furthermore, it was demonstrated by the groups of Hardie,⁷ Chand,⁸ and Crowley^{4c} that 4-dimethylaminopyridine (DMAP) can be used to convert $[\text{Pd}_6\text{L}_8]^{12+}$ and $[\text{Pd}_2\text{L}_4]^{4+}$ structures into the more stable $[\text{Pd}(\text{DMAP})_4]^{2+}$, and that the disassembly process can be reversed by addition of *para*-toluenesulfonic acid. The latter reactions represent a more complex version of the system depicted in Scheme 1b. However, it should be noted DMAP is a highly basic N-donor ligand. In acetonitrile, the $\text{p}K_a$ of the corresponding acid is more than 5 units higher than that of protonated pyridine (17.95 vs. 12.53, respectively).⁹ The ligands which are typically used for the construction of $[\text{Pd}_n(\text{N-donor})_m]^{2n+}$ assemblies are significantly less basic than DMAP, and it was not clear how the stability of Pd complexes is affected by more subtle changes in ligand basicity.

Figure 1 depicts the ditopic N-donor ligands which we have employed for our studies. The bent bipyridyl ligand L_1 is known to form $[\text{Pd}_2(\text{L}_1)_4]^{4+}$ complexes,¹⁰ whereas the linear ligand L_2 gives tetrahedral $[\text{Pd}_4(\text{L}_2)_8]^{8+}$ complexes¹¹ upon combination with Pd^{2+} . The ligands L_3 and L_4 contain electron-donating methoxy groups in para position to the N-donor atom. Therefore, they represent more basic analogues of L_1 and L_2 . For comparison, the $\text{p}K_a$ values of pyridine and *p*-methoxypyridine in acetonitrile differ by 1.7 units (12.53 vs 14.23, respectively).⁹ When mixed with $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$, ligand L_3 was found to give a dinuclear $[\text{Pd}_2(\text{L}_3)_4]^{4+}$ complex, similar to what was observed for L_1 . For the linear ligand L_4 , we observed the clean formation of a double-walled $[\text{Pd}_3(\text{L}_4)_6]^{6+}$ macrocycle instead of a tetrahedral cage as observed for L_2 .¹²

It is worth noting that trinuclear $[\text{Pd}_3\text{L}_6]^{6+}$ complexes and tetrahedral $[\text{Pd}_4\text{L}_8]^{8+}$ structures can easily be distinguished by NMR spectroscopy, because the latter have a reduced symmetry (double set of signals for the ligands). The new complexes $[\text{Pd}_2(\text{L}_3)_4]^{4+}$ and $[\text{Pd}_3(\text{L}_4)_6]^{6+}$ were also characterized by high-resolution mass spectrometry (see the Supporting Information, SI). The metalloligand

L5 contains a chemically inert Fe²⁺ clathrochelate complex.¹³ The reaction of **L5** with Pd²⁺ is known to give an octahedral [Pd₆(**L5**)₁₂]¹²⁺ complex.¹⁴

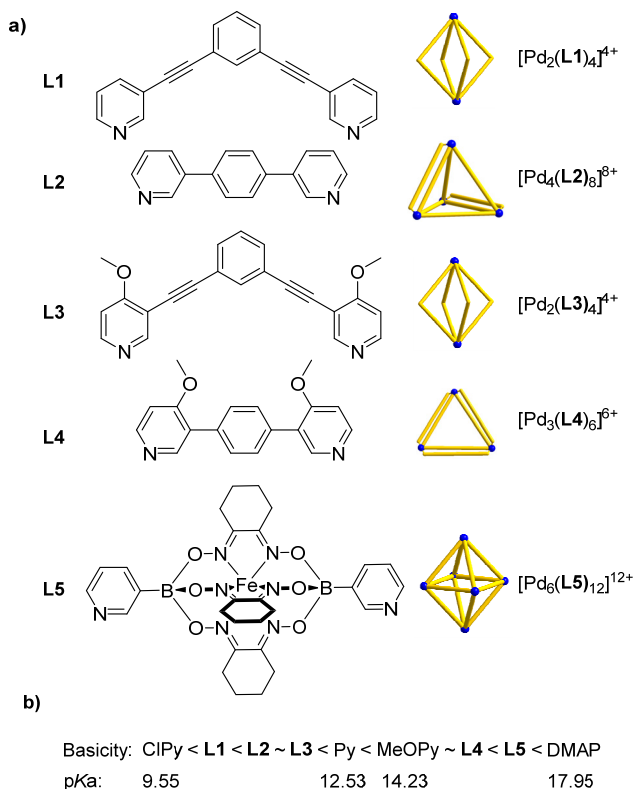


Figure 1. a) Structures of the N-donor ligands used in this study and the corresponding complexes with Pd²⁺; b) The relative basicity of the ligands. The pK_a values (acetonitrile) of the pyridine reference compounds are taken from ref. 9.

The relative basicity of the ligands **L1**–**L5** was determined by NMR spectroscopy. For this purpose, we have performed nine titration experiments with pairs of ligands and trifluoroacetic acid (TFA) in either CD₃CN or a 1:1 mixture of CD₃CN and CD₂Cl₂ (**L4** and **L5** are poorly soluble in pure CD₃CN).¹⁵ The simple monodentate ligands DMAP, 4-methoxypyridine (MeOPy), pyridine (Py), and 3-chloropyridine (ClPy) were included as references (for details, see SI).

The ligands **L1**–**L3** were found to be more basic than 3-chloropyridine but less basic than pyridine, with **L1** being the least basic of the three, and **L2** and **L3** displaying comparable basicity (Figure 1b). Ligand **L4** has similar basicity to 4-methoxypyridine, but it is less basic than the metalloligand **L5**. The high basicity of the latter was noticed earlier,¹⁶ and it can be attributed to the presence of a tetra-coordinated boronate ester group.¹⁷ Still, **L5** was found to be significantly less basic than DMAP.

The donor strength of the ligands was evaluated by determining the Huynh Electronic Parameter (HEP).¹⁸ In order to do so, we have prepared Pd complexes featuring an N-heterocyclic carbene ligand in *trans* position to the N-donor (for details, see SI). Solutions of the complexes in CDCl₃ were analyzed by ¹³C NMR spectroscopy. The HEP corresponds to the chemical shift of the carbene C-atom. The value provides a quantitative measure for the σ-donor strength of a ligand, with higher numbers indicating a better donor capability.¹⁸ The values for **L1**–**L5** are given in Table 1. It is evident that there is a good match with the relative basicity of the ligands, with both the HEP values and the basicity increasing in the order **L1** < **L2** ~ **L3** < **L4** < **L5**. The HEPs of the reference compounds are aligned accordingly: the lowest value is found for 3-chloropyridine

(158.7), followed by pyridine (160.1),¹⁸ 4-methoxypyridine (160.5), and finally DMAP (162.1).

Next, we have examined the relative stability of the Pd assemblies derived from **L1**–**L5** by performing competition experiments with pyridine. Solutions of the five complexes were prepared by dissolving an appropriate amount of [Pd(CH₃CN)₄](BF₄)₂ together with the corresponding ligand ([L_x] = 9.0 mM) in a mixture of CD₃CN and CD₃NO₂ (8:2). Addition of one equivalent of pyridine-*d*₅, with respect to each N-donor atom in the assembly, resulted in partial destruction of the assembly. The extent of pyridine-induced disassembly after an equilibration time of 2 h at 60 °C was determined by ¹H NMR spectroscopy (Table 1).

Table 1. Disassembly of the Pd complexes upon addition of TFA (4 eq.) or pyridine-*d*₅ (1 eq.), and the HEP values of the ligands.^a

L#	Assembly	Disassembly (%) TFA	Disassembly (%) pyridine- <i>d</i> ₅	HEP (ppm)
L1	[Pd ₂ (L1) ₄] ⁴⁺	<5	68	159.4
L2	[Pd ₄ (L2) ₈] ⁸⁺	44	20	159.8
L3	[Pd ₂ (L3) ₄] ⁴⁺	49	29	159.8
L4	[Pd ₃ (L4) ₆] ⁶⁺	65	<5	160.4
L5	[Pd ₆ (L5) ₁₂] ¹²⁺	>90	<5	161.4

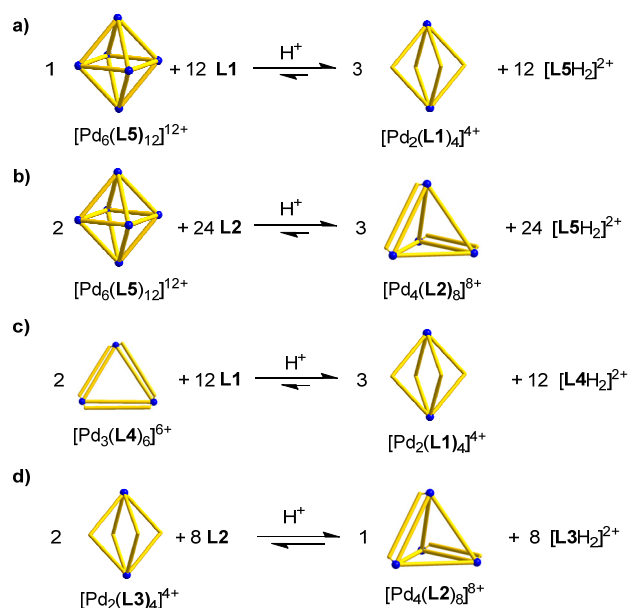
^a The disassembly experiments were performed in CD₃CN and CD₃NO₂ (8:2), whereas the HEP values were determined in CDCl₃.

The addition of pyridine had the largest effect on the dinuclear complex [Pd₂(**L1**)₄]⁴⁺, with 68% of the assembly being broken, as determined by integration of the ¹H NMR cage signals with respect to an internal standard (TMS). Significantly smaller values of 20 and 29% were observed for [Pd₄(**L2**)₈]⁸⁺ and for [Pd₂(**L3**)₄]⁴⁺, and no significant disassembly was detected for [Pd₃(**L4**)₆]⁶⁺ and [Pd₆(**L5**)₁₂]¹²⁺ (below 5%). One can observe a correlation between the stability of the assembly and the basicity/σ-donor strength of the N-donor, with more donating ligands leading to more stable assemblies. It is noteworthy that entropy is apparently a less important factor for the stability, because the hexanuclear complex [Pd₆(**L5**)₁₂]¹²⁺ is significantly more stable than the entropically favored dinuclear complexes [Pd₂(**L1**)₄]⁴⁺ and [Pd₂(**L3**)₄]⁴⁺.

The acid resistance of the Pd complexes was determined in a similar fashion using TFA (4 eq. with respect to the amount of N-donor atoms) instead of pyridine. Now, the correlation between stability and ligand basicity was inverted: the hexanuclear complex [Pd₆(**L5**)₁₂]¹²⁺ was found to be the most acid-sensitive assembly (nearly full disassembly), and extended acid resistance was observed for the dinuclear complex [Pd₂(**L1**)₄]⁴⁺ (Table 1).

The results of the competition experiments suggested that an acid-induced switch between different [Pd_nL_{2n}]²ⁿ⁺ structures could be possible.¹⁹ First, we examined the conversion of the most acid-sensitive assembly [Pd₆(**L5**)₁₂]¹²⁺ into the most acid-resistant assembly [Pd₂(**L1**)₄]⁴⁺ (Scheme 2a). A prerequisite for such a switch is the structural integrity of [Pd₆(**L5**)₁₂]¹²⁺ in the presence of an excess of **L1**. The superior stability of [Pd₆(**L5**)₁₂]¹²⁺ suggested that the octahedral cage might be the preferred assembly in a competition situation with **L1**. When an equilibrated solution of **L1** (2 eq.), **L5** (2 eq.) and [Pd(CH₃CN)₄](BF₄)₂ (1 eq.) in CD₃CN/CD₃NO₂ (8:2) was analyzed by ¹H NMR spectroscopy, we indeed observed the selective formation of [Pd₆(**L5**)₁₂]¹²⁺ along with 'free' ligand **L1** (Figure 2a). When TFA (4 eq.) was added to the mixture, we could observe the interconversion of the octahedral cage into the dinuclear complex [Pd₂(**L1**)₄]⁴⁺. After an equilibration time of 2 h at 60 °C, the transformation of [Pd₆(**L5**)₁₂]¹²⁺ into [Pd₂(**L1**)₄]⁴⁺ was complete (> 90% according to ¹H NMR, Figure 2b). Using a metastable-state photoacid instead of TFA, we were also able to induce the structural change by light (Figure S57, SI). The experiments with the photoacid also showed that the structural interconversion is fully reversible: when the sample was kept in the dark at 60 °C

for 6 h, we observed the back-conversion of $[\text{Pd}_2(\text{L1})_4]^{4+}$ into $[\text{Pd}_6(\text{L5})_{12}]^{12+}$.



Scheme 2. Acid-induced interconversion of different $[\text{Pd}_n\text{L}_{2n}]^{2n+}$ complexes.

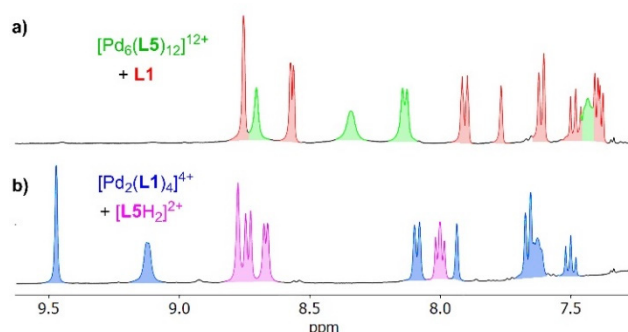


Figure 2. a) Aromatic part of the ^1H NMR spectrum ($\text{CD}_3\text{CN}/\text{CD}_3\text{NO}_2$; 8:2) of a mixture of **L1** (2 eq.), **L5** (2 eq.) and $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$ (1 eq.) after equilibration; b) Spectrum of the same solution after addition of TFA (4 eq.) and equilibration.

An acid-induced interconversion of $[\text{Pd}_n\text{L}_{2n}]^{2n+}$ structures was also possible for the ligand pairs **L5/L2** and **L4/L1**. In the former case, ligand exchange transformed an octahedral cage into a tetrahedral cage (Scheme 2b), whereas in the latter case, a double-walled triangle was converted into a dinuclear cage structure (Scheme 2c).

Furthermore, we examined the behavior of a mixture containing **L2** and **L3** (Scheme 2d). These ligands display a comparable basicity and, according to the HEP, the same σ -donor strength (Table 1). When combined with $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2$, the ^1H NMR spectrum showed the preferential formation of the entropically favored dinuclear complex $[\text{Pd}_2(\text{L3})_4]^{4+}$, but small amounts of the tetramer $[\text{Pd}_4(\text{L2})_8]^{8+}$ could also be detected. No ligand scrambling was observed by ^1H NMR or MS. Upon addition of acid, the relative abundance was inverted, with $[\text{Pd}_4(\text{L2})_8]^{8+}$ being the dominant metal-ligand assembly in solution (Figure S54, SI). These results show that even small differences in ligand basicity can be exploited to generate a large bias in the structures expressed by self-assembly. Other ligand combinations like **L1/L3** and **L2/L4** were also tested, but ligand scrambling was observed, and more detailed investigations were therefore not performed.

In summary, we have investigated the stability of five different $[\text{Pd}_n(\text{N-donor})_{2n}]^{2n+}$ assemblies (four cages and one macrocycle) by performing disassembly experiments with pyridine and with TFA. The susceptibility towards degradation by pyridine was found to be inversely correlated to the acid resistance. The most acid-resistant complex $[\text{Pd}_2(\text{L1})_4]^{4+}$ was disassembled to a large extent upon addition of pyridine (68%), whereas the most pyridine-resistant cage $[\text{Pd}_6(\text{L5})_{12}]^{12+}$ was very sensitive to acid. The contrasting behavior upon addition of pyridine or TFA can be linked to the basicity of the N-donor ligand. Interestingly, ligand basicity seems to be a more dominant factor for the stability of the assembly than entropy. For example, we observed the selective formation of the hexanuclear cage $[\text{Pd}_6(\text{L5})_{12}]^{12+}$ in the presence of **L1**, even though **L1** can form the entropically favored dinuclear $[\text{Pd}_2(\text{L1})_4]^{4+}$ complexes.

The context-dependent stability of Pd-based metal-ligand assemblies should be considered for applications of these complexes as drug delivery systems.^{4,20} The possibility to use the pH for a (reversible) switch between different supramolecular structures could also be of interest for application in materials science.^{5c-f} Evidently, the stability of metal-ligand assemblies is influenced by numerous factors, the ligand basicity/donor strength being just one of them. Therefore, it will be interesting to investigate if an inverse correlation between acid and pyridine resistance can be observed for metallocage structures other than $[\text{Pd}_n\text{L}_{2n}]^{2n+}$ complexes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information (containing experimental details, NMR and MS spectra) is available free of charge on the ACS Publications website at DOI: XXX

AUTHOR INFORMATION

Corresponding Author

E-mail: kay.severin@epfl.ch

ORCID

Suzanne M. Jansze: 0000-0003-2979-2630

Kay Severin: 0000-0003-2224-7234

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The work was supported by the Marie Curie Initial Training Network “ResMoSys”, and by the Ecole Polytechnique Fédérale de Lausanne (EPFL). We thank Dr. Mark Chadwick for providing the Pd complex for the HEP measurements, and Dr. Alexander J. Stephens for valuable suggestions on the manuscript.

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