Trapped Ion Mobility Mass Spectrometry is able to resolve minor size differences in supramolecular structures

Ion Mobility Mass Spectrometry has started to spread from analytical and omics research fields to other areas, including supramolecular chemistry.

Abstract

Besides its power to differentiate between isomeric analytes, ion mobility mass spectrometry offers the possibility to quantify the gas-phase collisional cross section (CCS, in Å^2) of ionic supramolecular assemblies, thereby delivering precious information about their size, shape and conformational dynamics. For example, dynamically self-assembled structures can be distinguished in complex mixtures and information about specific host-guest interactions can be retrieved. The comparison of experimental results with theoretically derived CCS values, determined by molecular modelling, adds valuable new methodology to the analytical toolbox of scientists in supramolecular and nano chemistry.

Keywords: Supramolecular chemistry, Nano Cages, Collisional Cross Sections, Molecular Modelling, Ion Mobility Mass Spectrometry, Trapped Ion Mobility Spectrometry (TIMS), timsTOF

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Introduction

Coordination-driven self-assembly of tailor-made organic building blocks and suitable transition metal cations with matching binding geometries allows for a simple construction of complex nanosized architectures, including molecular cages with an accessible cavity. Applications span from the selective recognition of guest molecules, aimed at compound separation tasks or diagnostic systems, over enzyme-mimicking catalysis to nano-machinery and light-harvesting devices. As these self-assembled structures are becoming increasingly complex in terms of structure and composition, the demands for powerful analytical techniques are rising, constantly. We recently reported a library of heteroleptic coordination cages based on the combination of four banana-shaped, bis-monodentate ligands, whose backbones only slightly differ in shape and length, with tetracoordinate palladium(II) cations (Figure 1) [1]. Pure *cis*-[$Pd_2L_2L'_2$] assemblies form after addition of Pd^{II} cations to a 1:1 mixture of matching pairs of shape-complementary ligands. When all four ligands are used in combination, however, the unambiguous discrimination of all individual species in the product mixture becomes difficult. Due to steric constraints, the system is restricted to the formation of ten different coordination cages in total, two of which are isomeric (Figure 2). While diffusion ordered (DOSY) NMR spectroscopy is a powerful tool for the discrimination of individual components in a complex mixture, it fails to deliver unambiguous answers when larger objects show only small size differences as in the present case.

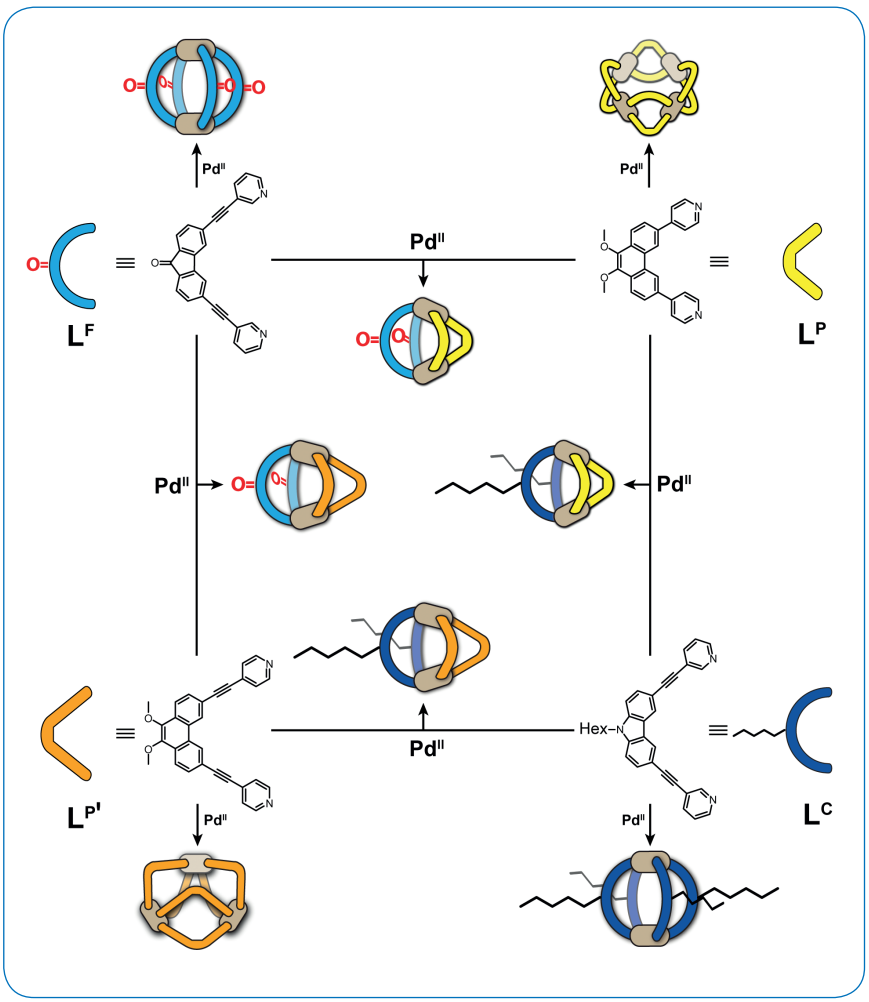

Figure 1: Schematic overview of bis-monodentate ligands L^F, L^P, $L^{P'}$ and L^C reacting with Pd^{II} cations to form homoleptic cages or rings and – by pairwise combination – heteroleptic cages.

Instrumentation

All herein described ion mobility measurements were performed on a Bruker timsTOF instrument combining a trapped ion mobility (TIMS) unit with a time-of-flight (TOF) mass spectrometer in one instrument.

After the generation of ions by electrospray ionisation (ESI, analyte concentration: 0.7 mmol, solvent: DMSO/MeCN (1:20), capillary voltage: +3600 V, end plate offset voltage: 500 V, nebulizer gas pressure: 0.3 Bar, dry gas flow rate: 3.0 L/min, dry temperature: 200°C), the desired ions were orthogonally deflected into the TIMS cell consisting of an entrance funnel, the TIMS analyser (carrier gas: N_2, temperature: 305 K, entrance pressure: 2,59 mbar, exit pressure: 0,89 mbar, IMS imeX ramp end: 1.90 $1/K_0$ [detect mode] and 1.03 $1/K_0$ [ultra mode], respectively, IMS imeX ramp start: 0.5 $1/K_0$ [detect mode] and 0.87 $1/K_0$ [ultra mode], respectively) and an exit funnel. As a result, the ions are stationary trapped. After accumulation (accumulation time: 5.0 ms), a stepwise reduction of the electric field strength leads to a release of ion packages separated by their mobility. After a subsequent focussing, the separated ions are transferred to the TOF-analyser.

Results and Discussion

A sample of the coordination cage library was prepared by mixing one equivalent of every ligand (4 eq. in total) followed by the addition of two equivalents of Pd^{II} cations. Due to the specific design based on a shape-complementary combination of two ligands, each, from the L^C and L^F family (sharing a converging orientation of the coordination vectors) and the L^P and $L^{P'}$ family (with diverging orientation of the coordination vectors) we expected the formation of ten distinct coordination cages of which two are isomeric, i.e. carrying a combination of all four ligands in a *cis*- (L^F next to L^P) or trans- (L^F opposite to L^P) arrangement around the metal centers.

The differentiation of eight species of the library is possible based on their differing mass alone. This, however, does not apply to the two isomers which do not only have the exact same mass but also a very similar shape and size. The measurement shows that distinguishing all ten cages by high resolution trapped ion mobility is indeed possible, including the isomeric cis- and trans-$[Pd_2L^CL^FL^PL^{P'} + BF_4]^{3+}$ (Figure 3a) species with an *m/z* value of 656.15 (Figure 3a–c). It should be noted that these isomers differ by only 4.3 $Å^2$ (0.8% with an achieved resolution of up to 160) in their collisional cross sections.

TIMS analysis shows that the species containing the fluorenone-based ligand L^F (species a–c in Figure 3c) have an overall lower ion mobility, and thus a smaller collisional cross section, serving as an isotropic measure for comparing cage dimensions, than the species with the carbazole-based ligand L^C (species g–h in Figure 3c). While they share a very similar backbone structure, they only differ in the size of the appended substituent (Figure 1).

Furthermore, ion mobility analysis allows the detection of quite small size differences. For example, compounds $[Pd_2L^F{}_2L^{P'}{}_2 + BF_4]^{3+}$ (species c in Figure 3c) and $[Pd_2L^C{}_2L^P{}_2 + BF_4]^{3+}$ (species g in Figure 3c) show only a small mobility difference. Nevertheless, trapped ion mobility mass spectrometry allows their clear differentiation for two reasons: (a) their different mass allows the superposition of mass-selected mobilograms even when both species are part of the same sample and (b) the high resolution of the TIMS analyser yields a clear separation of the peak maxima.

We were further able to assign the isomeric species by a computational analysis and comparison of calculated CCS values with the experimental data. The structures have been optimized using Grimme's GFN-xTB methodology followed by calculation of theoretical CCS values using the programs MOBCAL and IMoS (for details see reference [1]).

Furthermore, we have recently applied trapped ion mobility mass spectrometry for the discrimination of photo-switchable cage isomers and their host–guest complexes [2] and the visualization of the guest-induced expansion/contraction of helicene-based coordination cages [3].

Table 1: Instrument setup and experimental conditions

Syringe Pump	KDScientific KDS900
Flow rate	180 µL/min
MS	timsTOF mass spectrometer, Bruker Daltonics
Scan mode	Full scan TOF MS with IMS in Detect and Ultra mode
Ionization	ESI +3600 V
MS-Calibration	Agilent ESI tune mix
IMS-Calibration	Agilent ESI tune mix

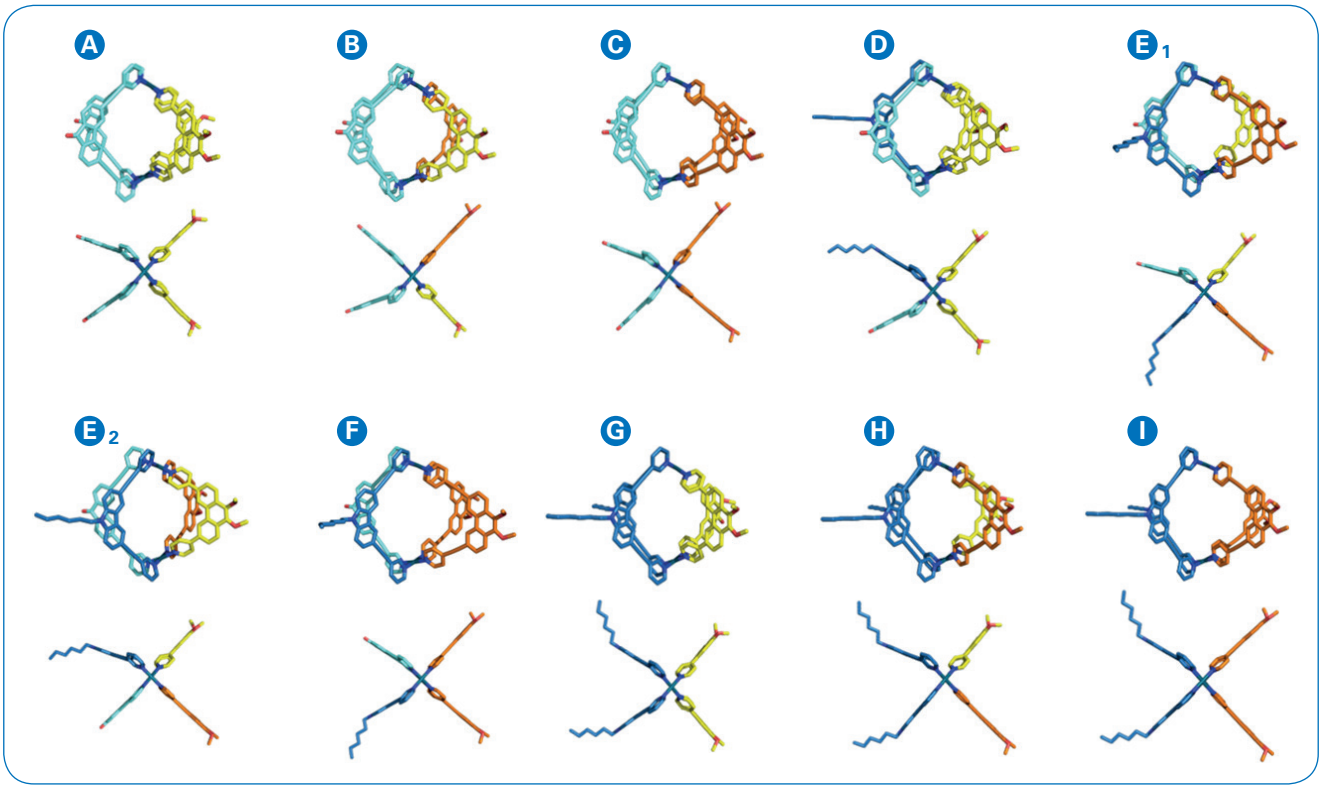

Figure 2: Geometry optimized structures of Ⓐ $[Pd_2L^F{}_2L^P{}_2]^{4+}$; Ⓑ $[Pd_2L^F{}_2L^P{}_1L^{P'}{}_1]^{4+}$; Ⓒ $[Pd_2L^F{}_2L^{P'}{}_2]^{4+}$; Ⓓ $[Pd_2L^CL^FL^P{}_2]^{4+}$; Ⓔ$_1$ cis-$[Pd_2L^CL^FL^P{}_1L^{P'}{}_1]^{4+}$; Ⓔ$_2$ trans-$[Pd_2L^CL^FL^P{}_1L^{P'}{}_1]^{4+}$; Ⓕ $[Pd_2L^CL^FL^{P'}{}_2]^{4+}$; Ⓖ $[Pd_2L^C{}_2L^P{}_2]^{4+}$; Ⓗ $[Pd_2L^C{}_2L^P{}_1L^{P'}{}_1]^{4+}$ *and* Ⓘ $[Pd_2L^CL^FL^{P'}{}_2]^{4+}$ *(each in top and side view).*

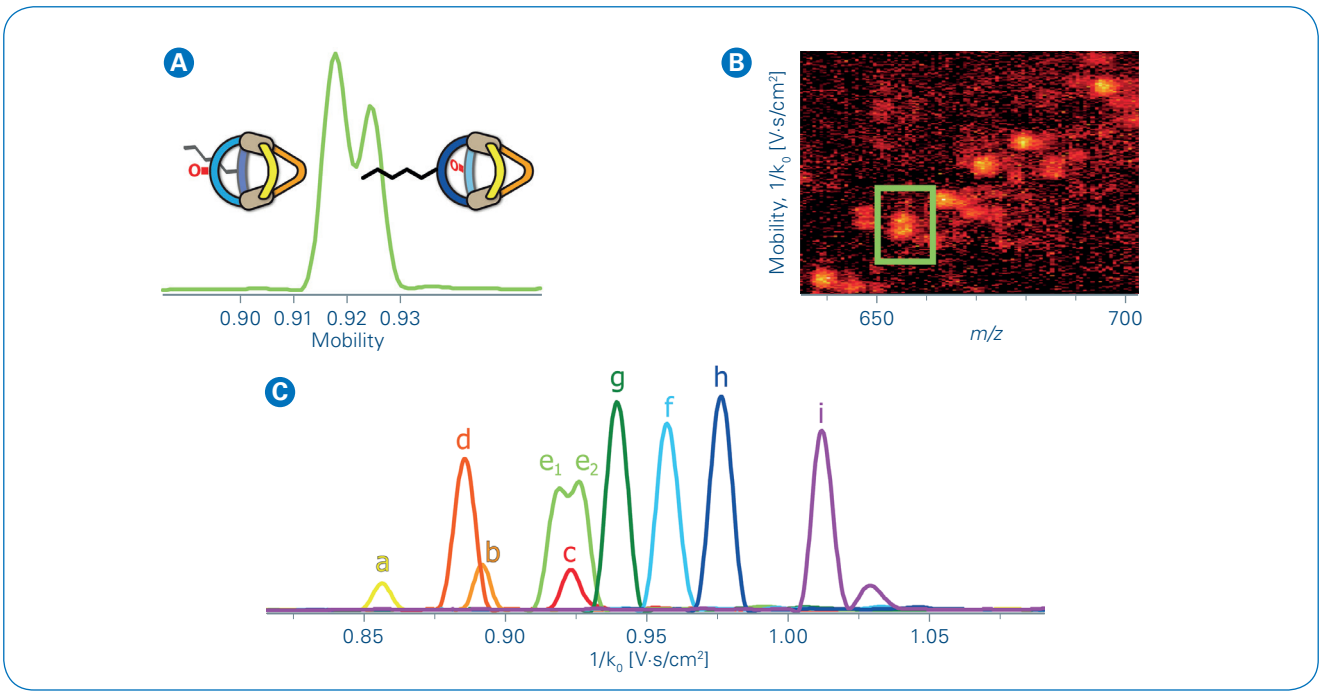

Figure 3: Ⓐ *High resolution TIMS mobilogram allowing the discrimination of* cis-$[Pd_2L^CL^FL^PL^{P'} + BF_4]^{3+}$ *and* trans-$[Pd_2L^CL^FL^PL^{P'} + BF_4]^{3+}$; Ⓑ *partial heat map and* Ⓒ *full mobilogram of the simultaneous ion mobility measurement of a mixed sample containing all ten coordination cages shown in Figure 2.*

Conclusion

- Ion mobility measurements with the timsTOF method offer the possibility to reveal very small size differences between self-assembled nano cages.
- Ion mobility proved to be a valuable tool for analysing complex supramolecular systems. It allowed us to show that discrimination of individual species is possible from a ten-component library whose members feature differences in their averaged radii of less than 0.1 Å.
- The theoretical calculation of collisional cross sections allowed us to reproduce the experimentally found size trends and their CCS values.

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