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Inert-Atmosphere MALDI-MS

Shining New Light on an Old Problem: Retooling MALDI Mass Spectrometry for Organotransition-Metal Catalysis**

*Melanie D. Eelman, Johanna M. Blacquiere, Maeve M. Moriarty, and Deryn E. Fogg**

Over the past two decades, discoveries in homogeneous catalysis have transformed organic chemistry and materials science. New catalytic methodologies for assembling and elaborating carbon–carbon and carbon–element bonds have had a profound impact on sectors ranging from pharmaceuticals to specialty polymers and "green" feedstocks.[1] Underlying these advances is an enormous body of work directed at synthesis, understanding, and iterative redesign of molecular transition-metal catalysts. A major obstacle, however, remains the simple problem of structure elucidation. Despite steady advances in our understanding of the rich chemistry of transition-metal complexes, reduction of planned syntheses to practice is still non-trivial, and novel pathways and unexpected products are commonplace. Identification of actual, as opposed to intended, products of organometallic syntheses typically takes considerably longer than the reactions themselves, while elucidation of catalytic mechanisms occurs on a timescale of years.

Structural identification in organic chemistry is greatly simplified by the use of mass spectrometry (MS) to identify molecular composition from mass-to-charge (m/z) ratios and isotope patterns. However, the standard high-energy MS ionization methods suitable for organic analysis typically induce decomposition of sensitive organometallic molecules.[2] "Soft" ionization techniques such as electrospray ionization (ESI)[3] and matrix-assisted laser desorption/ionization (MALDI),[4] which can ionize fragile complexes with minimal fragmentation, have tremendous potential to simplify and expedite analysis. Pioneering work by the groups of Chen, Traeger, Henderson, and others has demonstrated the power of ESI-MS for structural elucidation and mechanistic analysis in organometallic chemistry and catalysis.[2,5–7] This method is ideally suited to analysis of soluble, ionic complexes. Insoluble molecules are intractable,[8] while neutral species require introduction of charge by gas-phase cleavage of a covalent bond, cationization by an added proton (for hazards, see below) or other cation source, or prior modification of the complex to incorporate a charged surrogate ligand. The complementary technique of MALDI-TOF-MS (TOF = time-of-flight) permits analysis of ionic or neutral species, but transition-metal complexes commonly decompose during sample preparation, introduction, or analysis.[2,9] Herein, we show that these limitations are not inherent, and that appropriate modifications transform MALDI-MS into a powerful tool for insight into the identity and reaction chemistry of organometallic molecules.

Samples for MALDI-MS analysis are generally prepared by co-crystallizing the analyte with a matrix compound bearing a chromophore suitable for absorption of laser irradiation (most commonly an N_2 laser; emission at 337 nm). Decomposition of air-sensitive organometallic molecules can be minimized by preparing samples under inert atmosphere and rapidly transferring them to the MS loading chamber under a stream of nitrogen or argon gas.[2] This procedure can work well for relatively robust complexes, particularly coordinatively saturated complexes of the late transition metals, but reactive species remain susceptible to degradation during transfer. We resolved this problem by interfacing a MALDI-TOF mass spectrometer to an inert-atmosphere glovebox (Figure 1).[10] Samples can then be prepared in a rigorously anaerobic and anhydrous environment, enabling straightforward analysis of air- and water-sensitive compounds, whether these are isolated or intercepted by analyzing aliquots from reactions carried out in the glovebox.[11]

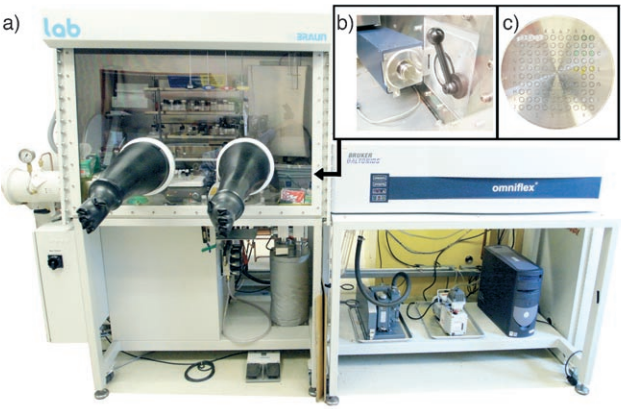

Figure 1. a) Inert-atmosphere MALDI-TOF mass spectrometer; b) open loading chamber projecting into the glovebox; c) target plate.

A major additional challenge lies in the identification of a suitable matrix. The dominant application of MALDI-MS is analysis of biopolymers, which are conveniently ionized by

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[*] M. D. Eelman, J. M. Blacquiere, M. M. Moriarty, Prof. D. E. Fogg
Department of Chemistry
University of Ottawa
Ottawa, ON, K1N 6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: dfogg@uottawa.ca
Homepage: http://www.science.uottawa.ca/~dfogg/default.htm

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protonation at polar sites by aromatic acid matrixes. An alternative ionization mechanism is desirable for transition-metal complexes, which (as Lewis acid–base adducts) are susceptible to protonolysis of metal–ligand bonds.[12] We were intrigued by the possibilities of charge-transfer (CT) ionization, which could exploit the rich redox chemistry of the transition metals. McCarley, Limbach, and co-workers have successfully applied CT-MALDI-MS to a number of redox-active species, including calixarenes, conducting polymers, and—most notably, in the present context—ferrocene derivatives.[13] In this approach, photoabstraction of an electron from a matrix compound possessing a large extinction coefficient at 337 nm (often polyaromatic hydrocarbons) generates a radical cation, which in turn abstracts an electron from the analyte. Ferrocene derivatives present a favorable test case, given their robustness and facile oxidation. Nevertheless, the ionization energies of transition-metal complexes are often low unless the metal is in its highest oxidation state, and we thus considered that the approach might be generalizable. As the examples below show, anaerobic CT-MALDI-MS can permit observation of the intact molecular cations even for highly reactive organometallic catalysts, whether ionic or neutral.

We prepared samples of discrete metal complexes by dissolving them with pyrene or anthracene in a suitable, volatile solvent (CH_2Cl_2, C_6H_6) and spotting microliter aliquots onto the MALDI target plate. Rapid evaporation left a film of the sample dispersed in the matrix, on which MALDI-TOF mass spectra were measured. Because single ionization is characteristic of MALDI analysis, the molecular weight of the analyte can be inferred directly from the *m*/*z* value for the molecular ion. The spectra of **1**–**3** (Figure 2) exhibit prominent signals for the intact molecular ions, despite the challenges presented by high oxygen sensitivity (particularly for titanium(III) complex **1**, an ethylene polymerization catalyst),[14] and high reactivity (**2**·BF_4, for example, is an exceptionally active catalyst for olefin metathesis,[15] while **3** constitutes the resting state in metathesis of α,ω-dienes by the first-generation Grubbs catalyst[16]). In each case, the base peak is the $[M]^{+\bullet}$ (or $[M]^+$) signal: its isotope pattern corresponds precisely to that simulated for the intact molecular cation, providing unequivocal confirmation of molecular composition. The complexity of these patterns, a function of the high natural abundance of certain isotopes (titanium has five, ruthenium seven, and chlorine two), gives direct insight into the number and identity of metal and halide atoms present. Matrix signals (pyrene: 202.1, anthracene: 178.1) are also present, though well below the mass range for these transition-metal complexes.

The assembly in Figure 1 is also highly convenient for assaying air-sensitive reactions, simply by removing aliquots, mixing them with matrix, and spotting on the target plate. Subsequent analysis provides a snapshot of the species present at the moment of evaporation. Figure 3 shows spectra from the completed syntheses of rhodium(I) dimer **4**[17] and paramagnetic copper(II) complex **5**.[18] Observation of intact **4** is hampered by the lability of such edge-bridged $\{M_2(\mu\text{-}Cl)_2\}$ structures. This lability is fundamental to the catalytic activity of **4**, an exceptionally versatile precatalyst for asymmetric

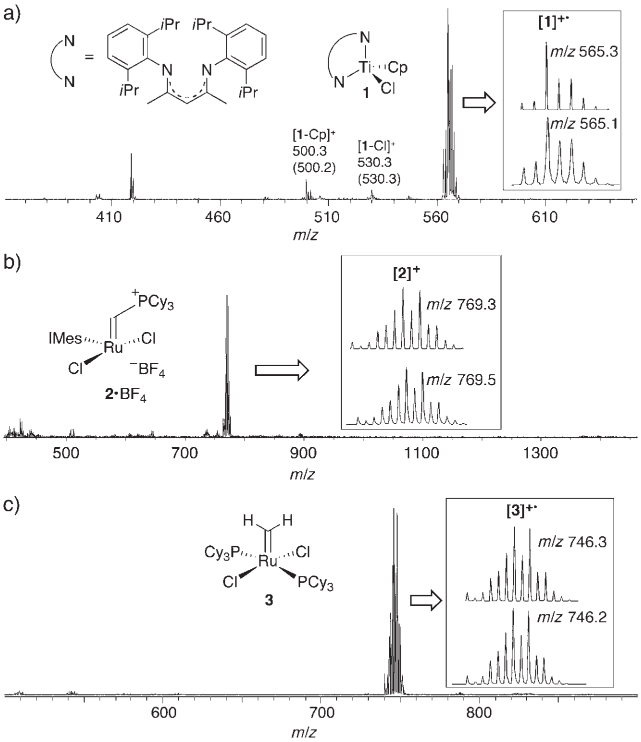

Figure 2. MALDI mass spectra of isolated complexes. a) An oxophilic Ti^{III} complex[14] (pyrene matrix); b) the Piers metathesis catalyst **2**·BF_4[15] (pyrene); c) a first-generation Grubbs catalyst[16] (anthracene). Labels give found (calculated) *m*/*z* values. Insets show isotope patterns for the molecular ions (top: simulated, bottom: observed). Cp = C_5H_5, IMes = *N*,*N*′-bis(mesityl)imidazol-2-ylidene, Cy = cyclohexyl.

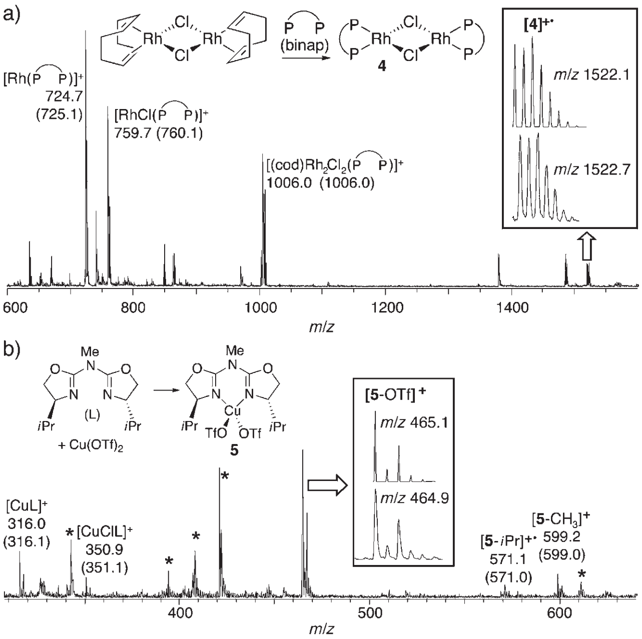

Figure 3. MALDI mass spectra of reactions (pyrene matrix). Labels give found (calculated) *m*/*z* values; [*] denotes Cu-free species. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = cycloocta-1,5-diene, OTf = CF_3SO_3.

hydrogenation, cyclodimerization, and addition reactions of olefins, among other transformations.[19] The signal for the "monomer" unit, unsurprisingly, is significantly greater in intensity; notably, however, the molecular cation $[\mathbf{4}]^{+\bullet}$ can be observed (Figure 3a).[20]

A different challenge is presented by **5**, a precatalyst for asymmetric cyclopropanation.[18] Because the Cu^{II} center in neutral **5** is in its highest common oxidation state, it resists one-electron oxidation to yield the cation. In the absence of a readily oxidized site on the ligand framework, therefore, we expect intact **5** to be invisible by electron-transfer MALDI. Indeed, no $[M]^{+\bullet}$ signal is observed, the base peak being due to loss of triflate. This finding reflects the lability of the Cu−OTf bond, triflate being widely used as a weakly coordinating counterion. Smaller signals in both spectra in Figure 3 indicate the presence of additional species in the crude reaction mixtures, as well as fragment ions and matrix adducts. While inorganic components are easily identified for the Cu-based reaction,[10] their assignment in Figure 3a is complicated by the monoisotopic nature of rhodium, which erodes the distinction between signals arising from metal-containing versus organic species. The natural occurrence of multiple isotopes for most of the transition metals is clearly advantageous for structural elucidation by MS methods.

The requirement of sample solubility imposes limitations on MALDI-MS analysis. Direct analysis of solid samples is desirable as a means of characterizing insoluble species, of establishing their identity where reaction in solution is suspected, of correlating solution- and solid-state structures, and, for partially soluble samples, of ensuring that "solution structures" are representative of the bulk. Solvent-free analysis of polymeric solids has been achieved by grinding with solid matrix and analyzing the powder.[21] We modify this approach by adding paraffin oil (Nujol) to promote matrix–analyte mixing and subsequently applying a thin layer of the amorphous mull to the target plate. Increased laser power is required (perhaps because inhibiting co-crystallization of analyte and matrix impedes desorption), but high-quality spectra can be obtained. Analysis of **3** by this method, for example, yields a spectrum essentially identical to that of Figure 2c.[10] This experiment is of added interest for the higher sample homogeneity attainable with amorphous films. The limited shot-to-shot reproducibility characteristic of MALDI-MS analysis, which severely impedes quantitative analysis, is believed to be due in large part to the inhomogeneity of the crystalline sample spots.[22]

Inert-atmosphere, charge-transfer MALDI-TOF-MS is strongly complementary to ESI-MS, enabling analysis of neutral, charged, or insoluble metal complexes with minimal perturbation. It is likewise complementary to X-ray and NMR analysis, permitting analysis of crystalline or amorphous, paramagnetic or diamagnetic species, and providing insight into the composition of the molecules within which spectroscopic data must be integrated. Indeed, the elements least readily interrogated by NMR methods in **1–4** (the metals, other than Rh, and the halides) present exceptionally convenient handles in MALDI-MS. Finally, use of inert-atmosphere MALDI-MS as a time-resolved method offers new ways to simplify the study of catalyst activation and deactivation pathways. Such studies are underway and will be reported in due course.

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[10] See the Supporting Information for experimental procedures, details of the glovebox–spectrometer integration, and additional spectra with signal assignments.
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[12] Important exceptions include late transition-metal complexes (particularly coordinatively saturated, 18-electron species) containing nonlabile, multidentate ligands. The heightened stability associated with these features improves the probability that the complex survives sample preparation and introduction and diminishes its susceptibility to gas-phase ligand exchange. See a) M. F. Wyatt, B. K. Stein, A. G. Brenton, *Anal. Chem.* **2006**, *78*, 199–206; b) S. W. Hunsucker, R. C. Watson, B. M. Tissue, *Rapid Commun. Mass Spectrom.* **2001**, *15*, 1334–1340.
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[20] The experimentally observed *m/z* value is midway between those for $[\mathbf{4}]^{+\bullet}$ and $[\mathbf{4}+\mathrm{H}]^{+}$, suggesting the alternative possibility of protonation, rather than charge transfer, as an ionization mechanism for this complex. Elsewhere, we find that $[M-\mathrm{L}]^{+\bullet}$ signals can predominate. Pyridine complexes related to **2**, for example, are observed as $[M-\mathrm{py}]^{+\bullet}$ species, while signals for matrix adducts dominate the spectra of two-coordinate Pd or Au complexes.

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