Fishing for Catalysts: Mechanism-Based Probes for Active Species in Solution

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Dedicated to *Albert Eschenmoser* on the occasion of his 75th birthday

A combination of derivatization with charged substrates and electrospray-ionization mass spectrometry is used to fish out the active species in a catalytic reaction. The observed species in the mass spectrometer corresponds to the resting state of the catalyst. Data for the ring-opening metathesis polymerization (ROMP) of norbornene by $(Cy_3P)_2Cl_2Ru{=}CHPh$ (Cy = cyclohexyl) are used to illustrate the method.

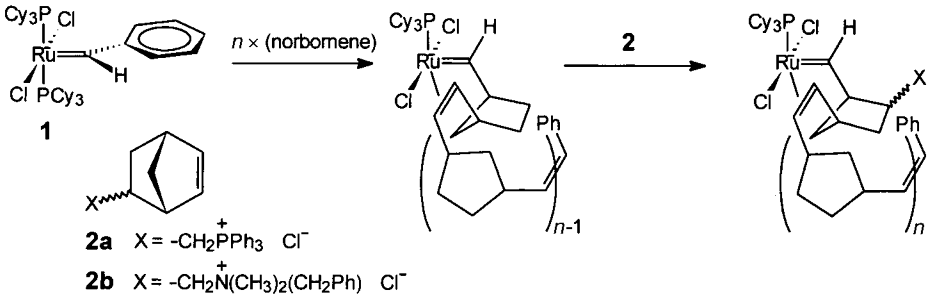
We report an electrospray-mass-spectrometric method for the identification of an uncharged active species in a solution-phase catalytic reaction based on derivatization of the active species with a charged substrate. The identification of the active species, as opposed to the procatalyst and any other related complexes that may be simultaneously present, is nearly always a challenging task. As had been elegantly demonstrated by *Halpern* [1], the most abundant complex in solution does not need to be a part of the catalytic cycle; it may represent, in fact, a dead end. Moreover, mechanistic considerations can suggest several active species that may be present. A method by which their *a priori* different levels of activity or selectivity could be quantitatively assayed would be of great utility. The present report represents a new methodology which can both identify and assay catalytically active species in solution by selectively transferring them to the mass spectrometer after trapping with a 'labeled' substrate. The demonstration is done with the well-characterized $(Cy_3P)_2Cl_2Ru{=}CHPh$ olefin-metathesis catalyst [2] as a model system.

Because electrospray (for a complete monograph on the technique, see [3]) transfers charged species from solution to the gas phase, a reaction which derivatizes active species with a charge becomes a selective probe. In this sense, the method is related to other derivatization strategies that pull out a desired species by way of radioactive or fluorescent tags, or pendant binding groups, as labels. In the present example, one fishes for the active species using a tagged substrate molecule as the fishhook.

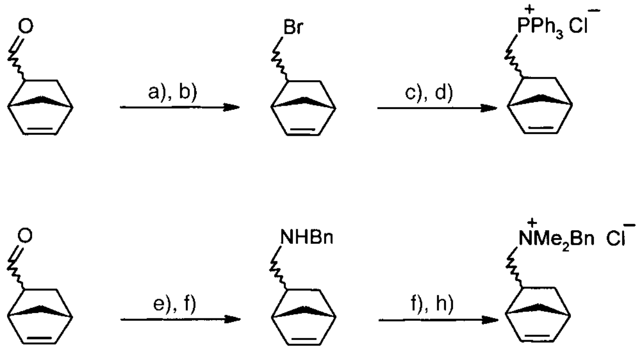
The test reaction is olefin metathesis or ring-opening metathesis polymerization (ROMP), catalyzed by the neutral complex $(Cy_3P)_2Cl_2Ru{=}CHPh$ (Cy = cyclohexyl; **1**), presumably *via* a monophosphine active complex (*Scheme 1*) [2][4]. Two different fishhooks, both cationized norbornenes, were synthesized straightforwardly according to *Scheme 2*.

ROMP Reactions were performed by adding a solution of 4.7 mg of norbornene in 0.5 ml of CH_2Cl_2 to a solution of 8.2 mg of **1** in 0.5 ml of CH_2Cl_2, stirring at 25° for

Scheme 1



Scheme 2[a]



a) $LiAlH_4$ (0.27 equiv.)/Et_2O, 1 h 0°, 2 h reflux, extraction; 93%. b) Br_2P (0.55 equiv.)/cat. pyridine/Et_2O, 0°, 30 min 25°, ice and 10% $NaHCO_3$, 0°, extraction, flash chromatography (silica gel; pentane; R_f 0.7); 27%. c) Ph_3P (3 equiv.)/DMF, 24 h 150°, precipitation with Et_2O; 28%. d) Ion-exchange with *Amberlite IRA 400* (Cl^- form; MeOH); quant. e) $BnNH_2$ (1 equiv.), no solvent, 2 h 25°, distillation, 200°, 8 mbar; 87%. f) $LiAlH_4$ (0.26 equiv.)/Et_2O, 1 h 0°, 2 h reflux, H_2O (1.2 equiv.), 0°, extraction; 92%. g) K_2CO_3 (1.5 equiv.)/MeOH, MeI (6 equiv.), 12 h reflux, recrystallization from MeOH; 25%. h) Ion-exchange with *Amberlite IRA 400* (Cl^- form; MeOH); quant.

15 min, and finally, addition of 0.1 equiv. (relative to ruthenium) of the cationized norbornene. The solution was then diluted 100-fold with CH_2Cl_2, and analyzed by electrospray-ionization mass spectrometry in a modified *Finnigan MAT TSQ-700* spectrometer as described in [5] [6].

The resulting mass spectra are shown in *Figs. 1* and *2*. As mentioned previously, only charged species, either cationic or anionic, depending on whether the spectrometer is run in positive-ion or negative-ion mode, are transferred to the gas phase. Accordingly, the mass spectra correspond to the selective detection of the catalyst-bound, charge-labeled substrate (the fishhook). The observed species should represent the resting state of the complex involved in the catalytic cycle. While our previous work has shown that a cationic catalyst can be observed by electrospray-ionization mass spectrometry [5], the mass spectrum in *Fig. 1* shows the detection of an electrically neutral catalyst by trapping with cationized substrate. The difference is significant. For a cationic catalyst,

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[a] All chemicals were obtained from *Fluka* and used without any further purification. Bicyclo[2.2.1]hept-2-ene-2-carbaldehyde was used as racemic *endo*/*exo*-mixture.

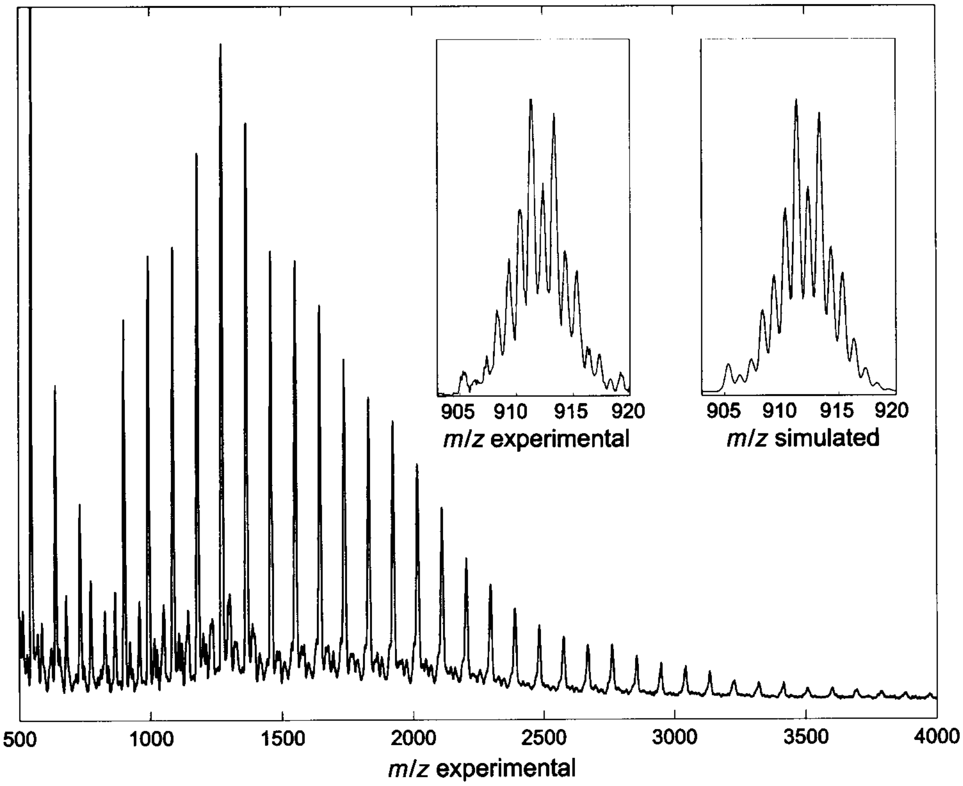

Fig. 1. *ROMP of 5 equiv. of norbornene with* **1** *and* **2a** *as fishhook.* The polymer distribution with $n = 0$ starts at m/z 911. The ESI-MS was performed on a *Finnigan MAT TSQ-700* by electrospraying at 10^{-5} M solution of the labelled living catalyst in CH_2Cl_2 in high-mass mode. Tube lens voltage was 170 V. The two insets show the experimental and computed isotope distributions for one of the oligomer peaks, which indicate, along with the mass, that the complex has one ruthenium, one phosphine, two chlorines, and one unit of the cation in **2a**.

all complexes, whether active or not, are detected. For a neutral catalyst and cationized substrate, only those complexes which bound and reacted with the substrate are detected.

For a polymerization reaction, control experiments can be done by addition of further monomer[1]) to establish that the detected species is still a competent catalyst after reaction with the charge-labeled fishhook. For the particular case of ROMP by **1**, the reaction should be reversible, with a ring-closing metathesis, leading to cyclic oligomers, known as 'back-biting' products, and a truncated catalyst-bound oligomer chain. Indeed, reversibility was demonstrated in our previous reports [5], indicating that the ion in the mass spectrometer was a competent carbene-ruthenium complex. The mass spectrum in *Fig. 1* also confirms that, subsequent to initiation, the catalytic cycle proceeds through the monophosphine complex without further significant involvement of a bis-phosphine complex, *i.e.*, the resting state of the catalyst in ROMP

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[1]) ROMP of norbornene by **1** has been shown to be living polymerization in which block copolymers can be prepared by sequential addition of different monomers.

is the monophosphine complex as opposed to the bis-phosphine resting state in acyclic olefin metathesis. In the earlier study of the related complex $(Cy_2PR)_2Cl_2Ru{=}CHPh$ ($R = CH_2CH_2NMe_3^+$), the doubly-charged molecular ion was observed by direct electrospray of a solution of the dicationic complex [5]. Loss of one phosphine in the electrospray mass spectrometer required collisional activation, even with the additional coulombic repulsion of the two positively charged phosphines. Moreover, a control experiment, in which a solution of **1** was treated with (hex-5-enyl)triphenylphosphonium hexafluorophosphate (an acyclic metathesis reaction) and then electrosprayed, showed a peak due to $(Cy_3P)_2Cl_2Ru{=}CH(CH_2)_4PPh_3^+$. The absence of bis-phosphine in *Fig. 1* within the 100:1 signal-to-noise of the spectrum is consistent with our earlier conclusion, based on kinetic arguments, that the resting state of the catalyst in ROMP is an intramolecular π-complex, in which an olefinic moiety on the catalyst-bound oligomeric or polymeric chain is bound to the metal center. With our earlier estimate of 3 kcal/mol for the intramolecular binding energy in the case of the ROM product with norbornene, a simple equilibrium calculation (assuming, of course, that the mass-spectrometric peak intensities represent solution-phase concentrations, and the CH_2Cl_2 itself does not bind significantly) suggests an upper-bound for the phosphine binding energy[2]) of 8.5 kcal/mol, which is consistent with expectations of phosphine binding for the sterically demanding tri(cyclohexyl)phosphine ligand.

One possible pitfall in the method is seen in *Fig. 2*. Clearly visible are two series of peaks, both displaying the characteristic *m/z* 94 spacing of catalyst-bound norbornene oligomers. One is tempted to attribute the presence of two series as evidence for two propagating species in the ROMP reactions of **1**, probed by addition of **2b**. However, as seen in *Fig. 1*, only one propagating species is evident when **2a** is used as a probe. By matching both the mass and the distribution of isotopic peaks, the second series in *Fig. 2* can be definitively attributed to a structure with the composition corresponding to $(Cy_3P)_2Ru_2Cl_5({=}CHPh)_2(\text{norbornene})_n(\mathbf{2})_2$, which is present when **2b**, but not **2a**, is used as a fishhook. We propose that the second series is a Cl-bound dimer of two monophosphine complexes, perhaps μ-Cl-bridged, associated norbornene units, and (in total) two cationized norbornenes. The coulombic interaction holding together the Cl-bound dimer is presumably more favorable for the small ammonium cation in **2b** compared to that for the larger phosphonium cation in **2a**. While dinuclear species [7] have been suggested in olefin metathesis, the particular series including **2b** is clearly an artifact created by the trapping method.

The ROMP reaction of norbornene by $(Cy_3P)_2Cl_2Ru{=}CHPh$ (**1**) has been used as a model for the demonstration of a mass-spectrometric method by which an active catalytic complex may be identified in solution. Synthesis of cationized norbornenes has yielded selective probes that tagged the ROMP-active catalyst-bound oligomers in the solution-phase polymerization. Transfer of only charged species to the gas phase by electrospray completed the analysis. The method has potential for application in a wide range of catalytic reactions, in which a generalized derivatization according to the catalyzed reaction itself can lead to selective detection of active species.

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[2]) The calculation was performed assuming $\Delta G = -3$ kcal/mol for the formation of the intramolecular π-complex, equilibrium at 298 K in solution, a total concentration of Ru species (after dilution) of 10^{-4} M, and [bis-phosphine]/[monophosphine] < 0.01.

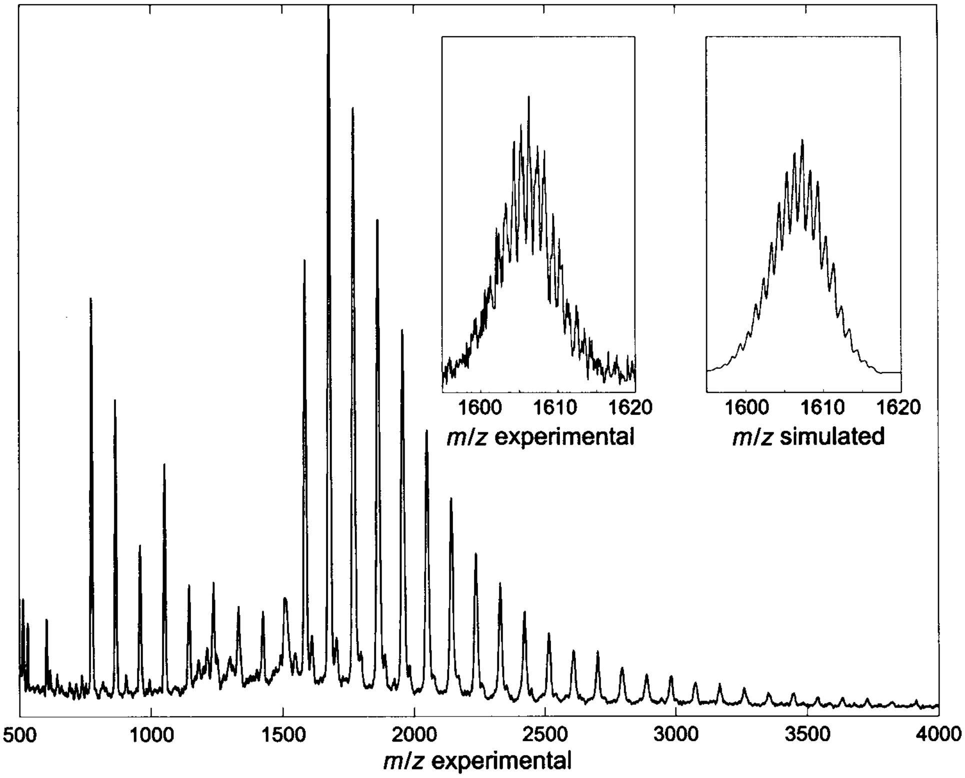

Fig. 2. *ROMP of 5 equiv. of norbornene with* **2b** *as fishhook.* In addition to the first series starting at *m/z* 784, a second series of a Cl-bound dimer of two monophosphine complexes starting at *m/z* 1606 is seen. The two insets show experimental and computed isotope distributions for one of the peaks in the second series, which indicate, along with the mass, that the complex has two rutheniums, two phosphines, five chlorines, and two units of the cation in **2b**.

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