

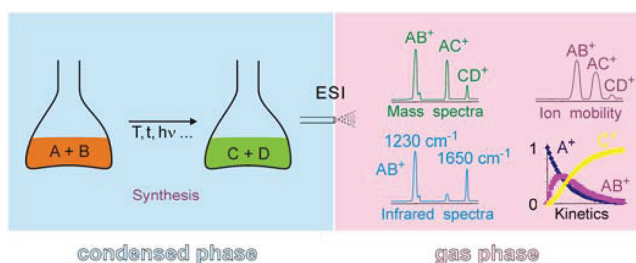
Applications of Electrospray Ionization Mass Spectrometry in Mechanistic Studies and Catalysis Research

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CONSPECTUS



Mechanistic studies form the basis for a better understanding of chemical processes, helping researchers develop more sustainable reactions by increasing the yields of the desired products, reducing waste production, and lowering the consumption of resources and energy overall. Conventional methods for the investigation of reaction mechanisms in solution include kinetic studies, isotope labeling, trapping of reactive intermediates, and advanced spectroscopic techniques. Within the past decade, electrospray ionization mass spectrometry (ESI-MS) has provided an additional tool for mechanistic studies because researchers can directly probe liquid samples by mass spectrometry under gentle conditions.

Specifically, ESI-MS allows researchers to identify the molecular entities present in solution over the course of a chemical transformation. ESI-MS is particularly useful for investigations of organic reactions or metal catalysis that involve ionic intermediates. Accordingly, researchers are increasingly using ESI-MS in mechanistic studies and catalyst development. However, a further understanding of the ESI process and how it can facilitate mechanistic studies has not accompanied this increased use of the technique. Therefore, at least in part the ESI-MS method not only has offered great promise for the elucidation of reaction mechanisms but also became a black box with the occasional risk of misinterpretation.

In this Account, we summarize applications of ESI-MS for synthetic and mechanistic research. Recently researchers have established direct linkages between gas-phase data obtained via ESI-MS and processes occurring in solution, and these results reveal qualitative and quantitative correlations between ESI-MS measurements and solution properties. In this context, time dependences, concentration series, and counterion effects can serve as criteria that allow researchers assess if the gas-phase measurements correlate with the situation in the solution. Furthermore, we report developments that bridge the gap between gas-phase and solution-phase studies. We also describe predictions derived from ESI-MS that have been verified with solution-phase chemistry experiments.

1. Introduction

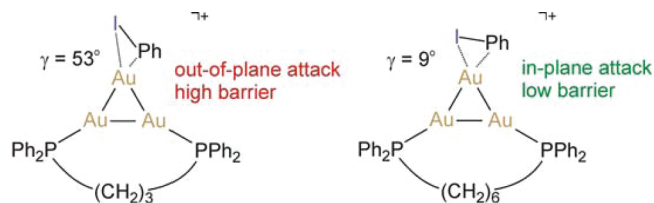
Mechanistic studies form the basis for advances in chemical processes and technology and thereby contribute to the development of more sustainable processes in terms of increasing yield of the desired products, reducing waste production, and enabling less consumption of resources as well as energy. Conventional methods for the investigation of reaction mechanisms in solution

include kinetic studies, isotope labeling, trapping of reactive intermediates, and advanced spectroscopic techniques.¹ Within the past decade, electrospray ionization mass spectrometry (ESI-MS)² became an additional tool in mechanistic studies with rapidly increased applications, not only by mass spectrometrists but also by practitioners in catalysis.^{3,4} In ESI-MS, liquid samples can directly be probed by mass spectrometry under

typically quite gentle conditions. To this end, the sample solution is pumped (typical flow rates of a few microliters per minute) through a capillary into an ESI source in which, assisted by a high voltage and a surrounding flow of nitrogen gas, a spray of small droplets is formed. Depending on the polarity applied, the droplets carry a small excess charge, which determines their net polarity and thereby that of the resulting ions. From the initial spray formed at atmospheric pressure and room temperature, the ionic species pass a differential pumping system until they reach a mass spectrometric analyzer operated in vacuum.⁵ A crucial aspect of ESI-MS is that unlike most other ionization methods no harsh ionization event (electron or photoionization, laser impact, etc.) is involved. Moreover, also complex mixtures can rapidly and sensitively be studied in an efficient way. A decisive advantage of ESI-MS, which makes it complementary to many condensed-phase techniques, is the direct information about the stoichiometry and type of molecular species involved. It is important to realize, however, that despite the common view of ESI as a gentle ionization method, chemical reactions can be drastically accelerated in the charged droplets.⁶ Hence, in terms of analytical purposes, the ESI process may not be “innocent” in that the sampling itself might significantly influence the results obtained.

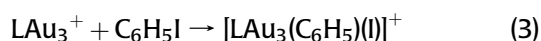
As an example for an application of ESI-MS in mechanistic research, let us consider a recent study of the gold-mediated C–I bond activation of iodobenzene relevant in the Sonogashira coupling. Thus, Robinson et al.⁷ prepared gold(I)-phosphine complexes in solution, transferred them into the gas phase using ESI and then probed the reactions of the mass-selected cations with iodobenzene. While the bisligated mononuclear species $\text{Au}(\text{PMe}_3)_2^+$ is unreactive, the monoligated cation $\text{Au}(\text{PMe}_3)^+$ shows a competition of adduct formation with iodobenzene (reaction 1) and loss of neutral AuI to the corresponding phosphonium ion (reaction 2). In contrast, trinuclear gold clusters LAu_3^+ with bisphosphine ligands ($\text{L} = \text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$, $n = 3-6$) promote C–I bond cleavage concomitant with the formation of gold–carbon bonds (reaction 3), as demonstrated by MS/MS experiments.⁷ The rate of reaction 3 is three orders of magnitude lower for the bisphosphine with the smallest linker ($n = 3$) compared with that with $n = 6$. Along with complementary theoretical studies, Robinson et al. thereby resolve a current controversy in the gold-mediated Sonogashira coupling⁸ by demonstrating that in the gas phase the formation of Au–C bonds does not occur for bisligated mononuclear

SCHEME 1. Rationalization of the Different Reactivities of LAu_3^+ Clusters with Bisphosphino Ligands Having a Different Number of Bridging Methylene Groups via the Computed Transition Structures^a



^aThe angle γ is the dihedral between the Au–Au–Au and the Au–I–C(Ph) planes.⁷

gold(I) cations but requires the presence of clusters.

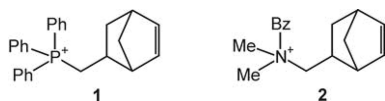


Aside from the mere reactivities themselves, a key advantage of these gas-phase studies is that they also provide conceptual understanding of the phenomena observed. Thus, Robinson et al.⁷ could explain the trends in the reactivity of the LAu_3^+ ions by reference to the modulation of the “biting angle” of the triangular Au_3 core by the bisphosphine ligands, which leads to a lower barrier for the larger linker (Scheme 1).

This Account aims to briefly summarize the contributions of ESI-MS to mechanistic research in solution with the primary intention to convince colleagues from inorganic and organic chemistry about the perspectives of the method. Accordingly, neither technical aspects of the mass spectrometric methods nor ion formation during electrospray are detailed, but the focus lies on the chemical implications of ESI-MS for preparative research. In order to provide a wider overview, recent examples from various researchers are presented in a rather condensed form, which of course comes at the expense of details for which the readers are referred to the original references.

2. Enthusiasm

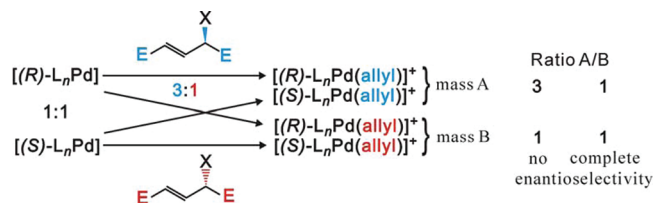
While there had been some earlier reports, the use of ESI-MS for the direct sampling of metal-catalyzed reactions was pioneered by Chen and co-workers.⁹ In an elegant contribution, Adlhart and Chen investigated the ring-opening metathesis polymerization (ROMP) of norbornene mediated by $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$ and described a strategy to “fish” reactive intermediates out of complex mixtures.¹⁰ To this end, they not only applied online monitoring of a reacting

SCHEME 2. Charge Tagged Substrates Used in Online Monitoring of ROMP¹⁰

solution but also introduced “charge tagging” as an important technology in catalysis research via ESI-MS.^{11,12} The idea behind charge tagging is that ESI-MS preferentially samples ionic species, whereas neutral components in the reaction mixture might either be discriminated or even escape detection. To this end, Adlhart and Chen added traces of the “charge tagged” norbornenes **1** or **2** (Scheme 2) to a mixture of norbornene and the catalyst and then probed the samples using ESI-MS, which allowed them to follow the ROMP process to oligomers with $n > 30$.

In this context, it is important to note that the charge tag is best used only as a cosubstrate and not as the major reactant itself. In the above example of ROMP, not only would exclusive usage of **1** or **2** as substrates represent a major perturbation of the polymerization, but moreover, the sampling via ESI would be very much affected, because the resulting oligomers would be multiply charged, which not only would complicate the analysis, but may even allow the highly charged species to escape detection due to fragmentations as a response to the high charge density. Another simple method of cationization is the addition of traces of alkali salts to the samples, which leads to the corresponding alkali cation adducts of neutral compounds.¹³

The team of Pfaltz is another pioneer in this area, though with the different objective to use ESI-MS for screening and optimization purposes in synthesis and catalysis¹⁴ with a particular emphasis on enantioselective processes.^{15,16} Recently, they developed a protocol for the determination of the enantiomeric excess in palladium-catalyzed allylation reactions, which can be applied to racemic catalysts by the use of artificial racemates in non-1:1 ratios.¹⁷ In an ideal artificial racemate, two enantiomers are differentiated by means of isotopic labeling and then mixed in equal proportions. Due to the mass difference (Δm) introduced by the label, the enantiomers occur at different mass-to-charge (m/z) ratios in the mass spectra and possible enantioselective processes can thus directly be identified by comparison of the measured ion abundances with the initial ratio of the enantiomers. In order to avoid the laborious preparation of isotopically labeled substrates, Ebner and co-workers differentiated the chiral substrates by different ester functions, that is, methyl esters (blue in Scheme 3) and ethyl esters

SCHEME 3. Determination of the Enantioselectivity of Chiral Catalysts by ESI-MS Screening of the Racemic Forms According to Ebner et al.¹⁷

(red in Scheme 3), leading to $\Delta m = 28$ in the products.¹⁷ If the Pd-mediated reaction occurs without enantioselectivity, the products are formed in the ratio of the reactants (3:1), whereas for a reaction having 100% enantioselectivity, the products occur in the ratio of the catalysts (1:1). The experimentally measured ratios between these extremes can then be used to determine the enantioselectivity of a given catalyst/substrate combination in a simple and rapid mass spectrometric screening assay.

Recently, also organometallic compounds sensitive to air and hydrolysis have been successfully studied via ESI-MS (e.g., cyanocuprates),¹⁸ and new sampling techniques for sensitive compounds were introduced,¹⁹ such that the scope of ESI-MS is likely to be extended to even more fragile metal organyls. Further, ESI can nowadays also be performed at low temperatures.²⁰ In the other extreme, ESI-MS has found several promising applications for organocatalyzed reactions in protic solvents, including mildly acidic media.²¹ Strong acids and bases yet pose some experimental problems associated with too high conductivities of the sample solutions leading to loss of the high voltage via the sample reservoir and instrumental limitations due to corrosion. These issues are, however, mostly of a technical nature, which can be solved provided sufficient interest of researchers and thus market volume for the manufacturers.

Advanced tools in mass spectrometry bring additional prospects for establishing correlations between solution chemistry and the gas phase. Particularly remarkable is the progress in the spectroscopy of gaseous ions during the past decade, infrared-multiphoton dissociation (IRMPD) in particular.²² More recent developments in two-photon spectroscopy even further extend the perspectives toward new spectral ranges at simultaneously substantially enhanced resolution.^{23,24} As an example, Figure 1 shows the infrared patterns of a binuclear gold–oxo cluster as measured for the neutral salt $\{[(\text{bipy})\text{Au}(\mu\text{-O})_2\text{Au}(\text{bipy})]^{2+} \cdot 2\text{PF}_6^-\}$ and mass-selected $[(\text{bipy})\text{Au}(\mu\text{-O})_2\text{Au}(\text{bipy})]^{2+}$ in the gas phase along with the computed spectrum of the free dication.²⁵ The reasonable agreement between the spectra not only

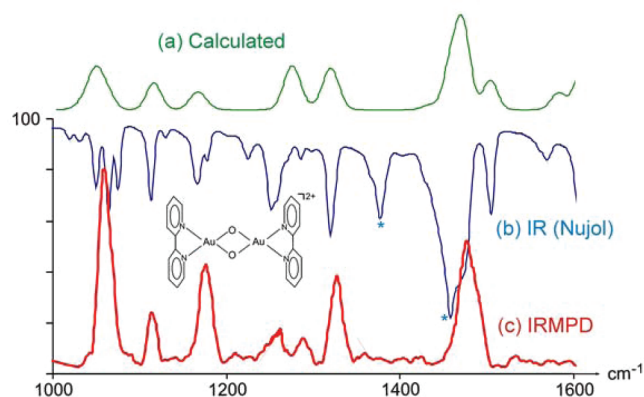


FIGURE 1. Infrared spectra of the dinuclear gold–oxo cluster $[(\text{bipy})\text{Au}(\mu\text{-O})_2\text{Au}(\text{bipy})]^{2+}$: (a) calculated IR spectrum of the free dication, (b) IR spectrum of the neutral salt (with hexafluorophosphate counterions) in nujol matrix (matrix peaks labeled with *), and (c) IRMPD spectrum of the mass-selected dication in the gas phase.²⁵

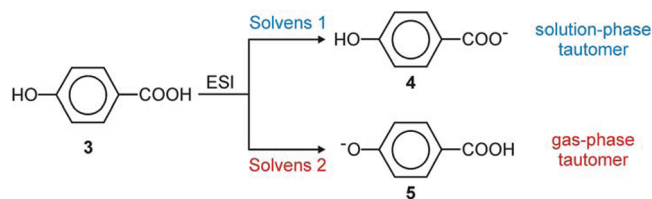
demonstrates the performance of these advanced gas-phase techniques but further indicates that the structure of the dicationic core remains intact upon desolvation and transfer of the free dication into the gas phase.

Notwithstanding this success story, in fact even a consequence of it, a grain of salt is to be added to the current status of ESI-MS. Within the past decade, remarkable advances in technology and thus largely facilitated usage as well as decreased market prices made ESI-MS a widespread tool in chemical research, such that it is not only used by mass spectrometrists but also by more synthetically oriented chemists. On the one hand, such a spread of the method is highly desired because it increases the knowledge base, leads to new applications as well as challenges, and boosts the general relevance of the field.^{3,26} On the other hand, there is the risk of ESI-MS being used as a black box without understanding of the underlying principles and concepts.²⁷ In combination with the success orientation of today's research, this may lead to cases in which the observation of a peak at the mass-to-charge ratio of an expected intermediate is presented as a proof of existence of this very species.²⁸ However, the mere mass and isotope pattern of an ion do not provide any information about its structure and its relevance as a reaction intermediate. In a hypothetical reaction of an ion \mathbf{A}^\pm with a neutral molecule \mathbf{B} via an intermediate \mathbf{C}^\pm to afford the products \mathbf{D}^\pm and \mathbf{E} , an ion having a mass corresponding to the sum of masses of the reactants could be the reactant complex \mathbf{AB}^\pm , the “desired” intermediate \mathbf{C}^\pm , or the product complex \mathbf{DE}^\pm . Even isotopic labeling techniques do not provide any insight in this respect, whereas several well-established mass spectrometric

methods (e.g., collision-induced dissociation, ion/molecule reactions, and threshold measurements) are able to distinguish isomeric ions. Advanced tools such as ion spectroscopy and ion mobility further extend the repertoire of structurally specific methods in MS. Common to all of them is, however, that their realization as well as interpretation requires deeper knowledge of the underlying foundations and the technologies involved.

3. Skepticism

For various justified reasons, a considerable share of condensed-phase chemists have reservations against an uncritical acceptance of results from ESI-MS. First of all, mass spectrometrists might be tempted to involve the ESI process itself as a mere monitoring step, but the changes in concentration, pH, solvation, etc. occurring upon successive evaporation of the droplets are indeed not just a minor perturbation, but instead a major change.²⁹ Moreover, the speed of response of the system to these changes in the spray is an important factor.³⁰ For anybody who knows from experience how large effects small variations in reaction conditions (temperature, solvents, additives etc.) can have on the outcome of a synthesis, the neglect of these changes does not really appear appropriate.³¹ Second, ESI-MS preferentially samples charged species (both anions and cations), whereas neutral compounds are only detected if they undergo efficient cationization (or deprotonation) during ESI. In many cases, this does not pose a problem because ESI-MS is very sensitive such that even small amounts of ionic products formed upon autoheterolysis in solution can be detected with good signal-to-noise ratios. Moreover, application of charge tagging can make the neutral species “ready for flight”. However, even when the expected signals are detected qualitatively, a priori there is no warranty that the sampling in ESI-MS occurs in a 1:1 fashion. In fact, huge discrimination effects can occur in that, for example, a neutral substrate is detected much less efficiently than an ionic species already existing in solution.³² The same holds true for different neutral substrates when ionized, and once again, these discrimination effects are not just a perturbation but can span several orders of magnitude. In addition, electrochemical processes in ESI³³ and the ionization conditions can substantially affect the resulting mass spectra.³⁴ Another quite fundamental reservation concerns the relevance of processes observed in the gas phase for equilibria in solution or reactions therein.³⁵ In the gas phase, reactions are often driven by the net charge of the system and further accelerated by the limited (or even absent)

SCHEME 4. Different Tautomers of Deprotonated *p*-Hydroxy Benzoic Acid Generated upon ESI of the Free Acid from Two Different Solvents³⁷

solvation of the reactive centers. Consequently, chemical processes might be triggered that otherwise are impossible in solution.^{6,36}

With regard to the question of whether ESI-MS is sampling solution structures, recent studies of the seemingly simple case of *p*-hydroxy benzoic acid (**3**) demonstrates particularly well the problems that might occur.^{37,38} In solution, **3** is well-known to be deprotonated at the acid, whereas deprotonation of the phenolic group is preferred in the gas phase.³⁹ Depending on the solvent used in ESI (e.g., acetonitrile or methanol/water), the gas-phase ions consist of either **4** or **5** (Scheme 4). Moreover, the two research teams engaged in this topic^{37,38} agree on the switching of the tautomers upon the change of the solvent but disagree on the actual assignment of the tautomers. One possible explanation of the different populations is based upon reversible protonation/deprotonation steps within the ESI source, which can occur with a protic solvent (methanol/water), whereas this option does not exist for the aprotic acetonitrile.

At this stage, I may add a more personal reflection because one reviewer of this Account and others on different occasions⁴⁰ considered me as being too critical about the correlations between ESI-MS and “real” chemistry. At first, I generally tend to prefer understatement over exaggeration. Second, an overly positive presentation of a new method in science may also delay its general acceptance by a wider audience, if counterarguments are not appropriately acknowledged. In the case of a controversy, researchers are likely to stick to reservations from their own field, rather than recognizing the promises offered by new developments from outside.⁴¹ Last but not least, there exists an important difference between the actual research done in the various laboratories and the published results. In our own experience, about half of the mechanistic projects we begin to study using ESI-MS are abandoned at an early stage and hence never get published. The reasons are manifold (most frequent are alkali contaminations in the substrates and instability of the intermediates of interest under ESI

SCHEME 5. Time-Dependent Ion Signals of the First Step (Activation of Iodobenzene) in a Suzuki–Miyaura Coupling^a

[L ₂ Pd(Cl)(CH ₃ CN)] ⁺	Reaction time in solution		
	5 min.	30 min.	60 min.
[L ₂ Pd(Cl)(CH ₃ CN)] ⁺	90	38	15
[L ₂ Pd(C ₆ H ₅)] ⁺	10	62	85

^aThe color code serves for the distinction of the operations in solution (blue) and the ions observed in the gas phase (pink).⁴³

conditions), but the take-home message is that ESI-MS can be very helpful in the elucidation of elementary steps, the identification of reaction intermediates, etc. but is not guaranteed to be so.

4. Links between Gas Phase and Solution Chemistry

From the above considerations, it is obvious that ESI-MS can provide quite useful insights into reactions occurring in the condensed phase. However, one cannot a priori be certain whether the data obtained via ESI-MS indeed sample the situation in solution or whether specific gas-phase properties predominate. Hence, some criteria are needed that may allow one to decide whether the situation in solution is sampled. Given the a priori unknown perturbation of the situation in solution by processes occurring in the ESI process itself, it is a crucial challenge to find systems in which the mass spectra respond to deliberate variations of the liquid sample. Irrespective of the actual role of the ESI process in ion formation and the sampling of the various species present in solution, any response of the ESI-MS spectra to these variations in solution establishes direct correlations between the liquid phase and the MS data. The presence or absence of such “responses” can hence be used as criteria indicating to what extent the solution-phase situation is sampled via ESI-MS, thereby providing a rational basis for the connections between both regimes.

4.1. Kinetics and Time Dependences. As far as chemical transformations are concerned, a first and obvious variation is the change of the reaction time in solution.⁴² For a transformation **A** → **B**, in such a case all conditions in ESI-MS monitoring remain constant, except for the ratio of **A** and **B**. Provided **A** and **B** are sampled with comparable efficiencies, the associated ion signals should thus change with time.

Scheme 5 illustrates such a case by reference to the C–I activation of iodobenzene as the first step in a Suzuki–Miyaura coupling mediated by a palladium(II) complex

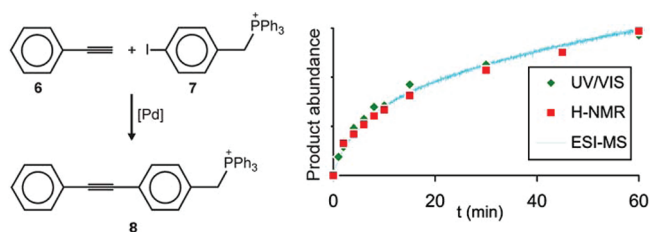


FIGURE 2. Kinetics of a Sonogashira coupling followed by UV/vis, NMR, and ESI-MS.⁴⁴

L_2PdCl_2 ($L =$ dipyridyl-cyclohexyl-phosphine).⁴³ ESI-MS of the catalyst precursor in acetonitrile leads to a $[L_2Pd(Cl)(CH_3CN)]^+$ cation via heterolysis of one Pd–Cl bond. After addition of iodobenzene and heating to 80 °C in the presence of K_3PO_4 as a base, the signal of $[L_2Pd(Cl)(CH_3CN)]^+$ decreases with a half-life of about 20 min in favor of $[L_2Pd(C_6H_5)]^+$, as the generally assumed active aryl-transfer reagent in Suzuki–Miyaura couplings. Crucial in the present context is the dependence of the ion signals in ESI-MS from the reaction time. Because time is the only variable, irrespective of all conceivable perturbations in ion formation and detection, the ESI measurements obviously sample the progress of the reaction in solution.

Elaborating on Scheme 5, it should be possible to follow reaction kinetics in solution using ESI-MS. A nice example has recently been reported by McIndoe and co-workers, who investigated the Sonogashira coupling of phenylacetylene (**6**) with the charged-tagged aryl iodide **7** to the cationic product **8** and followed the progress of the reaction in solution by stepwise sampling with NMR and UV/vis along with continuous online sampling via ESI-MS.⁴⁴ Figure 2 demonstrates that ESI-MS gives data of a quality similar to the two classical condensed-phase methods, while the (destructive) sample consumption in ESI-MS monitoring is much lower than the needs in UV/vis or NMR.

The example in Figure 2 is a particularly fortunate case, however, which is not at all accidental, but precisely because the charge-tagging technique is applied. Without charge tagging, reactants and products are likely to be sampled with different efficiencies in ESI-MS, such that comparison to data from conventional analysis could only be made after explicit consideration of these differences.⁴⁵

4.2. Concentration Dependence. The mass-action law is a fundamental concept in chemistry already taught in schools. If ESI-MS is supposed to sample the situation in solution, it should therefore depend on the concentrations of the components.⁴⁶ At first sight, this requirement seems to be trivial, but the ESI process may involve reactions that do

not occur in solution or species that are formed only in the spray itself, and the general characteristics of the spray largely fall into the regime of nonequilibrium thermodynamics.⁴⁷ Moreover, ESI is a charge-limited process in that the number of ions in the spray cannot exceed a certain critical value due to Coulomb repulsion of ions with the same charge. Therefore, the existence of correlations between the concentrations in solution and the ion abundances in ESI-MS is of crucial importance. In this context, we have derived an empirical calibration between the concentration in solution and the effective concentration in the spray for aqueous solutions of uranyl(VI) nitrate,⁴⁸ which has then successfully been applied to equilibria between mono- and dinuclear palladium(II)-allyl complexes in acetonitrile.⁴⁹ Hence, quantitative correlations between ESI-MS data and solution-phase properties are not just a vision anymore but represent experimentally testable issues.

With respect to the applicability of the mass-action law in ESI-MS, it is referred to a competition experiment in anion complexation by the bambus[6]uril (BU)⁵⁰ macrocycle (Figure 3a). In BU, the accumulation of dipoles of the multiple carbonyl groups creates an environment that favors the binding of anions in the central cavity (Figure 3b). Figure 3c describes an experiment in which aliquots of an equimolar mixture of $[Et_4N^+Br^-]$ and $[Et_4N^+PF_6^-]$ are added in a stepwise fashion to a sample of $[BU \cdot Cl^-]$.⁵¹ Of the three anions competing for the BU receptor, Cl^- is the worst, Br^- the best, and PF_6^- in an intermediate position. When adding the above mixture to pure $[BU \cdot Cl^-]$, both anions effectively replace the weaker Cl^- , and hence the abundances of $[BU \cdot Br^-]$ and $[BU \cdot PF_6^-]$ both increase at the expense of $[BU \cdot Cl^-]$. Once one equivalent of the mixture is added, however, the better Br^- “wins the fight”, and upon further addition $[BU \cdot Br^-]$ increases also at the expense of $[BU \cdot PF_6^-]$. The overall result is an exponential decrease of $[BU \cdot Cl^-]$ and an increase of $[BU \cdot Br^-]$ in a (roughly) reciprocal fashion, while the progression of $[BU \cdot PF_6^-]$ has a maximum at about 0.5 equiv. The abundance profiles of the three anions in ESI-MS not only obey this qualitative deduction but also can quantitatively be reproduced by a microkinetic model.^{52,53} The take-home message is that kinetic modeling based upon equilibrium considerations (solid lines in Figure 3c) can reasonably well reproduce the ESI-MS results (data points in Figure 3c).

4.3. Counterion Effects. A third criterion for establishing correlations between condensed- and gas-phase data is more specific. Let us consider a process in the condensed phase, an equilibrium or a chemical transformation, which

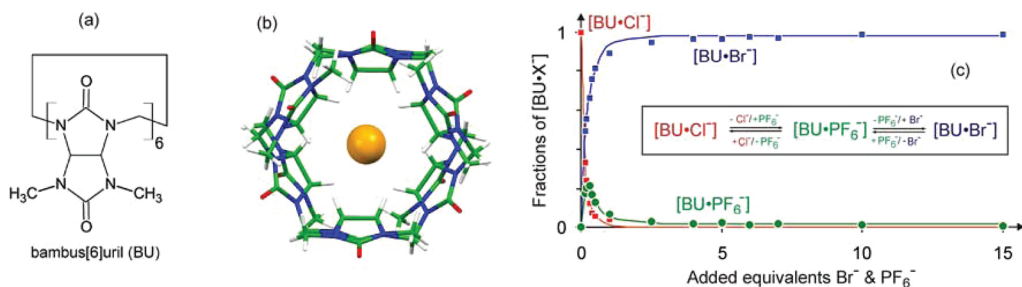


FIGURE 3. (a) Schematic formula of bambus[6]uril, (b) structure of the $[\text{BU} \cdot \text{Cl}^-]$ adduct, and (c) concentration profile of $[\text{BU} \cdot \text{X}^-]$ ions with three different anions X^- upon addition of a 1:1 mixture of Et_4NBr and Et_4NPF_6 to a $[\text{BU} \cdot \text{Cl}^-]$ solution as monitored via ESI-MS. The dots in the diagram are the measured data points, while the solid lines represent microkinetic modeling based on equilibrium considerations.⁵¹

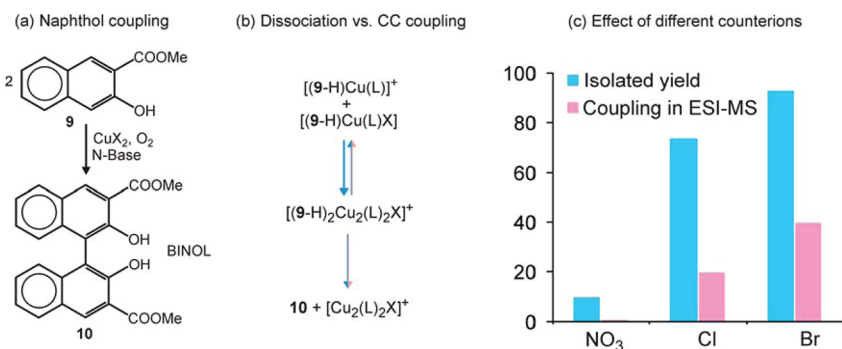


FIGURE 4. (a) Oxidative coupling of the naphthol **9** to the corresponding BINOL **10**, (b) competition of dissociation and C–C coupling in the binuclear cluster in the gas phase (pink arrows) and in solution (blue arrows), and (c) counterion effects observed in the condensed phase (isolated yields, blue)⁵⁶ and upon ESI-MS/MS (fraction of C–C coupling, pink).^{55a}

shows pronounced effects upon variation of the solvent, the presence of additives, or different counterions. In such a case, it is a key question whether these effects are reproduced in the gas phase. In some of the above examples, also significant effects of additives (e.g., triethylamine in the Sonogashira coupling)⁴⁴ or solvents (e.g., in anion complexation by BU)⁵¹ have been reported.

Here, a particular case of a counterion effect is addressed that has a direct correlation in its condensed-phase variant and is of importance for the synthesis of chiral bisnaphthol (BINOL) ligands.⁵⁴ Extensive ESI-MS studies of the coupling of the naphthol **9** to the BINOL **10** (Figure 4a) indicate that the actual coupling step is mediated by dinuclear copper clusters with a bridging anion ligand.⁵⁵ These dinuclear species contain two deprotonated naphthols (**9-H**), two copper atoms, two nitrogen ligands L, and a bridging anion, which is the counterion X of the CuX_2 salt used as precursor. When energized, the clusters can either dissociate back into mononuclear species or undergo C–C coupling to afford BINOL (Figure 5b). Nitrate, as the worst bridging ligand, leads to facile dissociation to mononuclear species and gives the lowest amount of the coupling product in ESI-MS/MS experiments, whereas for chloride and bromide the coupling is

significantly more efficient. The branching ratios in the gas phase show a clear correlation with the preparative yields in the condensed phase when using different CuX_2 salts ($\text{X} = \text{NO}_3, \text{Cl}, \text{Br}$) as the catalysts (Figure 5c).⁵⁶

5. Bridging the Gap

The above examples reveal several close correlations between ESI-MS data and condensed-phase chemistry. Nevertheless, there exists a considerable gap between both regimes as far as concentrations, pressures, reaction times, and conditions are concerned.⁵⁷ In this section, two examples are presented in which the gap between solution and the gas phase is partially bridged.



The first case concerns palladium–phosphine complexes, which are frequently used in transition-metal catalysis, C–C coupling reactions in particular. Frequently, the first step is the insertion of a Pd^0 species into the $\text{Ar}'\text{—X}$ bond of an aryl halide, tosylate, etc. (reaction 4). In several catalytic systems, a loss of the initial catalyst performance occurs due to a scrambling between aryl groups of the phosphine ligands (Ar) and aryl moieties (Ar') bound to palladium.

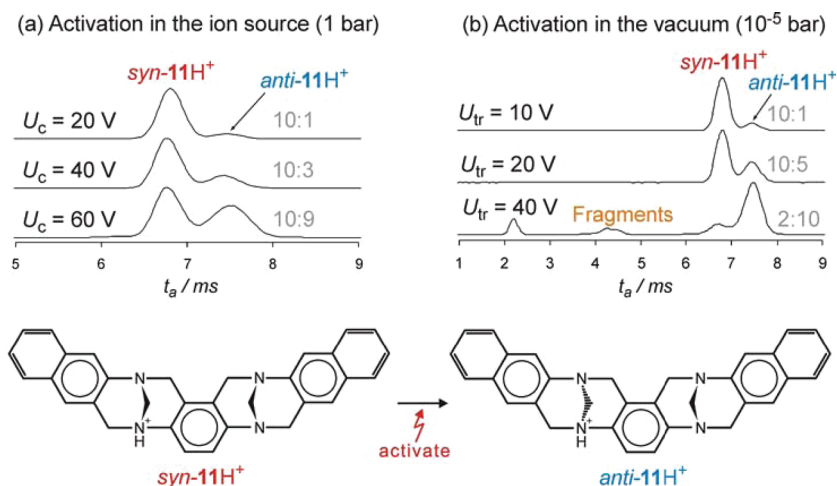
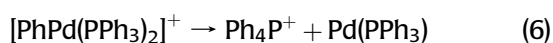
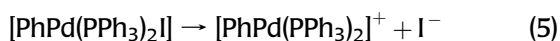


FIGURE 5. Interconversion of the *syn*-diastereoisomer of the protonated Tröger base $11H^+$ into the *anti*-isomer: (a) collisional heating in the liquid/gas interface by variation of the cone voltage (U_c) and (b) collisional excitation of mass-selected $11H^+$ at different voltages of the ion trap (U_{tr}) in front of the ion-mobility section.⁶¹

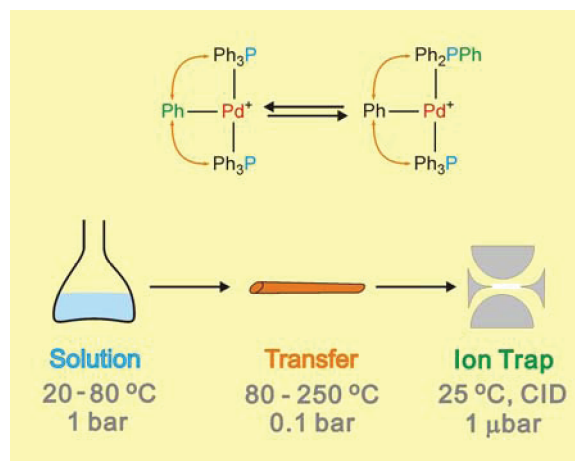
Hence, with the progress of the catalytic process a specifically tailored phosphine ligand on Pd is replaced by another phosphine with inferior activity or selectivity. As a model, we investigated the scrambling of phenyl groups in phenyl bis(triphenylphosphine)palladium iodide $[\text{PhPd}(\text{PPh}_3)_2]\text{I}$. Upon ESI-MS in the positive ion mode, the neutral compound gives rise to an abundant $[\text{PhPd}(\text{PPh}_3)_2]^+$ cation as the quasi-molecular ion of the neutral compound formed via heterolysis (reaction 5).⁵⁸ Upon collisional activation, this formal Pd^{II} cation undergoes reductive elimination to afford neutral Pd^0 concomitant with a phosphonium ion (reaction 6).



The exchange of the phenyl groups can be monitored via isotope labeling, which allows a distinction of the phenyl group bound to palladium from those on phosphorus and thereby a translation of the degenerate scrambling into measurable mass differences upon ion fragmentation (upper panel in Scheme 6).

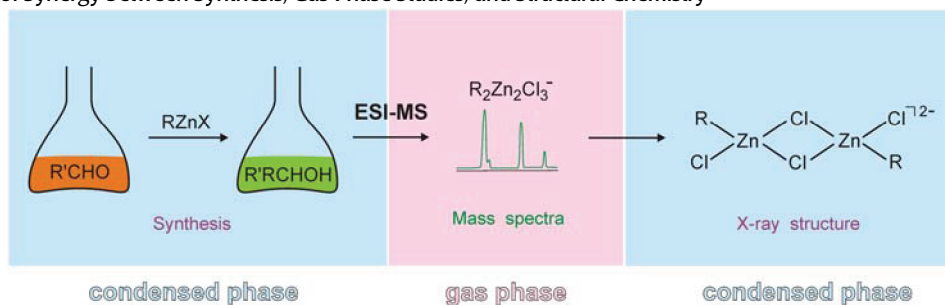
In the gas phase, collision-induced dissociation of $[\text{PhPd}(\text{PPh}_3)_2]^+$ is accompanied by statistical scrambling of the phenyl groups. Consequently, the barrier associated with the exchange of the aryl moieties is lower than the threshold for fragmentation via reaction 6. Hence, we speculated that the aryl exchange between Pd and P can also be induced in solution. Indeed, heating a solution of $[\text{C}_6\text{H}_5\text{Pd}(\text{P}(\text{C}_6\text{D}_5)_3)_2]^+$ in acetonitrile to 80 °C for 16 h led to a complete equilibration of the C_6H_5 and C_6D_5 moieties; notably, only the phenyls exchanged, while no C–H(D) bond activations are

SCHEME 6. Example of Exchange of Aryl Groups in a Phenyl-Palladium Complex, Where the Same Reaction Can Be Induced by (i) Heating to 80 °C in the Condensed Phase for 16 h, (ii) Heating of the Droplets in the Transfer Capillary of the ESI Source, and (iii) Collisional Activation within the Mass Spectrometric Analyzer⁵⁸



involved.^{58,59} Given this analogy between the gas-phase experiments and solution chemistry, we further tried to induce the phenyl scrambling in the evaporizing droplets and managed to trigger the degenerate exchange by heating the transfer capillary of the ESI source to 250 °C (lower panel of Scheme 6). This example thus demonstrates that the same process can be induced by gentle heating in solution for an extended period, by elevated temperatures in the transfer region, and by collisional heating in the mass spectrometer itself.

A related example touching the interface between gas- and condensed-phase chemistry applies ion-mobility mass spectrometry (IM-MS) for ion analysis; in this mass

SCHEME 7. Example of Synergy between Synthesis, Gas-Phase Studies, and Structural Chemistry^{65–67}

spectrometric technique ions are differentiated not only by their m/z ratios but also by means of their shapes, in that of two isomers the more extended one has a lower mobility and hence a larger arrival time (t_a).⁶⁰ In solution, the bis-Tröger base **11** undergoes pseudoepimerization upon heating in acidic media. By means of IM-MS, not only a previous controversy about the mechanism of the epimerization could be decided in favor of a proton-catalyzed process, but also a link between the gaseous and condensed regime was established.⁶¹ To this end, the diastereomers of **11** were subjected to ESI and the protonated ions **11H**⁺ probed via IM-MS. Under soft conditions of ionization, the more compact *syn*-compound shows a predominating signal at $t_a < 7$ ms, corresponding to *syn*-**11H**⁺, whereas the more extended and thus less mobile *anti* compound gives a clearly separated feature well above 7 ms. When *syn*-**11H**⁺ is energized either in the ion source (Figure 5a) or in front of the ion-mobility unit (Figure 5b), an isomerization of *syn*-**11H**⁺ into *anti*-**11H**⁺ is observed; analogous data are obtained when starting from *anti*-**11H**⁺.⁶¹ While the method of detection substantially differs from that in the previous example (Scheme 6), the conclusion is the same in that the reaction of interest can be induced either by heating in solution, by collisional activation in the liquid/gas interface, or by collisional excitation in the gas phase. In addition to the implications for the actual specific chemical problems, these two examples demonstrate that the so-called pressure gap⁵⁷ is not insurmountable anymore.

6. Predictions of ESI-MS for Solution Chemistry

This raises the question whether ESI-MS can also predict mechanistic scenarios or reaction intermediates in condensed-phase reactions. One example for novel intermediates predicted by ESI-MS is the Morita–Baylis–Hillman reaction,^{21a,62} in which the mechanistic proposals derived by Eberlin and co-workers from gas-phase studies have

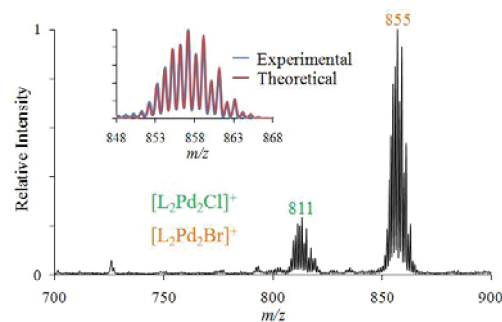


FIGURE 6. ESI mass spectrum of a reaction mixture of a Suzuki–Miyaura coupling of PhBr and PhB(OH)₂ using L₂PdCl₂ as a catalyst after the reaction is completed. The major signals correspond to binuclear palladium clusters [L₂Pd₂X]⁺ (X = Cl, Br; m/z 811 and 855, respectively) with formal Pd^I. The inset shows the experimental and theoretical isotope pattern of [L₂Pd₂Br]⁺.⁴³

found acceptance in the synthetic community.⁶³ Another case is the direct detection of cation-radical intermediates in SOMO catalysis.⁶⁴ With regard to organometallic chemistry, a particularly nice example deals with organozinc reagents widely used for C–C coupling reactions in organic synthesis.⁶⁵ In 2009, Koszinowski and Böhrer investigated solutions of such zinc reagents by means of ESI-MS and *inter alia* predicted the existence of chloro-bridged dinuclear clusters of the type R₂Zn₂Cl₃[−] (Scheme 7).⁶⁶ Only a year after that report, some of these complexes were indeed isolated and structurally characterized by X-ray analysis.⁶⁷

In our investigation of the Suzuki–Miyaura coupling (Scheme 5),⁴³ we *inter alia* observed the formation of binuclear palladium clusters [L₂Pd₂X]⁺ (L = phosphino ligand, X = Cl, Br) at the end of the catalytic transformation (Figure 6). Formally, the stoichiometry of the cluster implies palladium to be present in the unusual oxidation state Pd^I; alternatively Pd⁰Pd^{II} might be assigned to the dinuclear species. Interestingly, the solution containing [L₂Pd₂X]⁺ is still able to act as a catalyst in the Suzuki–Miyaura coupling when new reagents are added, suggesting the dinuclear cluster as a potentially catalytically active compound. While attempts to isolate the

cluster were unsuccessful, parallel to our ESI-MS studies a related cluster with a Pd^I dimeric core was isolated in a Pd-catalyzed *ortho*-bromination of anilides and characterized via X-ray analysis.⁶⁸

7. Conclusions and Outlook

Electrospray-ionization mass spectrometry represents a powerful tool for mechanistic studies in solution chemistry, these being related to classical organic chemistry or transition-metal catalysis. In particular, ESI-MS can provide a rapid overview about the stoichiometries of the species present in solution, and in combination with MS/MS experiments or more advanced techniques (e.g., spectroscopy of mass-selected ions) also specific structural information can be obtained. In this respect, the isolation of bulk compounds first predicted via ESI-MS may serve as an example (Scheme 7). Moreover, with the charge-tagging method otherwise neutral components in a reacting mixture can be sampled efficiently. ESI-MS can also be used for the online monitoring of reactions occurring in a time span of minutes to hours and can easily be combined with a variety of other techniques. As far as quantitative aspects are concerned, some reservations are indicated because in the course of droplet evaporation in ESI many parameters change^{29,30} and the process may not follow equilibrium thermodynamics.⁴⁷ Nevertheless, quantitative information can be gained from concentration series or via determinations of ionization efficiencies. If the changes in concentration during the spray process are acknowledged, even simple quantitative modeling of the ion abundances based upon the mass-action law can be applied.^{48,51} A crucial task for future research in this area is to refine the existing and define new criteria for correlations between the condensed phase and the gaseous regime. Such efforts will also allow a major step forward in direct kinetic studies of chemical reactions using ESI-MS, which still face difficulties, unless the charge-tagging technique is used. If realized, the direct monitoring of reaction kinetics using ESI-MS would allow for a parallel investigation of multiple samples with minimal manpower and consumption of reagents as well as solvents, thereby potentially contributing to more sustainable process optimization in applied chemistry. Moreover, ESI-MS can substantially contribute to shrink the gap between gas-phase model systems and chemical reactions in the liquid phase, including the gas/liquid interface.⁶⁹ Parallel to these efforts, promising developments in desorption electrospray ionization (DESI)⁷⁰ permit the investigation of liquid and solid samples on a substantially reduced time scale.⁷¹

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Detlef Schröder studied chemistry at the TU Berlin and earned his Ph. D. with Prof. Helmut Schwarz. Since 2006, he has worked at the IOCB in Prague, where he was appointed a Distinguished Chair in 2011. His interests in gas-phase ion chemistry range from fundamental questions on diatomic molecules via organic reaction mechanisms and inorganic chemistry to astrochemical or biochemical problems. In 2009, he received an Advanced Grant of the European Research Council, which is focused on links between mass spectrometry and condensed-phase chemistry.

FOOTNOTES

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