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Mechanistic insight into organic and catalytic reactions by joint studies using mass spectrometry and NMR spectroscopy

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Utilization of NMR spectroscopy and mass spectrometry for joint mechanistic and structural studies is a well-known practice. Several opportunities have appeared in recent years because of new hardware development and design of novel experimental procedures. Recent progress in this area and leading examples of new development, as well as already distinguished techniques, are discussed.

Over the past decades, the development of mass spectrometry and NMR spectroscopy has revolutionized modern chemistry. Structure determination of a typical organic or organometallic compound with a molecular mass of up to ~3000 Da (natural products, drugs, organic derivatives, transition metal complexes, *etc*.) became a routine task, which, in principle, can be carried out in a semiautomatic manner. The power of mass spectrometry[1,2] in determining chemical composition was successfully combined with establishing atomic connectivity (COSY, TOCSY, HSQC and HMBC) and three-dimensional structure analysis (NOESY, ROESY and coupling constants) by NMR.[3] Coupling of LC-NMR-MS hardware extended the analytical power of these methods to cover a broad range of mixtures.[4] The design and synthesis of derivatizing agents made it possible to determine enantiomeric purity and chirality based on spectral data.[5] The experience of spectral measurements gained for regular solutions was successfully transferred to the studies of non-standard liquid phases and melts, which are of much importance in view of new synthetic methods development according to green chemistry requirements.[6,7]

In spite of well-established experience in the structure determination of stable compounds, mechanistic studies and the nature of transient species are still the field of debates and questions. Most of the dedicated mechanistic investigations carried out so far were done by either of the methods. Getting chemically reliable and mutually consistent mechanistic data by both methods for chemical reactions studied under the same conditions until recently was quite rare and remained a challenging problem. The importance of the development of a proper methodology for such joint studies is unquestionable in order to facilitate the solution of long-standing mechanistic problems and achieve further progress in the development of organic synthesis.

Here, we review joint mechanistic investigations performed by NMR spectroscopy and mass spectrometry. Since an attempt to provide a comprehensive literature on these very diverse subject would be impractical, a selected most relevant examples are discussed instead with the main idea to highlight a concept to enhance mechanistical studies. Some of the well-known points discussed in the article are illustrated with tutorial examples.

An important prerequisite for a joint study with two different physico-chemical methods is to set up correct experimental conditions suitable for both methods. The amount of a sample needed and the concentration range are the first conditions to be defined (Table 1). For X-ray structure analysis, typically, tens of milligrams of a sample are required to obtain suitable high-quality single crystals *via* recrystallization from solution. The advanced methods for protein crystallization may operate with 1–3 mg of a sample, but these methods are not currently available in organic chemistry.[8] Unfortunately, X-ray analysis cannot be carried out directly in solution where organic reactions take place.

Superior sensitivity of mass spectrometry makes it possible to carry out the analysis of trace amounts of samples on a routine hardware (Table 1). The development of atmospheric pressure

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Table 1 Sample and concentrations required for structure determination with the most frequently used methods in organic and organoelement chemistry.

Method	Minimal amount of sample, mg		Concentration range/mol dm^{-3}
	Routine	Advanced	
X-Ray single crystal analysis	50	10	Not applicable
NMR spectroscopy	0.01–5	10^{-6}–10^{-2}	10^{-6}–1
Mass spectrometry	10^{-6}–10^{-3}	10^{-12}–10^{-6}	10^{-12}–10^{-5}

ionization, particularly, electrospray ionization (ESI), provided an excellent tool for studying liquid solutions by mass spectrometry. Indeed, the method was successfully applied to solve various mechanistic and structural problems.[9,10] Until recently, the sensitivity limit was a stumbling block in the NMR detection of transient species, which are formed in solution in very small quantities. However, recent developments of new electronic hardware,[11] microfabricated NMR probes[12] and inverse detected experiments[13] increased the sensitivity (and decreased the amount of sample needed) by several orders of magnitude (Table 1). Even better sensitivity can be expected according to the recent results: ^{1}H NMR spectra were recorded during a few minutes from the samples in a nanogram scale.[14]

Another important question is the concentration range for the chemical reaction in solution. NMR spectroscopy perfectly fits for a concentration range of reagents, catalysts and products used in organic reactions (Table 1). Quantitative NMR measurements usually can be easily performed. The concentration range of organic reactions is too high for mass spectrometry, and the samples should be diluted. Dilution of samples is acceptable for stable organic molecules; however, it should be applied with care for transient species and organometallic compounds. Due to equilibrium shifts, some compounds may appear/disappear after dilution as compared to the original conditions. In addition, quantitative measurements with mass spectrometry cannot be carried out with the same ease and efficiency as with NMR.

Although only some selected mechanistic studies comply to these conditions with routine hardware, we anticipate the scope will increase tremendously in nearest years, when advanced hardware will become more and more available to research laboratories. As the first necessary step for NMR studies, inverse detection experiments were made widely available and corresponding pulse programs are nowadays supplied by all hardware manufacturers. The idea of inverse (indirect) detection is to measure the NMR properties (chemical shifts and coupling constants) of unfavorable for detection low-sensitivity nuclei *via* magnetization transfer and detection of the most sensitive nuclei in the molecule (usually, ^{1}H).[15]

The application of indirect detection to organic structure determination was very well described.[3,13] Excellent opportunities are also available for functionalized and organoelement compounds. For example, ^{1}H–^{29}Si HMBC NMR experiment was carried out to identify silyl derivatives and to mechanistically study their transformation by joint NMR spectroscopy–mass spectrometry.[16] Different reactivity pathways of Pt/phosphine complexes were studied by ^{1}H-^{31}P HMQC and ^{1}H-^{195}Pt HMQC in combination with ESI-MS.[17]

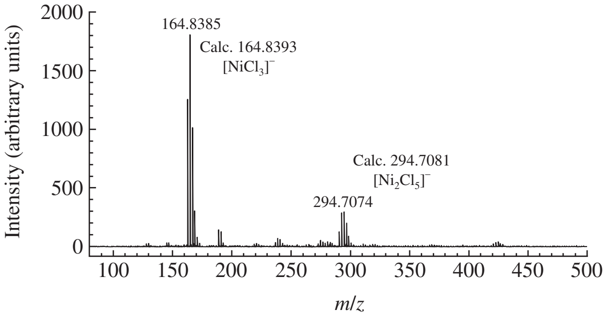

Figure 1 ESI-MS spectrum of $NiCl_2$ in acetonitrile solution (negative ions polarity mode).

The approach was found useful in the studies of catalytic reactions in organic synthesis. The idea is to detect selectively only intermediate metal complexes consisting of organic molecules bound to the catalyst (0.01–5 mol% with usual catalyst loadings) and to eliminate other undesired signals of unreacted compounds, product, solvent, *etc.* from the spectrum. In the mechanistic study of alkyne triple bond fictionalization by a Pt catalyst, the intermediate metal complex was detected by 2D ^{1}H-^{195}Pt HMQC NMR experiment.[18,19] A special GBIS-HMQC NMR experiment was developed to measure spin–spin coupling constants between the metal and bound organic group, $J_{^{195}Pt-^1H}$ and $J_{^{195}Pt-^{13}C}$, which provided unambiguous information on the nature of the transient species.[20]

An important advantage of the NMR measurements needed for correct interpretation of the mechanistic studies is a direct correlation between the signal intensity in the spectra and the amount of substances presented in the mixture in solution.[3,13]

In principle, the amount of species in solution and the intensity of the corresponding signals in the ESI-MS experiment should also be related. In practice, the intensity of the detected signals may change dramatically due to the complexation of ions. As a clear example, we can consider $NiCl_2$-catalyzed reactions in organic synthesis.[21] In the ESI-MS study, the signals were observed for the [Ni_2Cl_5]$^-$ and [$NiCl_3$]$^-$ ions resulted from the

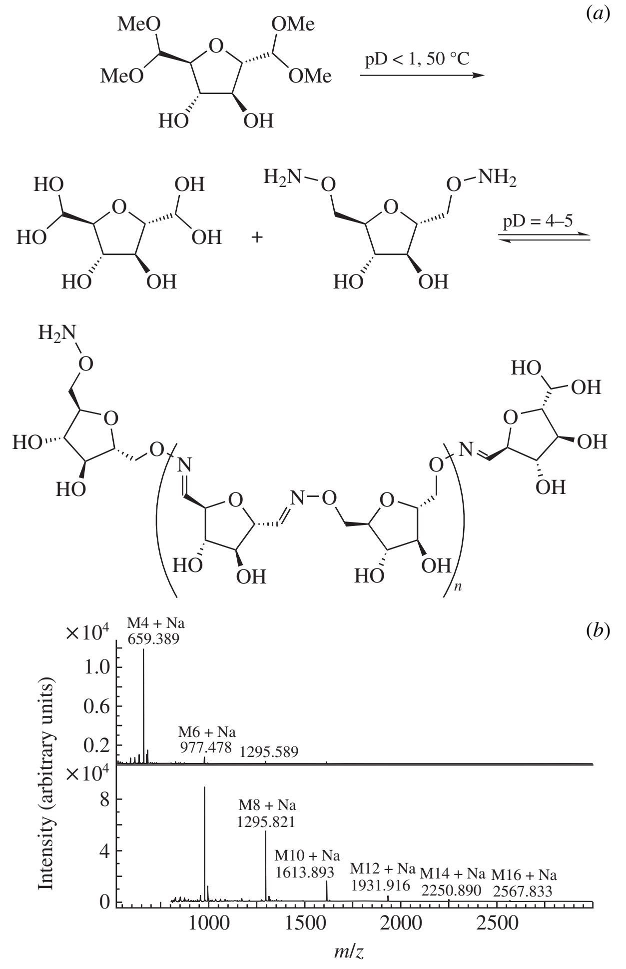

Figure 2 (*a*) Structural dynamics of analogs of arabinofuranoside oligosaccharides and (*b*) the mass spectrum of this sample (Na$^+$ adducts with oligosaccharides of 4 to 16 sugar units). Figure from ref. 22 ©2007 Wiley Periodicals, Inc. Reproduced with permission.

[nNiCl$_2$ + Cl$^-$] complexation, where $n = 1$, 2 (Figure 1). The experimental studies can hardly suggest involvement of such complexes as reaction intermediates. Clearly, a rigorous verification is necessary to find out whether the species detected by ESI-MS do really present under experimental conditions of chemical transformation and to what extent they are involved as intermediates on the reaction path. In the following examples, we will show how the above problems can be solved, if both methods are applied to complement and verify each other.

Diffusion ordered NMR spectroscopy (DOSY NMR) and mass spectrometry is a very efficient combination to reveal the nature of complexation. Mass spectrometric analysis of a solution of polycondensation products of sugars have suggested the formation of polymers with the degree of polymerization up to $n = 14$ (Figure 2).[22] Independent measurements with DOSY NMR estimated the molecular weight of species in solution, which was in an excellent agreement with the mass spectrum. Thus, the dynamic nature of the system was confirmed by both methods, and it demonstrated the formation of complex oligomeric structures in solution.[22] None of the methods along would provide sufficient evidence in such a case: DOSY NMR estimates molecular weight but is unable to give precise molecular formula; mass spectrum gives precise molecular weight but suffers from the formation of complex structures of larger size.

Mass spectrometric analysis of Zn^{2+} complex with the terpyridine–phenanthroline ligand (L) indicated the presence of the dimer [Zn$_2$L$_2$]$^{4+}$ (Figure 3).[23] Calculated isotopic distribution proved the structure of the complex, but the question arose whether the dimer was present in solution or it was formed during mass spectral measurements. DOSY NMR carried out in the methanol solution has revealed the presence of a single compound (Figure 3) with diffusion coefficient $D = 470$ µm^2 s^{-1} and hydrodynamic radius $r_H = 8.5$ Å. Comparison with the corresponding values for the monomeric ligand L ($D = 1000$ µm^2 s^{-1}, $r_H = 5.3$ Å) and computational simulations confirmed that the sole product of the reaction is the dimer [Zn$_2$L$_2$]·4OTf.[23]

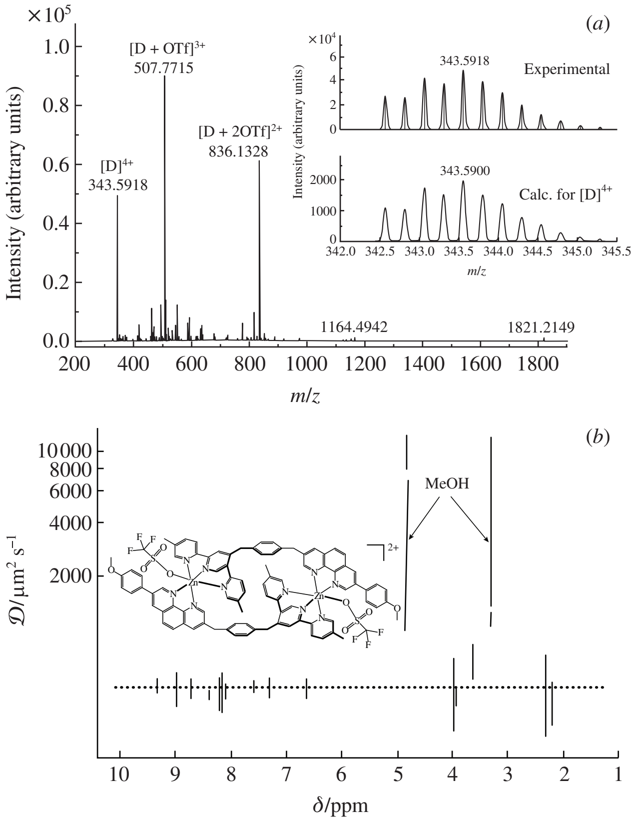

Figure 3 (*a*) ESI-MS spectrum with the [D]$^{4+}$, [D + OTf]$^{3+}$ and [D + 2OTf]$^{2+}$ peaks and (*b*) DOSY NMR spectrum in the methanol solution and structure of the dimer D (D = [Zn$_2$L$_2$]$^{4+}$). Figure from ref. 23 ©2008 The Royal Society of Chemistry. Reproduced with permission.

Generation and equilibrium of monomeric and dimeric species formed from zwitterionic organic species was characterized by ESI-MS and FAB-MS, as well as DOSY NMR in DMSO solution and DMSO–water mixtures.[24] The potential of this approach was demonstrated in the study of hydrogen-bonded and metal-linked dimers.[25]

Mechanistic studies of the formation of dimers and larger aggregates are of key importance to understand the self-organization and supramolecular chemistry of organic and metal-organic systems. A powerful combination of mass spectrometry and diffusion NMR measurements has shown an increasing scope to study these fascinating systems.[26]

After revealing the nature of the dimers (aggregates), the next step is to establish the three-dimensional structure of these complex species. An appropriate solution was provided by the combination of mass spectrometry and NOESY NMR. The NOESY NMR experiment is based on the nuclear Overhauser effect, which arises due to resonance line-intensity changes caused by dipolar cross-relaxation from neighboring spins with perturbed energy level populations.[27] The intensity of the signal is proportional to the inverse sixth power of the distance between the atoms, $I \sim 1/r^6$. Therefore, NOESY data provide straightforward information about intra- and intermolecular interactions and can be used for stereochemical assignment.[28] For some molecules, rotating frame measurements (ROESY) are carried out as a more sensitive alternative of the NOESY NMR experi-

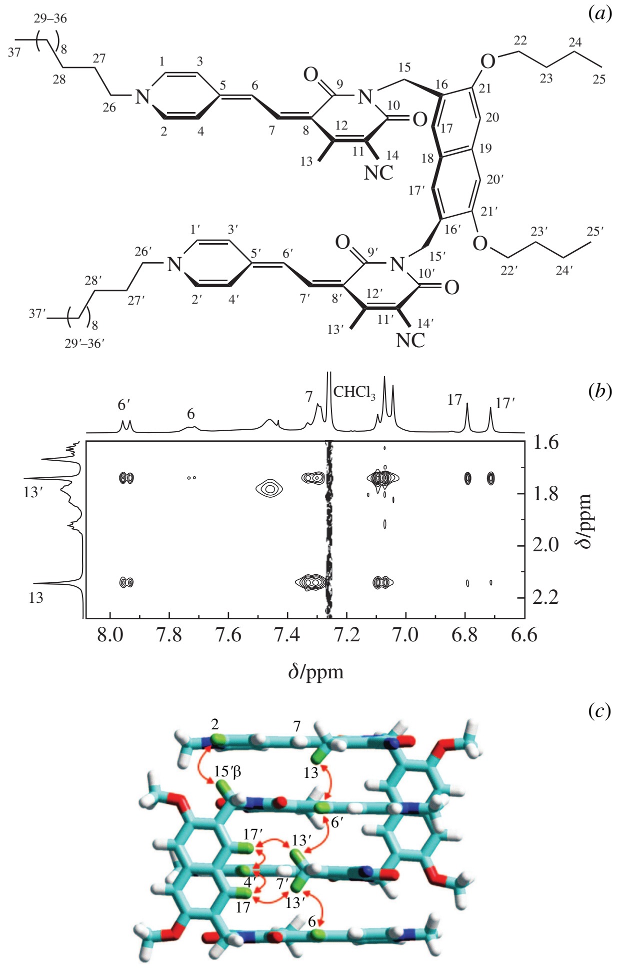

Figure 4 (*a*) Bis(merocyanine) monomer, (*b*) selected representative area of the 2D ROESY NMR spectrum with signals assignment and (*c*) three-dimensional structural model of the dimer with intermolecular contacts marked by arrows. Figure from ref. 29 ©2009 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

ment, which may not give a spectrum due to unfavorable correlation time.

In the study of bis(merocyanine) tweezers formation, the first evidence for self-assembly was obtained by mass spectrometry, which showed the presence of singly charged monomer and dimer cations.[29] Structure elucidation of the dimer was carried out in two step NMR analysis: (i) complete line assignment in the ^{1}H spectrum carried out by 2D COSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMQC NMR; and (ii) molecular structure determination by ROESY NMR and computational simulations. For the assigned ^{1}H signals of the bis(merocyanine) monomer, several intermolecular contacts were resolved in the ROESY spectrum, and the spatial arrangement of the structural units was established (Figure 4).[29]

A combination of mass spectrometry and NOESY (ROESY) NMR was applied to a wide range of structural problems including natural products,[30] transition metal complexes,[31] ligand-cation interaction,[32] analysis of mixtures and compounds identification.[33]

The chemistry of carbohydrates has especially benefited from the combination of these structural methods. The NMR spectroscopy[34] and mass spectrometry[35] of carbohydrates are well developed areas of research and their combinations have already been widely utilized.[36] On the example of oligosaccharides, it is useful to mention the application of total correlation NMR spectroscopy (TOCSY) to simplify signal assignment and analysis of NOESY signals in 2D spectrum (Figure 5).[36(*a*)] These NMR experiments complement each other very well: TOCSY spectra reveal the protons of localized (isolated) spin systems, that is, the protons of sugar residues, while NOESY spectra show the signals from the protons at the geometric distance of < 5 Å (independently on the number of chemical bonds between them). For carbohydrates, this allows one to implement sugar analysis based on COSY, TOCSY and NOESY spectra and to establish the sequence of residues (taking into account inter-residue correlations in the NOESY or ROESY spectra).[36(*a*)]

Important to note that both mass spectrometry and NMR spectroscopy can be connected directly with chemical reactors to carry out *in situ* mechanistic studies.[†] The first example of

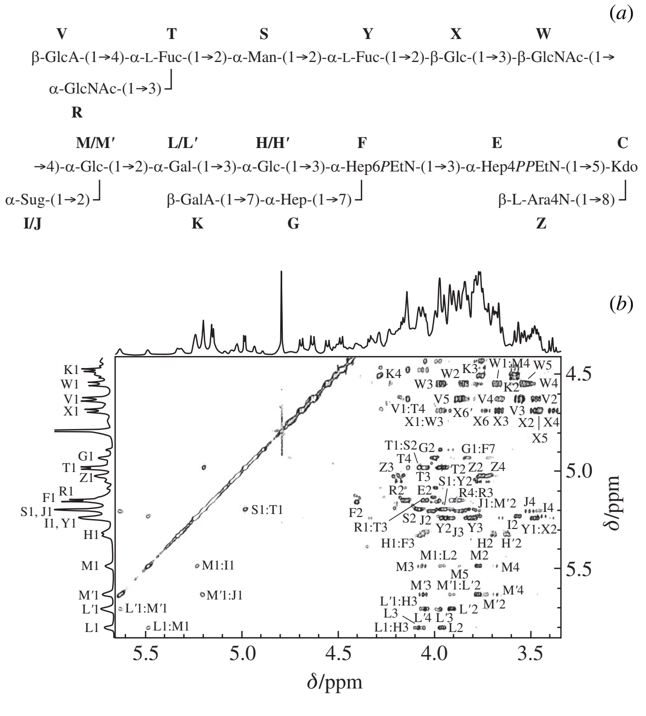

Figure 5 (*a*) Structure and (*b*) selected regions of two-dimensional NOESY and TOCSY (black and gray, respectively) spectra of the oligosaccharides with corresponding ^{1}H projections shown along the axis. Figure from ref. 36(*a*) ©2008 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

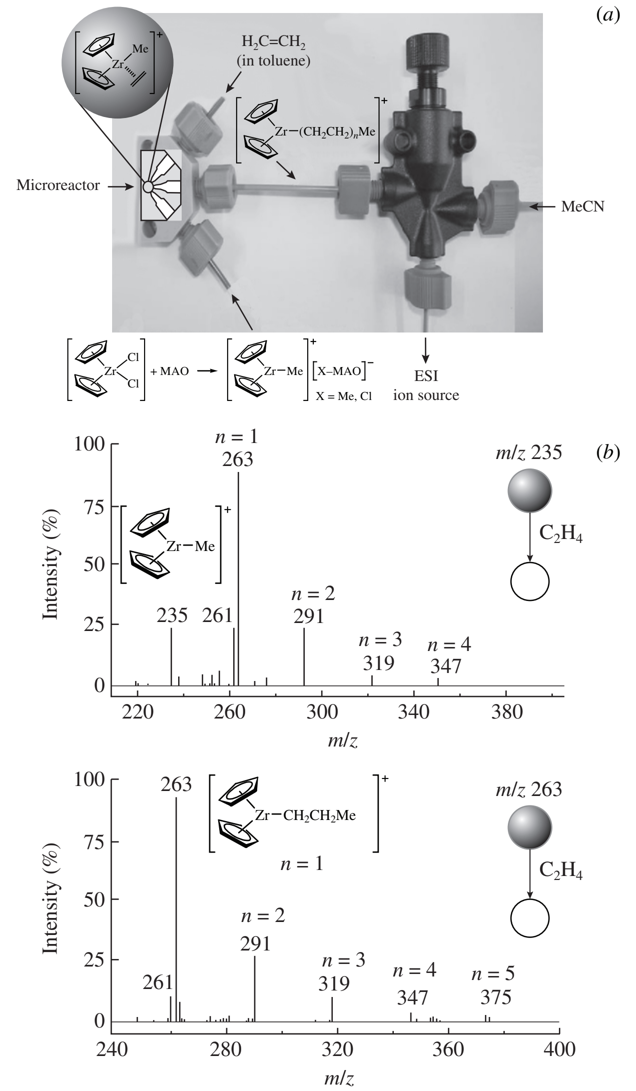

Figure 6 (*a*) Microreactor coupled with ESI-MS and (*b*) detection of transient metal species in the mass spectra. Figure from ref. 37 ©2006 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

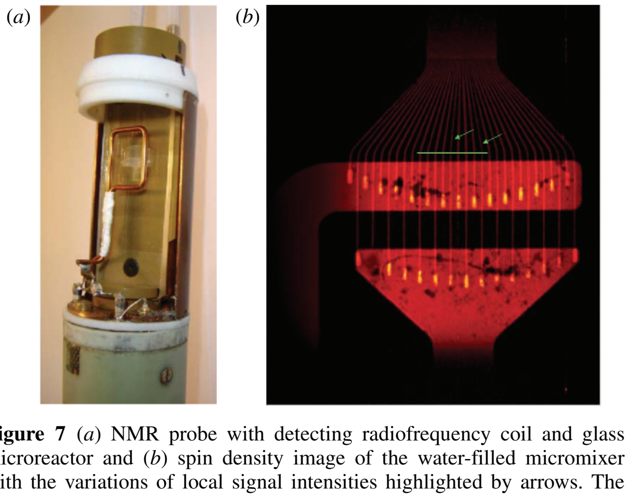

Figure 7 (*a*) NMR probe with detecting radiofrequency coil and glass microreactor and (*b*) spin density image of the water-filled micromixer with the variations of local signal intensities highlighted by arrows. The figure from ref. 39 ©2006 The Royal Society of Chemistry. Reproduced with permission.

[†] Standard hardware for LC-NMR-MS coupling available at the moment was designed for biomolecular samples (screening of pharmaceuticals, metabolomics, medical applications, *etc.*) and it is hardly suitable for mechanistic studies.[4] Separate transfers of the samples to NMR and MS instruments or home-made coupling devices were used in the studies discussed in the present focus article.

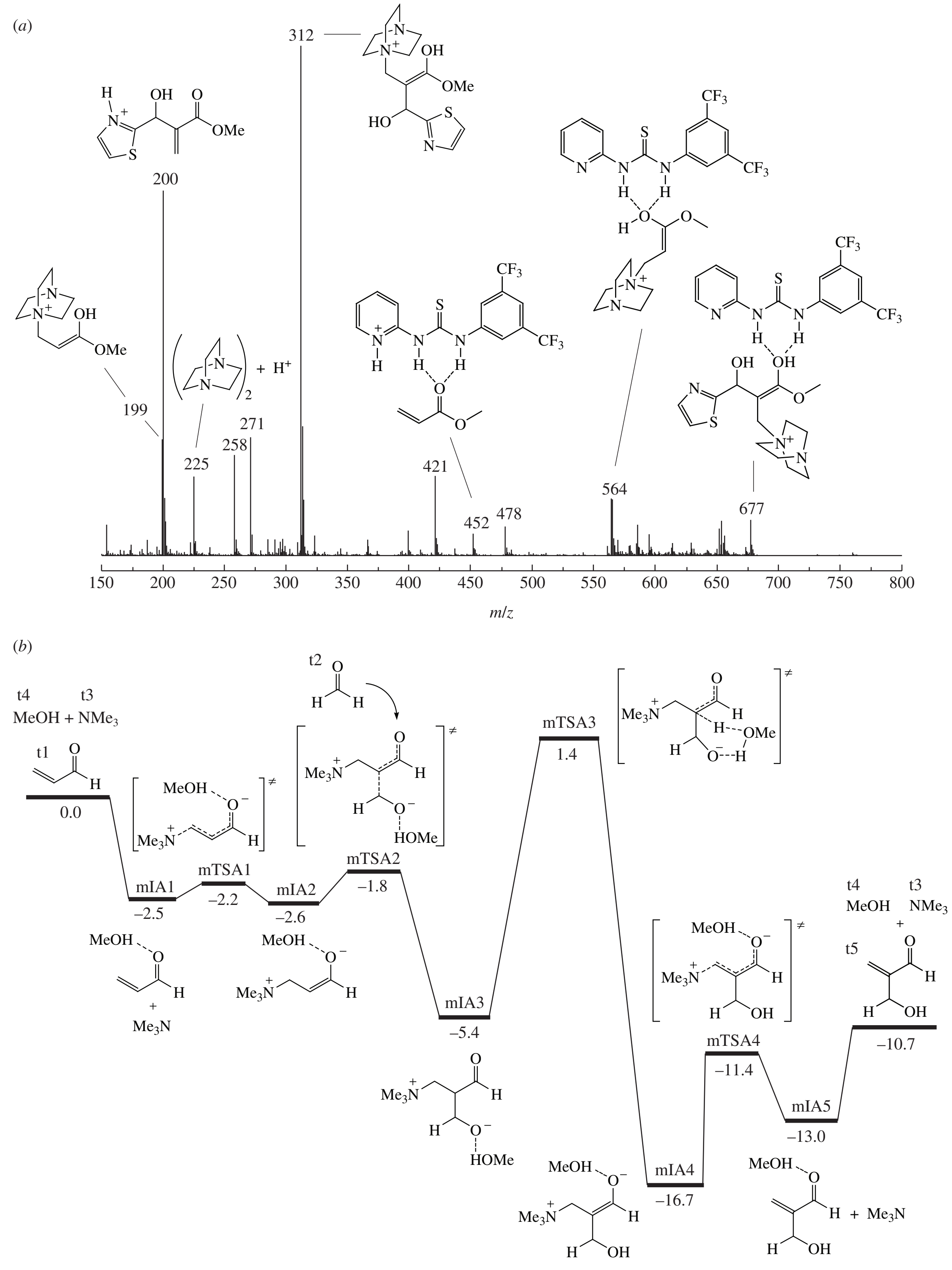

Figure 8 (*a*) ESI-MS spectrum of the reaction mixture with detected species and (*b*) calculated energy surface for the model reaction in methanol (energy in kcal mol^{-1}). Figure from ref. 46 ©2009 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

the microreactor coupled with ESI-MS instrument was demonstrated and utilized to investigate homogeneous Ziegler–Natta polymerization.[37] Within this experimental set up, a toluene solution of the catalyst precursor and ethylene were mixed and the polymerization reaction was initiated in the capillary, followed by quenching with acetonitrile and transferring directly to the ESI source (Figure 6). The study has shown that the $[Cp_2ZrMe]^+$ ion is indeed the catalytically active species, which reacts with ethylene molecules and produces $[Cp_2Zr(CH_2CH_2)_nMe]^+$ metal-terminated polymeric chain. Corresponding metal species with $n = 1–31$ were observed in the mass spectra.[37]

The conditions for NMR spectral characterization do not require direct contact between the studied solution and detector. Therefore, it is much easier to couple chemical reactors with NMR hardware for *in situ* mechanistic studies – the studied solution can flow through the NMR probe with various arrangements of the solenoids around the capillary.[38,39] The solution is not consumed during the NMR measurements and can be returned back to the chemical reactor.

Moreover, a mixer can be placed inside the NMR probe, thus providing the possibility to monitor directly the flow inside the microchannels and carry out immediate *in situ* studies. It was shown that the flow properties of individual channels can be observed using NMR with sufficient flow resolution (Figure 7).[39] The further improvement of this NMR hardware, particularly combining spatial resolution of the micromixers and microchannels together with chemical-shift and coupling constants resolved information about the species presented in solution, will undoubtedly furnish development of a dream analytical method for studying reaction mechanisms.

In the studies of catalytic reactions, an efficient multifunctional tool for the investigation of the properties of materials, transport processes and mechanisms was developed using multinuclear magnetic resonance imaging.[40]

Clearly, as discussed above, several possibilities exist to carry out joint mechanistic studies involving mass spectrometry and NMR spectroscopy. Even more opportunities are anticipated in the nearest future facilitated by the rapid development of modern NMR and MS hardware. Both methods can be coupled to on-line experimental monitoring of chemical reactions with outstanding potential for design of chemical reactors and industrial applications.

As a general outline, the following strategy can be proposed for joint NMR/MS mechanistic studies: (1) reaction monitoring, kinetic and equilibrium constant measurements should be carried out by ^{1}H and heteronuclear (^{19}F, ^{31}P, ^{13}C, *etc.*) NMR; (2) investigation of transient (intermediate) species formed in a reasonable concentration should be done by sensitive NMR techniques and mass spectrometry; and (3) the characterization of species formed in a low concentration should be performed by mass spectrometry, and their reliability for the reaction pathway should be verified.

The verification of the reliability of detected intermediates and assessment of their role deserves a special note. Theoretical calculations are helpful to evaluate structures, to estimate the stability of observed intermediates and to predict their NMR and mass spectrometric properties. Reliable theory levels and bases sets were established for a wide range of systems from pure organic compounds to transition metal complexes with the accuracy of the calculations similar to those observed experimentally.[41] With conventional computational approaches, accurate calculations at high level are applied for relatively small systems. For large chemical systems, the ONIOM computational methodology is a better choice to speed up the calculations and to ensure high accuracy and reliability of the results.[42]

Theoretical studies of the generation and detection of transient species,[43] stability and dissociation of molecular ions, proton affinity, complex ions formation and fragmentation pathways[44] are well-recognized representative examples in mass spectrometry. The scope of theoretical calculations in mass spectrometry is wide, and general applications of different approaches have been reviewed.[45]

Theoretical calculations of the potential energy surface of a chemical transformation involving the location of transition states is one of the most important tools to understand the mechanistic role of particular intermediate species observed experimentally. An excellent example was recently described dealing with ESI-MS and DFT studies of the catalytic Morita–Baylis–Hillman reaction.[46] In the study, the intermediate species were characterized by mass spectrometry combined with reaction pathway modeling at the B3LYP/6-31+G(d) level (Figure 8). The calculations have revealed the role of thiourea as an organocatalyst in the studied reaction. It was found that thiourea forms bidentate hydrogen bonds and, in the rate-limiting proton-transfer step, it acts as a Brønsted acid stabilizing transition state *via* interaction with oxygen center.[46]

Impressive achievements in the design of dedicated processor chips were demonstrated in recent years with a special emphasize to speed up certain mathematical operations. As a leading example, a performance increase of two orders of magnitude was reported in theoretical calculations using the GPU hardware architecture.[47] Implementation of such a calculation strategy into the everyday chemical practice would provide an efficient computational platform for the routine evaluation of potential energy surfaces to compare them with those studied in the experiment.

To conclude, we have considered the strategy for a joint NMR/MS study. The important experimental approaches to combined studies with these methods can be summarized as follows: (i) MS and inverse detected NMR correlations (HMQC, HSQC, HMBC) can be used to select the species of interest and to determine their structures; (ii) MS and DOSY NMR can be used to study the formation of complex species and ions and to investigate aggregation, assembly, self-organization or dissociation; and (iii) MS and NOESY (ROESY) NMR are of particular importance to determine three-dimensional structures of molecular systems. As far as signal assignment is concerned, full range of MS/MS and homo/heteronuclear NMR experiments can also be carried out to support these approaches.

Based on the rapid progress in hardware development for both methods, we anticipate even more synergetic applications of mass spectrometry and NMR spectroscopy in the near future to address structural and mechanistic problems.

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