doi.org/10.1002/celc.202000442

Special Collection

Recent Developments in Electrochemistry–Mass Spectrometry

Thomas Herl and Frank-Michael Matysik*[a]

Hyphenation of electrochemistry and mass spectrometry is an attractive method to investigate oxidation and reduction processes. By using mass spectrometry, electrochemically generated products can be identified. In this Review, different approaches to electrochemistry–mass spectrometry will be summarized, including hyphenation of electrochemical flow cells to mass spectrometry as well as integration of separation steps between electrochemical reactions and detection of products. Fields of application range from bioanalytical studies to studies regarding corrosion, electrosynthesis and energy carriers. Important historical developments will be highlighted, followed by an overview of terminology and instrumental setups and discussion of developments within recent years (2017–2020).

1. Introduction

Detailed characterization of electrochemical reactions demands coupling of electrochemical systems to advanced detection techniques so that it is possible to identify oxidation or reduction products and elucidate reaction pathways. Mass spectrometry (MS) is ideally suited for this purpose as it can be used in combination with electrochemical flow cells as well as separation methods like high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE). Furthermore, it offers valuable information for the identification of substances in terms of molecular ion masses, mass fragments, and isotopic patterns. Recent reviews covered different aspects of this topic such as bioanalytical and metabolic studies[1–4] as well as instrumental aspects,[5–11] organic electrosynthesis under flow conditions,[12] and electrocatalysis research.[13] Herein, the most important developments of electrochemistry-mass spectrometry (EC-MS) since its beginnings will be shortly summarized. Aspects of terminology and instrumentation will be highlighted followed by the latest developments in this topic from 2017 to early 2020. Main focus will be put on online approaches (i.e. electrochemical cells with two- or three-electrode setups and externally controlled potential are directly coupled to separation systems or MS). In-source electrochemistry (i.e. part of the ion source of MS system serves as electrochemical cell) will not be covered in detail.

1.1. Historical Developments

One of the main challenges of the investigation of electrochemical reactions is the rather small amount of products generated by electrochemistry compared to solution chemistry,[14] so that the transfer of analytes from electrode to detection system plays an important role. Mass spectrometric characterization of electrochemically generated species started in 1971 when Bruckenstein and Gadde[15] collected gaseous reaction products in a vacuum system before they were transferred to electron ionization mass spectrometry (EI-MS). Wolter and Heitbaum[16] improved the setup to the first online EC-MS approach and named it differential electrochemistry mass spectrometry (DEMS) to distinguish from offline sampling methods. Reaction products formed at a porous electrode were directly transferred to MS via a porous membrane. Due to the direct transfer, so-called mass spectrometric cyclic voltammetry (MSCV) could be accomplished as the MS response could be directly correlated with faradaic current. Thus, typical information gained in DEMS experiments is the MS signal development during potential sweeps. However, this approach for fast and direct analysis of electrogenerated products was limited to volatile compounds that could be transferred through the membrane.[16] After progress in interfacing technologies, Hambitzer and Heitbaum[17] were the first to analyze non-volatile oxidation products by online EC-MS using thermospray ionization. A scheme of the corresponding instrumental setup is depicted in Figure 1.

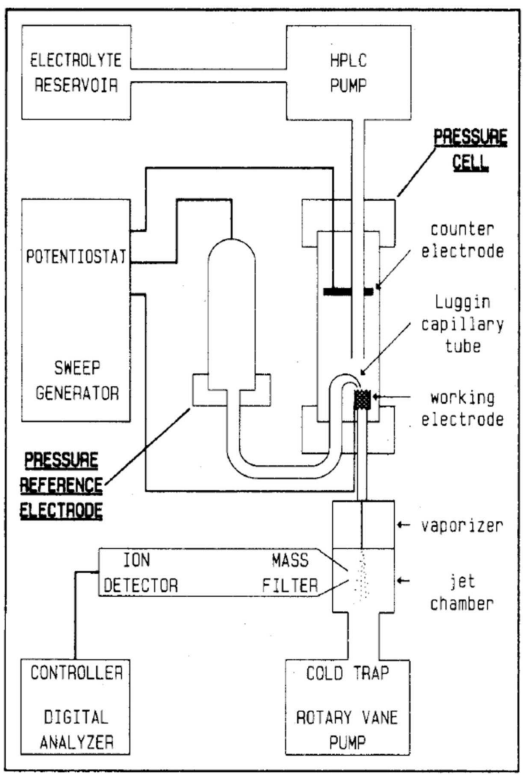

Figure 1. Schematic setup of an online EC-MS setup with thermospray ionization. Reprinted with permission from Ref. [17]. Copyright 1986 American Chemical Society.

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The electrooxidation of N,N-dimethylaniline was investigated by recording MSCVs. The dead time of this flow cell approach was 9 s and was proposed to be reduced to 1 s, which was supposed to allow for kinetic studies if the transfer time was varied.[17] This shows that the idea of real-time EC-MS which is of high interest nowadays arose already quite early. Rotating disk electrodes were also successfully coupled to mass spectrometry.[18] In 1988 Volk et al.[19] applied the methodology in bioanalytical context. The oxidation of uric acid and 6-thioxanthine was investigated and the usefulness for characterizing redox reactivity of drugs and xenobiotics was proposed. One year later, in 1989, further studies on uric acid oxidation were published by the same group and reaction intermediates and products were described together with proposed reaction pathways.[20] In the same year, the first online coupling of electrochemistry and high performance liquid chromatography to separate stable products was described[21] (Figure 2).

Further studies were concerned with the application of online-EC-HPLC-MS to study the oxidation of thiopurines.[22,23] A significant drawback of thermospray ionization is the risk of thermal decomposition of labile analytes in the ion source.[24] Electrospray ionization (ESI) represents an alternative ionization method facilitating the investigation of such thermally labile compounds.[25] After some studies on the inherent electrochemistry of ESI were published,[26–30] Dupont et al.[31] were the first to use electrochemistry to allow for the ESI-MS detection of neutral compounds by generation of stable oxidation or reduction products, however, in an offline approach. Fullerenes were used as model compounds. The applicability of in-source electrochemistry and offline electrochemistry to detect neutral species in ESI was compared. Zhou and Van Berkel[32] first described online coupling of different types of electrochemical flow cells (thin-layer electrode flow-by cell, tubular electrode flow-through cell, and porous electrode flow-through cell) to ESI-MS and addressed challenges and applications of this approach. First attempts to online electrochemical oxidation after HPLC separation were carried out by Karst and co-workers[33] with the goal of detecting ferrocenecarboxylic acid esters of different alcohols and phenols (Figure 3).

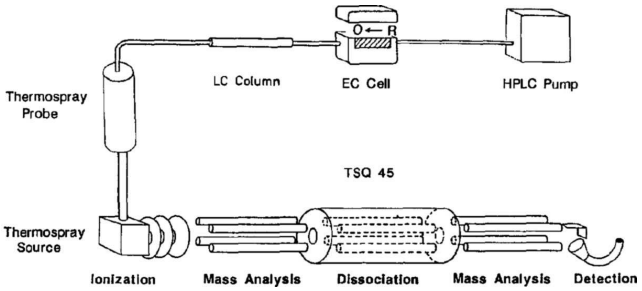

Figure 2. Illustration of an online EC-LC-thermospray-MS system. Reprinted with permission from Ref. [21]. Copyright 1989 Elsevier.

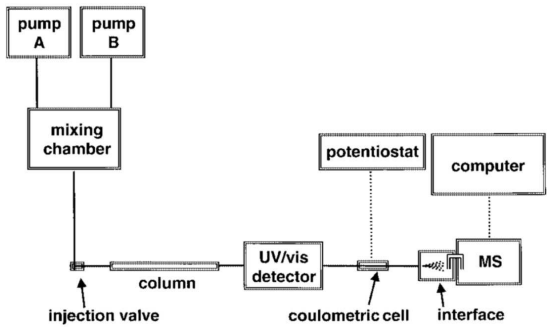

Figure 3. Scheme of an HPLC-EC-MS setup. Reprinted with permission from Ref. [33]. Copyright 2001 Royal Society of Chemistry.

Coulometric oxidation allowed for detection of these non-polar species in ESI-MS by generation of charged oxidation products. Next to HPLC, capillary electrophoresis (CE) is an alternative separation method suitable to be coupled with EC-MS. In 2003, Esaka et al.[34] and Matysik[35] independently described first electrophoretic separations of online electrogenerated species. Esaka et al. focused on the characterization of electrochemically generated anion radicals of phenanthrenequinone and anthraquinone while Matysik proposed so-called electrochemically assisted injection as an online sample preparation method for enhanced separation performance in CE and detectability of non-polar analytes in ESI-MS. The latter was

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demonstrated by online EC-CE-MS measurements of Scholz and Matysik[36] in 2011, when different ferrocene derivatives were analyzed by EC-CE-ESI-MS. Since then, the different methodologies of online EC-MS, EC-HPLC-MS, HPLC-EC-MS and EC-CE-MS have been widely applied, as several reviews show.[1,2,11,37–39,3–10]

1.2. Terminology

Different kinds of data can be derived from EC-MS depending on the measurement mode and the denotation of the data is not uniform. By online EC-MS, so-called mass spectrometric cyclic voltammograms,[16,17,40] mass spectrometric hydrodynamic voltammograms,[20,21] online linear sweep voltammetry-electrospray mass voltammetry measurements,[41] extracted ion voltammograms[42] or mass voltammograms[43–48] have been described. The potential-dependent mass intensity was measured and correlated to the potential. This method is perfectly suited to assign formed product species to the respective potential regions. Prerequisite for this is a fast transfer from the electrochemical cell to MS in order to directly correlate potential and mass intensity to each other. An alternative method is the application of constant potential steps,[17,20] which is the method of choice to characterize the instrumental setups regarding time-delays between generation and detection of products. Constant current and anodic stripping modes have also been applied.[32]

Considering mass voltammograms, two different modes of data acquisition have to be taken into account: (i) the potential is swept at a certain scan rate and the MS response is recorded in real time and correlated to the faradaic current[17,40,41] and (ii) the potential is increased step wise and the corresponding MS response is recorded. The discrete data points are collected to a mass voltammogram.[20,21,24,32] The first approach demands short dead times (below 1 s[17]). Already in the first online EC-MS studies a quantitative correlation between faradaic current and mass intensity was proposed as a source of information on current efficiency and number of transferred electrons.[17] However, in many cases, the current response of the electrode is not considered in data evaluation and only the mass intensity versus potential is presented. Considering the term voltammetry, which was introduced by Laitinen and Kolthoff[49] in 1941 as a description for determination and interpretation of current-voltage curves, a complete mass voltammogram should include both mass and current intensity to give comprehensive information and fully fit the term mass voltammogram. Due to time-resolution of the separation step, EC-HPLC-MS and EC-CE-MS experiments are usually carried out after constant-potential electrolysis as potential sweeps cannot be directly transferred to the separation system. Figure 4 shows an example of how a comprehensive mass voltammogram could be presented. The oxidation of ferrocenemethanol (FcMeOH) in a thin-layer flow cell equipped with a thin-film gold electrode is depicted and the current response as well as the mass intensity are drawn in dependence of the applied potential.

1.3. Instrumental Setups

In this section, a rough overview of different instrumental approaches to EC-MS will be presented. A straightforward method for EC-MS characterization of electrogenerated species is offline electrolysis followed by HPLC-MS or CE-MS.[45,51] However, it is combined with a loss of time resolution and experimental effort in sample preparation. Thus, online approaches are preferred when fast analysis is required. DEMS as the most traditional method is still relevant today. Gaseous products of electrochemical reactions can be detected after passing a porous membrane, usually consisting of polytetrafluoroethylene (PTFE), which separates the electrochemical cell from the MS system.[52] Different electrochemical cell configurations such as thin-layer flow cells or cells based on coated PTFE membranes exist as reviewed by Abd-El-Latif et al.[52] DEMS is characterized by very fast response times but is limited to gaseous reaction products.[52] In direct EC-MS of liquid solutions, mostly coulometric flow-through cells and amperometric thin-layer flow cells are used as previously described.[1]

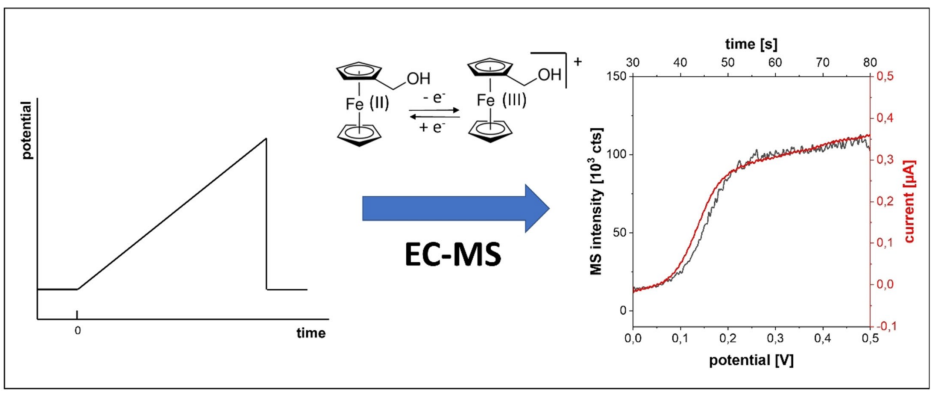

Figure 4. Example of a mass voltammogram for the oxidation of FcMeOH to $FcMeOH^+$. Hydrodynamic linear sweep voltammogram of 1 mM FcMeOH in ACN/1 mM HOAc/10 mM NH_4OAc (red, 10 mV s^{-1}, Micrux ED-SE1-Au electrode, 16 µL min^{-1}) recorded parallel to MS signal of $FcMeOH^+$ (black, m/z 216.06) with a PEEK thin-layer flow cell equipped with a thin-film electrode. The cell was coupled to ESI-TOF-MS via a fused silica capillary (50 µm × 21 cm). Experimental setup based on Ref. [50]. Unpublished work.

Different configurations are available on the market. ESA analytical cells,[42,53,54] electrochemical guard cells[55,56] and conditioning cells[48,55] as well as Antec ReactorCells[44,45,47,57] and µ-prepCells[51] equipped with different electrode materials have been quite popular in the last years. HPLC pumps (typically applied flow rates up to 50 µL min^{-1})[42,53,55] or syringe pumps (typically applied flow rates 5–20 µL min^{-1})[44–47,51,54] are used for transport of solutions. EC-HPLC-MS measurements are achieved by coupling the aforementioned flow cells to HPLC-MS by direct infusion into injection loops of the HPLC system[46,48,57] so that samples can be electrochemically pretreated on-line. Online EC-CE-MS measurements have been carried out either by injection from electrolytical batch cells[36] or disposable electrodes[58,59] with the advantage that no valve-based systems are needed as a direct injection into the separation capillary is possible. Especially in bioanalytical context EC-MS and EC-CE-MS offer the advantages that physiological conditions can be simulated by using the corresponding (MS compatible) aqueous electrolytes. This is not valid for HPLC separation, where typical separation conditions are very different from the electrolytes so that ongoing reactions during separation might not be representative for the behavior in close-to physiological solutions. However, if electrochemistry is coupled to CE systems, care has to be taken to decouple the electrochemical cells from the separation high voltage to avoid interferences and damage of the potentiostat. Miniaturization of electrochemical systems also plays an important role in instrumental developments. As reviewed by van den Brink et al.,[8] miniaturization offers the advantages of high conversion efficiencies at low sample consumption based on rapid diffusive mass transport in micro-volumes, reduced transfer times to MS, and compatibility to nano-LC and nano-electrospray conditions due to the low flow rates. Experiments that would be associated with critical conditions in conventional cells with larger amount of sample such as reactions of highly reactive compounds or reactions under high pressure can be carried out at low risk.[8] Micro and nanoscale cells of different materials such as ceramics, glass, or plastics with volumes ranging from low µL to even pL have been reported using flow rates in the range of several hundred µL min^{-1} down to low nL min^{-1}.[8] However, not all cells have been coupled to MS and many configurations are in the prototype status.[8] A further aspect of miniaturization is the combination of electrochemistry and electrospray ionization in one device.[8] Next to the methods mentioned above, a lot of innovative concepts are in development as will be shown in the following sections. Interfacing electrochemistry and mass spectrometry is another important issue. While membrane-based interfaces and electron ionization (EI) are used for analysis of volatile compounds in DEMS,[6] mostly electrospray ionization (ESI)[4,6] and inductively coupled plasma (ICP)[13] are used as interfacing strategies for liquid samples. ESI is a soft ionization method characterized by low fragmentation and is especially suited for analysis of bioanalytically relevant compounds of all sizes such as drugs, peptides and proteins, as covered in different reviews.[1,4,6] However, the electrochemical cell has to be decoupled from the ionization voltage of several kV, and the inherent electrochemistry of the ESI source has to be kept in mind.[6] As reviewed by Kasian et al.,[13] ICP-MS is characterized by high sensitivity and the possibility of multielement analysis, particularly of trace metals. Therefore, it was widely applied for stability studies of electrode materials in the context of electrocatalysis in fuel cells and water electrolyzers and the authors pointed out that it is also promising for stability studies in other fields of research.[13] As a drawback, however, it is not possible to determine the oxidation state of the respective dissolved species by ICP-MS alone.[13]

2. Latest Developments and Applications

In this section, developments and applications of mainly the last three years (2017–2020) will be shortly summarized. Table 1 shows the reported methods and fields of application. However, the different methods are often used in combination and a large variety of different topics are addressed so that the given classification is just intended to present a rough overview.

2.1. DEMS

DEMS is an important method for research in the context of energy carriers as recent publications show. Figure 5 illustrates a DEMS cell that was developed by Bell and coworkers.[60] It enabled the real time quantification of electrochemically generated products of CO_2 reduction, which was taking several hours with conventional methods. For the first time, DEMS could be used to quantify most of the major products of the CO_2 reduction reaction on polycrystalline copper within one hour. The cell was intended to be used for screening of the potential-dependent activity and selectivity of novel electro-

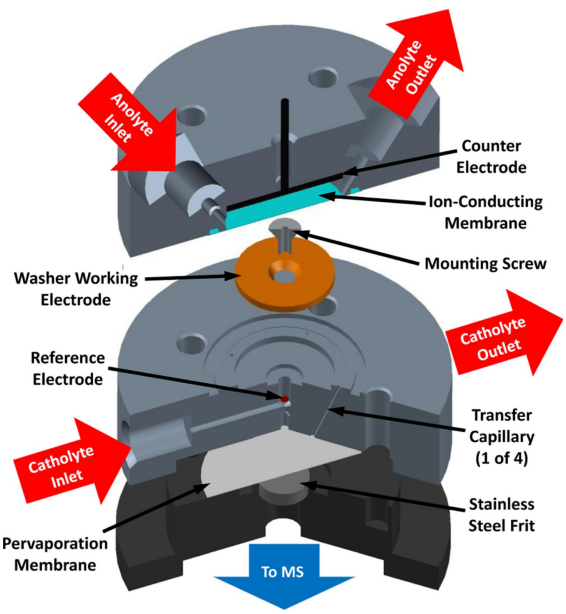

Figure 5. Exploded view of a DEMS cell applied for the investigation of CO_2 reduction. Reprinted with permission from Ref. [60]. Copyright 2015 American Chemical Society.

Table 1. Reported methods and fields of application.

Method, advantages and disadvantages	Fields of application	Refs.
DEMS[a]		
Pro:	CO_2 reduction	[60,61]
Fast response, separation of products from electrolyte	Lithium-ion batteries	[62]
Contra:	Methanol oxidation	[63]
Limited to volatile products	Carbon corrosion	[64]
	Hydroxylamine oxidation	[65]
EC-MS[a]		
Pro:	Energy carriers	[66–70]
Fast, rather simple setup, high instrumental flexibility and diversity of setups	Alloy corrosion	[71,72]
Contra:	Electrode corrosion	[73–77]
Suppression effects by electrolyte salts or product mixtures possible, compatibility of EC and MS conditions prerequisite (e.g. electrolyte salts and concentrations)	Interfacing	[78–80]
	Electrosynthesis	[81–85]
	Simulation of metabolism	[86–94]
	Protein cleavage	[95]
	Detection of complexes	[50]
	Reduction of quinones	[96]
	Disulfide bond mapping	[97]
	Location of double bonds	[98]
	Antibiotics degradation	[99]
EC-HPLC-MS[a]		
Pro:	Simulation of metabolism	[100–103]
Separation, retention time as additional information, identification via analytical standards	Quantification in MS	[104–106]
Contra:	Coupling reactions	[107]
Instrumentally complex, loss of time resolution, analytical standards often not available	Protein digestion	[108]
EC-CE-MS		
Pro:	Separation of complexes	[109]
Separation, migration time as additional information, suited for small charged compounds (orthogonal to HPLC)	Nucleobase oxidation	[110,111]
Contra:		
Instrumentally complex, limited sensitivity due to small injected volume, decoupling of EC and CE voltage necessary		

[a] Commercial setups available.

catalysts and to characterize the activity and sensitivity over time. The same group investigated the concentration of carbon dioxide and reaction products in the immediate vicinity of the cathode surface.[61] The electrocatalyst was directly coated onto the pervaporation membrane and volatile species were directly sampled from the electrode-electrolyte interface. Thus, the reaction conditions close to the electrode surface could be characterized. Ag and Cu were used as electrode materials. Shen et al.[62] used online continuous flow differential electrochemical mass spectrometry and in situ X-ray diffraction to investigate Li-rich layered oxide materials. The structure transformation during charge and discharge processes was characterized. High-energy nickel-manganese-cobalt cathode materials with different Co/Ni ratios showed different initial medium discharge voltages and voltage decays upon cycling. DEMS was used to detect gaseous products (CO_2, O_2) released from the electrodes during the initial cycle. Mateos-Santiago et al.[63] investigated the anodic oxidation of methanol on nanostructured Pt/C and Pt/WO_3—C electrode materials under acidic conditions. Methanol oxidation was different on both electrodes. The addition of WO_3 to the electrode support matrix led to an increased direct oxidation of methanol to CO_2 and the formation of formic acid. The electrochemical corrosion of carbon electrode materials at high anodic potentials in alkaline electrolytes was investigated by Möller et al.[64] by DEMS for the first time. By a modified DEMS system, the initially generated CO_3^{2-} could be detected as corrosion marker in form of CO_2 by in situ acidification in front of the DEMS membrane (Figure 6). Using highly active oxygen evolution reaction (OER) catalysts, carbon oxidation could be reduced. DEMS under forced convection was used by Pozniak et al.[65] to determine absolute faradaic efficiencies for the generation of nitrogen by oxidation of hydroxylamine on polycrystalline gold electrodes. N_2 and N_2O were found as main products in acidic and neutral media and NO as well as N_2O in alkaline media.

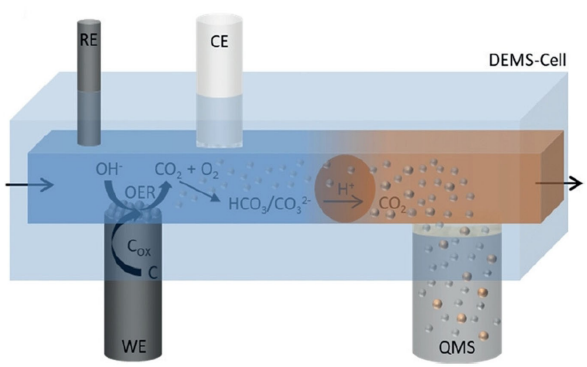

Figure 6. Setup for the investigation of carbon corrosion at high anodic potentials in alkaline electrolytes by DEMS. CO_2 was detected as corrosion marker after conversion to CO_3^{2-} due to the alkaline pH and release as CO_2 by in situ acidification. Adapted under the terms of the Creative Commons Attribution License (CC BY) from Ref. [64]. Copyright 2020 The Authors.

2.2. EC-MS

2.2.1. Energy Carriers and Corrosion

Cheng et al.[66] investigated the generation of formaldehyde by oxidation of methanol in the context of fuel cell research. Online EC-desorption electrospray ionization (DESI)-MS was used as method. The oxidation at Pt, Au, and Pt/C electrodes was characterized in acidic and alkaline solution. Formaldehyde was detected after online derivatization with phenylhydrazine. Liu et al.[67] developed a Y-shaped dual-channel microchip to investigate the reduction of oxygen by decamethylferrocene or tetrathiafulvalene under catalysis of tetraphenylporphyrin at a water/oil interface by EC-ESI-MS, which is important for electrochemical energy conversion. The electrochemical reaction steps were either induced by applying an external potential to glass microchips with integrated electroplated platinum line electrodes or by lithium tetrakis(pentaflourophenyl) borate in a polyimide-based microchip. The same topic was addressed by Gu et al.,[68] who investigated the oxygen reduction reaction by ferrocene under catalysis of cobalt tetraphenylporphine. Gel hybrid ultramicroelectrodes were developed that worked as electrochemical cells and nanospray emitters. Spray formation was achieved via a piezoelectric pistol. The agar-gel and PVC-gel components worked as liquid/liquid interface between aqueous and organic phase (agar-gel/dichloroethane, water/PVC-gel). Real time analysis of the oxygen reduction reaction was possible. Other investigations were concerned with the development of methods for the evaluation of water splitting catalysts. Electrolysis was coupled with mass spectrometry to measure the faradaic efficiency of water splitting at planar metal electrodes, metal-foam-based electrodes and porous electrodes with carbon additive under real time conditions.[69] Gaseous products were transferred to MS during electrolysis by a nitrogen carrier gas. In contrast to DEMS, transfer to MS was not achieved via a gas permeable membrane but an exhaust system. The anode and cathode chambers were separated by an ion exchange membrane. During slow potential scans the produced gases were quantified by MS while accumulation in the cell was minimized. Xu et al.[71] reported the investigation of alloys by so-called electrochemical ionization mass spectrometry (ECI-MS). A microelectrolytic cell equipped with platinum wire working and auxiliary electrode and a silver/silver chloride reference electrode was used for the investigations and the metal of interest was either connected to the anode or operated as bipolar electrode. By applying suitable potentials, the alloy components were selectively dissolved to the corresponding metal ions, which were complexed by ligands in the electrolyte and detected by mass spectrometry. The method was suggested to investigate organic compounds and alloys for example in the context of engine abrasion and engine oil analysis or cast post analysis in the context of dental treatment. The same method was applied to the analysis of metal impurities on the surface of objects with irregular shape such as necklaces and rings. Non-destructive sampling with sample consumption in the nanogram range was achieved by potential-dependent formation of metal ions from the sample followed by mass spectrometric detection.[72] Jovanovič et al.[73] investigated the corrosion of gold materials by measuring the potential-resolved dissolution of gold from a gold disc electrode and a carbon disc electrode coated with gold nanoparticles by EC-ICP-MS based on an electrochemical flow cell which has been previously applied for characterization of platinum electrocatalysts.[74] Online dissolution profiles of gold were obtained during cyclic voltammetry depending on the amount of simulated chloride impurities (Figure 7). Nanostructured gold on carbon supports was more stable against corrosion as less dissolution was observed. Another study was concerned with the investigation of platinum and gold dissolution in an organic methanol-based electrolyte. A modified EC-ICP-MS setup was used.[75] Ledendecker et al.[76] investigated the optimization of the iridium utilization during the acidic oxygen evolution reaction while reducing the noble metal content, which is important for future large scale applications. The stability of iridium oxide layers on tin oxide based support materials was investigated by dissolution experiments utilizing a flow cell coupled online to ICP-MS. Kasian et al.[77] used a scanning flow cell coupled to ICP-MS and online electrochemical mass spectrometry to investigate the oxygen evolution reaction on iridium and iridium oxide electrodes and the associated electrode degradation pathways. Three different dissolution mechanisms were identified. The reported measurements described above showed a trend towards miniaturization of electrochemical cells and interfacing systems. In many cases, two-electrode setups are used. However, no commercial standard systems have been established yet. As demonstrated in several studies, EC-MS is an attractive method to investigate and optimize the corrosion stability of coatings and electrocatalysts especially if electrochemistry is coupled to ICP-MS.

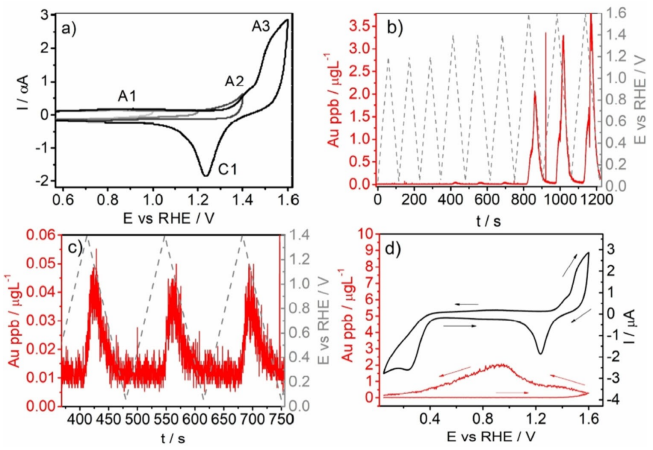

Figure 7. a) Cyclic voltammograms of 0.05 M H_2SO_4 on a polycrystalline Au electrode with increasing anodic potential limits (scan rate 20 mV s^{-1}). b,c) EC-ICP-MS measurements of Au dissolution during potentiodynamic cycling at 20 mV s^{-1}. d) Au dissolution profile (red) and current signal (black) during potentiodynamic cycle (20 mV s^{-1}). Reprinted under the terms of the Creative Commons Attribution License (CC BY) from Ref. [73]. Copyright 2018 The Authors.

2.2.2. Electrosynthesis and Metabolism Studies

Brajter-Toth and coworkers[78] investigated the ionization process in liquid sample (LS)-DESI and characterized an in-line LS-DESI configuration in comparison to common angled LS-DESI-MS systems, electrosonic spray ionization (ESSI) and ESI. As main advantage of the in-line LS-DESI-MS approach, a higher tolerance of the interface towards electrolyte solutions was described, avoiding contamination or clogging of the sprayer as it can occur in regular ESI. The MS intensity was found to be lower in LS-DESI-MS compared to ESI-MS but the ion signal stability was higher in LS-DESI-MS. The compatibility of the used electrolytes to the MS system is an important aspect as volatile electrolytes have to be used. However, in electrochemistry often high concentrations of electrolytes are preferred while low concentrations are better for MS to avoid suppression effects in the ionization process.[32] Miniaturization of electrochemical systems plays an important role for electrosynthesis processes. Folgueiras-Amador et al.[81] developed an electrochemical flow microreactor for organic electrosynthesis as improved version of their previous design.[82–84] Due to the small dimensions, the addition of high amounts of supporting electrolytes can be avoided. Among other studies, the cyclization of amides to isoindolinones was investigated and the number of electrons for a complete conversion was determined by inline mass spectrometry. This approach is interesting as minimizing the amount of supporting electrolyte avoids time consuming clean-up procedures and facilitates high-efficiency electrosynthesis of product solutions that can directly be investigated by further techniques such as NMR without interferences by electrolyte salts. Next to Fenton-like oxidation and UV irradiation, online as well as offline EC-ESI-MS was used to investigate the phase I metabolism of the mycotoxins citrinin and dihydroergocristine and results were compared to in vitro metabolites by Koch and coworkers.[86] Even if the Fenton-like reaction was the better suited method to predict phase I metabolites, the products generated by EC were suggested to be potentially interesting for future research. The same group investigated transition products of monensin by EC-MS and compared the results with microsomal metabolism and hydrolysis experiments of monensin.[87] Subsequent HPLC-MS/MS studies were used for further investigations. Decarboxylation, O-demethylation and acid catalyzed ring-opening reactions were found to be the main processes. By electrochemistry, some products formed in the microsomal assay could be reproduced but also additional products could be found. Colombo et al.[88] used online EC-ESI-MS to simulate oxidative injury of three phosphatidylethanolamines with a boron-doped diamond (BDD) working electrode and suggested an oxidation mechanism mediated by hydroxyl radicals. EC-ESI-MS was demonstrated to be able to reproduce oxidative metabolism by reactive oxygen species. Rohn and coworkers[89] analyzed the redox properties of various phenolic compounds such as chlorogenic acid or caffeic acid on a boron-doped diamond electrode and used EC-MS for investigation of adduct formation of oxidized phenolic compounds to food proteins by reaction of oxidized chlorogenic acid with peptides of alpha-lactalbumin. The same group reported the electrochemical simulation of phase-I and phase-II metabolism of cholecalciferol and ergocalciferol in the context of vitamin D metabolism.[90] Electrochemical investigations as well as binding studies to glucuronic acid were carried out and products of in vivo studies could be simulated. Additionally, EC-MS was suggested as a promising method for generating reference compounds. Oxidative metabolism of the antimicrobial agent triclosan was investigated by Zhu et al.[91] An electrochemical flow cell with a boron-doped diamond electrode was coupled to MS to identify possible metabolites. Additionally, the toxicity of triclosan and the simulated metabolites was investigated with modelling tools and bioassays on zebrafish embryos. The results demonstrated potential harmfulness of triclosan and its metabolites. Though far less frequently applied, investigations of reductive processes are also carried out. Pietruk et al.[92] investigated the reduction reactions of the azo-dyes Sudan I–IV and 4-nitroaniline at a glassy carbon electrode. Possible metabolites were identified by a flow cell approach. For further confirmation of the products, LC-MS/MS measurements were carried out after offline electrolysis. A novel paper based electrochemical cell was developed by Narayanan et al.[80] A filter paper coated with carbon nanotubes and equipped with printed silver paste electrodes was used to convert thiols to disulfides, to functionalize polycyclic aromatic hydrocarbons, detect radical cations of metallocenes and polycyclic aromatic hydrocarbons and to investigate the oxidation of glucose. van den Brink et al.[95] developed a glass-based microfluidic electrochemical cell with an integrated boron-doped diamond electrode for specific electrochemical protein cleavage. The cell volume was 160 nL. The potential-dependent cleavage was investigated by recording mass voltammograms and selectivity was proposed to be tunable by the selection of the potential. Cleavage of bovine insulin and chicken egg white lysozyme was demonstrated. The microfluidic cell was suggested as a purely instrumental approach to protein analysis and proteomics studies by high electrochemical conversion efficiency and mass spectrometric detection. The timescale of investigations can be reduced and reactions can be carried out under conditions not suitable for enzymatic cleavage.[95] Figure 8 illustrates the chip design. The reported studies show that instead of pure electrochemical investigations more and more additional experiments are carried out such as toxicity studies of electrogenerated compounds or conjugation studies of electrogenerated intermediates.

2.2.3. Real-Time EC-MS

The idea of fast real time analysis of electrochemical reactions was already present in the beginnings of EC-MS. However, in the last years this idea was reactivated and several developments towards real-time detection of electrogenerated species were described by different working groups. Matysik and coworkers[50] used amperometric thin layer flow cells with integrated disposable electrodes for direct coupling to ESI-TOF-MS. The dead volume for the transfer to MS was minimized by using short fused silica capillaries with low inner diameters and

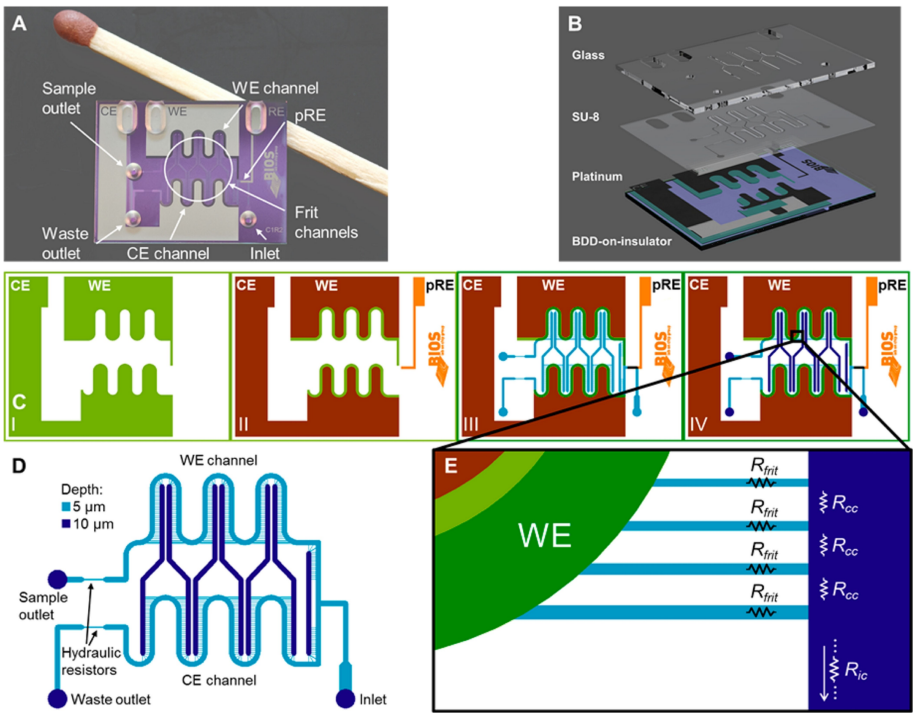

Figure 8. Microfluidic electrochemical cell used for electrochemical protein digestion. A) Photograph of assembled chip. B) Exploded view of the different chip layers. C) Structures of BDD working electrode and counter electrode (I), Pt pseudo reference electrode and contact pads (II), SU-8 layers (III), and microfluidic structures and access holes (IV). D) Scheme of fluidic structures. E) Expanded view of a part of the working electrode and frit channel network. Reprinted with permission from Ref. [95]. Copyright 2016 American Chemical Society.

an ESI interface commonly used in CE-MS. By appropriate flow rates, short transfer times in the range of 1 s could be achieved. However, this approach is limited to ESI compatible electrolytes. Wang et al.[79] described the real time investigation of ascorbic acid oxidation by the previously developed so-called in situ liquid secondary ion mass spectrometry (in situ liquid SIMS[112,113]). A radical intermediate could be detected and dynamic double layer processes at the electrode-electrolyte interface could be investigated by coupling a vacuum compatible microfluidic electrochemical cell with integrated gold film working electrode to TOF-SIMS. Secondary ions were directly sampled from the electrode-electrolyte interface by a primary Bi^{3+} ion beam that was penetrating a silicon nitride membrane as illustrated in Figure 9.

Khanipour et al.[70] presented a method for time- and potential-resolved investigation of liquid and gaseous products of electrochemical reactions by electrochemical real time mass spectrometry (EC-RTMS). The CO_2 reduction reaction on pristine and anodized copper was investigated. A scanning electrochemical flow cell with extraction capillary was coupled to mass spectrometry. Though instrumentally quite complex because of the parallel use of two MS systems, this method allowed for highest flexibility as volatile and non-volatile species could be investigated. The first was achieved by gas extraction through a hydrophobic membrane and detection by electron ionization quadrupole MS while the latter was realized by nebulizing the electrolyte solution and coupling to direct analysis in real time (DART) TOF-MS (Figure 10). Using DART ionization this approach

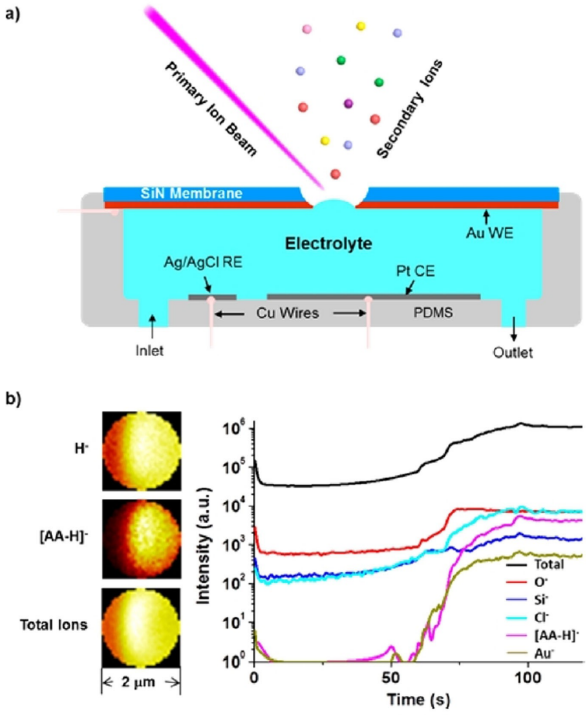

Figure 9. a) Illustration of an electrochemical cell for in situ liquid SIMS. b) Depth profiles of different ions obtained during drilling a hole through a SiN membrane and an Au film electrode in a solution of 0.5 mM ascorbic acid (AA) in 10 mM HCl. Reprinted with permission from Ref. [79]. Copyright 2016 American Chemical Society.

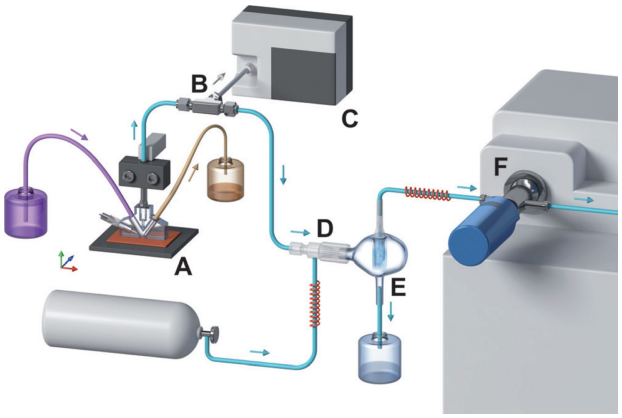

Figure 10. Setup for real time EC-MS consisting of a scanning flow cell (A), a degasser with hydrophobic tubing for gas-liquid separation (B), an electron-ionization quadrupole MS for gas analysis (C), a nebulizer (D), a spray chamber (E), and a direct analysis in real time-TOF-MS for liquid analysis (F). Reprinted with permission from Ref. [70]. Copyright 2019 Wiley-VCH.

was more robust towards electrolyte salts than regular EC-ESI-MS techniques.

Though it is contentious in some cases,[114] in-source electrochemistry or electrochemical systems combining electrochemistry and spray formation controlled by the ionization high voltage represent other variants of real-time EC-MS. However, in most cases the thermodynamic redox potentials cannot be investigated as no classical electrochemical cells with three-electrode system are used. Precise control of electrochemical potentials may be difficult in such systems and mechanistic findings have to be transferred to regular electrochemical cells carefully. Because of that only a few applications will be mentioned and not discussed in detail. Pei et al.[96] investigated corona discharge-induced reduction of various quinones by negative mode ESI-MS. Cramer et al.[97] used in-source reduction for disulfide bond mapping. Wan et al.[85] developed a real-time electrochemical reaction platform to monitor picomole-scale electrosynthetic reactions by nano-ESI-MS. Tang et al.[98] used electro-epoxidation in nano-ESI-MS controlled by the spray voltage. By fragmentation in tandem MS the capability to locate double bonds in lipids was demonstrated. He et al.[99] investigated the real-time monitoring of electrochemical degradation of ciprofloxacin by electrochemical mass spectrometry. Oxidation and spray formation by high voltage based on a platinum slice electrode placed on an ITO glass chip was used. Another application was demonstrated for dopamine[93] as well as DOPA and adrenaline.[94] Oxidation was either carried out by the ESI spray high voltage of 3 kV or by an integrated electrochemical cell using the stainless-steel electrospray emitter as working electrode and a second stainless-steel capillary as counter electrode that was connected by Teflon tubing. The voltage of the electrochemical cell was supplied by a battery and a variable resistor and the cell voltage was floated on the ESI high voltage.[94] Intermediates were detected in real time with a specified response time of about 3 ms.[93,94]

2.3. EC-HPLC-MS

Offline and online HPLC-MS and HPLC-MS/MS are often applied to support findings of EC-MS studies. On the other hand, EC-MS is regularly used to optimize oxidation conditions to get the highest possible yields of the products that should be analyzed by consecutive HPLC-MS so that both instrumental approaches are mostly applied in combination. By evaluation of the retention behavior, additional information on the polarities of analytes can be obtained and suppression effects in the ionization source can be avoided. In the following, recent online studies with focus on hyphenation of electrochemistry to chromatographic methods and mass spectrometry are summarized. Karst and coworkers[100] analyzed the oxidative transformation or roxarsone by EC-MS and EC-hydrophilic interaction liquid chromatography (HILIC)-MS using an electrochemical thin-layer cell with boron-doped diamond electrode. ESI and ICP were used as ionization methods. Adduct formation experiments were also carried out. By HILIC polar analytes could be separated using liquid chromatography, which shows the flexibility and universality of modern HPLC techniques. Using ICP-MS additionally to ESI-MS not only identification of organic substances but also speciation and quantification of inorganic constituents is possible. Another study was concerned with reduction of prodrugs based on Pt(IV) in the context of anticancer agents (Figure 11).[101] Electrochemistry was presented as alternative to chemical reducing agents where in some cases the reduction kinetics are very slow. Different platinum complexes were reduced and analyzed by EC-MS, EC-HPLC-ESI-MS and EC-HPLC-ICP-MS.

Mekonnen et al.[102] developed an automated EC-HPLC-MS method for electrochemical simulation of biotransformation products of the insecticide chlorpyrifos and compared the electrogenerated products with in vitro generated metabolites of rat and human liver microsomes. Six products could be identified with both methods while the authors emphasized the time that could be saved by the instrumental approach due to the missing sample preparation steps (matrix removal). Oxidations were carried out on boron-doped diamond and glassy carbon electrodes and the oxidation potential was optimized by EC-MS. The same group reported the investigation of biotransformation of the fungicide fluopyram.[103] Several known phase I metabolites could be simulated by electrochemical oxidation on a boron-doped diamond electrode, but also new metabolites were predicted by electrochemistry and studies based on human and rat liver microsomes. Additionally, mechanistic reaction steps were proposed. Xu et al.[104] used electrochemical oxidation for quantification in HPLC-MS without the need of standard compounds or calibration curves (electrochemical mass spectrometry) in a dual detection-like method. By evaluating the faradaic current in an LC-EC-MS approach the amount of oxidized analyte could be calculated, and the yield of oxidation was determined by comparing the MS signal before and after electrolysis. No quantitative electrolysis was needed as it would have been the case for coulometric quantification. Applications were demonstrated for determination of dopamine, norepinephrine, rutin, and glutathione as

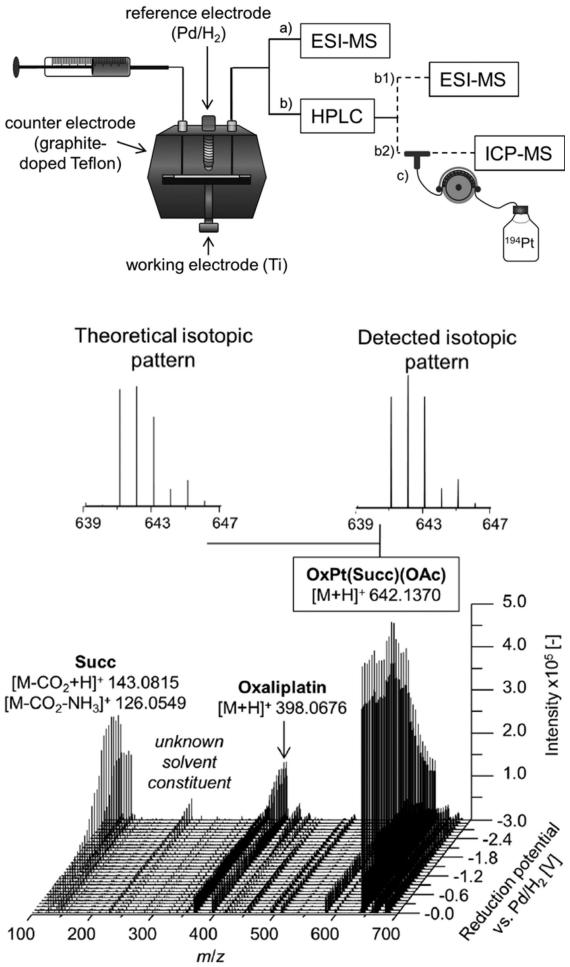

Figure 11. Top: Experimental setup used for reduction of Pt(IV) compounds either by EC-ESI-MS (a) or EC-HPLC-ESI-MS (b1)/EC-HPLC-ICP-MS (b2). Bottom: Mass voltammogram obtained for the reduction of OxPt(Succ)(OAc) on a Ti cathode during a potential ramp at a scan rate of 10 mV s^{-1}. Adapted under the terms of the Creative Commons Attribution 3.0 Unported License from Ref. [101]. Copyright 2018 The Authors.

well as uric acid in urine. The same method was used for quantification of tyrosine containing peptides.[105] However, in both cases it is mandatory to know the oxidation mechanism and the number of transferred electrons as well as the number of oxidizable groups of each target molecule. The method was also applied to purified samples where no separation was needed and the sample could directly be analyzed and quantified without separation step.[106] A novel approach to online dual electrochemistry coupled to LC–MS was presented by Karst and coworkers.[107] Two liquid streams were combined for online derivatization of a disulfide reduced to a thiol and a phenol oxidized to a benzoquinone. The coupling products were evaluated by HPLC separation and mass spectrometry. In future studies the concept is intended to be used for online protein labelling. Bischoff and coworkers[108] developed a method for electrochemical digestion of proteins. Next to digestion, chemical labeling of the cleavage products by introduction of reactive spirolactone groups was addressed. Cu (II) ions were used to stabilize spirolactone containing peptides which were subsequently labeled with biotin and enriched by avidin affinity chromatography. Identification was carried out by mass spectrometry. LC-MS measurements after the different reaction steps are shown in Figure 12. The method was applied to the analysis of chicken egg white lysozyme. The results show that electrochemical reaction steps can be effectively included into sample preparation and derivatization procedures. Overall it can be stated that various applications of rising complexity are reported. Usually different techniques are combined. The general redox behavior of analytes is often investigated and optimized by EC-MS while HPLC-MS is used for characterization based on the retention behavior and mass of products. Different ionization methods are applied for characterization of organic and inorganic constituents. In most cases methods based on electrochemistry are not used independently but are still compared to conventional methods leading to the conclusion that this field is still not fully established. A vast amount of applications is concerned with metabolic and biomimetic studies and the biggest advantage of electrochemistry is the rather simple setup and well controllable reaction conditions. Compared to regular assays the effort of sample preparation is significantly reduced and timescales of analysis are much shorter.

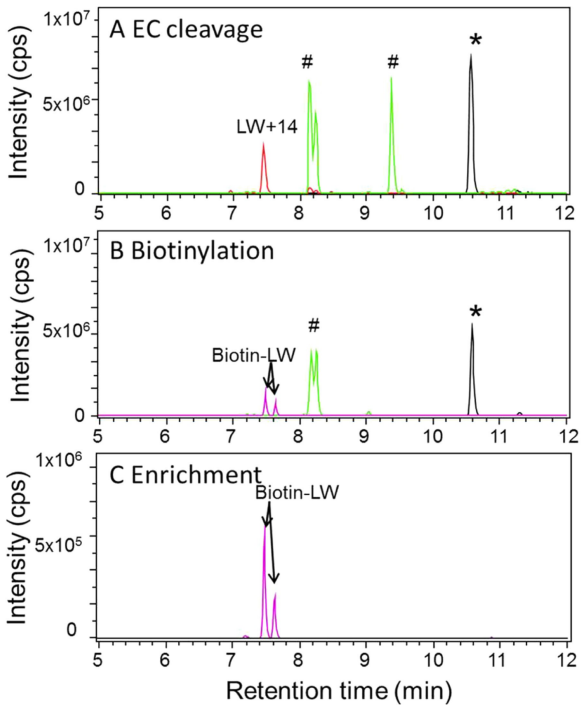

Figure 12. A) LC-MS of the electrochemically digested tripetide LWL, B) measurement of the reaction mixture after biotinylation and solid-phase extraction, and C) measurement of the biotinylated LW + 14 fragment after enrichment on monomeric avidin agarose. Extracted ion chromatograms of unoxidized LWL (*, m/z 431.26), uncleaved isomeric oxidation products LWL + 32 (#, m/z 463.26), LW + 14 (m/z 332.16), and biotinylated LW + 14 (m/z 706.37). Reprinted with permission from Ref. [108]. Copyright 2017 American Chemical Society.

2.4. EC-CE-MS

Capillary electrophoresis is a complementary separation method that can be used as an alternative to HPLC. However, it is much less frequently applied. Matysik and coworkers established an online EC-CE-MS system based on direct injection into the CE system from screen-printed electrodes. The capillary tip was directly placed on the working electrode surface for hydrodynamic injection.[58,59] This allows for a fast and efficient transfer of electrochemically pretreated solutions to the separation step without the need of quantitative oxidation or reduction. The approach was limited to aqueous electrolytes due the screen-printed electrode materials that are not resistant against organic solvents. To extend the applicability to non-aqueous solutions, a miniaturized electrochemical injection cell based on disposable thin-film electrodes was developed and characterized. The instrumental setup is illustrated in Figure 13.[109] Very low amounts of sample (below 10 µL) could be oxidized and characterized online by CE-MS as demonstrated for different ferrocene derivatives.[109] Next to guanosine and 8-oxo-7,8-dihydroguanosine[115] and cyclic nucleotides,[116] cytosine[110] and thymine[111] oxidation was investigated by online EC-CE-MS based on screen-printed carbon electrodes. Contrary to HPLC, the same electrolyte can be used for oxidation and separation in the case of CE. This has the advantage that the migration behavior in CE is representative for the state of charge of the analyte in the electrolyte as no solvent exchange takes place. Physiological conditions can be simulated also in the separation step, which is not possible in reversed-phase HPLC.

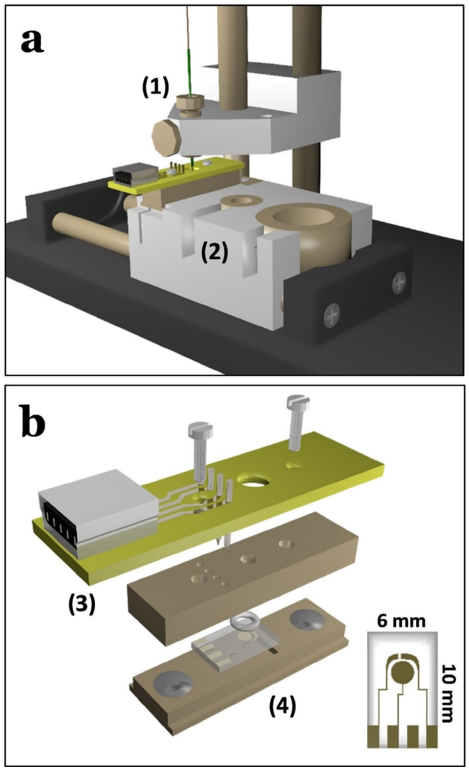

Figure 13. EC-CE-MS setup based on an injection cell equipped with disposable thin-film electrodes. a) Injection device at injection position. The separation capillary (1) is moveable vertically and the base unit with integrated electrochemical injection cell and electrolyte reservoirs (2) is moveable horizontally. b) Exploded view of the electrochemical injection cell consisting of a cover with electrical contacts (3) and base with electrode slot (4). Reprinted with permission from Ref. [109]. Copyright 2018 Springer Nature.

2.5. Further Studies

In Table 2, further recent studies from 2017–2020 are shortly summarized.

3. Summary and Outlook

EC-MS is an attractive method for characterization of redox processes and identification of oxidation and reduction products. A vast amount of the EC-MS investigations is concerned with the electrochemical simulation of oxidative metabolism, oxidative stress, or degradation processes. But also, electrochemical sample preparation, for example in the context of

Table 2. Further EC-MS studies from 2017–2020.

Category	Method	Content	Refs.
Metabolism	EC-MS, EC-HPLC-MS	– Simulation of oxidative metabolism of antitumor-active compounds	[117,118]
Metabolism	EC-MS	– Simulation of oxidative metabolism of nucleosides and nucleotides by EC-ESI-MS	[119]
Metabolism	EC-MS, EC-HPLC-MS	– Simulation of the oxidative metabolism of cardiovascular drugs – Conjugation to glutathione and comparison to in-vivo experiments	[120,121]
Protein analysis, interfacing	EC-MS	– Disulfide bond electroreduction and tagging by electrochemical-mass spectrometry	[122]
Protein analysis	EC-MS, EC-HPLC-MS	– Disulfide linkage assignment of disulfide-rich peptides by electrochemical reduction on a lead electrode – Alkylation of peptides followed by alkylated peptide sequencing	[123]
Metabolism, degradation, remediation	EC-MS, EC-HPLC-MS	– Simulation of metabolism and degradation of polycyclic aromatic hydrocarbons – Comparison to UV irradiation and microsomal incubation	[124]
Metabolism	EC-MS	– Simulation of enzyme-mediated metabolism processes of phosphatidylethanolamines	[125]
Energy carriers	EC-MS	– Screening of CO_2 reduction electrocatalysts by scanning flow cell and pervaporator	[126]
Metabolism	EC-HPLC-MS	– Aromatic hydroxylation of lidocaine to 3-hydroxylidocaine at a Pt electrode – Identification of oxygen source by experiments with ^{18}O labelled water	[127]

corrosion studies, plays an important role. While instrumental setups for EC-MS and EC-HPLC-MS are already established and commercially available, new developments in recent years dealt with interfacing strategies and development of real-time analytical systems and electrochemical interfaces combining electrochemistry and ionization for MS. However, potential control and evaluation of thermodynamic redox information is barely possible with such systems, as often two-electrode setups are applied and the potential drop within the ionization system is used for the electrochemical conversion. One crucial part of EC-MS is the identification of oxidation products. Evaluation of the masses and molecular formulas by MS is straightforward but deriving structural features is difficult. EC-MS systems are therefore often combined with separation techniques to obtain additional information on the retention or migration behavior. Tandem MS experiments can be applied to identify structural features by characteristic fragments. However, a lot of valuable data can be obtained this way but in many cases structures can still only be proposed because there is often a lack of analytical standards for comparison. Another difficulty is the low amount of product species generated by EC. Thus, producing enough sample for preparative separation and offline analysis, for example by NMR, is difficult. Especially if long electrolysis times are applied, one significant advantage of EC-MS, the short timescale of analysis, is lost. A lot of follow up reactions of primary oxidation products will take place and the composition of the reaction mixture will change significantly over time, which makes analysis quite complex. This may be a problem especially in studies with biological context as there is often interest in reactive intermediates. In the future, additional techniques for structural identification will be in demand for more detailed characterization of oxidation and reduction products.

In one of the main fields of application, investigations in bioanalytical context, metabolism studies showed that some characteristic processes can be simulated by electrochemistry. Different electrode materials can simulate different mechanisms like direct electron transfer or radical mediated processes. A current trend is that not only oxidation or reduction products are identified to simulate phase I metabolism but also conjugation studies for simulation of phase II metabolism are carried out. Applications of rising complexity are reported, and even dual electrochemical approaches are already established. In more and more investigations, microsomal experiments and toxicity studies of electrochemically generated metabolites are carried out additionally to electrochemical studies so that EC-MS slowly develops from pure proof-of-concept studies to an applied technique in this field. EC-MS is an attractive approach for preliminary screening procedures that can be carried out on a reduced time scale compared to in vitro assays and animal studies might be reduced. However, a lot of electrogenerated products are artificial and probably won't be present in in vivo metabolism so that conclusions have to be drawn carefully. One important issue especially for routine and high-throughput analysis is electrode maintenance. Electrodes need to be cleaned and polished properly to avoid artifacts and electrode fouling. This is time-consuming and demands experienced users. The application of disposable electrodes can be attractive in this case as electrodes can in principle be replaced by new ones after each measurement so that a constant performance can be ensured.

While in the past many instrumental developments in electrochemical cells and hyphenation to separation techniques have been established, future developments should deal with more powerful methods for online structural identification such as NMR.[128] Additionally, final steps from proof-of-concept to standardized applications should be done.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: hyphenated techniques · electrochemistry · mass spectrometry · liquid chromatography · capillary electrophoresis

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Manuscript received: March 24, 2020
Revised manuscript received: May 4, 2020
Accepted manuscript online: May 5, 2020