

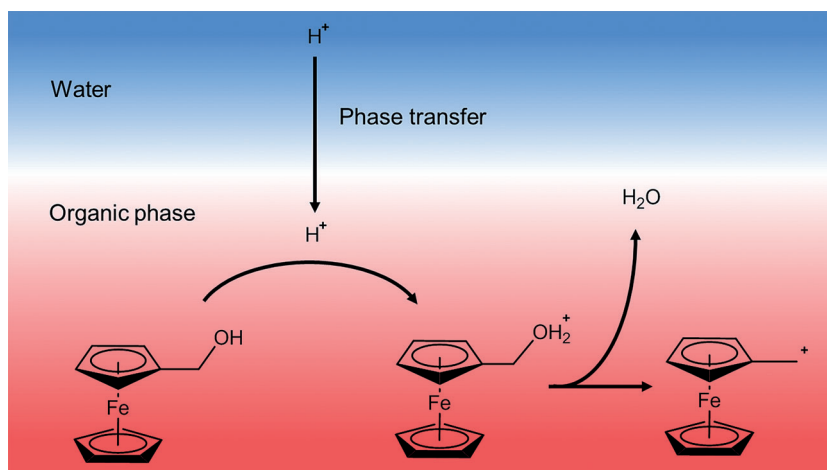
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Electrochemically Controlled Proton-Transfer-Catalyzed Reactions at Liquid–Liquid Interfaces: Nucleophilic Substitution on Ferrocene Methanol

Pekka Peljo,^[a] Liang Qiao,^[b] Lasse Murtomäki,*^[a] Christoffer Johans,^[a] Hubert H. Girault,^[b] and Kyösti Kontturi^[a]

Phase-transfer catalysis (PTC) is a widespread synthetic method to catalyze reactions between reagents soluble in immiscible phases. In a typical PTC reaction, the addition of a “phase-transfer catalyst”, typically a tetraalkyl ammonium cation, facilitates the transfer of reactive anions from an aqueous phase to an organic phase, allowing the reaction to occur.^[1] The standard textbook explanation is that the quaternary ammonium cations shuttles the reactant anions and the corresponding anions produced in the reaction across the liquid–liquid interface.^[1] The “electrochemical” interpretation is that the partition of the “phase-transfer catalyst” between the phases defines the Galvani potential difference across the interface according to the Nernst–Donnan equation.^[2] This interfacial polarization is the driving force for other ion-transfer reactions that controls the distribution of ions between the phases. The validity of this interpretation has been established by using a potentiostat instead of a partitioning ion to adjust the Galvani potential difference and hence the rate of the reaction.^[3]

Herein, we demonstrate an electrochemically driven S_N1 reaction, where a proton transferred into the organic phase either electrochemically or by a “phase-transfer catalyst” catalyzes an S_N1 substitution on ferrocene methanol (FcMeOH, also known as hydroxymethylferrocene). This model reaction was chosen because of the remarkable stability and ease of preparation of α -ferrocenyl carbocations by protonation of FcMeOH, leading to elimination of the hydroxyl group, presented in



Scheme 1. Proton-transfer-catalyzed interfacial formation of α -ferrocenyl carbocations from ferrocene methanol.

Scheme 1.^[4] Moreover, nucleophilic substitutions on ferrocenyl alcohols have recently been the subject of renewed interest,^[5] for example, nucleophilic substitutions to optically active ferrocenyl alcohols “on water” (poorly soluble ferrocenyl alcohols suspended in water at 80 °C) have given reasonable yields.^[5b] Additionally, we outline the utilization of the biphasic electrospray ionization mass spectrometry (ESI-MS)^[6] to characterize the reaction products.

Electrochemical control of proton transfer into the organic phase can be realized in two ways: i) by using a potentiostat to apply a suitable Galvani potential difference across the interface in a four-electrodes cell comprising two reference and two counter electrodes. ii) by addition of lithium tetrakis(pentafluorophenyl) borate (LiTB) into an acidic aqueous phase.^[7] In this case TB^- can be considered as a “phase-transfer catalyst”. As it is highly hydrophobic (with a standard free energy of transfer from aqueous to 1,2-dichloroethane phase $\Delta G_{tr}^{w-o} = -68.5 \text{ kJ mol}^{-1}$),^[8] it will transfer into the organic phase. To maintain electroneutrality, an equal amount of protons is extracted into the organic phase.

The behavior of FcMeOH in a four-electrodes cell under potentiostatic control shows that FcMeOH facilitates proton transfer across the liquid–liquid interface, even in the absence of a phase-transfer catalyst, as under electrochemical control the electroneutrality of the adjacent phases is maintained by the reactions at the two counter electrodes. The proton transfer is followed by an irreversible chemical reaction (see the Supporting Information for additional details).

[a] P. Peljo, Dr. L. Murtomäki, Dr. C. Johans, Prof. K. Kontturi
Department of Chemistry, Aalto University
P.O. Box 16100, 00076 Aalto (Finland)
Fax: (+358) 9 470 22580
E-mail: lasse.murtomaki@aalto.fi

[b] L. Qiao, Prof. H. H. Girault
Laboratoire d'Electrochimie Physique et Analytique
Ecole Polytechnique Fédérale de Lausanne (EPFL)
Station 6, 1015 Lausanne (Switzerland)

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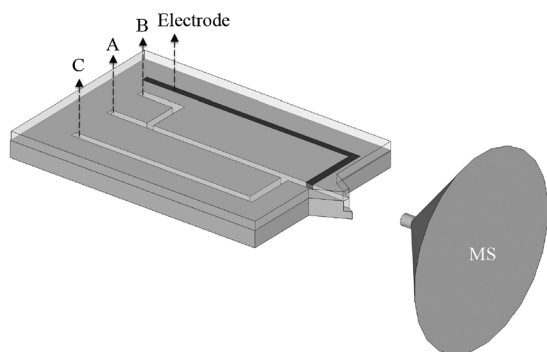


Figure 1. Microchip for MS characterization of the biphasic reaction products. Channel A was used for infusing the organic phase, and the aqueous solution was infused via channel B. The ESI buffer was infused via channel C.

The two-phase reactions were also studied by biphasic electrospray ionization mass spectrometry (ESI-MS). A dedicated three-channel microchip, shown in Figure 1, was used as an emitter in ESI-MS to analyze the reaction products. An aqueous phase containing 5 mM LiTB and 10 mM HCl was introduced in channel A and 1,2-dichlorobenzene (DCB) containing 5 mM FcMeOH was introduced in channel B. The results are shown in Figure 2, and the relative abundance of the species as a function of reaction time is shown in the Supporting Information. The maximum reaction time achieved with the chip was 3 min, and therefore, samples taken from batch reactions were analyzed to identify the products after longer reaction times (see the Supporting Information for experimental details).

The special isotope distribution of Fe (54, 6.3%; 56, 100%; 57, 2.4%; 58, 0.3%) was used to identify the iron-containing species. In the mass spectrum of FcMeOH (5 mM in DCB infused via channel A, channel B was not used), significant peaks around 216 Th (m/z) were observed corresponding well to the isotope distribution of FcMeOH (214, 6.3%; 215, 0.8%; 216, 100%; 217, 14.5%; 218, 1.4%), indicating the generation of FcMeOH⁺ ions (the oxidation of Fe^{II} to Fe^{III}) during ESI. Also significant peaks showing the typical isotope distribution of iron were observed

around 199 Th, indicating a reaction product from FcMeOH. The shift of m/z (–17 Da) corresponds to the elimination of the hydroxyl group and formation of a carbocation (FcCH₂⁺, m/z = 199). If channel B was infused with 10 mM HCl solution, the relative abundance of the peaks at 199 Th increased. This indicates that FcMeOH can partition slightly into the aqueous phase (partition coefficient P = 82, see Supporting Information) and react with protons. The protonation of the OH[–] group was followed by fast elimination of water to generate the carbocation FcCH₂⁺ observed with ESI-MS. This carbocation is stabilized by the high electron-donating property of the ferrocenyl group.^[4a,c] The generation of carbocation cannot be avoided during ESI-MS, since the presence of protons is essential to induce electrospray of droplets. The protons are mainly from the acidic ESI buffer added via channel C, and can also be generated by oxidation of water on the electrode for ESI.

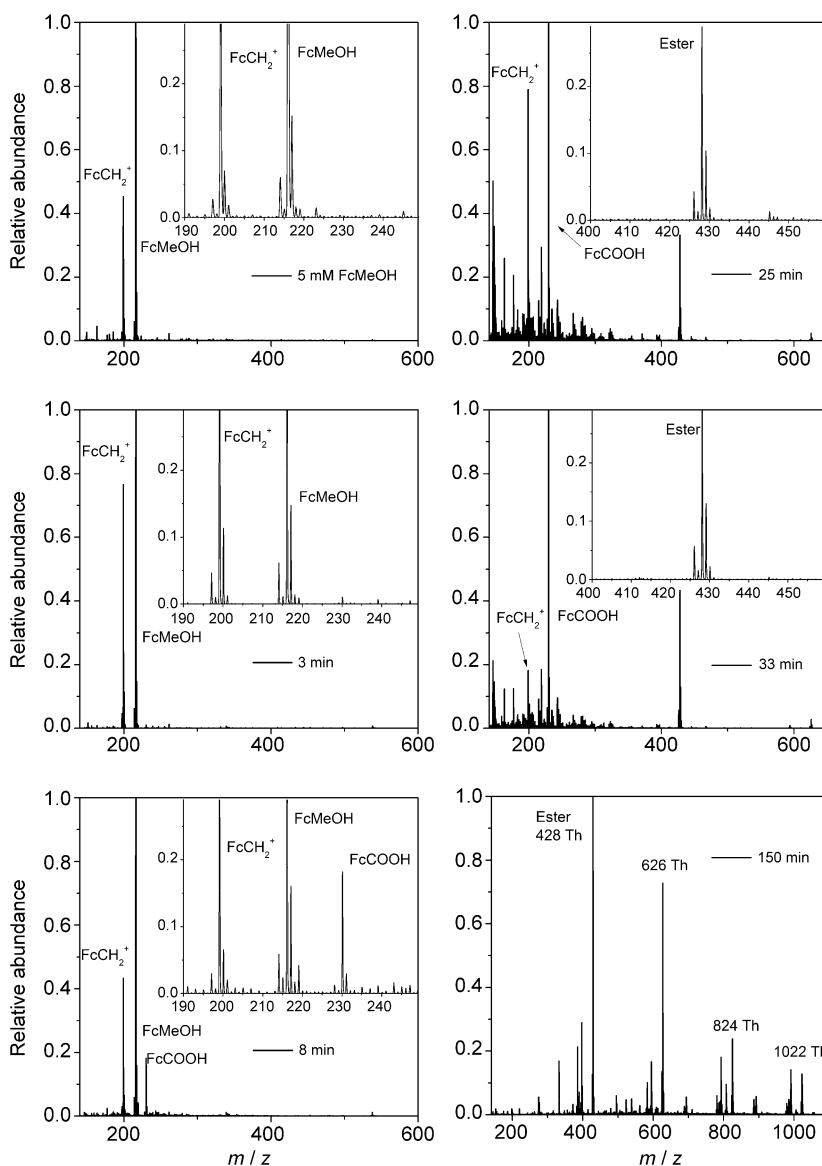
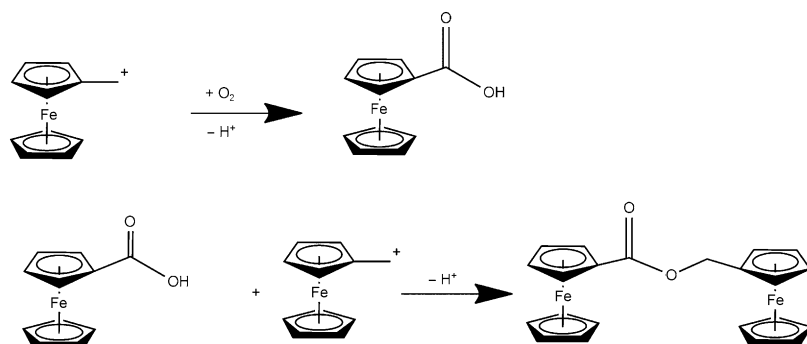


Figure 2. ESI-MS results of samples extracted from the reaction system at different reaction times. The insets show the observed isotope distribution of the peaks.

Additional peaks around 230 Th were observed in the sample taken from the oil phase of a batch reaction after 8 min of reaction showing the typical isotope distribution of iron (Figure 2). These peaks were assigned to ferrocene carboxylic acid FcCOOH and the results suggest that the carbocation can further react with molecular oxygen to produce ferrocene carboxylic acid FcCOOH ($m/z=230$). The production of FcCOOH was confirmed by ultramicroelectrode voltammetry (see the Supporting Information for details). The produced acid could then react with FcMeOH, forming the corresponding ester ($m/z=428$) observed after 25 min of batch reaction, but a more likely option is the reaction with the carbocation, as almost no ferrocene methanol was left when the formation of the ester began (Figure 2). The peak corresponding to the carbocation disappeared after 45 min, indicating that it is remarkably stable.

The reaction proceeded slowly after the ester formation by the additions of 198 mass units giving products with $m/z=626, 824$ and 1022 . This corresponds to the addition of the carbocation (and loss of one proton), probably by substitution of a proton in 1,2-, 1,3- and 1,1'-ringpositions, as in the case of ferrocenyl alcohol polymerization from melts under nitrogen.^[9] No hydrogen peroxide was detected after 1 hour of reaction with NaI or titanium oxalate methods,^[7a] proving that oxygen reduction did not take place in significant amounts. The proposed mechanism based on ESI-MS results and UME voltammetry (see Supporting Information) is shown in Scheme 2.

A similar mechanism has been suggested by Fomin et al.,^[10] who proposed that two carbocations can recombine producing 1,2-diferrocenylethane (DFcE²⁺), or the reaction with oxygen can lead to rather complicated chain radical oxidation resulting in the formation of ferrocene aldehyde and ferrocene



Scheme 2. Reactions of α -ferrocenyl carbocation in the shake-flask experiments.

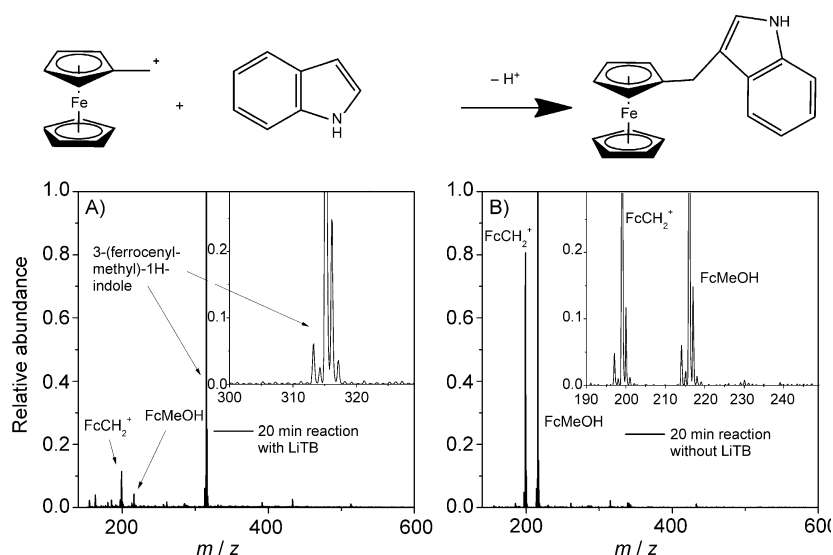


Figure 3. Top: The reaction between α -ferrocenyl carbocation and indole, producing 3-(ferrocenylmethyl)-1H-indole.^[5a-c] Below: The ESI-MS results of oil-phase samples from the shake-flask experiments with 5 mM FcMeOH and indole in DCB and 10 mM HCl with (A) and without (B) 5 mM LiTB in water after 20 min of reaction. The inset shows the observed isotope distribution of the peaks.

carboxylic acid. However, no aldehyde was observed experimentally in this study.

As an example of the reactivity of the carbocation formed by FcMeOH protonation, the nucleophilic substitution on indole (Figure 3)^[5a-c] was performed in a batch reaction and the results were analyzed by ESI-MS. After 5 min batch reaction between 5 mM FcMeOH and indole in DCB and 5 mM LiTB and 10 mM HCl in water the MS spectra showed the presence of a small amount of FcCOOH and 3-(ferrocenylmethyl)-1H-indole (315 Th). After 20 min of reaction the 3-(ferrocenylmethyl)-1H-indole peaks were dominant, as shown in Figure 3.

The control experiment with only 10 mM HCl in the aqueous phase was done to show that the polarization of the interface by the presence of a phase-transfer catalyst is critical to allow the reaction (Figure 3B). Indole cannot be charged under the ESI conditions, and hence it is not seen on the spectra. Figure 3 shows that the reaction described in the Scheme above proceeds relatively fast and with good selectivity, as no other reaction products are observed with ESI-MS. The described system is a model example of "proton transfer catalyzed" S_N1 substitution, where a phase transfer catalyst is first used to transfer protons into the organic phase, where they catalyze the carbocation formation. The same approach could be easily extended to other acid catalyzed reactions. Most previous investigations on acid catalyzed reactions rely on organic acids as proton sources, but in this case the reactivity is largely dependent on the acid strength. The approach described in this

paper allows the utilization of aqueous protons for acid catalysis.

The described system is very similar to the nucleophilic substitutions to ferrocenyl alcohols "on water",^[5a,b] but instead of a solid–water interface a liquid–liquid interface is utilized. This offers several advantages, like a better contact with the reactants resulting in shorter reaction times, and the possibility to turn the reaction on or off by adjusting the Galvani potential difference across the interface. A disadvantage is that an organic solvent is needed in these reactions. Also stereoselective reactions could be performed by the introduction of surface-active groups to the reactants: interaction with the interface would determine the orientation of the reactants, allowing more control over the stereoselectivity.

In summary, we have shown that proton transfer across the organic–water interface provides an excellent method for controlled "proton-transfer-catalyzed" ferrocenyl carbocation formation, which can be utilized in S_N1 substitution to ferrocenyl alcohols. The proton flux across the interface can be adjusted by adjusting the Galvani potential difference across the interface, either by a potentiostat or by an appropriate choice of salts. A controllable method for carbocation formation could be very beneficial for synthesis of a wide range of metallocene derivatives, as ferrocene derivatives have shown anti-aenemic and cytotoxic properties, and some show significant anticancer activity.^[11] Furthermore, these compounds are widely used in bio-organometallic chemistry.^[12] The synthesis taking place at liquid-liquid interfaces could also be used to control stereoselectivity of the reactions by introduction of suitable surface active groups to the reactant molecules. Biphasic ESI-MS was shown to be an efficient tool to understand and characterize biphasic reactions.

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Keywords: carbocations · electrochemistry · liquid–liquid interfaces · nucleophilic substitutions · proton transfer

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