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Electrochemical Control of Organic Reactions Involving Phase Transfer

by

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Abstract

Phase transfer catalysis reactions are reactions where the reactants are soluble in different solvents. The phase transfer catalyst facilitates the transfer of a reactant from one phase to another, hence enabling the reaction. This can be explained electrochemically: By partitioning between the phases, the catalyst establishes a potential difference across the interface, which drives the transfer of reagent into the other phase (usually an inorganic anion is being transferred into the organic phase), or controls the reaction at the interface. A similar potential difference can also be applied with electrochemical instrumentation and the reactions can be investigated in electrochemical systems. Electrochemistry at ITIES (Interface between Two Immiscible Electrolyte Solutions) provides a fast, convenient and simple way of investigating the electrochemistry of a synthetic phase transfer reaction. The organic syntheses were also carried out to confirm the electrochemical results.

Using an $\text{S}_\text{n}2$ reaction involving a catalytic step, it has been shown how to use electrochemical measurements of ion transfer across the aqueous-organic interface to understand the reactions following this ion transfer. The reaction investigated was the reaction between 2-bromo-3-methyl butyric acid and iodide and hydroxide. The experiments show that mechanistic details of consecutive steps in organic reactions, inseparable when carrying out the organic experiments, can be observed when the reaction is carried out electrochemically. Another reaction that has been investigated is a two-phase oxidation reaction, where cis-cyclooctene in an organic solvent is oxidised by aqueous permanganate. These experiments prove that ITIES can be used for investigations of two-phase reactions, which are too slow to be investigated on a normal cyclovoltammetric timescale. Again, the first reaction step can be investigated separately. In synthetic methods the further reaction of the intermediate makes the determination of the rate constant of the initial step difficult, whereas this rate constant is obtainable through simulations of the electrochemical experiments. Also, the experiments show that through electrochemical experiments at a liquid-liquid interface, it is possible to determine in which phase the initial step of a two-phase reaction takes place.
An $S_N1$ reaction has been investigated using synthetic methods. $S_N1$ reactions with a chiral substrate normally proceed by racemisation. The reaction chosen was the hydrolysis of $\alpha$-phenylethyl chloride. By using a two-phase system the reaction mechanism was altered to preserve optical rotation through inversion of configuration.
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1. Introduction

1.1 Phase Transfer Catalysis (PTC)

1.1.1 Introduction to PTC

Phase transfer catalysis is employed in reactions where the reactants are soluble in different solvents. The phase transfer catalyst acts to transfer one reactant into the phase of the other reactant, thereby enabling them to react. [1]

The phase transfer catalyst increases the yield dramatically: As an example can be mentioned the two-phase reaction between cis-cyclooctene and permanganate: When cis-cyclooctene is oxidised by permanganate to yield 1,2-cyclooctanediol, a yield of only 7% is reported in the absence of phase transfer agent. In the presence of the phase transfer catalyst benzyltriethylammonium chloride the yield is increased to 50%. [2]

Phase transfer catalysis provides mild reaction conditions. [2] For example it allows reactions to be carried out at lower temperatures. [3] It is an attractive alternative to the use of a solvent which dissolves both reactants. The use of such a solvent is often expensive on an industrial scale, [1] and also inconvenient for reactions where the difference in polarities of reactants is significant, [4] as well as for reactions where the solvent reacts with one of the reactants, as can be the case for example in permanganate oxidations.

Phase transfer catalysis (PTC) as a method offers considerable benefits to chemists and engineers. The advantages of PTC include increased yield, reduced reaction time and/or temperature, replacement or elimination of solvent, wider choice of raw materials, enhanced selectivity and higher safety. The reduced reaction time enhances productivity and hence promotes lower costs, and the elimination or replacement of solvent provides the facility to comply with stricter environmental standards. These factors, in combination with the wide range of organic and polymer reactions where PTC can successfully be used, make PTC popular in industrial applications.
The problems associated with PTC consist of lack of time to develop/optimise choice of catalyst, catalyst separation and other reaction or process parameters, as well as lack of expertise and confidence that the reaction will be successful. [5]

The transferred reactant is often an anion, which is transferred from an aqueous to an organic phase. By transferring a reactive anion into an organic phase various reaction can be conducted: displacement reactions, alkylation reactions, hydrolysis, oxidations and reductions are among the reactions that have been carried out catalysed by a phase transfer agent. [1]

1.1.2 Choice of catalyst

When choosing a catalyst factors that need to be taken into account are reactivity, catalyst stability, separation of catalyst from the product, achieved selectivity, cost, availability and toxicity, of which the two main criteria are reactivity and catalyst separation. [6]

Frequently used phase transfer catalysts are quaternary ammonium and phosphonium ions as well as crown ethers. [1]

Quaternary ammonium or phosphonium ions were found to dramatically increase the yield in two-phase displacement reactions, even in small amounts. These ions, the phase transfer agents, were not consumed, but continuously transferred the nucleophile into the organic phase. [7] Quaternary ammonium salts are cheap in comparison with crown ethers and can be simply removed by washing with water. [8]
Landini et al. investigated the two-phase reaction of n-octyl methane sulfonate with various inorganic anions in a PhCl/aqueous system [9].

\[
\text{Q}^+\text{Y}^- + n-C_8H_{17}\text{OSO}_2\text{Me} + KY \rightarrow n-C_8H_{17}Y+ \text{MeSO}_3K
\]

\[\text{PhCl-H}_2\text{O}\]

\(Y = \text{Cl, Br, I, SCN, N}_3, \text{CN}\)

The organophilicity of the catalyst was shown to be of major importance for its effectiveness, with a difference of up to two powers of ten in the pseudo-first order reaction rates depending on the structure of the phase transfer catalyst. The observed pseudo-first order rate constant was linearly related to the effective catalyst concentration in the organic phase. However, the second-order rate constants for this reaction, which take into account the concentration of the catalyst in the organic phase, differ only by an order of 2.5.

The anionic activity was found to increase only somewhat by replacing the phosphorous in the tetraalkylphosphonium catalyst with nitrogen, which increases the steric hindrance in the cation. It was concluded that the effectiveness of the catalyst mainly depends on its organophilicity. The reaction rate was found to increase with stirring up to 300 rpm, after which it remained constant, which illustrates the negligible effect of interfacial phenomena in this reaction. When the catalyst concentration was nearly equal to the substrate...
concentration, the second order rate constant increased somewhat when the concentration of the catalyst was decreased, which was attributed to the association of the quaternary ammonium salts. This effect was not found at lower quaternary ammonium concentrations, at which instead the reaction rate increased with increasing catalyst concentrations. It was hence concluded that at the lower concentrations of catalyst the limited number of water molecules associated with the quaternary salt in the organic phase was enough to suppress the formation of aggregates to a level which had no influence on reaction rates.

[9]

As well as transferring one reactant into the phase of the other reactant, the phase transfer catalyst must enable suitable reaction conditions for the transferred agent. Many anions show a very low reactivity when dissolved in organic solvents as sodium or potassium salts. When tetraalkylphosphonium or crown ethers are used to transfer the anion, the reactivity of the anion is remarkably improved. This is likely to be due to less interaction between the anion and the phase transfer agent, compared to the interaction between the anion and potassium, which results from a smaller distance of separation in the latter case. Uglestad et al [10] propose that relatively low cation-anion interaction energy in the ion pair, as can be expected between a quaternary ammonium cation and a halide, compared to a potassium halide, will promote the reaction in the organic phase. It has been postulated that the degree of dissociation is the same in the two cases, and that the reacting entity is the ion pair. [10] Other groups have shown that both the free anion and the ion pair it forms with the catalyst, or both, can be the reacting species. [11]

The extent of ion pairing is dependent on the size of the ions, and can be calculated using Bjerrum’s theorem. [12]

\[- \log \gamma_i = A\sqrt{\alpha_i c_i} / \left(1 + B\alpha_i c_i\right) \quad (1.1)\]

\[K_{\text{assoc}} = (1 - \alpha_i)c_i\alpha_i^2\gamma_i \quad (1.2)\]
where $K_A$ is the association constant of the salt, $A$ and $B$ are specific solvent parameters, $a$ is the distance of closest approach between the ions, $\gamma$ is the activity coefficient and $\alpha$ is the degree of dissociation.

Landini concluded that ion pair formation reaches an optimum degree of 'looseness', at least for a bromide salt in chlorobenzene for a quaternary ammonium salt having three ethyl groups and a long cetyl chain. [9]

Certain reactions, for example OH$^-$ initiated reactions which are conducted using PTC, show an increased reactivity with decreased organophilicity of the phase transfer catalyst. [13] An example of such a reaction is an alkylation reaction, which proceeds according to the Makosza mechanism. [14] In these reactions the first reaction step, occurring at the phase boundary, is a proton abstraction with the formation of a carbanion quaternary-ammonium cation ion pair.

Halpem et al concluded that shorter alkyl chains of the ammonium salts enhance the reactivity for these reactions better than long alkyl chains, and attributed this to the accessibility of the positively charged N site towards the association site of the anion. [15]

Halpem, as well as Starks [6, 16] consider that apparently contradictory conclusions on the effectiveness of different phase-transfer catalysts point to a variation in the mechanism of catalysis from one specific case to another, and that since the mechanism of phase transfer catalysis reactions can vary the cases mentioned above can all be right. [6]

The concept of phase transfer catalysis is general. It does not apply solely to anion transfer. With use of the right phase transfer catalyst, inorganic cations, acids, hydrogen peroxide and ammonia can all be transferred into the organic phase of a reaction mixture. [7]

1.1.3 Rate and mechanism of PTC

Phase transfer catalysis reactions involve at least two steps; the transfer of one of the reacting species across an interface, and the subsequent reaction of the two reactants. [1]
The rate determining step of the PTC reaction can be the transfer step ("T-reactions"), or the intrinsic reaction ("I-reactions"), or a combination of both, or alternatively another reaction step in some more complicated reaction such as many hydroxide reactions. [6] In T reactions, where the transfer of an ion is the rate determining step, the transfer of the reacting species can be the rate-limiting due to slow agitation, the use of highly hydrated anions, exceptionally high interfacial tension between the phases, or use of phase transfer catalysts that cannot properly approach the interface. [16]

Intrinsic reaction rates are increased by the organophilicity (increasing with increasing number of carbons on the quaternary ammonium cation), and by anion activation (increase by bulkiness of the quaternary ammonium cations) [6] as well as by adjusting temperature or organic solvent. [16]

In the 2-phase reaction of cyanide displacement on 1-chlorooctane, the anion transfer is the rate-limiting step below a stirring speed of 200rpm. Above 200rpm the stirring has no effect on the kinetics, indicating that the reaction in the organic phase has become the rate-limiting step. [16] The reaction rates of displacement reactions have been observed to be easily adjusted by changing the concentration of the phase transfer catalyst, [7] which is a mechanism in agreement with intrinsic reactions.

Two interpretations of the transfer step exist: One involves the transfer of the ion pair catalyst cation - reacting anion. The second interpretation assumes the permanent location of the quaternary cation in the organic phase, with only anions being transferred across the aqueous/organic interface. [16] The electrochemical interpretation of phase transfer catalysis is of the second type, but provides a different interpretation of the driving force for the anion transfer than that found generally in the literature of organic chemistry. [3]
1.1.4 Systems related to phase transfer catalysis

1.1.4.1 Interfacial reactions

Instead of being catalysed by a phase transfer agent, reactions can also occur at an interface between two phases. [17]

When carrying out a PTC reaction, there is often an interfacial reaction occurring in addition to the reaction in the organic phase. During every PTC reaction these mechanisms exist at various rates, and can be controlled by the reaction conditions. The truly interfacial reactions, or restricted-solution reactions (where a small part of the organic substrate is dissolved in the aqueous phase) can occur simultaneously with the phase transfer catalysed reaction. [16]

In reactions where at least one reactant is soluble in both phases the reaction rate depends on the diffusion of this reactant across the phase boundary, and is hence not due to surface phenomena. Dependence on stirring and interfacial tension can thereby be understood, since stirring changes the transport rate of species towards the interface and both stirring and interfacial tension control the breakup
of one phase into droplets dispersed in the other. In cases where two reactants are insoluble in the other phase the reaction will take place at the liquid/liquid interface and may depend upon the formation of adsorbed surface films. If the rate of the adjustment of adsorption equilibrium is slow in comparison to the rate of removal of molecules from the surface due to reaction, the reaction rate will be influenced by the stirring rate, since this affects the diffusion rate of molecules to the interface. However, if the reaction rate is only a function of the equilibrium of the surface layer, the stirring rate should have no influence. It has been found that oriented monomolecular films which are formed in solutions are not disturbed by moderate stirring. [18]

An organic molecule which is adsorbed onto an interface often experiences a different environment to the bulk phase. The dielectric constant, the concentration as well as the orientation of the molecule may vary from the molecule in the bulk phase. Whereas molecules in a bulk phase have a random orientation, the orientation of a molecule at an interface is often specified. [17] If a multifunctional molecule is positioned at a liquid/liquid interface so that only one of its labile groups is close to the interface this provides a possibility of reaction specificity. [19]

A significant paper in the field was published in 1928. [18] Benzoyl-o-toluidide in benzene was treated with permanganate in a neutral aqueous phase to produce benzoyl-anthralinic acid.

\[
\begin{align*}
\text{NHCOOC}_6\text{H}_5 \\
\text{CH}_3
\end{align*} \rightarrow \begin{align*}
\text{NHCOOC}_6\text{H}_5 \\
\text{COOH}
\end{align*}
\]

The solvent layers were stirred separately, and the oxidation was assumed to occur interfacially. Interestingly, the reaction rate was found to be independent on the stirring rate after a very short initial stage, which showed that the reaction rate was not dependent on the diffusion of either reactant towards the interface. The reaction rate was first order with respect to potassium permanganate and
above a certain level independent of the benzoyl-o-toluidide concentration. The authors concluded that the reaction occurred by permanganate striking an adsorbed layer of benzoyl-o-toluidide, and that the reaction rate was dependent only on the nature of the surface layer of the organic reactant as well as on the rate of impact of the permanganate ions. Very approximate calculations showed that only one in $10^7$ of the permanganate ions that reached the interface reacted with the organic substrate.

Another interfacial reaction that has been thoroughly investigated is the imidazole-catalyzed ester hydrolysis at a water-heptane interface. [19]

\[
\begin{align*}
\text{imidazole}_{\text{water}} &= \text{imidazole}_{\text{interface}} \\
\text{ester}_{\text{heptane}} &= \text{ester}_{\text{interface}} \\
\text{laurate anion}_{\text{water}} &= \text{laurate anion}_{\text{interface}} \\
\text{imidazole}_{\text{interface}} + \text{ester}_{\text{interface}} &\rightarrow \text{product}
\end{align*}
\]

When an aqueous imidazole solution is stirred rapidly under carefully controlled conditions with p-nitrophenyl laurate, ester hydrolysis takes place at the interface between the aqueous phase and the dispersed heptane droplets. In this case the hydrolysis rate is found to be a function of the stirring speed, concentration of reactants, temperature, viscosity of the organic phase, the volume of the phases, deuterium and salt content of the water, concentration of the organic reactant in the organic phase, presence of an amphiphile and structure of the catalyst. The reaction rate was found to be independent on the temperature and thus the authors concluded it to be diffusion controlled, instead of being kinetically controlled. The p-nitrophenyl laurate is insoluble in the aqueous phase. In this case the stirring was vigorous enough to disperse the hydrocarbon in order to produce a large interfacial area. Nevertheless, no more than 6% of the p-nitrophenyl of the heptane layer was hydrolysed in the experiments. The hydrocarbon-water interface was visualised as a three-dimensional region containing both water and hydrocarbon. It was postulated that the reaction between water and the ester was dependent on the ester molecule's location in this interfacial region.
The O- vs. C-alkylation of 1,1-dimethyl-2-indanone (4) is an example of a reaction where truly interfacial or restricted-solution reactions compete with PTC reactions, with different reaction products resulting from the different reaction pathways. [20] In the absence of a phase transfer catalyst the C-alkylation (6+7) is significant, and when a quaternary catalyst salt is added to the reaction, the O-alkylation (5) becomes the most significant reaction.

![Chemical Structures](image)

**Figure 1.3. Alkylation of 1,1-dimethyl-2-indanone**

1.1.4.2. Other systems

Quaternary ammonium salts with one or two large alkyl groups and two or three smaller alkyl groups possess good surfactant properties, and will produce micelles when added to a two-phase aqueous-organic system. The micelles provide a hydrophobic internal environment which dissolves nonpolar organic substrates, which then can react with anions which are attracted from the aqueous phase to the positively charged hydrophilic surface of the micelle. [1]
Other reaction systems related to phase transfer catalysis include the use of molten quaternary salts, catalysis by ion exchange resins, and preparative ion pair extraction. [1] Phase transfer catalysis with three phases has also been studied. A third phase may be formed when the phase transfer catalyst is insoluble both in the organic and in the aqueous phase. [21, 22, 23]

1.2. Electrochemical interpretation of phase transfer catalysis

The interpretation of phase transfer catalysis generally found in the literature of organic chemistry is based on the idea of extraction of anions as ion pairs into the organic phase which is due to an interfacial anion exchange process. [7] The selectivity of anion transfer is claimed to be determined by the association of the quaternary cation with the inorganic anion: quaternary cations in nonpolar environment will interact preferably with large anions as well as with anions that possess organic structure. [7]

The electrochemical view of phase transfer catalysis states that although ion pairing indeed may occur, and can be incorporated into the description of phase transfer catalysis, it is not a necessary condition. Electrochemically interpreted, the role of the phase transfer catalyst is to partition between the phases. By partitioning it will establish a Galvani potential difference (distribution potential) across the interface between the aqueous and the organic phase. The potential difference will drive the inorganic anion into the organic phase. [3, 24, 25] Since the driving force for the PTC reaction is an interfacial potential difference, it is possible to investigate PTC reactions using electrochemical instrumentation instead of a traditional phase transfer catalyst to establish the potential difference. The potential difference across the liquid-liquid interface in an ITIES system (Interface Between Two Immiscible Electrolyte Solutions) can act as the driving force for PTC reactions, as has been previously demonstrated. [3, 26]

Since all partitioning ions will contribute to the established potential difference [27, 28] the catalyst counterion and, if the reaction is slow, also the reacting inorganic anion, may contribute to the Galvani potential difference. The potential may alternatively act as the driving force for a redox reaction across the interface by facilitating interfacial electron transfer between a reductant in one phase and
an oxidant in the other. [24, 26] The interfacial potential difference then directly controls the reaction rate, just as in conventional electrochemistry with a metallic electrode.

The reason given for the poor transfer of hydroxide and fluoride into the organic phase, is claimed to be the high degree of hydration of these anions, in comparison with for example perchlorate and iodide. [29] It is noted in PTC theory that hydroxide is the most difficult anion to transfer into the organic phase. Furthermore any halide which is formed in the reaction greatly hinders the transfer of hydroxide. [16] These observations are in perfect agreement with the Gibbs free energies of transfer of these anions, and can be predicted from electrochemical calculations.

The concentration of the transferred ion should be less than that of the phase transfer catalyst salt so that the potential is determined by the phase transfer catalyst. Also the anion is of great importance for establishing the potential across the interface, and should therefore be carefully selected. It can be concluded that what is often seen as an ion pair extraction in organic chemistry would be more accurately described as an anion exchange. [3] However, the exact and careful establishment of potentials using a partitioning ion and different counter ions in the aqueous and organic phases is not always applicable in organic synthesis. As an example can be mentioned permanganate oxidations, where permanganate will oxidise tetraphenylborate, which often has been used as counterion in the organic phase. Another example is the case of substitution reactions, where counter ions such as chloride and bromide in the aqueous phase may influence the substitution reaction if transferred into the organic phase, given that these ions can react according to the substitution mechanism. [9]
1.3 Introduction to electrochemistry at the ITIES (Interface Between Two Immiscible Electrolyte Solutions)

1.3.1 General overview

Electrochemical experimentation at the ITIES (Interface Between Two Immiscible Electrolyte Solutions) is a relatively new field of electrochemistry. The research into ITIES has only been significant since the 1970s. It has featured at every meeting of the International Society of Electrochemistry for the last decade. The growing attention to the field is largely due to its wide range of applications. Research on processes at the ITIES includes charge transfer reactions, amperometric sensors, solvent extraction, pharmacokinetics, thermoelectricity, solar energy conversion and phase transfer catalysis.

In the present work electrochemical methods and concepts of the ITIES have been used to investigate ion transfer across an interface followed by homogeneous chemical reactions, as well as to investigate interfacial reactions. Hence this introduction will focus on the general properties of ITIES, ion transfer at ITIES as well as the investigation of biphasic reactions using ITIES.

1.3.2 Structure of the interface

The interface between two immiscible electrolyte solutions, separated by a density difference, can be assigned different structures depending on the time scale at which the observation is made. On a short timescale the interface is sharp, whereas seen on a longer time scale it must be described as diffuse. Also the thickness of the interface becomes a function of time. [30] The effect of the interface sharpness on two-phase reaction kinetics is not very well understood. It is estimated [16] that a hydrocarbon mixed with a concentrated aqueous salt solution has a very sharp interface (high interfacial tension), where interfacial mixing and hence the reaction rates of interfacial reactions are low. If the two solvents are partially miscible, the interface will be diffuse. In that case, the interfacial zone could also be assigned a concentration gradient from one side to the other. [16]
The liquid/liquid interface differs from the metal/electrolyte interface. Many suggestions for the structure of the liquid/liquid interface have been presented, such as models agreeing with the Gouy-Chapman theory with two back to back diffuse layers with a compact inner layer [31] as well as with ions penetrating into the inner layer. [32] A model was also proposed where the interfacial region consists of a mixed solvent region with a gradual change in the solvent properties, instead of being molecularly sharp, has been suggested. This model rejects the idea of an ion free inner layer. [33] Recent molecular dynamics simulations have indicated that the density of each liquid varies from its bulk value to almost zero over a distance of 0.7-0.9nm. The interface should be molecularly sharp, but with a roughness, which is attributed to protrusions, which are microscopic distortions of an otherwise sharp interface. Benjamin [34] showed that the roughness at a water/nitrobenzene interface is mainly due to protrusions of water molecules which are hydrogen bonded to the bulk water phase. These protrusions can have a length of up to 0.8nm and vary on the scale of tens of ps. There will be corresponding protrusions of nitrobenzene, but with a smaller amplitude. Fernandes et al used molecular dynamics simulations to investigate the interface between water and 1,2-dichloroethane. [35] They reported also for this system an interface which is sharp on the molecular level, with no mixed region, but with interpenetrating waves of one liquid into the other, hence broadening the interface. Neutron reflection measurements at the dichloroethane interface have indicated that the root mean square roughness should be less than 1nm. [36] There will be two interacting diffuse layers in both solvents, which will have dimension approximately 3nm at 0.01M salt concentration. Finally, concentration gradients of the transferring ions will be present over a distance scale on the order of μm. [37]

1.3.3 Polarisability of the interface

Liquid/liquid interfaces can be divided into polarizable and nonpolarizable interfaces. The polarizable interface, one where there is no reaction or ion transfer, facilitates external control of the potential difference across the
interface. [38] Although in practice all ions have certain solubility in both phases, thermodynamically an ideally polarizable interface means an interface where there are no common ions in the phases. [39] By choosing suitable supporting electrolytes, a potential range in which the interface can be electrically polarized with only a negligible current flow can be found. The small current which might flow can be explained by the transfer of the most easily transferable ion of the ions present in the two phases as well as by the charging current of the interface. [38] The polarized range of an interface is the range where ions existing in both phases do not significantly influence the electrochemical properties of the ITIES when investigated using a potentiostat. [40] By varying the supporting electrolytes, different potential ranges can be investigated by polarising the interface externally. [38]

A nonpolarized ITIES is defined as an interface between an aqueous and an organic phase which contain a common ion, and hence the application of a small potential will cause a large current to flow across the interface. Nonpolarized interfaces are utilised as reference interfaces between the organic phase of the ITIES and a reference aqueous phase, to which a reference electrode is connected. [38] The common ion is in this case often a hydrophobic cation which is dissolved in the organic phase as the cation of a hydrophobic salt and in the aqueous phase as a chloride salt.

1.3.4 Potentials across a liquid/liquid interface

The electrochemical potential, $\bar{\mu}_i$, of an ion $i$ present in a solution, can be arbitrarily divided into a chemical potential and an electrical potential. This division has no physical meaning, but is useful for the thermodynamic treatment of the system. The chemical potential of the ion $i$ in phase $\alpha$, $\mu_i$, can be described by

$$\mu_i = \mu_i^0 + RT \ln \alpha_i$$  \hspace{1cm} (1.3)
\(\mu_i^0\) refers to the standard chemical potential of the ion \(i\), where the solvent’s influence has been taken into account. \(a_i\) is the activity of the ion \(i\), \(R\) is the gas constant and \(T\) is the temperature expressed in Kelvin.

The ionic standard Gibbs energy of transfer of the ion \(i\) from phase \(\alpha\) to phase \(\beta\) can be written as [41]

\[
\Delta G_{i,\alpha\rightarrow\beta}^{0\alpha\rightarrow\beta} = \mu_i^{\beta} - \mu_i^{0\alpha}
\]

(1.4)

The contribution of the electrical potential to the electrochemical potential of the ion \(i\) in phase \(\alpha\) is described by the equation

\[
\mu_i^{\alpha,\phi} = z_iF\phi^\alpha
\]

(1.5)

\(\mu_i^{\alpha,\phi}\) is the electrical potential of the ion in phase \(\alpha\) and can be defined as the work required to bring the particle with the charge \(z_i e\) from infinity in vacuum to the inside of phase \(\alpha\). [40] \(\phi^\alpha\) is the inner potential of phase \(\alpha\).

When equations (1.3) and (1.5) are combined, the electrochemical potential of ion \(i\) in phase \(\alpha\) can be written as

\[
\bar{\mu}_i^{\alpha} = \mu_i^{\alpha,0} + RT \ln a_i^{\alpha} + z_iF\phi^\alpha
\]

(1.6)

If two phases, \(\alpha\) and \(\beta\), both containing the ion \(i\), are in contact with each other and at equilibrium, their electrochemical potential of the ion \(i\) is identical in both phases:

\[
\bar{\mu}_i^{\alpha} = \bar{\mu}_i^{\beta}
\]

(1.7)

According to equation (1.6), this can also be expressed as:

\[
\mu_i^{\alpha,0} + RT \ln a_i^{\alpha} + z_iF\phi^\alpha = \mu_i^{\beta,0} + RT \ln a_i^{\beta} + z_iF\phi^\beta
\]

(1.8)
Rearrangement gives:

\[
\left( \phi^\alpha - \phi^\beta \right) = \frac{1}{z_i F} \left( \mu_{i0}^\alpha - \mu_{i0}^\beta \right) + \frac{RT}{z_i F} \ln \frac{a_i^\beta}{a_i^\alpha}
\]  

(1.9)

Since \( \mu_i^\beta - \mu_i^\alpha \) is equal the standard Gibbs energy of transfer (equation (1.4)), equation (1.8) can also be written as

\[
\left( \phi^\alpha - \phi^\beta \right) = \frac{1}{z_i F} \Delta G_{i,i}^{0\alpha \rightarrow \beta} + \frac{RT}{z_i F} \ln \frac{a_i^\beta}{a_i^\alpha}
\]  

(1.10)

This is a means of calculating the Galvani potential difference, \( \Delta^*_\phi \), (the difference between the inner potentials of the phases, \( (\phi^\alpha - \phi^\beta) \)). [41]

The standard transfer potential is given by the equation

\[
\Delta^*_\phi_i^0 = \frac{1}{z_i F} \Delta^*_s G_{i,i}^0
\]  

(1.11)

This standard ion transfer potential describes the relative affinity of an ion for different phases in a standard state, which usually is 1 molkg\(^{-1}\) with unity activity coefficients assumed. [40] In assigning individual ions standard transfer potentials extra-thermodynamic assumptions have to be made. [41]

The standard Galvani potential scale is based on an extra-thermodynamic assumption. One example of such an assumption is the tetraphenylarsonium-tetraphenylborate assumption. [41] This assumption states that the difference between the solvation energies of tetraphenylarsonium and tetraphenylborate is negligible due to the similar structure of the ions.
The standard electrode potential in conventional electrochemistry, however, is based on the assumption that the free energy of the reaction $\text{H}^+ + e^- \rightarrow \frac{1}{2} \text{H}_2$ is zero. [41]

An ion which is partitioning between two phases will establish a Galvani potential difference (distribution potential) between these phases. This Galvani potential difference is related to the Gibbs free energy of transfer of the ion. According to definition, a negative potential difference means that the potential of the aqueous phase is negative with respect to the potential of the organic phase.

The Galvani potential difference established by a partitioning ion can be described by the equation: [41]

$$\Delta^\circ \phi = \Delta^\circ \phi_i^0 + \frac{RT}{z_i F} \ln \frac{a_i^w}{a_i^o} \quad (1.12)$$

The Galvani potential difference that is established by $\beta$ different partitioning ions can be calculated using eq (1.13) together with the conditions of conservation of mass and of electroneutrality in each of the phases, leading to:

$$\sum_{i=1}^{\beta} z_i C_i^{w,0} \frac{1}{1 + r \gamma_i e_i} + \sum_{i=1}^{\beta} r z_i C_i^{o,0} \frac{1}{1 + r \gamma_i e_i} = 0 \quad (1.13)$$
where \( r \) is the volume ratio between the organic and the aqueous phase, \( V^o/V^w \) and \( e_i = \exp \left( \frac{z_i F}{RT} \left( \Delta_{eq}^o \phi - \Delta_{eq}^w \phi^0 \right) \right) \)

Here \( \Delta_{eq}^o \phi \) is the equilibrium Galvani potential difference. \( c_i^{w,0} \) and \( c_i^{o,0} \) are the initial concentrations and \( \gamma_i^{w} \) and \( \gamma_i^{o} \) are the activity coefficients of the ion \( i \) in the aqueous and organic phase respectively. If the volume ratio, the standard transfer potentials for the ions, the starting concentrations of the ions in both phases and the activity coefficients are known, the only unknown factor is the equilibrium Galvani potential difference. This then can then be calculated. Alternatively, when the Galvani potential difference is known, the equilibrium concentration of a compound in the aqueous phase can be calculated from the equation (1.14). [27, 28]

\[
\frac{c_i^{w}}{1 + r \gamma_i^{w} e_i} = \frac{c_i^{w,0} + r c_i^{o,0}}{1 + r \gamma_i^{o}}
\]

(1.14)

The Galvani potential is the sum of the Volta potential (=the outer potential, \( \psi \)) and the surface potential (\( \chi \)).

\[
\phi = \psi + \chi
\]

(1.15)

The Volta potential difference between two phases equals the difference between the outer potentials of the phases, and is due to unequal distribution of ions in the two phases. [42]

The surface potential is due to the orientation of solvent and solute dipole molecules at the interface. Also the ions at the interface contribute to the surface potential. [41]
1.3.5 Ion transfer across a liquid/liquid interface

The potential where an ion will transfer across a liquid/liquid interface is determined by its Gibbs energy of transfer. When a Galvani potential is applied that provides enough free energy, by polarising the interface either using a potentiostat, [30] or a potential determining ion [3, 26] the ion will transfer into the other phase and the consequent current can be recorded.

The ion transfer can be divided into three phases:

- Mass transfer (mainly diffusion) in one phase towards the interface
- Ion transfer reaction
- Mass transfer in the other phase, away from the interface [30]

The mass transfer occurs over distances of micrometers and can be modelled using Fick’s laws. [30]

For ion transfer across a liquid/liquid interface both reversible and irreversible transfers have been described, as well as ion transfer modified by surfactants at the interface. [43, 44] Most ion transfer reactions can be considered reversible, and the similarity between equation (1.12) and the Nernst equation for redox reactions suggests that the theories used for redox processes are valid for ITIES, [30, 40] and that the electroanalytical methods which rely on the Nernst equation as a boundary condition for the solving of Fick’s diffusion equation can be applied to liquid/liquid interfaces. [30]

In cases where the supporting electrolytes have lower Gibbs free energies of transfer than the ion of interest, this ion will transfer outside the polarisation window. Usually this is the case with hydrated transition metal ions. However, when the metal forms a complex with a ligand in the organic phase, the Gibbs free energy of transfer for the metal is often reduced enough for the transfer to be observed. [45] Alternatively an interfacial complexation can occur, or the neutral ligand can be added to the aqueous phase and the complexation can occur in the aqueous phase with subsequent transfer. [30] Using complexing agents to alter the formal transfer potential of metal ions can be used for selective extractions of ions from an aqueous into an organic phase under controlled potential. [45]

Another area of interest for assisted ion transfer is the development of selective amperometric ion sensors. The transfer of a base in the form BH⁺ could be
regarded as an assisted proton transfer. Ion pairing could also be argued to fall into the category of assisted ion transfer. [30]

It has been found that the rate of polarisation and the concentration of the transferred ion have only a negligible effect on the ion transfer rate constant. The ion transfer rate constant is affected by the potential only by the indirect effect of the potential on the double layer structure. [46]

1.4 Phase Transfer Catalysis investigated at ITIES

Cunnane et al showed how the potential difference established by a potential determining ion acts as the driving force for electron transfer across a liquid/liquid interface. [26] Tin diphthalocyanine Sn(PC)\textsubscript{2} in the organic phase was oxidised by electron transfer into the aqueous phase where ferricyanide was reduced to ferrocyanide.

\[ \text{Sn(PC)\textsubscript{2} + Fe(CN)\textsubscript{6}\textsuperscript{3-} \leftrightarrow Sn(PC)\textsubscript{2}\textsuperscript{+} + Fe(CN)\textsubscript{6}\textsuperscript{4-}} \]

It was shown that a fast redox couple like ferri-ferrocyanide in an aqueous phase in contact with an organic phase gave virtually the same half wave potential for the electron transfer of tin diphthalocyanine as a metal electrode. The formal transfer potentials of tetraethylammonium and tetrapropylammonium were derived from cyclic voltammetry across a liquid/liquid interface. Different concentration ratios of these ions in the aqueous and the organic phase were then used to vary the Galvani potential difference across the interface. The established Galvani potential was calculated using electrochemical principles. Electron transfer across a liquid/liquid interface which was driven by the established Galvani potential difference was investigated in a two-phase gently stirred bulk experiment. The Galvani potential difference was varied to correspond to different points on the voltammogram for the oxidation of the diphthalocyanine. The logarithm of the ratio of the oxidized form of diphthalocyanine and the reduced form of diphthalocyanine (\( \log \frac{c(SnPC)\textsubscript{2}\textsuperscript{+}}{c(SnPC)\textsubscript{2}} \)) showed a Nernstian slope (close to 58 mV) when plotted versus the Galvani potential difference.
established by the partitioning ion. The potential of equimolar concentration (the half wave potential of the oxidation voltammogram of diphthalocyanine) was 40 mV more positive than the calculated value, which may have been due to approximations made in the calculations.

Girault et al studied the Williamson ether synthesis by polarising the interface between water and an immiscible organic solvent using a potentiostat. [3] The Williamson ether synthesis is an Sn2 reaction between alkoxide anion which acts as a nucleophile and an alkyl halide, alkyl sulfonate or alkyl sulfate. [47] When carried out homogeneously, the alkoxide anion must first be generated, usually by reacting an alcohol with a strong and expensive base such as Na metal, NaH or NaNH2. In phase transfer conditions 50% aqueous NaOH is sufficient to produce to alkoxide anion. The example chosen is the substitution of chloride in PhCH2Cl (benzyl chloride) by butoxide to form BuOCH2Ph (benzyl butyl ether) and HCl.

$$\text{BuOH}_{\text{water}} + \text{PhCH}_2\text{Cl}_{\text{org. phase}} \rightarrow \text{BuOCH}_2\text{Ph}_{\text{org. phase}} + \text{HCl}_{\text{water}}$$

The nonreactive solvent o-C6H4Cl was used to dissolve PhCH2Cl. The formal transfer potentials of BuO-, OH-, Bu4N+ and Br- were measured using o-C6H4Cl, which has physical properties similar to PhCH2Cl. These results were used to calculate the partitioning equilibrium concentrations in the aqueous and the organic phase in the absence of benzyl chloride, which illustrates how electrochemical calculations can be used to aid PTC reactions. They showed how electrochemical calculations explain how the catalyst cation and counter anion establish a potential difference across the interface. This potential difference then drives the anion transfer instead of the catalyst cation acting as a shuttle for the transferring anion. To prove the theory an electrolysis experiment was carried out, transferring BuO- across the interface using a potentiostat to establish the potential difference. Benzyl butyl ether was synthesised in a bulk electrolysis experiment using a potential difference which transfers BuO-. When a potential difference was established that was too positive to transfer BuO- no product was observed. [3]
Kontturi et al investigated the reaction between electrochemically transferred $H^+$ ion with tetraphenylborate and tetrakis(4-chlorophenyl) borate. [48]

$$H^+(w) + (\text{ClPh})_4B'(o) \leftrightarrow (\text{ClPh})_4BH(o)$$

$$(\text{ClPh})_4BH \rightarrow (\text{ClPh})_3B + \text{ClPh}$$

$[(\text{ClPh})_4B' = \text{TPBCl}]$

The techniques used were cyclic voltammetry and potential-step measurements. The rate constant of the homogeneous chemical reaction was obtained from cyclic voltammograms. TBATPB (tetrabutylammonium tetraphenylborate) or TBATPBCl (tetrabutylammonium tetrakis(4-chlorophenyl)borate were used as supporting electrolytes in the organic phase. In the case where TPBCl was used as base electrolyte, the positive side of the potential window was limited by the transfer of the hydrogen ion from the aqueous to the organic phase. When TPB$^-$ was used, this ion probably contributed to limiting the potential window on the positive side. It was shown that with increasing concentrations of HCl the potential window was shifted towards more negative values of potentials. At low sweep rates no return current could be observed at the positive side with TBACl$^-$. When the sweep rate was increased a return current could be observed. This occurred also when TPB$^-$ ions were used as supporting electrolytes in the organic phase. Using TPBCl$^-$ a return current could be observed also at lower sweep rates when the temperature was lowered to $+4^\circ C$. It is known that the decomposition of the tetraphenylborate acid, HTPBCl, proceeds slower at lower temperatures. From the solution of the diffusion problem describing the cyclic voltammetric wave the rate constant for the reaction following the charge transfer was evaluated. The first order rate constant for the decomposition of HTPBCl in the organic phase was found to be $1s^{-1}$.

Kakiuchi et al investigated the two-phase reaction between 2,4-dinitrofluorobenzene (DNFB) in nitrobenzene and OH$^-$ in an aqueous phase. [49] One of the products formed was 2,4-dinitrophenolate (DNP$^-$).
DNFB + OH⁻ ↔ DNP⁻ + F⁻ + H⁺

Cyclic voltammograms of 0.5M LiOH in an aqueous phase and 40 mM DNFB in nitrobenzene showed an increase of current with time, which indicated that the transferring species is generated due to contact of the two phases. The half-wave potential corresponded to the half-wave potential of DNP⁻. A polarogram where the potential was scanned from 500 mV to 100 mV showed a negative current. Two possible mechanisms proposed. The first was the partitioning of the DNFB into the aqueous phase where the substitution reaction occurs, with subsequent transfer of DNP⁻ into the organic phase when the potential is scanned in a negative direction. The second was the partitioning of OH⁻ into the organic phase with subsequent reaction. It was concluded to be unlikely due to the highly negative standard transfer potential of OH⁻. The third alternative for reaction mechanisms is an interfacial reaction. This alternative was excluded due to lack of influence of adsorbed positive surfactants at the aqueous side of the interface. This should increase the concentration of OH⁻ in close vicinity to the interface, which would result in an increased reaction rate and hence an increased current, provided that the reaction was truly interfacial. Since no such phenomenon was observed, the authors concluded that the likely mechanism is the partitioning of DNFB into the aqueous phase with subsequent reaction and transfer of DNP⁻.

Kakiuchi et al also investigated the substitution reaction between aqueous hydroxide and 1-p-toluenesulfonyl-2,4-dinitronaphtalene (TSDNN) in nitrobenzene. [50]

TSDNN + OH⁻ ↔ DNN⁻ + p-toluenesulfonate⁻ + H⁺

A polarographic technique was used to study the replacement of p-toluenesulfonyl with hydroxide. In the reaction 2,4-dinitronaphtalate (DNN⁻) was formed. A negative current was observed, as in the reaction between DNFB and OH⁻. It was concluded that the limiting current was kinetically controlled, since it was independent on the height of the aqueous reservoir. The limiting current was also proportional to the concentration of TSDNN and increased linearly with an
increased aqueous concentration of hydroxide. It was concluded that the mechanism was the same as previously described for DNFB: transfer of the organic substrate into the aqueous phase, substitution reaction in the aqueous phase with consequent transfer of an organic anion (in this case DNN') into the organic phase, monitored as a negative flow of current. Although the partition coefficient of TSDNN is one magnitude smaller than for DNFB \((3.4 \times 10^{-4} \text{ vs } 1.2 \times 10^{-3})\), it is enough to be significant. The rate constant was estimated to be \(1.03 \pm 0.23 \text{ M}^{-1}\text{s}^{-1}\).

Another reaction investigated by Kakiuchi et al is a two-phase azo coupling using an electrochemically established potential difference across the interface as the driving force. [51] Hydrophilic arenediazonium ions were transferred from an aqueous phase into a dichloroethane phase where an azo coupling reaction using different coupling components occurred.

\[
\begin{align*}
\text{Ar-N}_2^+ (W) &\leftrightarrow \text{Ar-N}_2^+ (\text{DCE}) \\
\text{Ar-N}_2^+ (\text{DCE}) + Y (\text{DCE}) &\leftrightarrow \text{Ar-N=Y}^+\text{-H (DCE)} \\
\text{Ar-N=Y}^+\text{-H (DCE)} + B &\rightarrow \text{Ar-N=Y (DCE)} + \text{HB}^+ (\text{DCE})
\end{align*}
\]

where \(Y\) is a coupling component and \(B\) is a base. The reaction in DCE is expressed as

\[
\text{Ar-N}_2^+ + Y \rightarrow \text{Ar-N=Y}^+\text{-H}
\]

for which the coupling reaction rate was measured. A coupling component in the organic phase significantly changed the reverse scan of voltammograms, with the height of the peak decreasing with decreasing scan rates. This suggests that the azo coupling reaction occurs in the organic phase. Also potential-step chronoamperometric measurements were carried out, where a diazonium ion was transferred into the organic phase using a potential step, and after a certain time transferred back into the aqueous phase by stepping the potential back to its original value. The peak for the back transfer was again diminished in the presence of a coupling component in the organic phase. The
rate of the coupling reaction was derived from the amperometric potential step experiments and was found to be 1.6-133.1 M⁻¹s⁻¹, depending on the compounds investigated.

1.5. Stripping voltammetry at ITIES

Stripping voltammetry has been used to investigate the charge transfer across the liquid/liquid interface. Huang et al used a vitamin B₁ ion selective microelectrode based on a water-DCE and water-NB interface. [52] They were able to detect trace vitamin B (4.6 *10⁻⁶M) in an aqueous sample solution using stripping voltammetry across the interface. Stripping voltammetry across a liquid-liquid interface has also been to study the transfer of poly(oxyethylene) alkyl and alkylphenyl ether non-ionic surfactants at trace levels. In a pre-electrolysis step the surfactant is transferred into the organic phase, assisted by a metal cation, followed by back-transfer into the aqueous phase. When pulse amperometry was used the stripping limiting current was proportioned to a surfactant concentration in the aqueous phase of 10nM. Heavy metals, for example Hg²⁺, Pb²⁺, Zn²⁺, Cd²⁺ and Pb²⁺ at trace level can be determined using stripping voltammetry across the interface between an organic gel and water. [53, 54]

In the present work, stripping voltammetry has been used to investigate the initial step of a biphasic reaction.

Reactions investigated in this work are the two-phase $S_{N}2$ reaction between 2-bromo-3-methyl butyric acid and the nucleophiles iodide and hydroxide, the two-phase oxidation reaction between permanganate and cis-cyclooctene as well as the two-phase interfacial reaction between water and α-phenylethyl chloride. Chapter 2 describes the background of these reactions. Chapter 3 describes the experimental conditions which were used. Chapter 4, 5 and 6 describe the results that were obtained. In chapter 7 the results are summarised, and suggestions for future work are made.
1.6 References


2. Background to the organic reactions studied

2.1 Permanganate oxidations

2.1.1 Permanganate as an oxidant

Permanganate is a strong and reversible, easily available oxidant which oxidises alcohols, alkenes, aldehydes, saturated C-H bonds as well as other functionalities. [1] Without phase transfer agents the use of aqueous permanganate as an oxidant for organic substrates is limited to substrates with at least a partial solubility in water. This is necessary in order to facilitate enough contact between the oxidant and the reductant. A way of overcoming this is using a polar organic solvent, which will dissolve both reactants. This requires a higher reactivity of the substrate than the solvent with permanganate. [2]

An alternative approach to permanganate oxidations of organic compounds is using a two-phase solvent system and a phase transfer agent. Quaternary ammonium salts, such as tetrabutylammonium bromide and benzyltriethylammonium have been used to solubilize permanganate in benzene ("purple benzene") and dichloromethane, respectively. [3, 4] Cyclic and acyclic polyethers can also be used as phase transfer agents. In these cases the polyether forms a complex with the potassium ion, and together with this complex permanganate is transferred into the organic phase. [2] Using crown ethers as the phase transfer agent, oxidations of olefins, alcohols, aldehydes and alkylbenzenes have been demonstrated. [5]

Huang et al recently reported the measurement of second order rate constants for the permanganate oxidation of perchloroethylene (0.035 ± 0.004 M\(^{-1}\)s\(^{-1}\)), trichloroethylene (0.80 ± 0.12 M\(^{-1}\)s\(^{-1}\)), dichloroethylene (1.52 to 48.6 M\(^{-1}\)s\(^{-1}\), depending on the isomer) [6] The permanganate oxidation of trichloroethylene is reported to proceed in the same way as the permanganate oxidations of alkenes (see below), the first intermediate being a cyclic hypomanganate ester. [7] These reactions could prove significant in the remediation of sites that are contaminated with chlorinated ethenes. [6]
2.1.2 Permanganate oxidations of non-terminal alkenes

Wagner in 1895 postulated that the first intermediate in permanganate oxidations of olefins is a cyclic manganate (V) ester (1). [8]

\[
\begin{align*}
\text{C} &= \text{C} \\
\text{O} &= \text{Mn} \\
\text{O} &= \text{O} \\
\end{align*}
\]

The oxygens are introduced into the olefin by permanganate, and not by the solvent, as has been shown using an oxidation of oleic acid by O\(^{18}\)-labelled permanganate. [9]

There seems to be general agreement regarding the first intermediate in permanganate oxidations of alkenes being this hypomanganate ester. [10,11,12,] The short life of this intermediate complicates its detection. Some authors claimed to have detected the hypomanganate ester using a stopped-flow technique. [11] Others, who used a stopped flow-chemical quenching technique claim that the hypomanganate ester intermediate is too short-lived to be detected using this technique, and that the intermediate detected at 415 nm is a soluble manganese (IV) species. [12] Attempts to observe the manganese (V) ester by \(^1\)H NMR and \(^{55}\)Mn NMR also failed, the reason given being that the oxidation of the manganese (V) ester to a manganese (VI) ester by electron transfer is very rapid. [5]. Indeed, as late as 1998, it was stated that no direct evidence had been given for a manganese (V) ester in olefin oxidation, [13] but that there at the time could be no doubt about the existence of both Mn (V) and Mn (VI) esters due to indirect evidence available from mechanistic studies.

Second-order rate constants have been measured for the permanganate oxidation of endo-dicyclopentadiene in dichloromethane using a quaternary ammonium ion
as phase transfer catalyst. Using spectrophotometry, a rate constant of $26.8 \pm 0.7$ units for the formation of the intermediate at 420nm and a rate constant of $27.3 \pm 0.5$ units for the disappearance of the permanganate at 525nm have been obtained at 298.2K. [14] These authors also pointed out the similarity between the spectra of the manganese dioxide and the manganate (V) ester, if compared at $\lambda > 300$nm.

The final reaction products of permanganate oxidations of non-terminal alkenes are highly dependent on reaction conditions. Acidic conditions yield cleavage products [11], basic conditions result in dihydroxylation [15] and neutral conditions lead to ketols. [15,16] Often a mixture of products is obtained. [11]

The variation in the products can be explained by the reaction mechanisms: Under acidic conditions the manganate (V) ester intermediate, 1, will decompose to give cleavage products and manganese (III), which is stable in acidic solutions. [11]

If a base is present, the manganate (V) ester can be hydrolysed:
Further hydrolysis of intermediate 2 could then occur, which would yield the 1,2-diol and manganese (V) as the final products.

\[
\begin{align*}
\text{MnO}_3^{2-} & \xrightarrow{\text{OH}^-} \text{MnO}_3^{2-} + \text{Mn}^V \\
2 & \quad + \quad 3
\end{align*}
\]

Alternatively, 2 could be oxidised by permanganate to a manganate (VI) ester, 3.

\[
\begin{align*}
\text{MnO}_3^{2-} & \xrightarrow{\text{MnO}_4^-} \text{MnO}_3^- \\
2 & \quad + \quad 3
\end{align*}
\]

The manganate (VI) ester, intermediate 3, could decompose to give the hydroxyketone and Mn (IV). [11]
Hence it would appear that hydroxide and permanganate compete for the same intermediate, 2, which can be either hydrolysed or oxidised, depending on the reaction conditions. This interpretation agrees with observations that formation of the diol is favoured by low permanganate concentration and relatively high base concentration, whereas the ketol formation is favoured by high permanganate concentration and relatively low base concentration. [9]

The first manganate (V) ester, 1, could also be oxidised to yield a manganate (VI) ester, 4.

\[
\begin{align*}
\text{Mn} & \quad \text{Mn} \\
\text{O} & \quad \text{O}
\end{align*}
\]

This manganate (VI) ester could then decompose to give cleavage products. [11]

\[
\text{R'} \quad \text{R''} \quad \text{Mn} \quad \text{O} \quad \text{Mn} \quad \text{O} \quad \text{R'} \text{CH} + \text{R''CH} + \text{MnO}_2
\]

The cleavage products could be oxidised by permanganate to form carboxylic acids. [2]
If the manganate (VI) ester, intermediate 4, is hydrolysed to intermediate 3, the hydroxyketone could also be formed via this ester. [11]

The above reaction schemes clearly illustrate that the final reaction products in permanganate oxidations are highly dependent on the reaction conditions, which therefore need to be carefully chosen when carrying out permanganate oxidations.

2.1.3 Further oxidation of diol

Alcohols are easily oxidised by permanganate in both aqueous and non-aqueous environments. [2] Vicinal diols are oxidised by acid permanganate to form products resulting from glycol bond fission. The oxidation of other diols result from oxidation of the hydroxy-group. There is a sharp increase in the rate of oxidation of vicinal diols with increasing acidity, which indicates that the oxidising species is permanganaic acid, HMnO₄. [17] The further oxidation of the alcohol is to be carefully avoided if the desired reaction product is the diol.

A large consumption of permanganate has been observed when treating ethanediol with excess permanganate. This may be due to eventual oxidation of ethanediol to carbon dioxide via formic acid. [17]

2.1.4 PTC oxidations

Permanganate oxidations of organic compounds are favourably carried out under two-phase reaction conditions. Crown ethers and quaternary ammonium salts as phase transfer catalysts have improved the yield in oxidation of olefins by
permanganate to 1,2 diols or carboxylic acids. [3, 4, 18] Good yields of oxidation of organic compounds using crown ethers have been reported. [3]

The potassium permanganate can be solvated directly in an organic solvent using an equimolar amount of quaternary ammonium salt [19], or solvated in an aqueous phase with subsequent transfer into the organic phase. [4] Alternatively, quaternary ammonium permanganate salts can be prepared and isolated. This salt can then be dissolved in the solvent which is used in the reaction. [20] When quaternary ammonium permanganate salts are isolated, care must be taken to avoid violent thermal decomposition. [21] The dangerous quaternary ammonium permanganate can be avoided by preparing it "in situ", as described above. Quaternary phosphonium and arsonium salts can also be used as phase transfer catalysts. [2]

As mentioned above, as an alternative approach to traditional PTC reactions quaternary ammonium salts can be used to solubilize potassium permanganate directly in dichloromethane, thereby providing an anhydrous environment for the oxidation of olefins solvated in the dichloromethane. [19] By quenching the reaction mixture with an aqueous solution, 1,2-diols or aldehydes were obtained, depending on the aqueous solution. When an oxidation of endodicyclopentadiene was quenched with an alkaline aqueous solution, 1,2-diols were obtained in good yield (83%). Using an acidic aqueous phase, aldehydes were obtained with 81% yield. When the pH of the aqueous phase that was used to quench the reaction was neutral, a mixture of the products was obtained. In a non-aqueous environment, aldehydes are the bond cleavage products, instead of carboxylic acids.

In homogeneous, non-aqueous organic solutions the organomanganese intermediates are more stable than in aqueous solutions, and last until the reaction is quenched with an aqueous solution. The intermediates are believed to be cyclic hypomanganate esters, as in aqueous systems. [8, 19] The high yield and selectivity in homogeneous, non-aqueous systems are likely to occur because the products are protected against secondary oxidations by permanganate through the formation of the stable organomanganese intermediate. [19]
Using this homogeneous, non-aqueous reaction environment and quenching the reaction with an alkaline aqueous phase, cis-cyclooctene was oxidised to the corresponding cis-diol in 70% yield. [19] In traditional two-phase phase transfer catalysis conditions, the yield is reported to be 50%. [4]

2.2 Substitution reactions

2.2.1 Substitution mechanisms

Nucleophilic substitutions, where an incoming nucleophile replaces a leaving group, often a halide, can be most distinctively classified into unimolecular (S\textsubscript{N}1) and bimolecular (S\textsubscript{N}2) substitutions. [22] In a bimolecular substitution the bond is exchanged in one act, whereas in unimolecular substitutions the bond is broken and a new bond is formed in a separate step. [23] Between these two cases, a number of reaction pathways can exist. [22] The classification of nucleophilic substitution reactions dates back to Ingold's original work in the 1930s. Depending on to which extent the rate of one type of substitution is favoured, one reaction route will be favoured over the other.

The pathway of a substitution reaction will be determined by the rates at which the unimolecular and the bimolecular substitution occur; if a molecule reacts rapidly according to the S\textsubscript{N}1 mechanism but slowly according to the S\textsubscript{N}2 mechanism, most of the molecules will react according to the S\textsubscript{N}1 mechanism, which hence will be dominating the reaction.

A number of factors will influence the rate at which the substitution reactions take place. The most important factors are structure of the substrate, the solvent, the concentration and reactivity of the nucleophile as well as the nature of the leaving group. [22]

A bimolecular substitution will occur with decreasing likelihood at the following carbon atoms: methyl > primary > secondary > (tertiary). [22] As the hydrogen atoms in a methyl halide are progressively replaced by alkyl groups, the mechanism is shifted from S\textsubscript{N}2 towards S\textsubscript{N}1. [23]
This occurs because bulkier groups at the seat of substitution will introduce steric hindrance in preventing the formation of the required transition state, which involves both the substrate and the nucleophile. A tertiary carbon atom at the seat of substitution will on the contrary favour a unimolecular substitution. [22]

Aryl groups are highly polarisable and hence a unimolecular substitution is favoured as substitution route at their adjacent carbon atom. The transfer of electrons in the initial bond-fission of an $S_{N}1$ reaction creates a large electron demand, which is why the capacity for electron-release of the aryl groups facilitates a unimolecular substitution. Aryl groups attached to the seat of substitution facilitate unimolecular substitutions more strongly than alkyl groups, which in turn, due to their electron-releasing properties facilitate unimolecular substitutions to a larger extent than hydrogen does. An aryl group at the seat of substitution will also promote racemisation if the seat of substitution is optically active, because the presence of an unsaturated group adjacent to the seat of substitution not only stabilises, but also flattens the carbocation. On the contrary, electron-attracting groups, such as undissociated carboxyl, ester and carboxylamide groups at the seat of substitution, will shift the substitution mechanism from $S_{N}1$ to $S_{N}2$. [23]

A unimolecular substitution is unaffected by the concentration or identity of the nucleophile, since the first, rate-determining reaction step involves only the dissociation of the leaving group from the seat of substitution. The rate of a bimolecular substitution is dependent on the concentration of the nucleophile as well as its identity. Due to its higher nucleophilic strength hydroxide will react more rapidly in a bimolecular substitution than water. [22]

Polar aprotic solvents, due to their lack of ability to form hydrogen bonds, do not solvate anions to an appreciable extent. Since the nucleophiles thus are poorly solvated, they will be less shielded and hence more reactive. Rates of bimolecular substitutions can increase up to million-fold in aprotic solvents, compared to when carried out in protic solvents capable of hydrogen bonding. A polar protic solvent on the other hand, will increase the rate of the initial rate determining ionisation step of $S_{N}1$ reactions, due to stabilisation of the carbocation. [22]
The unimolecular substitution is known to be considerably modified in a solvent with a low solvating power, such as benzene. In such a solvent the $S_{N\text{1}}$ reaction consists of two slow, rate determining steps and one intervening fast, product determining step: A slow ionisation, not entailing dissociation is succeeded by a fast, product-controlling dipole association, with consequent slow quadropole rearrangement. The first two steps are present in unimolecular substitution reactions occurring in highly solvating solvents, however in solvents with a low solvating power they are modified, which makes the third step necessary. [24]

The best leaving groups are the most stable molecules or ions after their departure. $S_{N\text{1}}$ is favoured by weak nucleophiles. Neutral molecules are weaker nucleophiles than anions.

The structure of the carbocation which is formed in the first step of a unimolecular substitution is trigonal planar. The substituting agent can hence react either from the frontside or from the backside of the carbocation. [23]

### 2.2.2 Stereochemical results of substitution reactions

In the present work substitution reactions have been investigated with focus on their stereochemical results. The stereochemical result of a substitution reaction is dependent on which reaction path that has been favoured by the reaction conditions, and hence on the mechanism of the substitution. The mechanisms of substitution reactions were studied using kinetic results, and subsequently kinetics were also used to investigate the stereochemistry of reactions.

It is known that bimolecular substitution reactions ($S_{N2}$) proceed with inversion of configuration, whereas unimolecular substitution reactions ($S_{N1}$) proceed with inversion with extensive, sometimes nearly complete, racemisation. [25]

The length of life of the carbocation will be of great importance for the mechanism and hence for the stereochemical result of the reaction. In cases where the dissociated anion produces a asymmetric shielding of the carbocation while the course of the substitution is determined, inversion of configuration will be the dominating stereochemical result. [23]
Hydrolysis of α-phenylethyl chloride was previously investigated by Ingold et al. [25], and was found to be unimolecular, and hence proceed with inversion with extensive, sometimes nearly complete, racémisation. The extent of racémisation was dependent on the solvent that was used: acetone/water. An increase in the content of inert acetone in the aqueous solvent resulted in an even higher extent of racémisation of the product. This is due to the concentration of the hydrolysing agent decreasing, resulting in a longer lifetime for the carbocation through the dilution of the reactive solvent with an unreactive solvent. [25] In a reactive medium, the carbocation is more short-lived, and will still be disymmetrically shielded by the leaving group when the course of the substitution is determined. [23] Semi-quantitative measurement showed that the rate of hydrolysis was independent of the potassium hydroxide concentration. [25]

Whereas unimolecular substitution was the only route for the hydrolysis of the optically active chloride, both unimolecular and bimolecular methoxylation occurred, and ethoxylation of the chloride proceeded almost solely according to the $S_{N}2$ mechanism. The shift in mechanism is due to a smaller ionising power of the methyl and ethyl alcohol compared to water, as well as to the methoxide and ethoxide ions being stronger nucleophiles than hydroxide. [25]

### 2.3 References


3 Experimental

3.1 Electrochemical experiments

3.1.1 Electrochemical instrumentation

The electrochemical measurements were carried out in a four-electrode cell using an Autolab electrochemical workstation (PGSTAT 100, Ecochemie, The Netherlands). The experimental set-ups used are described in schemes 3.1:

Scheme 3.1a Experimental set-up A

<table>
<thead>
<tr>
<th>Ag</th>
<th>AgCl</th>
<th>0.1mMTHPACl</th>
<th>10mMTHpATPB</th>
<th>0.5MLi2SO4</th>
<th>Hg2SO4</th>
<th>Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>org.ref. phase</td>
<td>org. phase</td>
<td>aq. phase</td>
<td>1,2-dichloroethane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aqueous solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scheme 3.1b Experimental set-up B

<table>
<thead>
<tr>
<th>Ag</th>
<th>AgCl</th>
<th>0.1mMBTPACl</th>
<th>10mMBTPATPB</th>
<th>0.5M KCl</th>
<th>AgCl</th>
<th>Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>org.ref. phase</td>
<td>org. phase</td>
<td>aq. phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aqueous solution</td>
<td>1,2-dichloroethane</td>
<td>aq. phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The area of the interface under study, denoted by $||$, was 0.2 $-0.27 \text{ cm}^2$, depending on which cell was used. The transferring ion was added to the aqueous phase. When a two-phase reaction was investigated, the organic reactant was added to the organic phase (1,2-dichloroethane).
3.1.2 Supporting electrolytes

For transfer of halides the experimental set-up A was used. The supporting electrolytes, tetraheptylammonium tetraphenylborate (THpATPB, Fluka, 98%) in the organic phase and Li$_2$SO$_4$ (Aldrich, 99+%) in the aqueous phase were chosen because of the hydrophobicity of the tetraheptylammonium and the hydrophilicity and salting-out efficiency of the sulphate ion. These properties expand the negative branch of the potential window, which is necessary to observe the transfer of halides. The transfer of the organic supporting electrolyte is often considered to limit the polarisation window. To remedy this, organic supporting electrolytes with high organophilicity were chosen. Alternatively the Gibbs energy of transfer of the organic supporting electrolyte ions can also be altered by salting out these organic ions by using suitable aqueous electrolytes. The aqueous electrolytes used alter the activity of the organic ion in the aqueous phase. It has been shown that when tetraphenylarsonium tetraphenylborate is used as supporting electrolyte in a dichloroethane, both Li$_2$SO$_4$ and MgSO$_4$ in concentrations above 0.1M considerably increase the potential window, and for a concentration of 2M MgSO$_4$, the polarisation window is extended to almost 700mV. [1]

In experimental set-up B, bis(triphenylphosphoranylidene)ammonium tetraphenylborate (BTPPATPB) and KCl were used as supporting electrolytes in the organic and the aqueous phases, respectively, and BTPPACl and KCl were the supporting electrolytes in the organic reference phase.

The cell potential is defined as shown in the scheme above, i.e. the potential of the aqueous reference electrode with respect to the organic reference electrode. Cell potentials were converted to potentials on the standard Galvani scale by the formula

$$\Delta\Phi / V = E_{\text{cell}} / V - E_{1/2} / V \text{ (database)},$$  \hspace{1cm} (3.1)

Equation 3.1 is derived by comparison of the half-wave potential for an ion transfer with the standard transfer potential of the ion ($E_{1/2}$) listed in a database.
[2] Positive current is defined as the transfer of a positive charge from the aqueous phase to the organic phase.

The ohmic drop in the solution was compensated by positive feedback. Since the organic Luggin capillary was situated very close to the interface, especially in the experiments where the halides were transferred, the amount of necessary ohmic drop compensation was rather small, typical values being 0-200 Ω for the halide transfer experiments. For the permanganate transfer experiments the compensation required was a bit higher (0-1000 Ω), and was checked prior to each scan. Due to the smaller dielectric constant and hence larger resistivity of the organic phase, the largest part of the ohmic drop occurs in the organic phase.

The measurements were carried out in a Faraday cage at room temperature (21 ± 3 °C).

The cell design is pictured in scheme 3.1.

δ represents the organic phase, γ represents the aqueous phase and β represents the organic reference phase.

Figure 3.1 Cell design used to investigate the electrochemistry at a liquid/liquid interface
3.1.3 Reference electrodes

As reference electrodes in the four electrode set-up two Ag/AgCl electrodes or one Ag/AgCl electrode and one Hg/Hg\_2SO\_4 were used. The Ag/AgCl electrode was made by applying a positive current (150 μA) on a silver wire in 0.5M HCl during 30 min. When making the Ag/AgCl electrode, a platinum wire was used as the counter and reference electrode. The potential of the Ag/AgCl electrodes were approximately -45mV against a saturated calomel electrode in a saturated KCl solution. The Hg/Hg\_2SO\_4 electrode was made in-house, as was a Hg/Hg\_2Cl\_2 electrode that was used as reference electrode to check the potential of the other electrodes. The potential of the Hg/Hg\_2SO\_4 electrode was 0.411V against a saturated calomel electrode in a saturated KCl solution. The inner solution of the calomel and mercury/mercury sulphate were saturated KCl and 1M Li\_2SO\_4, respectively. The electrodes were stored in the same solution as their inner compartment solution.

An attempt was made to make a Ag/AgI electrode in the same way that the Ag/AgCl electrode was made. The electrode would have been used as reference electrode when measuring the iodide transfer, since the iodide concentration in the bulk phase remains constant during the cyclic voltammetric experiment. This electrode, however, turned out to be highly unstable and was thus not used. The use of Ag/AgCl in the iodide transfer experiments was not possible due to interference of the chloride transfer with the iodide transfer.

3.1.4 Electrochemical techniques

3.1.4.1 Cyclic voltammetry

Cyclic voltammetry was used to observe ion transfer across the interface between an aqueous and an organic phase. Cyclic voltammetry experiments can be carried out at a liquid/liquid interface as well as at a metal/solution interface. The potential across the interface is swept from the potential E1 to E2, and then back to E1. The current resulting from the charge transfer across the interface is recorded as a function of the potential. The sweep rates used normally vary from
a couple of mV/s to a couple of hundreds of V/s. Cyclic voltammetry is a good experiment for initial investigations of a system. The appearance, variation and disappearance of different peaks at different values of potential limits and sweep rates give information about the system. Although kinetic data can only be obtained from the first scan, the variation among subsequent scans can provide valuable information about the system. [3]

Conventional cyclic voltammetry across the ITIES is mainly useful for determining diffusion coefficients and half-wave potentials. When the half-wave potential is measured, it is possible to estimate the standard Galvani potential for the ion, if certain factors are taken into account: The activity coefficients in both the aqueous and the organic phase are often assumed to be equal to unity, and this assumption has been made in the present work. The diffusion coefficient ratio is usually estimated to be the reciprocal of the viscosity coefficient ratio. However, when these assumptions are used for detailed interpretation and modelling of experimental data problems can arise.

Firstly, activity coefficients might be different from unity for large quaternary ammonium ions in water. The activity of ions might be different from unity in organic solutions with a low dielectric constant (such as dichloroethane), even in solutions as dilute as $10^{-3}$M. [4]

Such deviations will alter the activity of the ion that will be established according to the Nernst equation applied to the ITIES. This might be the reason why quoted values for Gibbs energy of transfer differ depending on the method that is being used for determining $\Delta G_{\text{tr}}$ (cyclic voltammetry or partitioning experiments). [2]

Another difficulty might be that ions will transfer hydrated from the aqueous to the organic phase in partitioning experiments, with the degree of the hydration depending on the ion. [5] This means that any ion pairing that might occur and which is generally accounted for by theory such as that due to Bjerrum [6] could be highly suppressed by water molecules transferred into the organic phase as hydration shells of the anion.

In cyclic voltammetry the process $O + ne^- \leftrightarrow R$ is recorded as the current flow. As an example, the case where initially only $O$ is present at a metal/electrolyte
interface is considered. As the potential of the electrode is scanned in a negative direction the species \( O \) will be reduced to \( R \) since the ratio of \( c_O/c_R \) in the Nernst diffusion layer is defined by the Nernst equation. The current is proportional to the diffusion of \( O \) to the electrode interface. When the potential is negative enough to convert all the interfacial \( O \) into \( R \), the concentration of \( O \) will be virtually zero in the vicinity of the interface, and the concentration gradient will have reached its maximum, which will lead to the characteristic peak in the cyclic voltammograms. Hereafter the concentration gradient starts to decrease due to diffusion, and the observed current will decrease. When the potential is reversed the current will flow in the same direction until the potential reaches the value where reoxidation starts to occur, \( E^{\circ} \). The magnitude of the current will be lower on the back scan than the forward scan, due to part of the electroactive species (\( R \)) having diffused into the bulk phase. When the cyclic voltammograms is solved mathematically using Fick's second law of diffusion for the electroactive species and the correct initial and boundary conditions as well as planar diffusion, the Randles-Sevcik expression (equation 3.2) is obtained for the peak current:

\[
I_p = -0.443 \ nF \left( \frac{nF}{RT} \right)^{1/2} c_0^{\infty} D^{1/2} v^{1/2} \tag{3.2}
\]

At 25° C this equation is reduced to

\[
I_p = -(2.69 \times 10^5) n^{3/2} c_0^{\infty} D^{1/2} v^{1/2} \tag{3.3}
\]

Where \( I_p \) is the peak current density in A cm\(^{-2}\), \( D \) is the diffusion coefficient given in cm\(^2\) s\(^{-1}\), \( v \) is the potential scan rate in Vs\(^{-1}\) and \( c_0 \) is the bulk concentration in mol cm\(^{-3}\).

If a cyclic voltammogram is reversible, the kinetics of the electron transfer (or ion transfer across a liquid/liquid interface) are fast enough for the current to be limited by diffusion to and from the interface, and the diffusion layer concentrations are at all potentials given by the Nernst equation. For a reversible
system O and R must also be stable. There are several indicators for a reversible system:

1. The peak separation $\Delta E_p$ is $59 / n \text{ mV}$. ($E^A_p - E^C_p$)

2. $E_p - E_{p/2} = 59 / n \text{ mV}$.

3. $I^A_p / I^C_p = 1$

4. $I_p$ proportional to $\nu^{1/2}$

5. $E_p$ is independent of $\nu$

6. At potentials beyond $E_p$, $I^2 \propto t$.

If the electron transfer kinetics are not fast enough to maintain the Nernst equilibrium at the surface of the electrode or in the diffusion layer the cyclic voltammogram changes, and becomes quasi-reversible or irreversible. One of the typical characteristics of an irreversible cyclic voltammogram is the absence of a reverse peak and an increase in the peak separation with the sweep rate. [3]

3.1.4.2 EC reactions

Cyclic voltammetry is highly suitable for investigating coupled chemical reactions. The chemical reaction can occur either before or after the charge transfer, or both before and after a charge transfer.

The EC mechanism, where the charge transfer is followed by a chemical reaction can be described by:

$$O + ne^- \leftrightarrow R \quad (3.4)$$

$$R \leftrightarrow Y \quad (3.5)$$

The shape of the cyclic voltammograms is dependent on both these steps. The charge transfer can vary from irreversible, in which no kinetic information about the chemical reaction can be obtained from the cyclic voltammograms, to completely reversible. The chemical reaction can vary from reversible to irreversible.
If the charge transfer is reversible and the chemical reaction is irreversible no reverse peak can be observed at low sweep rates, since R is rapidly reacting as it is forming. Also the cathodic peak potential is shifted towards more positive values than would be expected for a reversible charge transfer. This is due to more charge transfer having to occur in order to maintain the Nernst equilibrium at the interface, which is influenced by the homogeneous chemical reaction taking place after the charge transfer. [3] At higher sweep rate a reverse peak can be observed. The rate constant \( k \) for the chemical reaction can be derived from comparing experimental \( I_p^A / I_p^C \) ratios plotted as a function of \( \log k \tau \), where \( \tau \) is the time required to scan the potential from \( E_{1/2} \) to the switching potential at which the potential sweep is reversed. [7] To obtain correct values of \( k \) several switching potentials and sweep rates should be used. Alternatively the rate constant can be obtained using digital simulations, as has been done in the present work. [3]

3.1.4.3 Chiral surfactants used at a liquid/liquid interface

Chiral surfactants were used to modify the liquid/liquid interface in the electrochemical experiments where iodide was transferred across the interface with 2-bromo-3-methyl butyric acid in the dichloroethane phase. The surfactants used were a phenylalanine derived surfactant, a leucine derived surfactant as well as (10R, 11S)-(−)-N-Methyl-O-hexadecylquininium (figure 3.2).
Figure 3.2. Surfactants used to modify the interface: Phenylalanine derived surfactant (1), Leucine derived surfactant (2) and (10R, 11S)-(-)-N-Methyl-O-hexadecylquinium (3).

The concentrations used were 50-100 μM. Higher concentrations could not be used due to problems with interface stability.

3.1.4.4 Stripping voltammetry

In traditional stripping voltammetry the analyte, often a metal ion, is pre-concentrated in a Hg working electrode by application of a negative potential. After a certain time the potential is scanned in a positive direction. The pre-concentrated metal is oxidised and the anodic current which is measured as a result of the oxidation is proportional to the analyte concentration in the solution. [8]

An analogy of stripping voltammetry was used in this work to measure the rate constant of the first reaction step in the reaction between permanganate and cis-cyclooctene. Due to the slow kinetics of the reaction a potential profile analogous to that used for stripping voltammetry was applied. Permanganate was first transferred into the organic phase by scanning the potential moderately rapidly in the negative direction (scan rate \( ν=50 \text{ mV/s} \)). Then the potential was held constant for some time, typically 60 s, to allow \( \text{MnO}_4^- \) to react in the organic
phase, analogous to the preconcentration step in stripping analysis. Subsequently
the permanganate remaining was determined by transfer back into the aqueous
phase during the back scan (\(v=10\) mV/s). There was some small variability
(<20\%) in the charge passed during the transfer of permanganate into the organic
phase, which has not been found with the transfer of other, unreactive species
and which is perhaps associated with the formation of MnO\(_2\) near the interface.
To compensate for this effect in the data analysis, currents were renormalized by
dividing by the ratio of the amount of charge transferred into the organic phase
during the first 70s of the experiment to the charge transferred during that time in
a particular experiment taken as a standard for the series. Transfer of
permanganate into the organic phase by applying a potential step resulted in a
high degree of irreproducibility, and was thus not used in the present work. This
irreproducibility is attributed to an uncertainty in the large required IR drop
compensation, which is a result of the instant high current (0.25 mA - 1.0 mA)
which flows in the chronoamperometric experiments.
Over time, as the reaction proceeds, the interface became clogged with MnO\(_2\)
and the transfer current for MnO\(_4^-\) was diminished. The measurement time was
limited in the present work in order to minimise this effect.

3.1.5 Digital simulations

Digital simulations can conveniently be used to obtain kinetic parameters for
systems where an analytical solution would be too complicated to develop. The
differential equations that describe the system (mass transport and reactions) are
solved by converting these equations into difference equations, which are solved
to fit the experimental system by adjusting rate parameters. The parameters of
the systems are converted into dimensionless parameters, in order for one
simulation to cover a variety of experiments. [9] Digital simulations can also be
used for learning purposes: The simulations enables a clear understanding of how
concentration profiles change with time and applied potential or current. [3]
In this work, an approximate solution of the reaction/diffusion problem was
found by the standard method of explicit finite differences. [10] The distance
from the liquid/liquid interface was divided into small spaces, \(dx\), and the time
was divided into small time steps, \(dt\). The concentration profiles of the
permanganate in the aqueous phase and permanganate and cis-cyclooctene in the organic phase were obtained for each $dx$ during each $dt$. The concentration changes during each $dt$ in each $dx$ due to diffusion were calculated from Fick's laws of diffusion, and the concentration changes in the organic phase in each $dx$ which were due to reaction were calculated using the homogeneous reaction equation. The rate constant for the homogeneous rate equation was obtained by adjusting the simulation concentration profile to fit the experimental current. [3] The concentration of permanganate in the $dx$ closest to the interface was obtained from the Nemst relation between the activity of the species in the organic phase and in the aqueous phase (equation 3.6), analogous to the treatment of the boundary values for activity of the oxidised and reduced species at a metal electrode:

$$\frac{\alpha^{a}_{i}}{\alpha^{w}_{i}} = \exp\left[\frac{(\Delta^{a}_{i}\Phi - \Delta^{w}_{i}\Phi^{0}_{i})}{RT}\right]$$

(3.6)

The current density that was compared to the experiments was obtained from the concentration changes in the $dx$ closest to the interface, since

$$I = -nFd \left( \frac{\delta C_{i}^{a}}{\delta x} \right)_{x=0}$$

(3.7)

The potential profile of the simulations was adjusted to be identical to the potential profile of the experiments. The potential range was divided into three sectors, the forward scan, the constant potential and the back scan. The sweep rate in the simulations was obtained by dividing the whole experiment into time steps and giving each potential sector a fraction of the time steps proportional to its duration with respect to the whole experiment.

Errors in simulations may arise from two sources: an error in the code, or the approximations made when discretising the differential equations. Another cause of error is the sequential treatment [9] of diffusion and reaction in the explicit scheme, whereas they in reality occur simultaneously. This latter error was estimated by halving the time step and comparing the peak potential values for scans with reactant in the organic phase. The time step was chosen for which the
difference in the peak current was less than 0.7% for subsequently doubling of
the time step. In all simulations the time step was $\Delta t = 0.113$ (corresponding to $\Delta t = 0.000833s$) and the space interval $\Delta x = 0.057$ (corresponding to $\Delta x = 0.049cm$).

3.2 Organic chemistry experiments

3.2.1 Synthetic procedures for Phase Transfer Catalysis

*Hydroxylation of 2-bromo-3-methylbutyric acid (reaction 1):* S-(-)-2-bromo-3-methylbutyric acid (89.2 mg, 0.49 mmol) in 1,2-dichloroethane (50 cm$^3$) was stirred with aqueous KI (83 mg, 0.5 mmol in 50 cm$^3$, pH = 9) containing 5 mmol phase transfer catalyst (tetramethylammonium chloride or tetraphenylphosphonium chloride). The KI was added slowly during 15 min, after which the mixture was stirred for another 15 min. The phases were separated, the organic phase evaporated under reduced pressure and the solid (product and phase-transfer salt) was redissolved in CDCl$_3$ and the product identified by NMR spectroscopy (300 MHz). 2-bromo (or hydroxy) -3-methylbutyric acid were identified using $^1$H and $^{13}$C NMR analysis and comparing the results with NMR spectra of standard commercial samples available from Aldrich. [11] Attempts to prepare the iodo-acid with KI in acetone resulted only in the hydroxyacid: presumably the iodo-acid reacted rapidly with trace water in the acetone.

*Hydroxylation of triphenylmethyl chloride (reaction 2):* In these experiments nitrobenzene was used as solvent, due to the higher dielectric constant of nitrobenzene compared to dichloroethane, (34.8 and 9.2, respectively). [12] A high dielectric constant promotes separation of charge, which is necessary in a unimolecular substitution where the first reaction step is the formation of a carbocation and a counterion. Triphenylmethyl chloride (71 mg, 0.25 mmol) in nitrobenzene (25 cm$^3$) was stirred with aqueous KI (41.5 mg, 0.25 mmol in 25 cm$^3$, pH = 9). The KI was added slowly during 5 min, after which the mixture was stirred for another 25 min. The solution turned very yellow during stirring. The phases were separated, and the organic phase evaporated under reduced
pressure while heating to 70°C in order to remove the nitrobenzene. The solid (product and phase-transfer salt) was evaporated several times from toluene in order to remove the nitrobenzene, and were then redissolved in CDCl₃ and the product identified by NMR spectroscopy (300 MHz), as in the hydrolysis of 2-bromo-3-methyl-butyric acid. ¹H and ¹³C NMR analysis were used, and the results were compared with NMR spectra of standard commercial samples available from Aldrich. [12] An experiment where tetrapentylammonium chloride was used as phase transfer catalyst was also carried out. The triphenylmethyl chloride (28.4 mg, 0.1 mmol) in nitrobenzene (10 cm³) was stirred with aqueous KI (16.6 mg, 0.1mmol in 10 cm³, pH = 9) containing tetrapentylammonium chloride (67.5 mg, 0.2 mmol). The KI was again added slowly during 5 minutes, whereafter the reaction mixture was stirred during 25 minutes. The work-up was carried out identically to the experiment without a phase transfer catalyst.

3.2.2 Procedures for determining the transfer potential of hydroxide

10 ml 0.00158 M tetraheptylammonium chloride (the phase transfer catalyst, in dichloroethane) was equilibrated with 10 ml 0.00101 M KOH (aq. phase) during 3 minutes. The mixture was allowed to settle for 15 minutes, after which the pH of the aqueous phase was measured. The transfer potential of hydroxide can be calculated when the amount of transferred hydroxide is known. [13,14] In the calculations the activity coefficients for OH⁻ were obtained from tables, [15] and the activity coefficients were taken to be equal in the organic and the aqueous phases.

3.2.3 Permanganate oxidation in synthesis

11g (0.1 moles) cis-cyclooctene was dissolved in 100 ml dicloromethane, to which 100 ml 40% aqueous phase and 0.0044 moles phase transfer catalyst (1 g benzyltriethylammonium chloride, 1.22 g tetrabutylammonium chloride, 2.124 g tetraoctylammonium hydroxide) or alternatively 0.001 moles (0.165 g tetraethylammonium chloride) was added (reaction 3). The reaction mixture was cooled to 0°C, and 15.8 g (0.1 moles) permanganate was added during 2h. The
reaction mixture was left to stir overnight in an icebath (0°C). [16] The reaction mixture was filtrated with diethylether. The ether was then evaporated and the product was analyzed using NMR. In an alternative work-up the MnO₂ was reduced using SO₂. The organic phase was then separated and the aqueous phase was washed three times with diethylether which was added to the organic phase. The organic solvents were evaporated under reduced pressure and the products were analyzed using NMR.

Analysis of the aqueous phase required a separation of the organic products from inorganic salts. The aqueous phase was separated, acidified to pH~1, extracted first with dichloromethane (DCM) and second with toluene. The DCM and toluene-water mixtures were evaporated under reduced pressure. Chloroform was added to dissolve the product, was separated from the remaining salt by filtration, and then evaporated under reduced pressure. NMR, IR and GC-MS were used to identify the products from both aqueous and organic phases.

In equilibrium partitioning experiments, an aqueous phase containing permanganate (as KMnO₄) and PTC (as chloride) was shaken with DCE. After the phases had settled, the aqueous phase was removed and the permanganate concentration determined by uv-vis spectrophotometry.

3.2.4 Synthesis of α-phenyl ethyl chloride

The phenylethyl chloride was not commercially available, and was synthesised from 1-phenylethanol (reaction 4). Two syntheses were used (6 experiments). [17, 18] The temperature of both syntheses was modified in order to achieve a higher stereoselectivity. Both syntheses were also run over a shorter period of time in order to eliminate the possibility of racemisation with time. Success was achieved when the method according to Ingold [17] was used with modified concentrations.

0.5ml S-(-)-1-phenylethanol was added to 1.5ml thionyl chloride. [17] After 1 hour another 1ml thionyl chloride was added and the reaction mixture was left to stir overnight. The work-up was done using a column of 9:1 hexane:EtOAc. The sample racemised. Another reaction was carried out, taking samples after 1 hour,
5 hours and then left to run overnight. HPLC analysis showed that a racemisation had occurred already after 1 hour.

In order to achieve higher stereoselectivity, a reaction was carried out where the 0.2ml alcohol was added to 0.5ml thionyl chloride at -20°C while stirring with molecular sieves that had been activated by heating with a Bunsen burner under vacuum. After addition of the alcohol, the reaction mixture was left in the fridge over the weekend. The thionyl chloride was then pumped off during 3 hours at room temperature. The molecular sieves were filtered away, and the filterpaper and flask were washed with diethyl ether. The ether was rotary evaporated at room temperature. The thionyl chloride was pumped off, and the solid was filtered through a pipette with cotton and sand using hexane:EtOAc (9:1) in order to remove impurities. The solvents were evaporated and the product was analysed using HPLC, and turned out to be the racemised chloride.

In the successful synthesis of the chloride, 0.2g (0.00164 moles) commercial 1-phenylethanol was dissolved in 1 ml distilled CH$_2$Cl$_2$. 2.4 ml thionylchloride (0.033 moles, 20 equivalents with respect to the alcohol) was added at room temperature and the reaction mixture was allowed to stir for no more than 3 1/2 hours. The reaction mixture was then evaporated to dryness with a cold water bath. The product was isolated using a short column with 30:1 hexane:ethylacetate, the optical rotation was measured and the product was identified using NMR. It is likely that the attempts to analyze the optical rotation using HPLC failed due to a decomposition of the chloride on the silica. The purifications on silica columns were carried out very quickly.

Attempts were also made to carry out the synthesis of the chloride by reaction between 1-phenylethanol and phosphorous oxychloride [18]: 0.7ml (0.0058 moles) R-(+)-1-phenylethanol was added to 1.40 ml pyridine in 3.2 dry pentane. 0.53 ml phosphorus oxychloride (0.0058 moles) in 0.96 ml dry pentane was added dropwise at -20°C. The low temperature was achieved by dissolving dry ice (CO$_2$) in acetone. The solution was stirred in an icebath for 6 hours. The product was then washed with water, then twice with saturated NaHCO$_3$ solution, then water again, and then dried with MgSO$_4$ and filtered. The solvent was filtered to yield 0.462g solid. The solid was left under house vacuum for 3 hours to remove the pyridine, and was identified using HPLC.
To modify this reaction in order to obtain a higher yield and chirality, a reaction was carried out using 0.66ml S-(-)-1-phenylethanol and 0.51ml phosphorous oxychloride. The phosphorous oxychloride was added at -10°C, and then left in a fridge for 60 hours (over the weekend) Molecular sieves that had been activated by heating them in a flask with a bunsen burner under vacuum were added to the pentane and pyridine mixture at the beginning of the reaction in order to ensure that the conditions were anhydrous. When the reaction was finished, hexane was added to the reaction mixture and possible product was dissolved using ultrasound. The liquid phase was then filtered into an extraction funnel and the work-up was carried out as previously described. The product, 0.647g, was filtered through a pipette with cotton and sand using hexane:EtOAc, then evaporated and analysed by HPLC.

Attempts were also made to isolate one enantiomer of the chloride using several runs of the analytical HPLC. This failed, however, to isolate enough substrate to analyse on subsequent runs.

3.2.5 Hydrolysis of the chloride

The chloride was dissolved in DCE and the reaction mixture was stirred (reaction 5), varying the reaction times between 8 and 16 hours. The DCE phase was pipetted out, leaving a small part of the DCE phase in order to avoid water in the sample to be analyzed. The aliquot which was left in the reaction mixture was corrected for when calculated the yield. The DCE phase was evaporated to dryness and the product was run through a column using first 30:1 hexane:ethylacetate, which removed the chloride. A 10:1 hexane:ethylacetate gave the pure product, for which the optical rotation was measured, and the product was then identified using NMR. [11]

In experiments where the chloride dissolved directly in water without an organic phase present, the work-up was carried out by extracting the aqueous phase four times with ether. The ether was dried using MgSO₄ and was then evaporated, and the remaining product was analysed.
3.2.6 Synthesis of BTPPATPB

The supporting electrolyte, BTPPATPB (bis(triphenylphosphoranylidene)ammonium teraphenylborate), was synthesized from BTPPACl and NaTPB (sodium tetraphenyl borate) (reaction 6). Equimolar amounts of BTPPACl and NaTPB were dissolved in an aqueous phase and in a 2:1 mixture of water:ethanol, respectively. The phases were mixed and the solvents were removed from the formed BTPPATPB by filtration, after which the solid was thoroughly washed with water. The solid was recrystallised from acetone:ethanol.

3.2.7 HPLC

The α-phenylethyl chloride and the 1-phenylethanol were analysed used HPLC with UV detection. The wavelength of the detector was adjusted to 254nm, at which the aromatic compounds can be detected. The column used was an OD column for chiral compounds and the solvents used were hexane:propan-2-ol 9:1. Both solvents were HPLC grade. A few drops of compound were dissolved in approximately 0.5 ml DCM. After the baseline had been calibrated with only solvents, 1-5μl of this solution was injected into the HPLC.

3.2.8 Optical rotation measurements

The optical measurements were carried out using a polarimeter. Before each measurement the polarimeter was zeroed using the solvent in which the compound of interest was dissolved during the measurements. The compound was measured immediately after the zeroing of the polarimeter and the optical rotation of the compound was calculated from the reading:

$$ [\alpha]^{20} = \frac{x \times 100}{c} $$  \hspace{1cm} (3.8)

where $x$ is the reading from the polarimeter and $c$ is the concentration, calculated by
\[ \frac{m(g) \times 100}{V(ml)} \]  

\[(3.9)\]

where \(m\) is the mass of the compound and \(V\) is the volume of the solvent in which the compound is dissolved. [19]

The rotation of sucrose (Aldrich, 66°) was measured before each measurement by dissolving 50 mg sucrose in 5 ml in water. The optical measurements of the 1-phenylethanol were carried out by dissolving the alcohol in methanol (Aldrich, analar) and the chloride was measured in dichloromethane (distilled).

3.3 Chemicals

3.3.1 Chemicals – \(S_N^2\)

Tetraheptylammonium chloride (THpACl, Fluka, 98%), (R)-(+)2-Bromo-3-methylbutyric acid (Aldrich, 96%), (S)-(−)-2-Bromo-3-methylbutyric acid (Aldrich, 96%), KCl (BDH, analar), and KBr (BDH, spectrosol). The solvents used were 1,2-dichloroethane (Aldrich, 99.8%, HPLC grade) and Millipore MilliQ water (specific resistivity 18.2 MΩ cm).

3.3.2 Chemicals – permanganate

Tetraheptylammonium tetraphenylborate (THpATPB, 98% Fluka,), Li₂SO₄ (99+%, Aldrich), tetraheptylammonium chloride (ThpACl, 98%, Fluka,), LiCl (99+ %, Aldrich), KMnO₄ (BDH Chemicals Ltd, analar), cis-cyclooctene (95%, Sigma-Aldrich 95%), KOH (min 86%, Fisons scientific equipment) tetraoctylammonium solution (Fluka, 20% in methanol) were used as received. All solution were prepared from Millipore MilliQ water (specific resistivity 18.2 MΩ cm) and 1,2-dichloroethane (DCE, HPLC grade, Sigma-Aldrich).
3.3.3 Chemicals – interfacial reaction

Triphenylmethyl chloride (98% Aldrich), triphenylmethanol (Aldrich, 97%), nitrobenzene (Aldrich 99+) 1-phenylethanol (Fluka, chiraselect ≥ 99%), thionyl chloride (Aldrich, 99+%), TPPTPB (Fluka, selectophore), TPeACl (Fluka, ≥ 98%), phosphorous oxychloride, pyridine (distilled and dried), pentane (distilled and dried), sodium hydrogencarbonate (99%, Aldrich), magnesium sulfate (Aldrich, 99%) ethylacetate (GPR, 99%) petrol spirit (GPR, 99%), \( \text{CH}_2\text{Cl}_2 \) (distilled).

3.4 References


2] Database maintained by Lab. d'Électrochimie, Institute de Chimie Physique, École Polytechnique Fédérale Lausanne, Switzerland; on their web site: http://dcwww.epfl.ch/le

3] Southampton Electrochemistry Group, University of Southampton, *Instrumental Methods In Electrochemistry*, Ellis Horwood, 1993


11] Dr. H.C. Hailes, personal communication

4. An electrochemically investigated $S_N2$ reaction

4.1 Experimental results

4.1.1 Cyclic voltammetry of $\Gamma$

The reaction investigated was the reaction between 2-bromo-3-methyl butyric acid in an organic phase and iodide and hydroxide in an aqueous phase. Hence it was of interest to investigate the transfer of iodide across the liquid/liquid interface.

Cyclic voltammetry of 1mM iodide was carried out, with the scan rates varying from 5mV/s to 80mV/s, as shown in figure 4.1.a. The transfer was found to be reversible, with a transfer potential of 0.35V in the experimental set-up, which yields a term of 0.625 for conversion from the experimental to the Galvani scale. The cell potential is defined as the potential of the aqueous reference electrode with respect to the organic reference electrode. Cell potentials were converted to potentials on the standard Galvani scale by the formula

$$\Delta \Phi / V = E_{\text{cell}} / V - E_{1/2} / V \text{ (database)} \quad (4.1)$$

Equation 4.1 is derived by comparison of the half-wave potential for an ion transfer (iodide) with the standard transfer potential of the ion ($E_{1/2}$) listed in a database. [1] The literature values for the iodide transfer potential obtained using cyclic voltammetry is $E_{1/2} = -0.275V$, which, when compared to the experimental value 0.35V gave the conversion term 0.625V.
Figure 4.1.a Cyclic voltammetry of 1 mM iodide at different scan rates. \([\Gamma] = 1\) mM. Scan rates: \(v = 5\) mV/s (curve 1); \(v = 10\) mV/s (curve 2); \(v = 25\) mV/s (curve 3); \(v = 50\) mV/s (curve 4); \(v = 80\) mV/s (curve 5)

Significant noise occurred on the iodide transfer curve from the organic phase back into the aqueous phase, and a white precipitate could occasionally be observed at the interface. In order to investigate the cause of this noise, cyclic voltammetry was carried out using less concentrated iodide solutions. Figure 4.1.b shows the transfer of 0.5mM iodide. As the figure clearly illustrates, the noise is absent during the back transfer at this concentration of iodide.

Figure 4.1.b Cyclic voltammetry of iodide. \([\Gamma] = 0.5\)mM. Scan rate 10 mV/s.

Since the noise is absent at smaller concentrations of iodide, the cause noise is likely to be due to a complexation between the iodide and the tetraheptylammonium, which is the cation of the supporting electrolyte in the
organic phase. This illustrates how electrochemistry at liquid/liquid interfaces can be complicated by processes occurring across the interface due to contact between the two liquid phases.

### 4.1.2 Transfer of I with subsequent reaction

Cyclic voltammetry of 1mM iodide was carried out in the presence of increasing concentrations (1-3mM) of 2-bromo-3-methyl butyric acid (RBr) in the organic phase. The obtained voltammograms were compared with a cyclic voltammogram of 1mM bromide, as shown in figure 4.2. The transfer wave for the process $\Gamma^{\text{aq}} \rightarrow \Gamma^{\text{o}}$ is shifted towards that for the process $\text{Br}'^{\text{aq}} \rightarrow \text{Br}'^{\text{o}}$ and the peak current is increased as the concentration of the butyric acid, RBr in the organic phase is increased. The scans were very reproducible at these concentrations of iodide and RBr.

![Figure 4.2](image_url)

Figure 4.2 The effect of substrate (RBr) concentration on the apparent iodide transfer curve: $[\Gamma] = 1$ mM, no RBr (curve 1); $[\Gamma] = 1$ mM, [RBr] = 1 mM (curve 2); $[\Gamma] = 1$ mM, [RBr] = 2 mM (curve 3); $[\Gamma] = 1$ mM, [RBr] = 3 mM (curve 4); [Br'] = 1 mM, no [Gamma] (curve 5); baseline (curve 6). Scan rate 10 mV s$^{-1}$. 
The shift in the transfer wave can be explained by the reaction which is taking place between the transferred iodide and RBr:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHBr} \quad \text{COOH(} \text{o}\text{)} + \text{i}^- (\text{aq}) \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHCl} \quad \text{COOH(} \text{o}\text{)} + \text{Br}^- (\text{aq}) \\
\end{align*}
\]

As bromide is formed in the reaction, it will transfer from the organic into the aqueous phase during the beginning of the iodide transfer into the organic phase, hereby cancelling out the current which is caused by the iodide transfer in the other direction. This is due to a more negative transfer potential of bromide from the aqueous into the organic phase. Only when the potential is negative enough to keep the bromide in the organic phase, will no more bromide transfer into the aqueous phase occur, and the iodide transfer be observed.

The increase in the peak current is due to the reaction of hydroxide with RBr and RI(2-iodo-3-methyl butyric acid):

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHBr} \quad \text{COOH(} \text{o}\text{)} + \text{OH}^- (\text{aq}) \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHOH} \quad \text{COOH(} \text{o}\text{)} + \text{Br}^- (\text{aq}) \\
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHCl} \quad \text{COOH(} \text{o}\text{)} + \text{OH}^- (\text{aq}) \quad \text{H}_3\text{C} \\
\text{H}_3\text{C} & \quad \text{CH} \quad \text{CHOH} \quad \text{COOH(} \text{o}\text{)} + \text{i}^- (\text{aq}) \\
\end{align*}
\]

4.1.3 The effect of an increase in the iodide concentration; 2\textsuperscript{nd} order kinetics

According to the assumption that the substitution reaction between iodide and 2-bromo-3-methyl butyric acid follows the S\textsubscript{N}2 mechanism (second order kinetics), the shift in the iodide peak potential towards more negative potentials due to a cancellation of the current by the bromide transfer should occur also with increasing concentrations of iodide, while the RBr concentrations are kept constant. Figure 4.3 illustrates that this indeed is the case. No clear trend can be distinguished between the different RBr concentrations in the range of 0.35-
0.5mM. However, at these substrate concentrations the iodide peak potential is significantly shifted when the iodide concentration is increased from 1mM to 1.8mM.

![Graph showing the effect of an increase in iodide concentration on the apparent peak potential of the iodide transfer.](image)

**Figure 4.3** The effect of an increase in the iodide concentration of the aqueous phase on the apparent peak potential of the iodide transfer. Scan rate 25 mV/s. [I⁻] = 1 mM, [RBr] = 0.35 mM (curve 1); [I⁻] = 1 mM, [RBr] = 0.5 mM (curve 2); [I⁻] = 1 mM, [RBr] = 0.4 mM (curve 3); [I⁻] = 1.8 mM, [RBr] = 0.35 mM (curve 4); [I⁻] = 1.8 mM, [RBr] = 0.4 mM (curve 5); [I⁻] = 1.8 mM, [RBr] = 0.5 mM (curve 6)

In figure 4.4.a the butyric acid concentration is 0.5mM and the iodide concentration is varied regularly between 0.2mM and 1.8mM. Figure 4.4.b shows the same variation of iodide concentrations as in figure 4.4.a, with a butyric acid concentration of 0.35mM. As can be seen from figure 4.4.c, the shift in the peak potential is considerably smaller when the concentration of RBr is only 0.2mM in the organic phase. Figure 4.4.b and 4.4.c are directly comparable since the same scan rate, 10 mV/s, has been used in both experiments.
Figure 4.4 a The shift in the iodide peak potential with increasing iodide concentrations, due to the reaction of iodide with 0.5mM RBr in the organic phase. Scan rate 25 mV s⁻¹. [I] = 0.2 mM (curve 1); [I] = 0.5 mM (curve 2); [I] = 1 mM (curve 3); [I] = 1.2 mM (curve 4); [I] = 1.5mM (curve 5); [I] = 1.8mM (curve 6)

Figure 4.4 b The shift in the iodide peak potential with increasing iodide concentrations, due to the reaction of iodide with 0.5mM RBr in the organic phase. Scan rate 10 mV s⁻¹. [I] = 0.2 mM (curve 1); [I] = 0.5 mM (curve 2); [I] = 1 mM (curve 3); [I] = 1.2 mM (curve 4); [I] = 1.5mM (curve 5); [I] = 1.8mM (curve 6); [I] = 2mM (curve 7)
Figure 4.4c The effect of increasing iodide concentrations with 0.2mM RBr in the organic phase. Scan rate 10 mV/s. [I'] = 0.5 mM (curve 1); [I'] = 0.8 mM (curve 2); [I'] = 1 mM (curve 3); [I'] = 1.2 mM (curve 4); [I'] = 1.5mM (curve 5); [I'] = 1.8mM (curve 6); [I'] = 2mM (curve 7)

The effect of varying the scan rate while keeping the iodide and RBr concentrations constant is illustrated in figure 4.5. The scan rate varies from 5mV/s to 80mV/s. The concentration of butyric acid is 0.35mM and the iodide concentration is 0.2mM (a), 1.8mM (b). In figure 4.5.c the concentration RBr is only 0.2mM, and the iodide concentration is 1.5mM. The shift of the peak potential with increasing scan rates becomes more significant with increasing iodide concentrations or RBr concentrations. Again, this shift of the peak potential as a function of scan rate is absent at sufficiently low iodide concentrations or at sufficiently low RBr concentrations.
Figure 4.5.a The effect of varying the scan rate with an iodide concentration of 0.2 mM. [RBr] = 0.35mM, [I] = 0.2mM. Scan rates: \( v = 5 \text{ mV/s (curve 1)}; v = 10 \text{ mV/s (curve 2)}; v = 25 \text{ mV/s (curve 3)}; v = 50 \text{ mV/s (curve 4)}; v = 80 \text{ mV/s (curve 5)} \)

Figure 4.5.b The effect of varying the scan rate with an iodide concentration of 1.8 mM. [RBr] = 0.35mM, [I] = 1.8mM. Scan rates: \( v = 5 \text{ mV/s (curve 1)}; v = 10 \text{ mV/s (curve 2)}; v = 25 \text{ mV/s (curve 3)}; v = 50 \text{ mV/s (curve 4)}; v = 80 \text{ mV/s (curve 5)} \)
Figure 4.5c The effect of varying the scan rate at low concentrations of RBr. [RBr] = 0.2mM, [I-] = 1.5mM. Scan rates: \( v = 10 \text{ mV/s} \) (curve 1); \( v = 25 \text{ mV/s} \) (curve 2); \( v = 50 \text{ mV/s} \) (curve 3); \( v = 80 \text{ mV/s} \) (curve 4)

4.1.4 Effect of pH

The iodide transfer curves were found to depend strongly on the pH value of the aqueous phase. The current is significantly greater when the pH of the aqueous phase is 9, compared to when the pH is 3. This indicates that the iodide transfer wave consists partly of hydroxide transfer (figure 4.6.a). Figure 4.6.b shows that the pH dependence also can be observed without iodide present. In the absence of substrate and of iodide, the current consists only of the baseline, illustrating that, without subsequent reaction in the organic phase, the hydroxide transfer takes place outside the potential window. The baseline was obtained with only the supporting electrolytes present: 0.5M Li$_2$SO$_4$ in the aqueous phase \( (\text{pH} = 9) \) and 10 mM tetraheptylammonium tetraphenylborate (THpATPB) in the organic phase.
Figure 4.6.a The effect of pH on the iodide scans: [I] = 1 mM, pH 9 (curve 1); [I] = 1 mM, pH 3 (curve 2); baseline (curve 3). Scan rate 10 mV s^{-1}; [RBr] = 2 mM, except for the baseline.

Figure 4.6.b The effect of pH on the scans with no iodide present: no [I], pH 9 (curve 1); no [I], pH 3 (curve 2); baseline (curve 3). Scan rate 10mVs^{-1}; [RBr] = 2 mM, except for the baseline
At high RBr concentrations and low iodide concentrations the transfer wave consists mainly of hydroxide transfer when the pH of the aqueous phase is 9. As illustrated in figure 4.7, the transfer curve shifts notably towards more positive potentials when the iodide concentration is increased from 0.1mM to 0.5mM, and the iodide transfer becomes significant.

![Figure 4.7](image)

Figure 4.7 The effect of an increase in the iodide at low iodide concentrations and high RBr concentration (3mM). Scan rate 25 mV s⁻¹. [I] = 0.1mM (curve 1); [I] = 0.2mM (curve 2); [I] = 0.3mM (curve 3); [I] = 0.4mM (curve 4); [I] = 0.5mM (curve 5)

The difference voltammogram (pH9 - pH3) in figure 4.8 clarifies the influence of the hydroxide transfer on the voltammograms. The difference curves shown in the figure were obtained by subtracting the current of the voltammogram obtained when pH (aq. phase) = 3 from the voltammogram when pH (aq. phase) = 9. Apart from the difference in the pH values, the experimental conditions were identical. In the absence of iodide in the aqueous phase but with RBr in the organic phase, the difference curve 1 shows the current caused by the pH increase, due to an increase in the transfer of hydroxide (the only transferable ion present), which is facilitated by the reaction between hydroxide and RBr in the organic phase. The voltammograms for difference curve number 2 were recorded in the presence of both iodide in the aqueous phase and RBr in the organic phase.
Since the iodide concentrations in the voltammograms are identical, the amount of current that is caused by iodide is cancelled out by this subtraction. The difference voltammogram again shows the current that is due to the increase in hydroxide transfer when the pH value of the aqueous phase is increased from 3 to 9. Clearly, the hydroxide transfer takes place at more positive potentials when iodide is present in the aqueous phase. This can only be caused by a greater extent of the reaction of hydroxide in the organic phase, which is due to the presence of RI as an intermediate in the reaction. The catalytic effect of iodide in the $S_N2$ reaction occurring is clearly illustrated by these difference voltammograms.

Figure 4.8 Differential voltammograms: \(((\text{[I]} = 1 \text{ mM}, \text{pH 9}) - (\text{[I]} = 1 \text{ mM}, \text{pH 3}))\) (curve 1); \(((\text{no [I]}, \text{pH 9}) - (\text{no [I]}, \text{pH 3}))\) (curve 2); baseline (curve 3). Scan rate 10 mV s$^{-1}$; [RBr] = 2 mM, except for the baseline.

4.1.5 Hydroxide transfer potential

The transfer potential for hydroxide was of interest to measure, since it was an important parameter in the simulations from which the rate constants for the reactions were obtained. The hydroxide transfer potential was approximately measured using partitioning experiments with a phase transfer catalyst, measuring the change in the pH of the aqueous phase. It was found to be $\approx -0.56$V (details in the experimental section). This value is approximately 160mV
negative of the literature value for the bromide transfer potential which has been obtained using partitioning experiments \[1\]. The hydroxide potential was also estimated by correlation of the Gibbs energy of transfer for the halides with the ionic radius, and extrapolating to obtain an estimated Gibbs energy of transfer for hydroxide. The Gibbs energies of transfer for the halides vary linearly with the ionic radius for $\Gamma$, $Br^-$ and $Cl^-$. Smaller ions, such as $F^-$ and $OH^-$ are more strongly solvated than for example $\Gamma$ and $Br^-$, and therefore the solvated radius needs to be taken into account in the extrapolation. This is done by applying the same deviation from the relation between the radii and the Gibbs free energy of transfer for hydroxide as for fluoride. As can be seen from figure 4.9, this method yields a value for the standard transfer potential for hydroxide approximately 140mV negative of that for bromide, in reasonable agreement with the approximate measurement by partition equilibrium.

![Figure 4.9 Correlation between the Gibbs free energy of transfer and the ionic radii](image)

**4.1.6 Organic phase transfer catalysis experiments**

Organic phase transfer experiments were carried out to confirm that the potential difference indeed was driving the reaction (experimental procedure in chapter 3.2.1, reaction 1). The interfacial potential difference was controlled by the partitioning of a tetraalkylammonium salt and the organic phase was analysed
after 30 min reaction time, using NMR spectroscopy (details in the experimental section). When a potential difference of $\Delta^*\Phi = -0.403$ V was established, using tetraphenylphosphonium as phase transfer catalyst, the product was a mixture of the hydroxyacid and the bromoacid. In accordance with the electrochemical experiments this potential difference will transfer both iodide and hydroxide when the 2-bromo-3-methyl butyric acid is present in the organic phase. When tetramethylammonium was used as catalyst, the established potential difference across the interface was $\Delta^*\Phi = -0.075$ V. No detectable reaction occurred in this experiment. This is a potential region where, according to the electrochemical experiments, no ion transfer takes place. The transfer potentials used for the calculations (appendix C) were: potassium: 0.463 V, chloride: -0.467 V, hydroxide: -0.56 V, iodide: -0.273 V, tetraphenylphosphonium: -0.364 V, tetramethylammonium: 0.182 V. The concentrations used were: 0.01 M potassium iodide, $10^{-5}$ M potassium hydroxide and 0.1 M catalyst chloride. There was a small transfer of the neutral acid, $RBr$, into the aqueous phase; however the observation of negligible reaction at sufficiently positive interfacial potential difference confirms that the substitution reaction in the aqueous phase containing $RBr$ and iodide proceeded at an immeasurably slow rate.

4.1.7 Effect of surfactants

Attempts were made to modify the interface using chiral surfactants. The aim was to enable a stereoselective adsorption of the substrate at the interface and hereby achieve a stereoselectivity between the two butyric acid enantiomers in the react ion with iodide and hydroxide. The surfactants used were a phenylalanine derived surfactant, a leucine derived surfactant as well as (10R, 11S)-(−)-N-Methyl-O-hexadecylquinium (figure 3.2 in chapter 3.1.4.3).

Surfactant concentrations in the range of 50-100 μM were used. No difference in the iodide voltammograms could be seen between the experiments where the surfactant was added and the interface was left to equilibrate during 10-20 minutes before the voltammogram was run, and the experiments where no surfactant was added. An unstable interface and oscillations prevented the use of higher surfactant concentrations.
4.2 Discussion

Simulations of the system can be made in two limits: either the homogeneous reactions are considered irreversible or they are considered to be at equilibrium at all times. The aim is to interpret the unusual apparent shift of the iodide transfer wave in the presence of 2-bromo-3-methyl butyric acid and to draw conclusions about the occurring reaction mechanisms from the electrochemical results.

The interesting shift occurring in the iodide transfer wave when the butyric acid is present in the organic phase is due to an ECE process: The first electrochemical step is the transfer of iodide from the aqueous to the organic phase (E), followed by a homogeneous reaction of iodide with the 2-bromo-3-methyl butyric acid in the organic phase (C), with the reaction products 2-iodo-3-methyl butyric acid and bromide. As can be seen from figure 3.3, bromide has a more negative transfer potential than iodide, and will after its formation transfer from the organic into the aqueous phase (E) during the beginning of the iodide scan, hereby cancelling out the current. When the potential is sufficiently negative to keep the bromide in the organic phase, no further cancellation of the current will occur, and the transfer of iodide from the aqueous to the organic phase can be observed. A similar ECE interpretation can correctly be applied to the hydroxide transfer: The hydroxide ion transfers from the aqueous phase into the organic phase (E), reacts homogeneously in the organic phase with the bromoacid and the iodoacid that has been formed (C), hereby producing 2-hydroxy-3-methyl butyric acid, iodide and bromide. The bromide ion again transfers into the aqueous phase (E) until the potential becomes sufficiently negative.

The observed shift of the peak potential occurs with increasing concentrations of substrate as well as of iodide, which confirms that the reaction proceeds in the organic phase according to an $S_{N}2$ reaction mechanism. The reaction rate dependency on the concentration of both reactants is characteristic for a second order reaction. At these experimental conditions it is difficult to know the extent of the reaction at low concentrations of substrate (0.3-0.5mM) in the organic phase. At greater iodide concentrations (1.8mM), however, the presence of these low concentrations of substrate in the organic phase proves significant and shifts
the peak potential due to an increased amount of bromide transfer from the organic to the aqueous phase. A similar shift can be observed at increased scan rates as a consequence of a greater amount of iodide and hydroxide transferred. This has to be seen as very significant, since it verifies that the kinetics of the reaction indeed is second order, and can be modified by changing either the RBr concentration, or the iodide concentration that is transferred into the organic phase, which is influenced by the scan rate.

The simulations of the experiments were carried out by Dr. Lasse Murtomäki, Helsinki University of Technology, Finland. The diffusion-reaction problem was simulated using orthogonal collocation (OC), [2] which is a sufficiently stable numerical scheme so that even at high homogeneous reaction rates the calculated concentration profile does not begin to oscillate. The difficulty for exact modelling is the number of unknown parameters. However, it is possible to reach some estimates of the equilibrium constants for the reactions through simulations of the system. The key parameter is the standard transfer potential for hydroxide, which we have both approximately measured and also estimated using the correlation between ionic radii and Gibbs energy of transfer. Transfer of the base electrolyte hindered the measurement of the Gibbs energy of transfer for hydroxide using cyclic voltammetry, since in the absence of a consequent homogeneous reaction in the aqueous phase, the hydroxide ion transferred outside even the very negative potential window that was used.

If the homogeneous reactions are assumed to be irreversible, the voltammograms become determined by the transport of the butyric acid to the interface, since this transport becomes the rate-limiting step. When simulated this assumption does not reproduce the effect an increase in the substrate concentration has been observed to have on the voltammograms. The hydroxide transfer is not shifted into the experimental window regardless of the magnitude of the rate constant. In order to reproduce this effect the homogeneous reactions are required to be at equilibrium. Then, the process is analogous to an ion transfer facilitated by complexation in the organic phase, for which very large shifts in transfer potential can be achieved. [3] The present problem is more complicated because the current for transfer of hydroxide from aqueous to organic phase is superimposed on currents due to iodide and bromide, which, dependent on the potential, might go in either direction. The chief difficulty in the simulation is to
set up the initial conditions correctly. Equilibrium throughout the system was assumed and the initial condition calculated from the equilibrium constants (which are the parameters of the model), the added concentrations, and the mass balance. Figure 4.10 shows the simulated effect of increase of concentration of RBr in the presence of I. The apparent shift of the transfer wave to more negative potentials, and the increase in maximum current is illustrated.

Figure 4.10 Simulated voltammograms. Equilibrium constants: 
[ROH][Br]/([RBr][OH]) = 10^4; [ROH][I]/([RI][OH]) = 10^6; scan rate 10 mV s^{-1}, 
Area = 0.2 cm^2, pH = 9, [I] = 1 mM; [RBr]/mM = 0.1 (curve 1), 0.3 (curve 2), 1 (curve 3) and 3 (curve 4). \Delta^w \Phi_{OH}^0 - \Delta^w \Phi_{Br^-}^0 = -100 mV has been assumed.

The magnitude of the shift of the transfer wave is reproduced with values of equilibrium constants for reaction 1 approximately 10^4 and for reaction 2 approximately 10^6. The detail of the experimental curves was not reproduced, however, particularly the steady shift of the transfer wave along the potential axis with increase of concentration of RBr. A likely explanation is that one or more of the reactions was not completely at equilibrium. There are too many unknown parameters (six rate constants are needed for a complete description) to justify
attempts at more detailed simulation. The assumption of a high equilibrium constant for the reaction between RBr and OH to form ROH and Br was supported by partitioning experiments which attempted to measure the concentration of RBr at equilibrium with ROH in the presence of a large excess of Br: 0.001 M ROH (organic phase) and 0.3 M tetraphenylphosphonium chloride (phase transfer catalyst, also organic phase) were equilibrated for 30 minutes with 0.1 M KBr (aqueous phase). If the activity coefficients of the aqueous and the organic phase are assumed equal, the concentration of Br in the organic phase would have been 0.055 M, a 55-fold excess over ROH. No trace of RBr was found when the organic phase was analysed using NMR 300.

4.3 Conclusions

Information regarding mechanistic details of consecutive steps in organic reactions, inseparable when carrying out the organic experiment can be obtained through simulations of the electrochemical phase transfer catalysis experiments. The equilibrium constants of the reaction steps as well of whole reaction can be obtained. This opens up new possibilities for research that combines electrochemistry and organic chemistry, using electrochemistry as a tool for understanding, modelling and optimising phase transfer catalysis reactions.

4.4 References

[1] Database maintained by Lab. d'Électrochimie, Institute de Chimie Physique, École Polytechnique Fédérale Lausanne, Switzerland; on their web site: http://dcwww.epfl.ch/le


5. A two-phase permanganate oxidation reaction

5.1 Electrochemical investigation of the permanganate oxidation reaction

5.1.1 Cyclic voltammetry of permanganate

Figure 5.1. shows a cyclic voltammogram of permanganate, recorded in experimental set-up B (section 3.1.1.) The supporting electrolytes in this set-up are 0.5 M KCl in the aqueous phase, 10 mM BTPPATPB in the organic phase and 10 mM KCl as well as 0.1 mM BTPPACl in the organic reference phase. The transfer potential of permanganate on the Galvani scale, obtained using this experimental system is –0.03 V. The Galvani transfer potential is derived from the comparison of the experimental permanganate transfer potential with the experimental transfer potential of tetraethylammonium, which is 0.019V on the Galvani scale. [1] The standard transfer potential of permanganate could not be found in databases.

Figure 5.1 Cyclic voltammogram of permanganate, recorded in experimental set-up B. \([\text{MnO}_4^-]\) = 1 mM. Scan rate 50 mV/s.

Figure 5.2 shows three subsequent voltammograms of 1 mM permanganate, with 8 mM cis-cyclooctene present in the organic phase. The scan is recorded in experimental set-up A, similarly to the following amperometric experiments discussed in this chapter. The supporting electrolytes are 0.5 M Li_2SO_4 in the aqueous phase, 10 mM tetraheptylammonium tetraphenyliborate in the organic
phase, and 10 mM KCl as well as 0.1mM tetraheptylammonium chloride in the organic reference phase. The transfer potential for permanganate is, according to the first scan, 0.51 V in the experimental system. This corresponds to a potential of -0.115 V on a Galvani scale, derived by comparison of the experimental iodide transfer potential with the iodide transfer potential obtained from values in a database. [1] The difference in the Galvani transfer potential obtained from the two experimental systems is likely to be due to varying activity coefficients in the two systems. The current shows a diminution with subsequent scans. Over time, MnO₂, which is one of the reaction products, was observed to precipitate at the interface. So, one explanation for the diminution of current on successive scans, is that the MnO₂ is blocking the interface, thus preventing the transfer of charge.

![Figure 5.2 Cyclic voltammogram of permanganate. [MnO₄⁻] = 1mM, [cis-cyclooctene] = 8mM. Scan rate 25 mV/s. The voltammograms (A), (B) and (C) are subsequent scans.](image)

**5.1.2 Stripping voltammetry**

The oxidation of cis-cyclooctene in the organic phase by permanganate in the aqueous phase was found to be too slow to be investigated on a cyclovoltammetric time scale. Because of the slow kinetics a potential profile
similar to that used for anodic stripping voltammetry was applied. The permanganate was first transferred into the organic phase by scanning the potential rapidly in the negative direction, \((v=50 \text{ mV/s})\). The potential was then held constant for 60 s, to allow the permanganate to react in the organic phase, analogous to the preconcentration step in stripping analysis. The remaining permanganate was then subsequently stripped back from the organic into the aqueous phase at a scan rate of 10 mV/s, and its concentration in the organic phase was determined by this back scan. The cyclic voltammograms show a diminution of current for the transfer of permanganate from the organic phase back into the aqueous phase when cis-cyclooctene is present in the organic phase. This is due to the reaction of permanganate according to scheme 5.1. Since a fraction of the permanganate has reacted, the amount of permanganate which is available for back transfer into the aqueous phase has decreased. By comparing the values of the diminution in current with values obtained when the process is simulated as an EC process, it is possible to obtain an estimate of the rate constant for the first step of the homogeneous oxidation reaction.

\[
\text{MnO}_4^- + \text{cis-cyclooctene} \rightarrow \text{manganate(V) ester}
\]

Scheme 5.1 Reaction of permanganate with cis-cyclooctene to form a manganate(V) ester

There was some small variability (<20%, usually <10%) in the charge passed during the transfer of permanganate into the organic phase, which has not been found with the transfer of other, unreactive species and which is perhaps associated with the formation of MnO_2 near the interface. To compensate for this effect in the data analysis, currents were renormalized by dividing by the ratio of the amount of charge transferred into the organic phase during the first 70s of the experiment to the charge transferred during that time in a particular
experiment taken as a standard for the series. Attempts were made to carry out
the experiments in analogy with traditional stripping voltammetry, using a
chronoamperometric first step instead of sweeping the potential in a negative
direction. A chronoamperometric first step, however, turned out to be highly
irreproducible, and was therefore not used in the present work.

Figure 5.3 shows four experimentally obtained current-time traces with equal
concentrations of permanganate (1mM) in the aqueous phase and various
concentrations of cis-cyclooctene (0-30mM) in the organic phase. The backpeak
current, corresponding to the permanganate transfer from the organic phase back
into the aqueous phase, decreases with increasing concentrations of cis-
cyclooctene in the organic phase. The scan with no cis-cyclooctene present in the
organic phase shows the amount of permanganate that is transferred back into the
aqueous phase when no homogeneous reaction is occurring in the organic phase.
In this case the loss of permanganate in the organic phase is solely due to a
diffusion process. By comparing this measurement with the measurements where
cis-cyclooctene is present in the organic phase, it is possible to estimate the
amount of permanganate which has been diminished in the organic phase due to
the reaction with the cis-cyclooctene.
Figure 5.3 Experimental amperometry of permanganate transfer across the water/DCE interface, with current corrected for small variations between experiments as described in the text. [MnO_4^-] = 4mM for all experiments. [Cis-cyclooctene] = 30 mM (A), 15 mM (B), 8 mM (C) and 0 mM (D). Initial potential +0.7 V. Between t=0 and t=7s, scan rate 50 mV/s. Between t = 7 and 67 s, the potential was held at 0.35 V. Scan rate = 10mV/s for the scan backward to E = 0.7 V, starting at 67s.

5.1.3 Numerical simulation of the experiment

A numerical simulation of the experimental result was performed, assuming homogeneous second-order reaction of permanganate and cyclooctene in the organic phase.

An approximate solution of the diffusion/reaction problem was found by the standard method of explicit finite differences [2]. The differential equations describing the diffusion and reaction processes of permanganate and cis-cyclooctene at the interface were converted into difference equations and solved using Matlab. The potential profile for the simulations was divided into 3 vectors; the potential scan in the negative direction, the constant potential during which the transferred permanganate was kept in the organic phase, and the potential scan in the positive direction. The potential profile was dependent on
the scan rate of the potential scans. The effect of the scan rate on a potential vector was taken into account in the simulations by dividing the potential scanned during the vector with the fraction of time steps of that vector. The fraction of time steps of the vector was obtained by multiplying the fraction of the duration of the vector with respect to the whole experiment by the number of time steps in the experiment. The experimental potential profile is shown in figure 5.4a and the dimensionless potential profile obtained from the simulations is shown in figure 5.4b.

![Figure 5.4.a Experimental potential profile used in the stripping voltammetry](image)

![Figure 5.4.b Potential profile used in the simulations of the stripping voltammograms](image)
The potentials in the simulations were obtained by subtracting the transfer potential of permanganate in the experimental system (0.51V) from the experimental potentials which were simulated.

In the simulations the diffusion and reaction processes are treated as subsequent processes. [3] For each time step the permanganate concentration change which is due to the reaction is assumed to occur after the change which is caused by diffusion. This is an approximation and will introduce an error into the simulations, since in reality the reaction and diffusion processes occur simultaneously. The error, introduced by this sequential treatment of diffusion and reaction in the explicit scheme, was estimated by halving the time step and comparing the peak potential values for scans with reactant in the organic phase. The time step was chosen for which the difference in the peak current was less than 0.7% for subsequently doubling the time step. In all simulations the dimensionless time step was $\Delta t=0.113$ and the dimensionless space interval $\Delta \chi=0.057$.

Figure 5.5 presents current-time traces which are obtained by simulating the experimental conditions in figure 4.3. By fitting the simulated voltammogram to the experimental voltammogram, both in the absence of cis-cyclooctene, a diffusion coefficient of $1.4\times10^{-5}$ cm$^2$s$^{-1}$ for permanganate in the aqueous phase is obtained. This shows good agreement with the value from the literature ($1.632\times10^{-5}$ cm$^2$s$^{-1}$). [4] In the simulations the diffusion coefficients for permanganate were assumed to be equal in the aqueous and the organic phase. This assumption was justified, since the simulated results showed no effect as the diffusion coefficient in the organic phase was varied over a relatively wide range.
The initial reaction step between permanganate and cis-cyclooctene to form the manganate(V) ester is known to be slow. [5] The manganate ester can then react with permanganate or hydroxide in a subsequent fast reaction step. When simulating the process of the permanganate oxidation it is assumed that the concentration of the manganate ester that is formed is very low in comparison with the cis-cyclooctene, and that permanganate therefore reacts merely with the cis-cyclooctene.

5.1.4 Comparison of experiment and simulation of the two-phase oxidation

Figure 5.6 shows experimental peak currents of the permanganate transfer back from the organic into the aqueous phase, divided by the back peak current for the experiment where no cis-cyclooctene is present in the organic phase. The peak currents are normalised as described above. In figure 5.6 the concentrations of MnO$_4^-$ in the aqueous and cis-cyclooctene in the organic phase were the same as in the voltammograms presented in Figure 5.3. Average values of 5-9 measurements were used for the experimental points. The solid lines present values obtained by simulations, using rate constants of $k = 0.25, 1.5, 3$ and $10$ M$^{-1}$s$^{-1}$. 
Comparing the simulations with the experimental data it can be concluded that a rate constant $k$ between 0.25 and 3 M$^{-1}$s$^{-1}$ will give the best fit between the experimental and the simulated values. A value of $k = 1.5$ M$^{-1}$s$^{-1}$ was used in the simulation shown in Figure 5.5.

Figure 5.6. Comparison of experimental values of peak current for back transfer from the organic to the aqueous phase with values obtained through simulations (solid lines). The simulations were carried out using different values of $k$: (A) 0.25 M$^{-1}$s$^{-1}$, (B) 1.5 M$^{-1}$s$^{-1}$, (C) 3 M$^{-1}$s$^{-1}$ and (D) 10 M$^{-1}$s$^{-1}$. The experimental values are represented by symbols. Every series of values was normalised by dividing the experimental back peak current with the value of the back peak current with no cis-cyclooctene present in the organic phase.

Since the first reaction step in the oxidation reaction is assumed to be second order, the aqueous concentration of MnO$_4^-$ was also varied in order to verify this. Presuming that the first reaction step is second order, a variation of the aqueous MnO$_4^-$ concentration is expected to show a similar effect as the variation of the cis-cyclooctene concentration in the organic phase previously discussed. Experiments were carried out using 0 and 15mM cis-cyclooctene with 1, 2.5 and 4mM MnO$_4^-$. The result is shown in figure 5.7. Again, a simulated value of 0.25 M$^{-1}$s$^{-1} < k < 3$ M$^{-1}$s$^{-1}$ fits the experimental results. Hence it can be concluded that the first reaction step between permanganate and cis-cyclooctene to form a
manganate ester indeed is second order with a rate constant of \(0.25 \text{ M}^{-1}\text{s}^{-1} \leq k \leq 3 \text{ M}^{-1}\text{s}^{-1}\).

Figure 5.7 Comparison of experimental values (symbols) of the diminution in back peak current due to reaction of permanganate in the organic phase with values obtained through simulations (solid lines). The rate constants for the simulations are (A) 0.25 M\(^{-1}\)s\(^{-1}\), (B) 1.5 M\(^{-1}\)s\(^{-1}\), (C) 3 M\(^{-1}\)s\(^{-1}\) and (D) 10 M\(^{-1}\)s\(^{-1}\). The ratio between the experimental back peak current (org. \(\rightarrow\) aq. phase) between the scan where no cis-cyclooctene was present in the organic phase and the scan where 15 mM cis-cyclooctene was present was measured.

The effect of pH was also investigated. Experiments showed no difference when the pH of the aqueous phase was adjusted from 6.5 to 12. The concentration of permanganate and cis-cyclooctene in these experiments were 4 mM and 15 mM respectively.

5.1.5 Discussion

The permanganate was transferred into the organic phase using a potential scan (50 mV/s), since a chronoamperometric first step proved too irreproducible to be used in these experiments. The reason for this irreproducibility can be attributed
to large momentary currents. Since larger currents will cause a larger IR drop, one cause for this irreproducibility could be a faltering IR drop compensation. In the experiments without cis-cyclooctene present in the organic phase, the only diminution of the permanganate concentration in the organic phase is due to diffusion. The permanganate is transferred into the organic phase, and during the 60s it is kept there the diffusion layer in the organic phase will expand. As a result the apparent permanganate concentration in the organic phase that is available for permanganate transfer back into the aqueous phase is smaller than the concentration that has been established in the organic phase due to the imposed transfer. This voltammogram is taken as the model voltammogram and is compared with the scans where cis-cyclooctene is present in the organic phase. By dividing the backpeak current of the voltammograms with cis-cyclooctene present by the backpeak current of the voltammogram without cis-cyclooctene, the fraction of unreacted permanganate in the diffusion layer is obtained, from which the fraction reacted permanganate easily can be calculated. The value for this fraction can conveniently be used to compare experimental results with simulations.

The reaction between permanganate and cis-cyclooctene was simulated as a homogeneous reaction in the organic phase, and not as an interfacial reaction. This is based on the observation that the experimental voltammograms shown in Figure 5.3. show no difference in the peak potential and current of the forward scan for different cis-cyclooctene concentrations in the organic phase. This peak is attributed to the transfer of permanganate from the aqueous to the organic phase. An interfacial reaction with cis-cyclooctene would influence the peak height and shape of the forward peak, and hence it can be concluded that the reaction between cis-cyclooctene and permanganate is not interfacial, but takes place in the organic phase after the transfer of permanganate into the organic phase, and hence this approach in the simulations is justified.
5.2 Synthetic permanganate oxidation of cis-cyclooctene

The synthetic reaction of permanganate with cis-cyclooctene was studied with the aim of gaining an understanding of the impact of the potential which is established by the catalyst on the product distribution. Different synthetic experiments were carried out (experimental procedure in chapter 3.2.3, reaction 3), and the results are summarised in table 5.1.
5.2.1 The effect of different catalysts on the product distribution

Table 5.1 PTC = phase transfer catalyst; DCM = dichloromethane; DCE = dichloroethane; BzEt3N⁺ = benzyltriethylammonium; Et₄N⁺ = tetraethylammonium; Bu₄N⁺ = tetrabutylammonium; TOctA⁺ = tetraoctylammonium

<table>
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<tr>
<th>solvent</th>
<th>PTC</th>
<th>initial PTC concentration mole dm⁻³ (total)</th>
<th>initial KMnO₄ concentration mole dm⁻³ (total)</th>
<th>yield, % diol</th>
<th>yield, % further oxidised products aq. phase</th>
</tr>
</thead>
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<tr>
<td>DCM</td>
<td>BzEt3N⁺</td>
<td>0.022</td>
<td>0.5</td>
<td>9.4</td>
<td>not investigated</td>
</tr>
<tr>
<td>DCE</td>
<td>BzEt3N⁺</td>
<td>0.022</td>
<td>0.5</td>
<td>9.9</td>
<td>octanedioic acid, 4.9%</td>
</tr>
<tr>
<td>DCE</td>
<td>Et₄N⁺</td>
<td>0.000505</td>
<td>0.5</td>
<td>0</td>
<td>Among others: pentane- and hexanedioic acid; butane-, pentane- and hexanedioic acid diethyl ester</td>
</tr>
<tr>
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<td>n-Bu₄N⁺</td>
<td>0.022</td>
<td>0.5</td>
<td>8.8%</td>
<td>not investigated</td>
</tr>
<tr>
<td>DCM</td>
<td>TOctA⁺</td>
<td>0.022</td>
<td>0.5</td>
<td>0</td>
<td>not investigated</td>
</tr>
</tbody>
</table>
5.2.2 Transfer of permanganate into an organic phase using different catalysts

It was also of interest to investigate the amount of permanganate transferred into the organic phase as a function of the phase transfer catalyst used, as well as of the concentration ratio between the catalyst and permanganate. This was carried out in equilibrium partitioning experiments, where an aqueous phase containing permanganate (as KMnO₄) and PTC (as chloride) was shaken with DCE. After the phases had settled, the aqueous phase was removed and the permanganate concentration of the aqueous phase was determined by uv-vis spectrophotometry, from which the concentration of permanganate that had transferred into the organic phase could easily be calculated. It was presumed that the catalyst counterion (chloride) and the potassium did not transfer into the organic phase. The experiments were carried out using different ratios of the starting concentrations of permanganate and catalyst in the aqueous phase. The result is shown in figure 5.8.

![Figure 5.8 Experimental and calculated values of the transfer of permanganate into the organic phase using various phase transfer catalysts. Experimental values: Tetrabutylammonium (■) tetrapropylammonium (♦), benzyltriethylammonium (▲) and tetraethylammonium (●). Calculated values: tetrabutylammonium (curve 1), tetrapropylammonium (curve 2), benzyltriethylammonium (curve 3) and tetraethylammonium (curve 4).](image-url)
The standard transfer potentials on the Galvani scale for tetrabutylammonium ($\text{TBA}^+$: -0.255V), tetraethylammonium ($\text{TEA}^+$: 0.019V), and tetrapropylammonium ($\text{TPrA}^+$: -0.091V) could be calculated from the Gibb’s free energies of transfer that can be found in a database which is accessible through the world wide web. [1] The standard transfer potentials for benzyltriethylammonium ($\text{Bz(Et)}_3\text{A}^+$) was obtained by cyclic voltammetry, as shown in figure 5.9. In order to obtain a cyclic voltammogram of $\text{Bz(Et)}_3\text{A}^+$, a concentration of $10^{-4}\text{M}$ $\text{Bz(Et)}_3\text{A}^+$ in the aqueous phase had to be used, since at higher concentrations the interface was destroyed by the formation of an emulsion in the aqueous phase. This indicates that one function of $\text{Bz(Et)}_3\text{A}^+$ is the creation of an emulsion in the reaction mixture, which increases the interface between the aqueous and the organic phase. An increase in the interfacial area will naturally have a beneficial impact on the transfer of permanganate and catalyst between the phases.

Figure 5.9 Cyclic voltammogram of benzyltriethylammonium ($\text{BzEt}_3\text{A}^+$), obtained using experimental set-up B. $[\text{BzEt}_3\text{A}^+] = 0.1$ mM. Scan rate 50 mV/s. Potential shown are potentials on the cell scale.
As can be seen from figure 5.9, the transfer potential for Bz(Et)₃A⁺ on the cell scale is 0.18V. For transfer of TEA⁺ ion, there was a difference of -0.26V between the transfer potential measured by cyclic voltammetry (the transfer potential on the cell scale) and the transfer potential calculated from the database values for Gibb’s energies of transfer (the standard transfer potential on the Galvani scale). If the same difference is assumed for Bz(Et)₃A⁺, the standard transfer potential on the Galvani scale for Bz(Et)₃A⁺ is -0.08V.

Hence the standard transfer potentials of all the catalysts used were known. The standard transfer potential of permanganate was taken to be -0.09 V, approximately derived from experiments and treated as a parameter in the calculations. The starting concentrations of the ions in the both phases were known. The established potentials and the transfer of permanganate and catalyst were calculated by taking into account the electroneutrality and the standard transfer potentials of the permanganate ion and the catalyst. The activity coefficients in the aqueous phase were taken for convenience and without great loss of accuracy to be 1. Two different assumptions on the activity coefficients in the organic phase were made: The first was the simple assumption γ =1; that is, no ion association at all. The second was to allow for ion pairing, calculating the activities in the organic phase with the equation \( a_i = c_i \alpha_i \gamma_i \), where \( \gamma_i \) is the activity coefficient and \( \alpha_i \) is the degree of dissociation. \( K_A \), the association constant, was estimated using Bjerrum’s theory of closest approach, [6] after which \( \gamma_i \) and \( \alpha_i \) could be calculated by iteration.

It was found that calculations based on theory for activity coefficients and association constants gave a large discrepancy between the theoretical and the experimental values. In order to fit the experimental values to the theoretical values when taking ion pairing into account, a transfer potential for permanganate of -0.16 V was necessary, which showed too big discrepancies with the experimental values. We presume that, because there is a significant solubility of water in DCE, the ions in the organic phase are, in fact, solvated by water, at least in the primary solvation shell. It is justified to expect the permanganate ion to be highly solvated, since hydrogen bonding will occur between the permanganate oxygen atoms and the hydrogen atoms of water. This might prevent the strong ion pairing usually postulated. High solvation of the catalyst and the reacting anion has certainly been known to prevent agglomeration of the catalyst/anion. [7] However, at higher concentrations of MnO₄⁻ and PTC, a precipitate
formed in the organic phase, presumed to be the salt of permanganate and the organic cation.

The data in figure 5.8 can be used to interpret the data of table 5.1: the relative yield and product distribution for the different catalysts. A straightforward interpretation is that the diol is only slowly further oxidised, if at all, by permanganate in the organic phase, but is rapidly oxidised, to more water soluble products, by aqueous permanganate, either as a consequence of extraction of the diol into the aqueous phase or of reaction across the interface. Figure 5.8 can then be used to prescribe a method for maximising yield based on minimising the concentration of permanganate in the aqueous phase at every stage of the reaction. Firstly, TBA\(^+\) should be superior as a PTC; Table 5.1 certainly shows it to be equivalent to Bz(Et)\(_3\)A\(^+\). Secondly, the addition of MnO\(_4^-\) should be carefully controlled so that the ratio of concentration of PTC to MnO\(_4^-\) does not fall below 2.

Experiments were also carried out using SO\(_2\) to remove the manganese dioxide, instead of filtration, which has been used in the experiments above. The aim was to increase the yield. However, no difference in the yield could be observed.

It is likely that also the transfer of hydroxide is an important parameter for the final product distribution. None of the catalysts discussed above have a standard transfer potential which is sufficiently negative to transfer hydroxide, which has a very negative transfer potential, as discussed in chapter 4. Experiments were carried out using tetraoctylammonium as phase transfer catalyst. However, in these experiments no product could be found in the organic phase. The influence of the catalyst on the hydroxide transfer as well as the influence of hydroxide transfer on the final product will be discussed in the section on future work.

5.3 Conclusions

Two-phase reactions, which are too slow to be investigated on a normal cyclovoltammetric timescale, can be investigated at the ITIES using pre-electrolysis with back-transfer of the transferred reactant. ITIES can be used to obtain the rate constant for an initial reaction step, whereas in synthetic methods the further reaction of the intermediate makes the determination of the rate constant of the initial step
difficult. Through electrochemical experiments at a liquid-liquid interface, it is possible to determine in which phase the initial step of a two-phase reaction takes place. Electrochemical calculations can be used to predict the distribution of catalyst and transferred anion in a two-phase mixture.

5.4 References

[1] Database maintained by Lab. d'Électrochimie, Institute de Chimie Physique, École Polytechnique Fédérale Lausanne, Switzerland; on their web site: http://dcwww.epfl.ch/le


6. Use of a liquid-liquid interface to control stereochemistry in a nucleophilic substitution reaction

6.1 $S_N1$ reaction of triphenyl methyl chloride

For investigations into substitution reactions in a two-phase system it was of interest whether a unimolecular substitution ($S_N1$) could occur across the interface in an aqueous/organic solvent two-phase system. For this purpose, the two-phase $S_N1$ reaction of triphenyl methyl chloride was investigated (experimental procedure in chapter 3.2.1, reaction 2). The interfacial reaction conditions were compared with phase transfer experiments where the reacting ions are transferred from the aqueous to an organic phase using a phase transfer catalyst. In $S_N1$ reactions a carbocation is formed as an intermediate as a result of the departure of the leaving group. The departure of the leaving group requires the stabilisation of the carbocation + anion which are formed, and this formation is normally promoted by a solvent with a high dielectric constant, since such a solvent will be favourable for the necessary separation of charge. [1] Nitrobenzene was used as the organic solvent, due to its high dielectric constant ($\varepsilon = 34.8$). [2] Triphenyl methyl chloride was the chosen substrate, since it is well known to react according to the $S_N1$ mechanism in substitution reactions [3] due to the three phenyl groups which can stabilise the tertiary carbocation by conjugation. [4] Iodide and hydroxide were chosen as nucleophiles due to their known transfer potential, which was of interest for the phase transfer experiments. The transfer potential for iodide in nitrobenzene is -0.23V. [5] The transfer potential for hydroxide between water and nitrobenzene was obtained by comparison with the value for its transfer potential between water and dichloroethane, and was found to be -0.54 V. The comparison factor for the hydroxide transfer between water and 1,2-dichloroethane and water and nitrobenzene was obtained using the average value for this transfer factor of bromide, chloride and iodide. [5] The average difference between the Gibbs free energy of transfer between water and 1,2-dichloroethane and water and nitrobenzene for these ions was 5.43 kJmol$^{-1}$. 


In the experiments where iodide and hydroxide were transferred into the organic phase with subsequent reaction, tetrapentylammonium chloride was used as the phase transfer catalyst, with the established potential \(-0.29\text{V}\). The organic phase was analysed using NMR and the results were compared with commercial samples. [6] It was clear that the reaction had taken place already after 30 min. In order to investigate whether the reaction could take place across the interface between the aqueous and the organic phase, instead of in the organic phase, experiments were conducted without a phase transfer catalyst. The potential was established by the potassium hydroxide and the potassium iodide that was added to the aqueous phase. These ions will partition to a small extent and hereby establish the potential difference \(-0.1\text{ V}\). This potential is insufficient to transfer hydroxide or iodide into the organic phase, and hence any reaction occurring will be interfacial. The results showed the appearance of triphenyl methanol within 30 min, and hence was clear that a unimolecular substitution could occur across the liquid/liquid interface.

6.2. Substitution reaction of phenylethyl chloride

6.2.1. Introduction

The aim of the work described in this section was to explore the possibility that the properties of the liquid-liquid interface between water and an immiscible organic solvent could be exploited to alter the reaction mechanism at an asymmetric centre. The reaction between \(\alpha\)-phenylethyl chloride and water was chosen as a model reaction for the present work (scheme 6.1, experimental procedure in chapter 2.2.5, reaction 5). The reaction is known to proceed according to the \(S_N1\) mechanism and therefore with inversion with extensive racemisation when the chloride is dispersed in water. [7] By contrast, the work reported in this section has demonstrated that, when using a two-phase solvent system (water and dichloroethane), the stereochemistry of the reaction can be dramatically affected, leading to a high degree of inversion of configuration as opposed to inversion with extensive racemisation.
6.2.2. Additional experimental details

The α-phenylethyl chloride was not commercially available, and was synthesised from 1-phenylethanol, as described in chapter 3.2.4 (reaction 4), scheme 6.2.

The postulated mechanism involves the formation of an alkyl chlorosulphite, ROSOCl, which is formed with retention of configuration without breaking of the R-O bond. It is proposed that an ion pair, R^+OSOCl then is formed, with subsequent formation of an intimate ion pair between the carbocation and Cl^- Cl^- then forms a bond with the carbocation at the same side from which OSOCl^- departed, hence retaining the configuration. [8]
Achieving a successful asymmetric conversion proved to be a major difficulty. Ingold et al reports an intramolecular nucleophilic substitution [7], ‘Sní [8]’, using 1-phenylethanol and thionyl chloride. However, according to the report, variable optical rotation values for the product were obtained. When this procedure was repeated it was not successful. Similarly, the use of phosphorous oxychloride [9] also failed to deliver a high enough conversion to isolate the product. Interestingly, the literature yields of this method for the formation of the chloride is reported to be only 21%. Attempts to extend the reaction time also failed to deliver sufficient product (see chapter 2.2.4). The method according to Ingold [7] was chosen. However, two problems were demonstrated. First, a successful asymmetric synthesis required a variation in the procedure. Twenty molar equivalents of thionyl chloride with respect to the alcohol were used, instead of four, as reported in the literature. Also, the alcohol was dissolved in dichloromethane, and the reaction mixture was stirred for no more than 3.5 hours. [see chapter 3.2.4.] Secondly, in the literature distillation has been used for separation of the synthesised chloride and also for isolating the 1-phenylethanol, formed in the hydrolysis experiments [7,9]. In the present work distillation was not convenient given the small amounts that were used. Instead, purifications were carried out on silica columns and optical purity assessed by HPLC using a chiral column. It appeared that the α-phenylethyl chloride racemised using flash silica chromatography, which explains why attempts to measure the optical purity using HPLC failed. Success was only achieved when the purifications on silica columns were carried out rapidly, in order to avoid racemisation, and when the optical purity of the substrates was determined using
optical rotation measurements. One difficulty with this approach was the need to
determine rather small rotations given the small amounts of material available for
study. Repeat measurements and frequent calibration gave confidence in the
reliability of the results. Typical optical rotations obtained for the chloride were
22-26° in dichloromethane.

For the two-phase synthesis, two work-up procedures were used, superficially
similar but with drastically different results. In the first, whose results are
reported in detail below, the phases were separated and the organic phase was
analysed. In the second, the aqueous phase was extracted 3 times with
dichloromethane. This second procedure consistently gave only small optical
rotations in the product, as described in section 6.3.

6.2.3. Results

R- or S-α-Phenylethyl chloride in dichloroethane was stirred with an aqueous
phase, hereby enabling the chloride to react with water, and the product in the
organic phase was subsequently analyzed. The configuration of the product, 1-
phenylethanol was inverted with respect to the phenylethyl chloride starting
material (Table 6.2). As stated in the literature, it is presumed that the sign of the
optical rotation is identical for identical configurations of the alcohol and the
chloride. [7] This result is startlingly different from the expected outcome of an
$S_{N1}$ reaction, which is inversion with extensive, sometimes nearly complete,
racemisation.
Table 6.1. Control optical rotation measurements

<table>
<thead>
<tr>
<th>Sample</th>
<th>Polarimeter reading</th>
<th>$[\alpha]^{20}$</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial S(-)-phenylethanol</td>
<td>-0.293 (c = 0.58 g / 100ml)</td>
<td>-50.5°</td>
<td>Good agreement with value stated by Fluka: -45°.</td>
</tr>
<tr>
<td>Racemic chloride</td>
<td>0 (c = 0.26 g / 100 ml)</td>
<td>0°</td>
<td></td>
</tr>
</tbody>
</table>
Table 6.2. Optical rotation measurements

<table>
<thead>
<tr>
<th>Hydrolysis experiment number</th>
<th>Experimental conditions</th>
<th>Polarimeter reading (chloride)</th>
<th>[α]$_{20}^{\circ}$ chloride</th>
<th>Yield (%)</th>
<th>Polarimeter reading (alcohol)</th>
<th>[α]$_{20}^{\circ}$ alcohol</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absence of DCE. Neutral aqueous phase. Reaction run overnight. Started from S(−)-α-phenylethyl chloride</td>
<td>-0.082 (c = 0.26 g / 100 ml)</td>
<td>-26.5°</td>
<td>37.6</td>
<td>0.001 (c = 0.462 g / 100 ml)</td>
<td>≈ 0°</td>
<td>Alcohol measured before chloride from exp 4. Control: Racemisation of the alcohol agrees with the literature. [7]</td>
</tr>
<tr>
<td>2</td>
<td>Volume ratio DCE: water = 1:1. Neutral aq. phase. Reaction run overnight (≈20 h). Started from R(+)α-phenylethyl chloride</td>
<td>+0.055 (c = 0.344 g / 100 ml)</td>
<td>+15°</td>
<td>35.3</td>
<td>-0.061 (c = 0.2 g / 100 ml)</td>
<td>-61°</td>
<td></td>
</tr>
<tr>
<td>Hydrolysis experiment number</td>
<td>Experimental conditions</td>
<td>Polarisimeter reading (chloride)</td>
<td>$[\alpha]^{20}$ chloride</td>
<td>Yield (%)</td>
<td>Polarisimeter reading (alcohol)</td>
<td>$[\alpha]^{20}$ alcohol</td>
<td>Comment</td>
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</tr>
<tr>
<td>3</td>
<td>Volume ratio DCE: water = 1:1 Neutral aqueous phase. Reaction run overnight (15 ½ h) Started from $S(\cdot)-\alpha$-phenylethyl chloride</td>
<td>-0.433 (c = 0.636 g / 100 ml)</td>
<td>-61°</td>
<td>6.7</td>
<td>+0.063 (c = 0.143 g / 100 ml)</td>
<td>+44°</td>
<td>Alcohol measured after commercial alcohol (see table 6.3.) The high reading of the optical rotation of the chloride is likely to be an experimental error.</td>
</tr>
<tr>
<td>4</td>
<td>Volume ratio DCE: water = 1:1 Alkaline aqueous phase (pH 12.6) Reaction run during 8 hours. Started from $R(\cdot)-\alpha$-phenylethyl chloride</td>
<td>+0.040 (c = 0.182 g / 100 ml)</td>
<td>+22°</td>
<td>18.1</td>
<td>-0.043 (c = 0.128 g / 100 ml)</td>
<td>-34°</td>
<td>Alcohol measured directly after chloride from experiment 4 NMR not consistent but run after optical rotation and removal of solvent and appeared to be contaminated.</td>
</tr>
</tbody>
</table>
It is clear from the results presented in the tables that when the substitution reaction was carried out in a two-phase solvent system by stirring \( \alpha \)-phenylethyl chloride in dichloroethane with water, the steric orientation of the product, 1-phenylethanol was inverted with respect to the \( \alpha \)-phenylethyl chloride. High degrees of inversions were obtained for the alcohol.

The yield of the reaction varied highly. It is likely that the conversion factor was dependent on the stirring rate, since the stirring rate affects the amount of interface created in the two-phase solvent mixture. Low yields (6%) of interfacial reactions have been reported in the literature. [10] The alcohol generated was also volatile, and the yield was probably also affected during rotary evaporation. Complete evaporation of the solvent was necessary, however, since any remaining solvent would lower the measured optical rotation of the alcohol.

The optical rotation of the commercially available (S)-(\(-\))1-phenylethanol was measured and a value of \(-50.5^\circ\) was obtained, in reasonable agreement with the value of the \(-45^\circ\) that was stated by the manufacturer (Fluka).

Before every optical rotation measurement the optical rotation of sucrose (literature value +66°) was measured. The experimental optical rotation for sucrose was found to be between 59.9 and 71.9 degrees. (68.5, 71.1, 71.9, 59.9, 61.4, 62.3)

Since the optical rotation for sucrose varied, it is important to note that when measuring the alcohol formed from experiments 2, 3 and 4, the optical rotation of \( \alpha \)-phenylethyl chloride or the commercial alcohol were measured at the same time.

6.2.4 Discussion

Since, as previously discussed in chapter 3, the asymmetric carbon in the \( \alpha \)-phenylethyl chloride is a secondary carbon with a phenyl and an alkyl group attached to it, the \( \alpha \)-phenylethyl chloride can be expected to undergo hydroxylation according to the \( S_{N1} \) mechanism. [7]. Thus, according to the
literature [7], unimolecular hydroxylation is the only possible mechanism for the reaction between α-phenylethyl chloride and water in a reaction where the chloride is dispersed directly in water. Therefore inversion with extensive, sometimes nearly complete, racemisation of the product can be observed. This was experimentally verified; from α-phenylethyl chloride with an optical rotation of -26.5°, racemic 1-phenylethanol was obtained when the chloride was stirred in water. Therefore, the present results show that the presence of a water-dichloroethane interface influences the reaction, changing the stereochemistry by preserving the optical purity through inversion of configuration.

Since inversion of configuration was observed for the two-phase system where the chloride was dissolved in dichloroethane, the $S_n2$ mechanism is a likely route for the substitution reaction in this case. Water and hydroxide ion are the potential nucleophiles. The difference between water and hydroxide as nucleophiles were investigated by qualitative comparison of reaction rates and by comparing the optical rotation of the 1-phenylethanol that was obtained in a neutral aqueous phase with the optical rotation of the 1-phenylethanol that had also been synthesised in an aqueous phase with a pH value of 12.6. No significant trend of difference in the optical rotation of the alcohol could be observed, suggesting the mechanism (apparently $S_n2$) was the same in both cases. No noticeable difference in the rates of the reactions could be observed when the reactions were followed by TLC, which indicated that the nucleophile was not hydroxide. If the reaction proceeded according to the $S_n2$ mechanism with hydroxide as the nucleophile, a pronounced rate difference would be expected when increasing the hydroxide concentration in the aqueous phase by five-orders of magnitude.

Water is soluble in DCE: (0.86 %) [11]. One possibility is therefore that hydrolysis of the chloride could occur within the DCE phase. To investigate the effect of the water in dichloroethane, an experiment was carried out where the α-phenylethyl chloride was stirred for 72 hours in dichloroethane, which had been previously saturated with water. No reaction product could be detected by TLC. It can therefore be concluded that the interface is necessary to drive the reaction. The chloride and hydrogen ions which are formed will immediately partition into
the aqueous phase. Another possible scenario is a reaction according to a unimolecular substitution where the incoming nucleophile forms an ion pair with the carbocation before the leaving group is fully dissociated. [3] This reaction mechanism would also lead to an inverted product with respect to the starting material.

The water content in the dichloroethane phase (0.86%) [11] is kept throughout at its maximum by stirring the two phases in contact with each other. The hydroxide will partition to an extremely small degree into the organic phase. The transfer potential of hydroxide is highly negative (≈ -0.56V) and the transfer of hydroxide into the dichloroethane phase will therefore be negligible compared to the concentration of water in the organic phase.

Thus, the data suggests that water in dichloroethane is the nucleophile and that the reaction occurs at the interface with the product ions being immediately solvated and extracted into the aqueous phase as they are formed. Certainly it is possible to rationalise that water in solution in dichloroethane can be a sufficiently aggressive nucleophile. It is likely that the water molecules in dichloroethane form fewer hydrogen bonds to each other compared to water molecules in a homogeneous aqueous phase, since they are less hydrogen bonded and hence less shielded they will be more aggressive. If the reaction conditions are shifted towards more aggressive nucleophiles, the likelihood of an $S_{N2}$ reaction occurring increases. [12] because the incoming nucleophile will form a new bond faster than the carbocation can be stabilised. Also the stabilisation of the carbocation will be decreased due to the decrease in the dielectric constant of the medium. ($\varepsilon_{\text{H}_{2}O}=78.5$, $\varepsilon_{\text{DCE}}=9.2$) [2].

The proposed interfacial $S_{N2}$ mechanism is illustrated in scheme 6.3 below.
6.2.4. Mechanisms

The discussion above leads to some predictions concerning the course of the reaction with different solvents. First, the effect should depend on the solubility of water in the organic phase. If water is insoluble (as is expected for the pure phenylethylchloride) then one would expect formation of the carbocation at the interface with the aqueous phase, followed by its solvation and subsequent \( \text{S} \text{n} \text{I} \) reaction. The interfacial \( \text{S} \text{n} \text{2} \) requires a certain solubility of water in the organic phase. If on the other hand the water content of the organic phase were higher, then there is the possibility of \( \text{S} \text{n} \text{I} \) within the bulk of the organic phase.

In scheme 6.4, another possible rationale is illustrated: A stereo-selective \( \text{S} \text{n} \text{I} \) reaction, in which the interface serves to orientate the carbocation and determine the direction of attack of the nucleophile. If the substitution proceeded in this way according to the classical \( \text{S} \text{n} \text{I} \) mechanism, without ion pair formation, the interface might be expected to influence the stereochemistry of the reaction by influencing the shape of the carbocation intermediate of the \( \text{S} \text{n} \text{I} \) reaction. The carbocation, which is formed as an intermediate in an \( \text{S} \text{n} \text{I} \) reaction due to the dissociation of the displaced group, is planar in a one-phase reaction. This yields equal chances of the new bond forming on either side of the asymmetric carbocation, hereby leading to extensive loss of optical activity. [12] The varying hydrophilicity of the groups attached to the asymmetric carbon in \( \alpha \)-phenylethyl chloride could be expected to lead to a specific orientation of \( \alpha \)-phenylethyl chloride at the interface, with the hydrophilic groups (hydrogen and chloride) oriented towards the aqueous phase and the hydrophobic groups (phenyl and
methyl) oriented towards the organic phase. If the nucleophile (e.g., OH⁻) were present only in the aqueous phase, then this would result in a preferred stereospecific configuration for the bond between the incoming nucleophilic group and the carbocation. If the substitution reaction in a two-phase reaction was unimolecular, the substituting agent would be expected to approach the carbocation intermediate from the aqueous phase, hereby leading to preservation of the chirality of the substrate with the retention of configuration. This intriguing possibility has not been observed here.

Since inversion has been observed, instead of retention, it could be concluded that the substitution reaction is more likely to be bimolecular. A possible nucleophile is water which is soluble in the dichloroethane phase. Alternatively, the hydroxide ion, in the experiments where the aqueous phase was alkaline, could act as nucleophiles by a small partitioning into the organic side of the interface. Since no rate difference could be observed between the experiments where the pH of the aqueous phase was alkaline and the experiments where the aqueous phase was neutral, it can be concluded that the nucleophile is water. The change of mechanism from Sn1 to Sn2 is likely to be due to less shielded and hence more aggressive nucleophiles in the organic phase, resulting from a smaller extent of hydrogen bonding between the water molecules in the dichloroethane compared with the hydrogen bonding in the aqueous phase. Since no reaction could be observed when the α-phenylethyl chloride was stirred in dichloroethane which was saturated with water, it can be concluded that the liquid/liquid interface is required in order for water in dichloroethane (0.86%) to
act as a nucleophile. [11] The interface is likely to shift the reaction equilibrium because of the possibility of chloride and hydrogen to partition into the aqueous phase. Hence the presence of the aqueous phase is necessary in order for the reaction to occur.

Experiments were also carried out by Dr Soraya Manazaviar where the work-up was carried out by extracting the aqueous phase twice with dichloromethane. The dichloromethane and dichloroethane were then evaporated without drying over MgSO₄. In some cases the product was then left in the fridge overnight before the column was run. The optical rotation of the resulting alcohol was considerably lower than in the experiments where no extraction had been carried out: 3-11°.

It is likely that the water content of dichloromethane (1.32%) [11] has influenced the stereochemistry of the product. When the dichloromethane was evaporated, the water in the dichloromethane would remain in the product mixture. In order to test the reactivity of the chloride with a small amount of water, the chloride (≈ 60 mg) was left in the fridge with 1.5 ml water. It was clear that even at low temperatures some hydrolysis had occurred after 1 hour, and that a considerable amount of the chloride had reacted overnight. Due to the small volume of water, the aqueous concentration of the hydrogen ions which are formed in the reaction will be higher than in the aqueous phase of two-phase reaction. In an acidic environment, the oxygen of the hydroxide group in the alcohol might become protonated, in which case the protonated hydroxide might act as leaving group. If this occurs in a system where the only phase present is the substrate dispersed in an aqueous phase, it might lead to racemisation of the alcohol, since the H₂O⁺ can act as a leaving group [8]. Because of this, one hypothesis could be that a high conversion of the chloride to the alcohol should be avoided. TLC analysis of the 1-phenylethanol showed a minute partitioning of the alcohol into the aqueous phase, where the protonation with consequent increased racemisation might occur.
6.3. Conclusions and future work

Two-phase reactions provide a powerful means of altering the stereochemistry in substitution reactions by changing the mechanism due to changes in the reaction medium.

The importance of the results described certainly merit the investigation of two-phase substitution reactions using other nucleophiles. In cases of hydrophilic nucleophiles a phase transfer catalyst could be added to the reaction in order to facilitate a bond formation between the nucleophile and the substrate instead of hydrolysis of the substrate.

Phase transfer catalysis reactions are usually carried out by transferring one reactant across the liquid/liquid interface into the other phase. In the present work the interface was used as a means of shifting the reaction equilibrium by providing the possibility of partitioning of the hydrophilic reaction products into the aqueous phase.

6.4. References

[6] Dr. H.C. Hailes, personal communication


7. Conclusions and future work

7.1. Conclusions

This thesis presents an interdisciplinary approach to phase transfer catalysis reactions, involving electrochemical experiments at a liquid/liquid interface, simulations of these experiments, as well as organic synthetic experiments. The work demonstrates two examples of how electrochemistry across a liquid/liquid interface can aid organic synthetic chemistry, producing information that is very difficult to obtain using synthetic methods, and one example of how a liquid/liquid interface can be used to alter reaction mechanisms.

Electrochemical experimental results of the two-phase bimolecular substitution reaction between iodide and hydroxide in an aqueous phase and 2-bromo-3-methyl butyric acid in a 1,2-dichloroethane phase provide an insight into the mechanism of the occurring reactions. The simulations of the system, carried out by Dr. Lasse Murtomäki (Helsinki University of Technology, Finland) give approximate numerical data on the equilibrium constants of the occurring reactions. In the electrochemical set-up which was used it was possible to observe and obtain information regarding all the reactions as well as about ion transfer occurring of the reactions.

The two-phase permanganate oxidation of cis-cyclooctene provides information about the rate constant of the first reaction step, which has proven to be extremely difficult to obtain using synthetic methods, and is hence highly useful. It also clarifies the issue of where in a reaction mixture the initial reaction occurs, which is crucial information when optimising a reaction.

The work also demonstrates how electrochemical calculations can be used to predict a suitable phase transfer catalyst for a two-phase reaction. Currently the choice of catalyst is often tetrabutylammonium, because this choice usually works. [1] Some demands on the catalyst, such as providing a suitable reaction form for the transferred anion, need to be taken into account from an organic chemistry perspective [2], but it is certainly possible to postulate that catalysts could be screened, and suitable catalysts chosen on the basis of their ability to
transfer the reacting anion into the organic phase. This can easily be calculated using electrochemistry. The impact of the counterion on the transfer of the reacting anion could also be theoretically predicted, hence saving time and money when starting up new reaction projects.

Two-phase reactions are usually carried out by transferring one reactant into the other phase by using a phase transfer catalyst. Truly-interfacial reactions are less investigated, despite their highly interesting potential to alter reaction mechanisms and hence modify the outcome of reactions. [3] The interfacial reaction in this work (the hydrolysis of phenylethyl chloride) shows how the interface between an aqueous and an organic phase can be used to alter the stereochemistry of reactions, in this specific example by preventing racemisation and hence preserving chirality. Since separation of enantiomers is expensive, the possibility of preserving the chirality when the reaction is carried out would be highly useful on an industrial scale.

7.2 Future Work

It is clear that the interface between an aqueous and an organic phase can be used to alter the stereochemistry of organic reactions. For the hydrolysis of phenylethyl chloride which was carried out in this work, it is postulated that the incoming nucleophile is water in the dichloroethane phase. It would be of interest to investigate this reaction using the interface between water and various solvents with different water solubility, such as benzene (0.18 %), nitrobenzene (0.19%) or dichloromethane (1.32%). Since the reaction proceeds according to a bimolecular reaction mechanism, the rate of the reaction should be directly proportional to the content of water in the organic solvent.

The preservation of the chirality might decrease with high water solubility in the organic phase, such as for dichloromethane. This would confirm one hypothesis of this work, which postulates that if the water content of the organic phase is high enough, the reaction can occur in the bulk of the organic phase, hereby resulting in the same stereochemical outcome as a one-phase reaction (racemisation).
In the same reaction, different nucleophiles could be transferred into the organic phase using a suitable phase transfer catalyst, with the interface still acting to transfer ionic reaction products, such as Cl⁻, into the aqueous phase. It would be highly interesting to transfer an anion which can act as a nucleophile and investigate the proportion between the reaction of the substrate with the nucleophile and with water. An example of an anion that could be transferred is bromide \((\Delta G_{tr} = -35.5 \text{kJ/mol, dichloroethane})\). An example of suitable catalysts are tetrahexylammonium bromide (established potential = -0.42 V). It is necessary to use bromide as catalyst counterion, because if another halide is used as counterion and transferred into the organic phase, it might influence the reaction.

In the permanganate two-phase oxidation of cis-cyclooctene, increasing the yield of the cyclooctane diol in two-phase reactions presents a clear challenge. As can be seen from the reaction mechanisms in section 2.1.2, a high ratio of hydroxide/permanganate is desirable in the vicinity of the manganate(V)ester, since these two compete for the same intermediate with only the reaction between hydroxide and the intermediate resulting in the diol. The phase transfer catalyst currently used, benzyltriethyl ammonium chloride \([4]\), will transfer permanganate but not hydroxide into the organic phase. It can hence be concluded that the conditions are not optimised for producing the diol as the final product. A more suitable catalyst would be tetraoctylammonium hydroxide, which would establish a potential of \(-0.64 \text{ V}\) across the interface between an aqueous and a dichloroethane phase. At this potential hydroxide will transfer into the organic phase, since the estimated transfer potential of hydroxide is \(-0.56 \text{ V}\). (section 3.1.5.) Hydroxide is a more suitable counterion than the chloride which is normally used: The chloride will transfer into the organic phase more easily than hydroxide and hence hinder the hydroxide transfer into the organic phase.

In the experiments that were carried out using tetraoctylammonium hydroxide as catalyst and SO₂ to remove the manganese dioxide, no product was found in the organic phase. The starting material was consumed, which proves that a reaction had occurred, but possibly the products had been overoxidised to CO₂, indicating that the reaction time needs to be shortened. Important variables to optimise would be the permanganate/hydroxide ratio in the organic phase, as well as the
reaction time. It is likely that leaving the reaction overnight, as is custom [4], is not necessary, and might contribute to overoxidation of the product. Further development of the co-operation between organic synthetic chemistry and electrochemistry at a liquid/liquid interface could involve the use of electrodes to carry out the two-phase synthesis on a normal reaction scale. A reaction that could easily be used as an example to demonstrate proof of this principle is the two-phase $S_n2$ reaction between iodide and hydroxide in an aqueous phase and 2-bromo-3-methyl butyric acid in an organic phase. Electrodes that could be used are two platinum sheets, connected as a two-electrode set-up. For initial experiments, the two phases could be stirred using one magnetic stirrer: If the stirring speed is slow enough the phases will stir separately without mixing, enabling the establishment of a potential across the interface using the two electrodes. Further optimisation of the reaction could involve two thin layers of an aqueous and an organic phase, flowing in different directions, with a potential difference applied across the interface between them. The use of electrodes instead of phase transfer catalysts would eliminate problems with catalyst separation from the reaction product and allow very accurate establishment of the potential across the interface, as well as eliminate the effect of the catalyst counterion. Hence this could be seen as an attractive industrial alternative to the current use of phase transfer catalysts.

References

A.1.1. HPLC of the racemic \( \alpha \)-phenylethyl chloride
A.1.2. NMR of cis-cyclooctane diol
A.1.3. NMR of the commercial 2-bromo-3-methylbutyric acid and tetraphenylphosphonium ion (1:5 mole ratio)
A.1.4. NMR of the commercial 2-hydroxy-3-methylbutyric acid and tetraphenylphosphonium ion (1:5 mole ratio)
A.1.5: NMR of the product of the reaction between 2-bromo-3-methyl butyric acid and iodide and hydroxide with tetraphenylphosphonium as catalyst.
A.1.6. Commercial 2-bromo-3-methyl butyric acid
A.1.7. Commercial 2-hydroxy-3-methyl butyric acid
A.1.8. Product from reaction between 2-bromo-3-methyl butyric acid and iodide and hydroxide with tetramethylammonium as phase transfer catalyst
A.1.9 NMR of commercial triphenylmethyl chloride
A.1.10. NMR of triphenylmethanol
A.1.11. NMR of interfacial reaction between hydroxide and triphenylmethyl chloride
A.1.12 Synthesised α-phenylethyl chloride
A.1.13. Synthesised 1-phenylethanol
Appendix B

clear all;

z=-1;
F=96485;
R=8.314;
T=298;
f=F/(R*T);

Dmodel=input('Give Dm (< 0.5 for stability): ');
N=input('number of time steps: ');
Einitial=input('starting potential: ');
Ea=Einitial-0.51;
Ereverse=input('end potential of first sweep: ');
Eb=Ereverse-0.51;
Ec=Eb;
Eend=input('end potential: ');
Ed=Eend-0.51;
x1=sqrt(input('ratio of diffusion coefficients (DO/DW): '));
coct=input('concentration cis-cyclooctene: ');
cMn04=input('concentration permanganate: ');
k=input('k = ');

Xmax=6;
M=floor(6*sqrt(Dmodel*N))
deltaX=Xmax/N;
T=1/N:1:N+1;
K=k*1/N*cMn04*102;
dE1=abs(Ea-Eb)/(7*N)/102);
dE2=abs(Ed-Ec)/(35*N)/102);
E0=Eb*ones(1,floor(N*60/102));
E1=Ea:-dE1:Eb;
E3=Ec:dE2:Ed;

E=[E1 E2 E3];
theta=exp(z.*f.**(E));
cMn04=cMn04/cMn04;
coct=coct/cMn04;
cWold=cMn04*ones(1,M);
cOold=zeros(1,M);
coctOold=coct*ones(1,M);
for n=1:N,
    cWnew(1)=(48*(cWold(2)+xi*cOold(2))-36*(cWold(3)+xi*cOold(3)))+
              16*(cWold(4)+xi*cOold(4))-3*(cWold(5)+xi*cOold(5)))/...
              (25*(xi*theta(n)+1));
    cOnew(1)=theta(n)*cWnew(1);
    coctOnew(1)=(coctOold(3)/3-4*coctOold(2)/3);
    for (j=2:M-1)
        cWnew(j)=cWold(j)+Dmodel*(cWold(j-1)-
                            2*cWold(j)+cWold(j+1));
        cOnew(j)=cOold(j)+Dmodel*(cOold(j-1)-
                            2*cOold(j)+cOold(j+1));
        coctOnew(j)=coctOold(j)+Dmodel*(coctOold(j-1)-
                            2*coctOold(j)+coctOold(j+1));
    end

B.1. Mathcad simulation program used for simulation of the initial reaction step
of the two-phase reaction between permanganate and cis-cyclooctene
2*coctOold(j)+coctOold(j+1));
    kin=K*cOnew(j)*coctOnew(j);
    cOnew(j)=cOnew(j)-kin;
    coctOnew(j)=coctOnew(j)-kin;
end

cWnew(M)=CMn04;
cOnew(M)=0.0;
coctOnew(M)=Coct;
cWold=cWnew;
cOold=cOnew;
coctOold=coctOnew;

chi(n)=-(25*cWold(1)+48*cWold(2) . . .
    -36*cWold(3)+16*cWold(4)-3*cWold(5))/(12*deltaX);
end

figure;
hold;
plot(T,chi);
[chimax, Emax]=max(chi);
[chimin, Emin]=min(chi);
peak2peak=chi(Emax)-chi(Emin)
chimax
chimin
xlabel('T');
ylabel('dimensionless current');
title('Simulated voltammogram');
Calculation of established potential using tetraphenylphosphonium (TPP⁺) as phase transfer catalyst.

\( x = -0.2 \)

Given
\( x = -5 \)
\( x = 5 \)

\[ \frac{-0.1}{9.6483} + \frac{0.1}{9.6483} + \frac{0.00001}{9.6483} + \frac{-0.00001}{9.6483} + \frac{0.01}{9.6483} + \frac{-0.01}{9.6483} = 0 \]

\[ 1 + 2.7183 \cdot 3.141598 \]

\( a = \text{Find}(x) \)
\( a = -0.403 \)

Calculation of established potential using tetramethylammonium (TMA⁺) as phase transfer catalyst.

\( x = -0.2 \)

Given
\( x = -5 \)
\( x = 5 \)

\[ \frac{-0.1}{9.6483} + \frac{0.1}{9.6483} + \frac{0.00001}{9.6483} + \frac{-0.00001}{9.6483} + \frac{0.01}{9.6483} + \frac{-0.01}{9.6483} = 0 \]

\[ 1 + 2.7183 \cdot 3.141598 \]

\( a = \text{Find}(x) \)
\( a = -0.075 \)