



Faculty of Science



Electrochemical Organic Synthesis

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Electrochemical Organic Synthesis

Agenda

1. What is organic electrochemistry ?
2. Examples of conversions that may be accomplished by electrolysis
3. A brief discussion of the intermediates that are formed during an electrochemical process
4. Some technicalities related to the electrosynthesis of organic compounds
5. Recommended literature
6. Summary - Pros and cons



What is Organic Electrochemistry?

Organic electrochemistry is concerned with the exchange of electrons between a substrate and an electrode and the associated chemical reactions.

Organic electrochemical reactions are conceptually related to other organic reactions that include one or more electron transfer steps, such as

oxidation by metal ions (e.g., Cu^{2+} , Fe^{3+} and Ce^{4+})

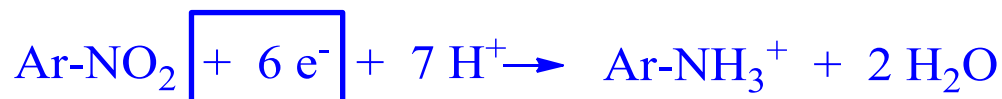
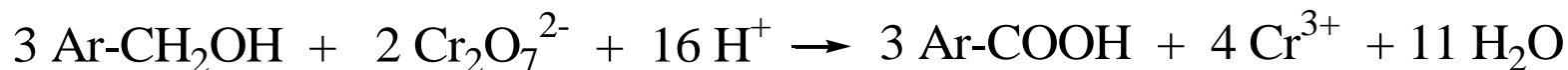
and

reduction by metals (e.g., Na, K, Zn and Sn).



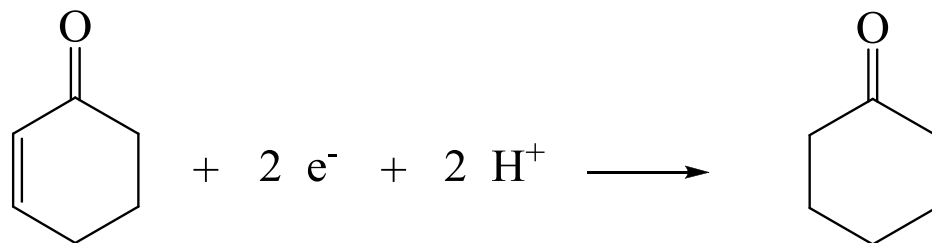
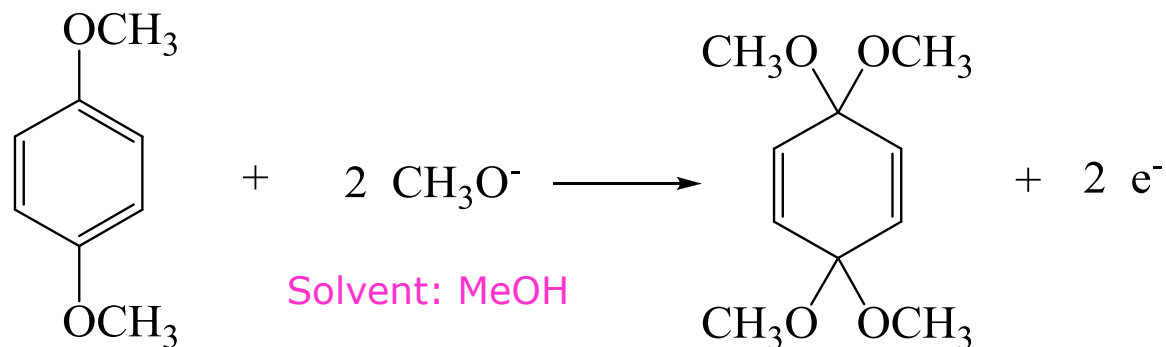
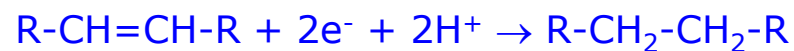
Conventional reactions *vis-à-vis* electrochemical reactions

In an electrochemical process, the **oxidation agent** is replaced by the **anode (+)** and the **reduction agent** by the **cathode (-)** here illustrated by functional group conversion.



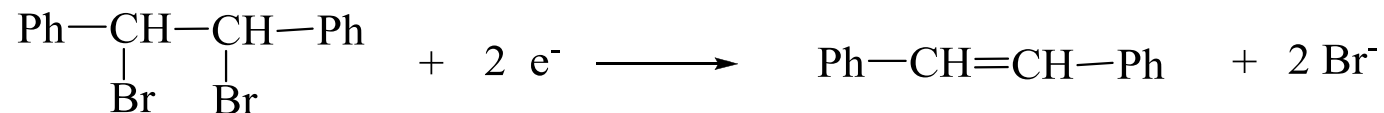
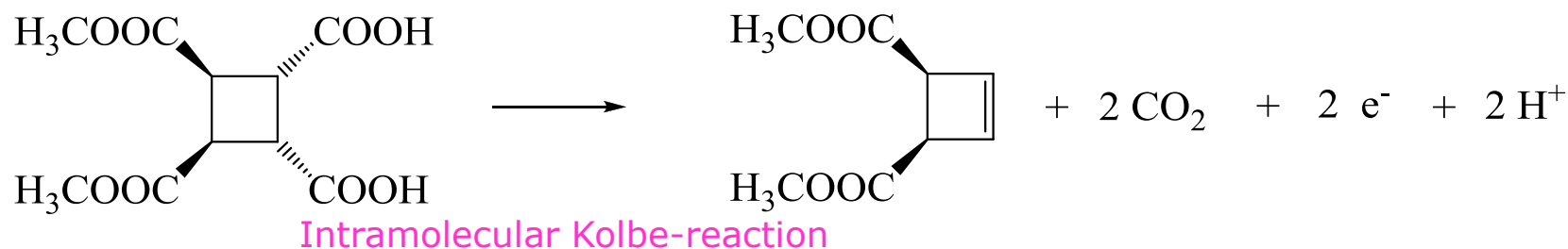
Organic electrochemical conversions

Additions:



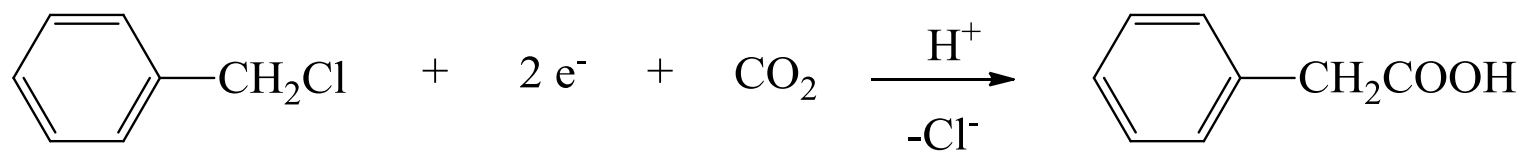
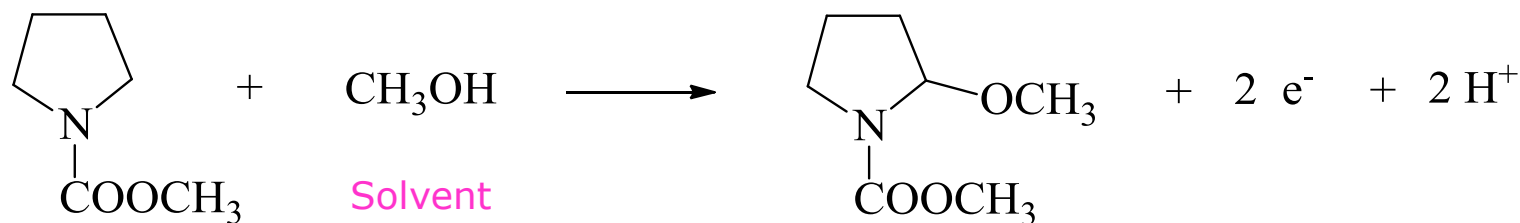
Organic electrochemical conversions

Eliminations:



Organic electrochemical conversions

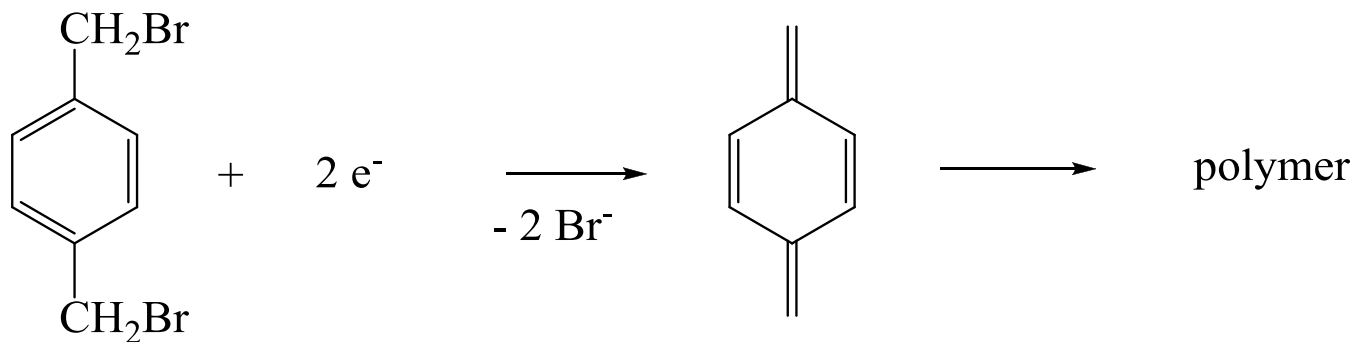
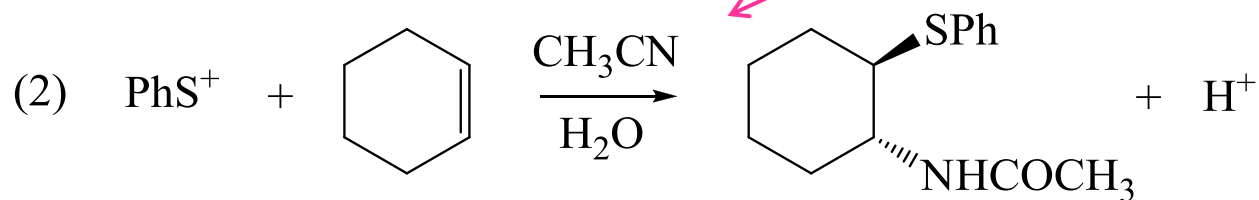
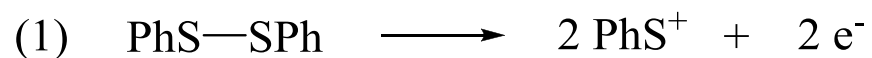
Substitutions:



'Umpolung' á la Grignard-reaction

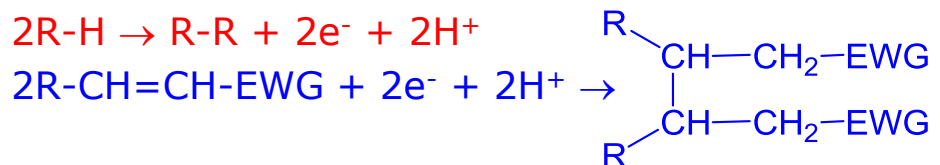
Organic electrochemical conversions

Cleavages:

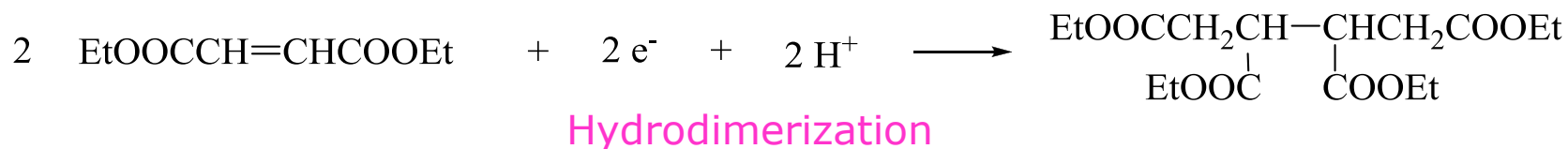
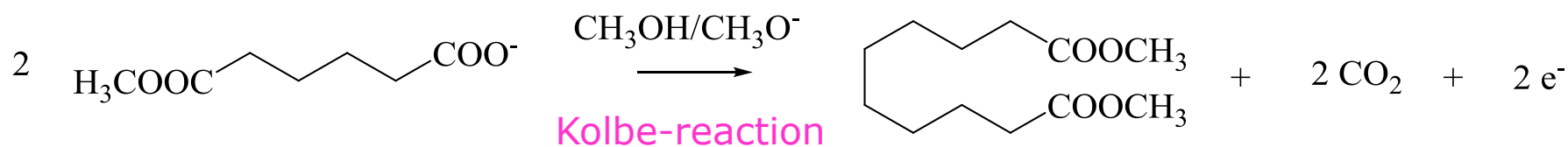
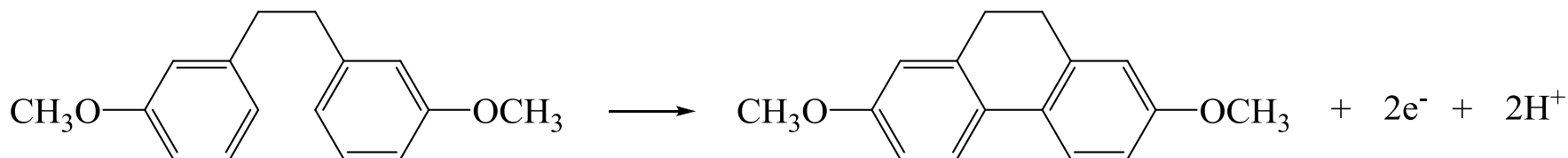


Organic electrochemical conversions

Couplings/dimerizations:

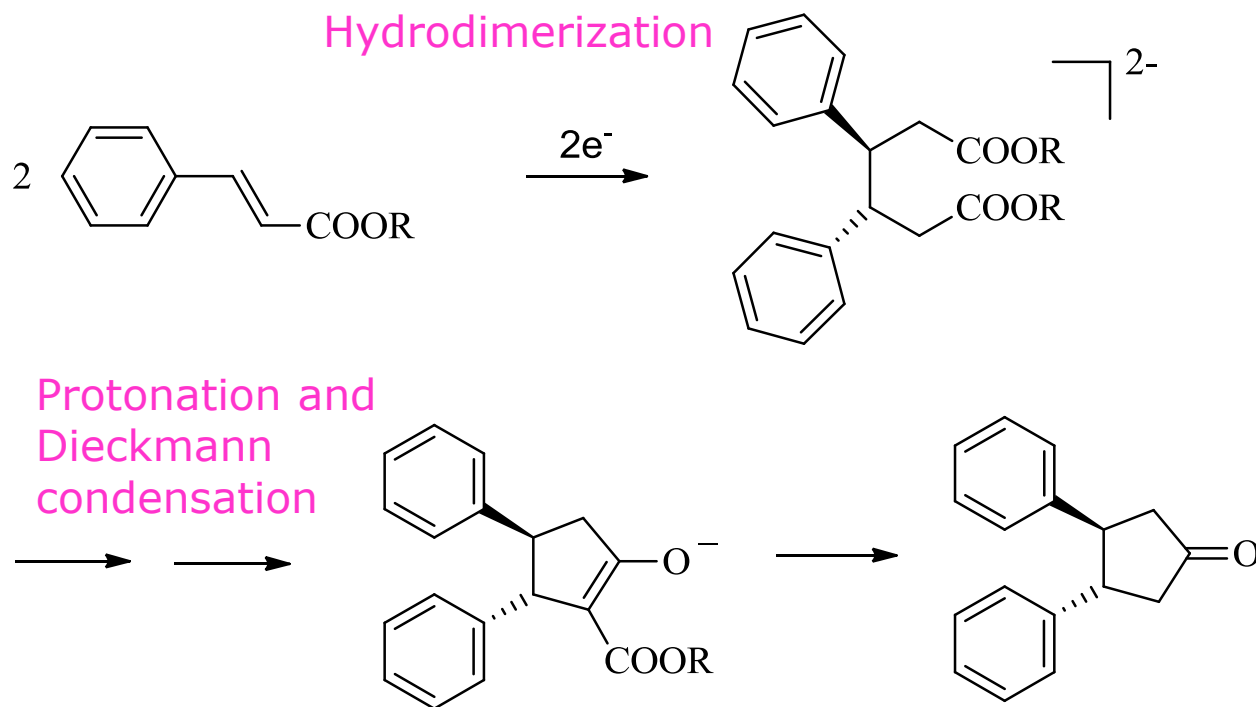
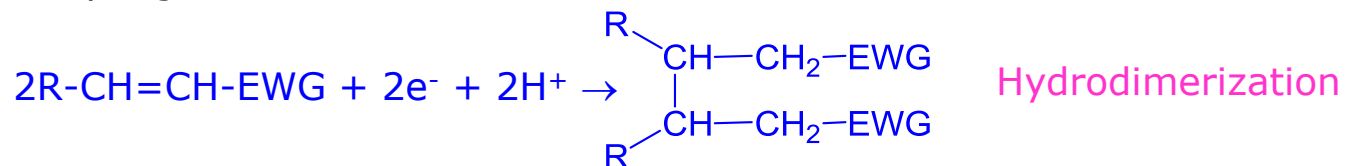


Hydrodimerization



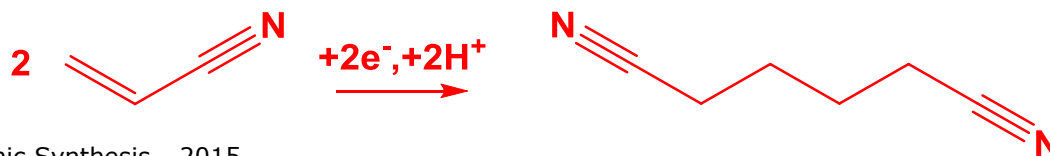
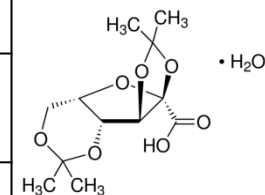
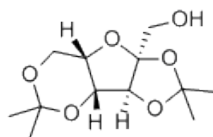
Organic electrochemical conversions

Couplings/dimerizations:



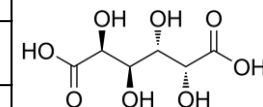
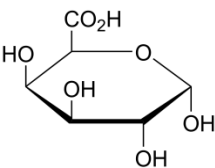
Some commercial processes

Starting material	Product	Company
Butanone	Acetoin (3-hydroxybutanone)	BASF
1,4-Butynediol	Acetylenedicarboxylic Acid	BASF
Acrylonitrile (hydrodimerization)	Adiponitrile (> 200.000 tons/year) (production of nylon 66)	Monsanto, BASF, Asahi Chemical
4-Cyanopyridine	4-Aminomethylpyridine	Reilly Tar
Anthracene	Anthraquinone	L. B. Holliday, ECRC
Nitrobenzene	Azobenzene	Several
Glucose	Calcium Gluconate	Sandoz, India
L-Cystine	L-Cysteine	Several
Diacetone-L-sorbose	Diacetone-2-ketogulonic Acid	Hoffman- LaRoche
Naphthalene	1,4-Dihydronaphthalene	Hoechst



Some commercial processes

Starting material	Product	Company
Furan	2,5-Dimethoxy-2,5-dihydrofuran	BASF
Monomethyladipate	Dimethylsebacate	Asahi Chemical
Hexafluoropropylene	Hexafluoropropyleneoxide	Hoechst
<i>m</i> -Hydroxybenzoic Acid	<i>m</i> -Hydroxybenzyl Alcohol	Otsuka
Galacturonic Acid	Mucic Acid	EDF
Hydrocarbons	Perfluorinated hydrocarbons	3M, Bayer, Hoechst
<i>p</i> -Methoxytoluene	<i>p</i> -Methoxybenzaldehyde	BASF
<i>p</i> - <i>tert</i> -Butyltoluene	<i>p</i> - <i>tert</i> -Butylbenzaldehyde	BASF, Givaudan
<i>o</i> -Hydroxybenzoic Acid	Salicylic Aldehyde	India
Maleic Acid	Succinic Acid	CERCI, India

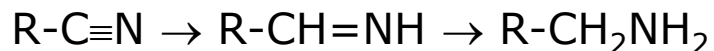
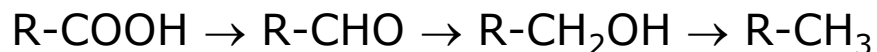
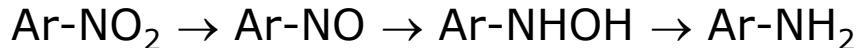


Organic redox reactions are usually written as 'two-electron processes'

Most persistent organic compounds have an even number of electrons

- **G.N. Lewis (1916):** A covalent bond is the result of two atoms or groups sharing an electron-pair

Examples of reductions: (+2H or +2H, -H₂O)

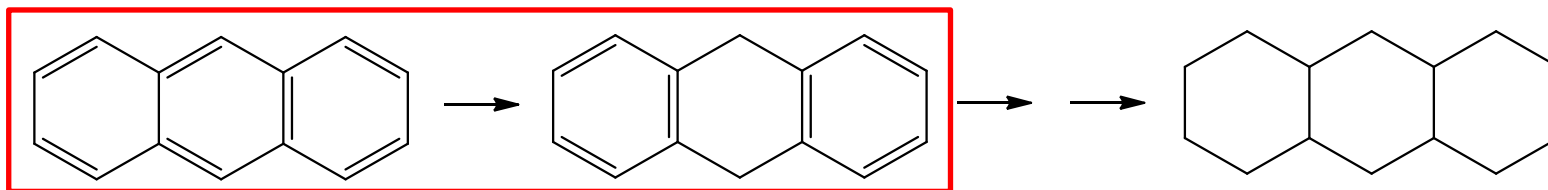


Organic redox reactions are usually written as 'two-electron processes', but they are 'one-electron processes'

Many organic redox reactions are comprised of a series of 'one-electron processes' often accompanied by a series of proton-transfer processes and, occasionally, with the elimination/uptake of water.

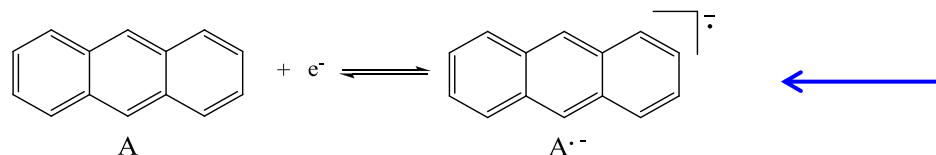
So, when we write $+2\text{H}$, we actually mean $+2\text{e}^- + 2\text{H}^+$, that is four steps.

Example, the reduction of anthracene in an aprotic, dipolar solvent:

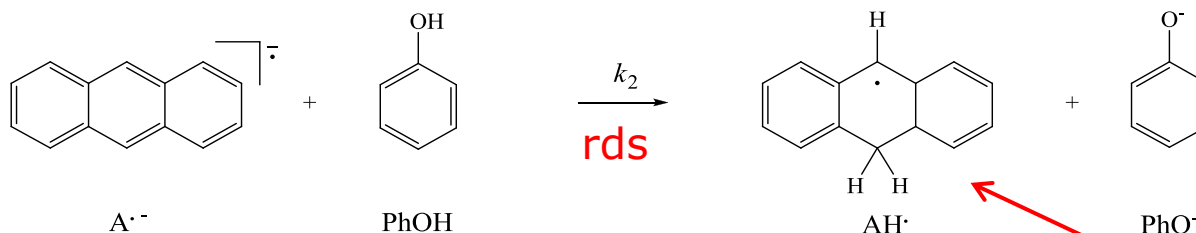


Organic electrochemistry is 'one-electron processes'

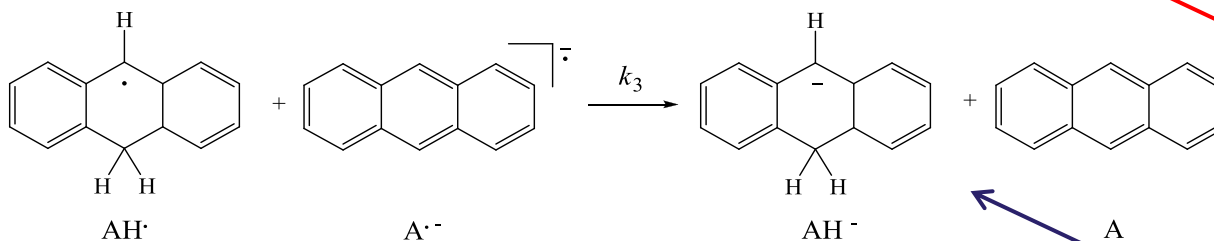
ET at the cathode



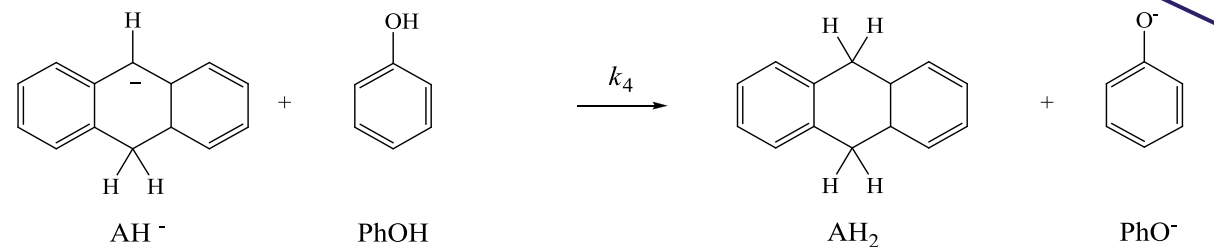
The first intermediate is a radical anion



ET in solution



The second intermediate is a neutral radical



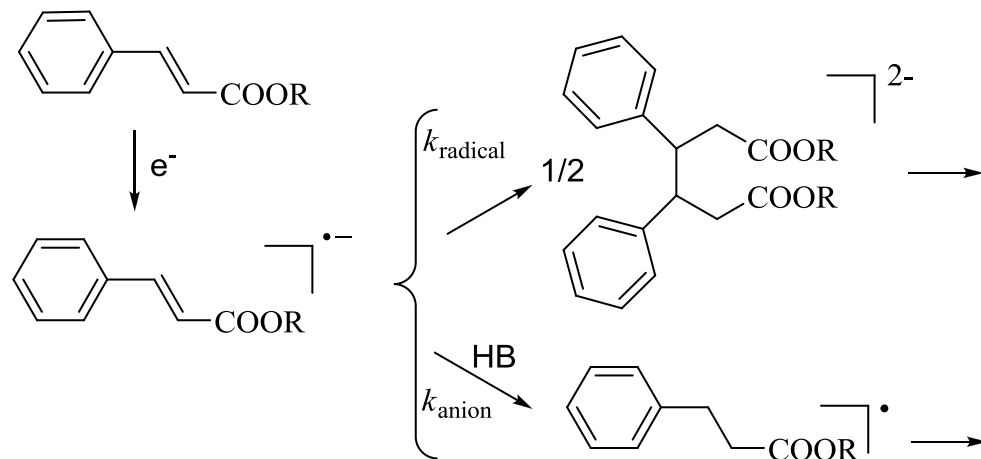
The third intermediate is a carbanion



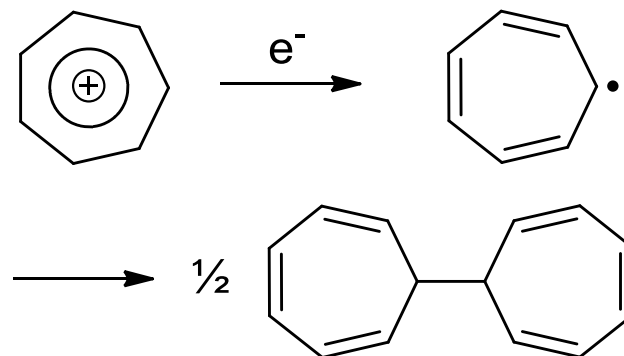
Organic electrochemistry is 'radical ion and radical chemistry'

For **neutral π -systems** the primary intermediates are **radical cations** and **radical anions**, i.e. the intermediates are radicals and ions at the same time.

The competition between the radical character and the cation or anion character depends on the conditions.

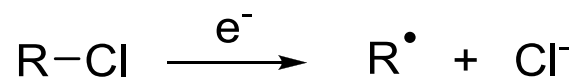


For **charged π -systems** the primary intermediates are **radicals** that may dimerize.

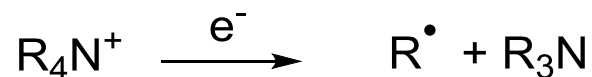


Organic electrochemistry is 'radical ion and radical chemistry'

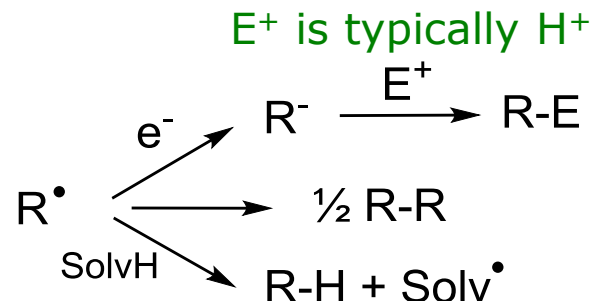
For **neutral σ -systems** electron transfer is dissociative resulting in **radicals** and **cations** or **anions**



For **charged σ -systems** dissociative electron transfer results in **neutral** fragments and **radicals**



The **radicals** may either dimerize, be further reduced or abstract hydrogen-atoms.



Radical ions and neutral radicals are reactive species

1. Electron transfer reactions

- Some organic solvents may be oxidized or reduced

2. Cleavage reactions

- Inherent - owing to bond weakening

3. Couplings/dimerizations

- Inherent - owing to the radical character

4. Reactions of radical cations with nucleophiles and of radical anions with electrophiles (electrochemical 'umpolung')

- Mostly non-inherent - owing to the ionic character
- Many organic solvents are nucleophiles and/or electrophiles
- Many organic solvents are bases and some are also Brønsted acids

5. Atom (hydrogen) abstractions

- Inherent - owing to the radical character
- Some organic solvents are hydrogen-atom donors



Important experimental parameters in electrochemistry

The number of experimental parameters that may be manipulated in electrosynthesis is large including the

- a) cell design (electrode surface area, separation of anolyte and catholyte – ‘divided cells’)
- b) electrode potential and cell voltage (driving force, rate of the ET process)
- c) current and current density (speed of conversion)
- d) electrode material (overpotential - catalysis)
- e) solvent (often the reagent) and the supporting electrolyte (conductivity)
- f) mass transfer to/from the electrodes (stirring/pumping rate)

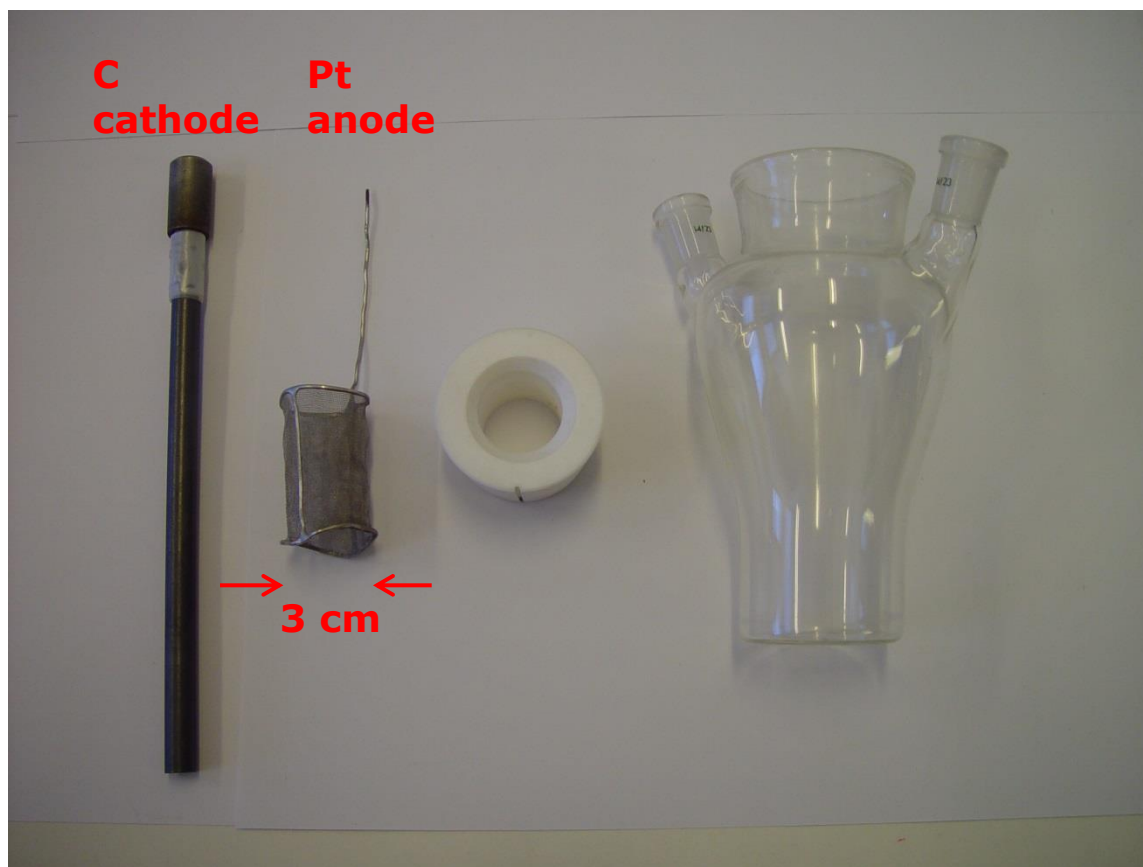
in addition to, e.g., temperature, pressure etc etc

Any of these parameters may affect which products are formed and/or the yields

Take-home-message: Do as told in the recipe !



Cell Design - Components of a simple, **undivided** cell



Notice: No reference electrode !

The undivided cell put together

cooling bath
(ice/water)



The power supply – constant current source



Voltage
(not potential)

Current

Undivided ? Divided ?

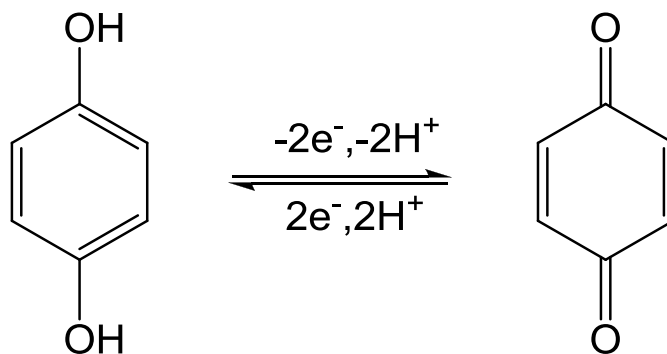
Two processes are going on in the electrochemical cell, always !

An oxidation at **the anode**

A reduction at **the cathode**

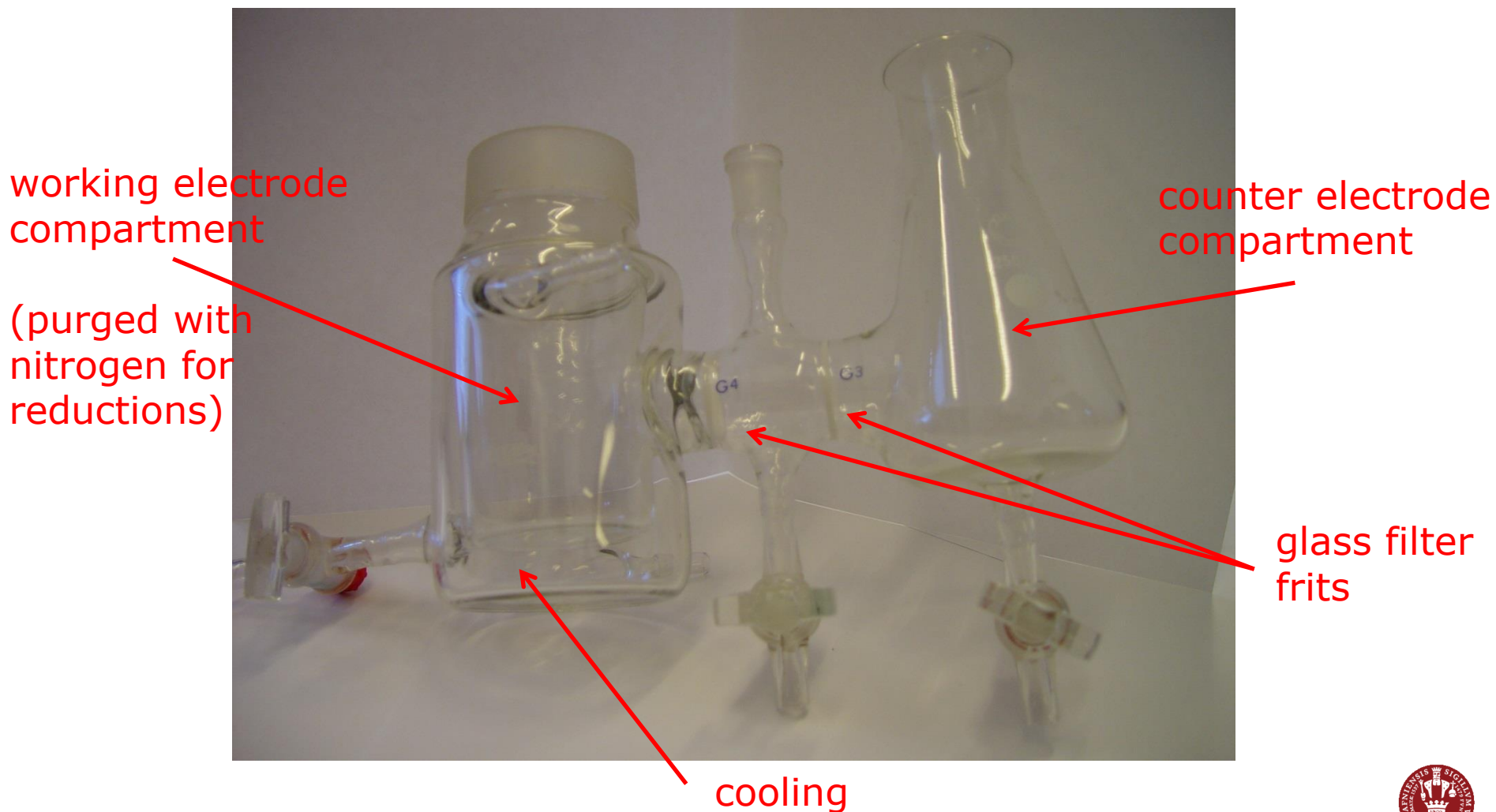
Potential problem:

The product formed by oxidation at the anode may undergo reduction (e.g., back to the starting material) at the cathode



In such a case a divided cell is needed

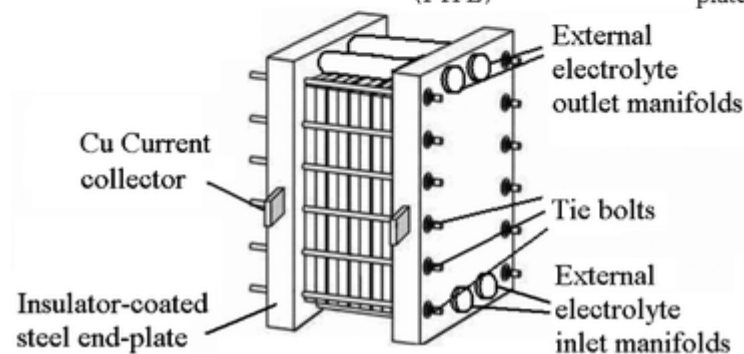
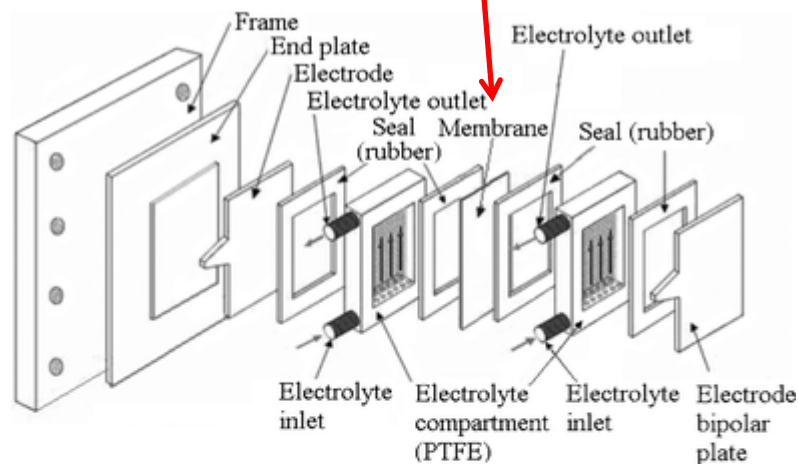
Cell Design - Classical, divided laboratory scale cell (H-cell)



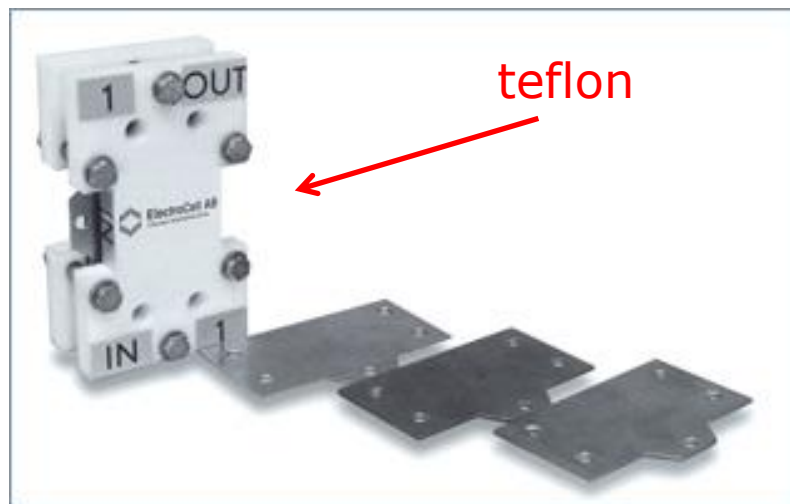
Cell Design – Membrane divided flow cell for laboratory use



ion exchange
membrane (nafion)



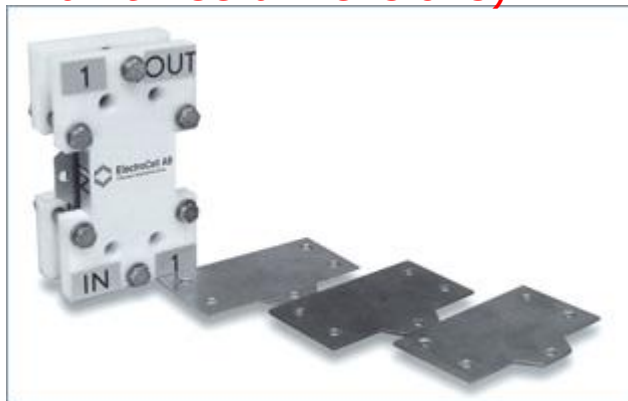
Small distance between the
electrodes => low resistance



teflon

From laboratory scale to industry scale

Electrochemical syntheses in flow cells are easily scalable (reaction vessels are expandable in all three dimensions)



Voltage and Potential – Solution resistance

Two-electrode system for electrochemical synthesis in an undivided cell

The *voltage difference*, ΔV , between the two electrodes is NOT the same as the *potential difference*, ΔE

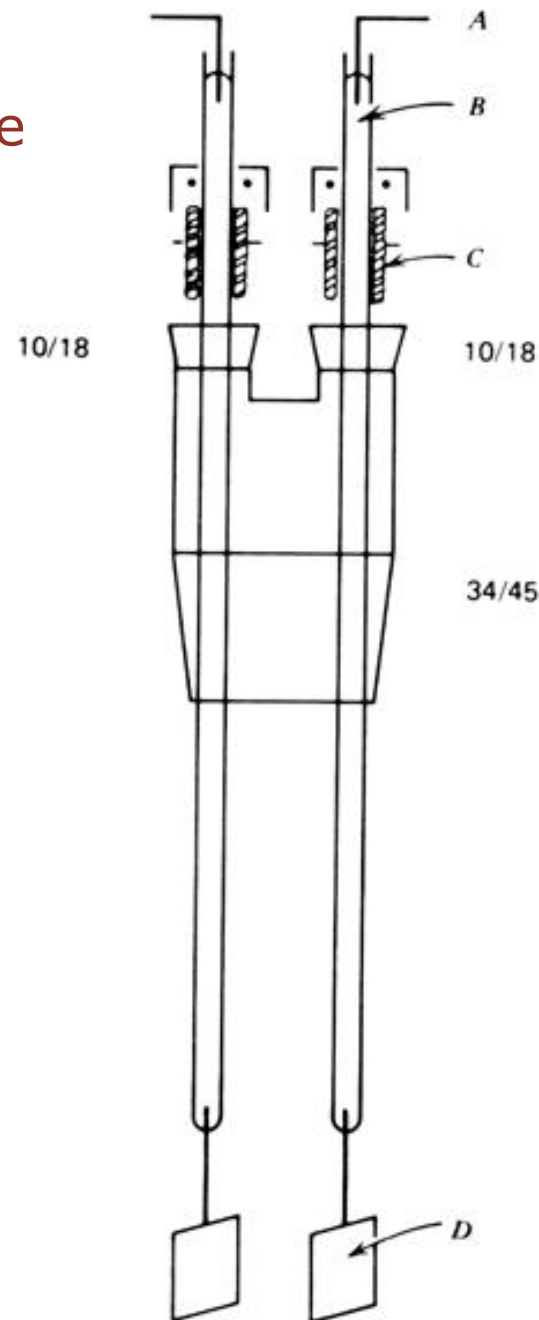
$$\Delta V = \Delta E + iR_s$$

i : the current

R_s : the **solution resistance**

iR_s : the ohmic drop (Ohm's law)

In organic solvents R_s may amount to several hundred ohms unless special precautions are taken.



Solution resistance - Power consumption

$$\Delta V = \Delta E + iR_s$$

If $i=1\text{A}$ and $R_s=100\Omega$ then $\Delta V = \Delta E + 100\text{V} \approx 100\text{V}$
100V may be dangerous !

Power consumption

$$100\text{V} \cdot 1\text{A} = 100\text{ W (= heat)}$$

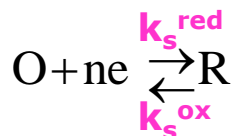
1. Waste of energy
2. Need for cooling (unless high temperature is an advantage)

Costs money !



Electrode potential – the driving force

- The **Nernst equation**
- The **standard potential**, E^0 and the **formal potential**, $E^{0'}$
 The heterogenous electron transfer rate constants, k_s^{red} and k_s^{ox}



$$E = E^0 + \frac{RT}{nF} \ln \frac{(\text{O})}{(\text{R})} = E^0 + \frac{RT}{nF} \ln \frac{f_{\text{O}}[\text{O}]}{f_{\text{R}}[\text{R}]}$$

$$E = E^{0'} + \frac{RT}{nF} \ln \frac{[\text{O}]}{[\text{R}]} \quad E^{0'} = E^0 + \frac{RT}{nF} \ln \frac{f_{\text{O}}}{f_{\text{R}}}$$

n is the number of electrons (for organic compounds, typically, $n = 1$)

R is the gas constant

T is the absolute temperature

F is the Faraday constant

Parentheses, $()$, are used for activities and brackets, $[\]$, for concentrations

f_{O} and f_{R} are the activity coefficients of O and R, respectively.

Most organic compounds are oxidized or reduced in the potential range +3 to -3 V



Current and current density – speed of conversion

The **heterogenous electron transfer rate constants**, k_s

$$k_s^{\text{red}} = k^{\circ} \exp[-\alpha nF (E - E^{\circ}) / (RT)]$$

$$k_s^{\text{ox}} = k^{\circ} \exp[(1 - \alpha)nF (E - E^{\circ}) / (RT)]$$

The **Butler-Volmer equation**

$$\begin{aligned} i &= nFA(k_s^{\text{red}}[O]_{x=0} - k_s^{\text{ox}}[R]_{x=0}) \\ &= nFAk^{\circ} \{ [O]_{x=0} \exp[-\alpha nF (E - E^{\circ}) / (RT)] - [R]_{x=0} \exp[(1 - \alpha)nF (E - E^{\circ}) / (RT)] \} \end{aligned}$$

The current (the conversion speed) is potential dependent

k° is the standard heterogeneous electron transfer rate constant

α is the **electrochemical transfer coefficient**

(corresponds in electrochemistry to the Brønsted coefficient in organic chemistry)

A is the electrode area

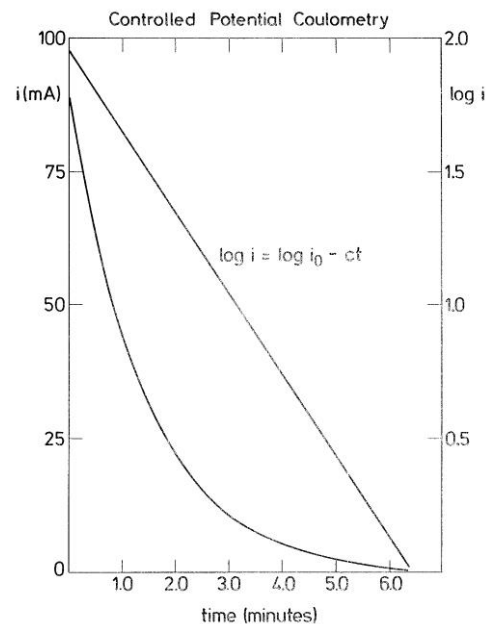
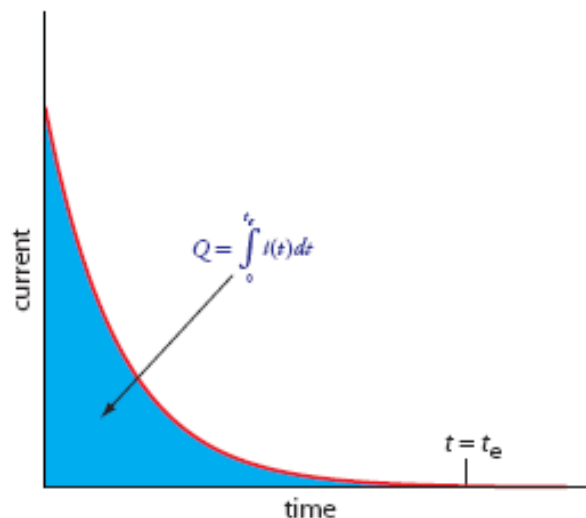
$[O]_{x=0}$ and $[R]_{x=0}$ are the **surface concentrations** of O and R, respectively
(the ratio of which is governed by the Nernst equation)

Efficient mass transport (stirring, pumping) is important

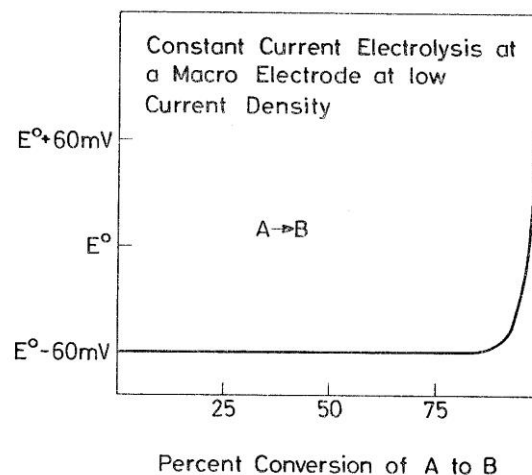
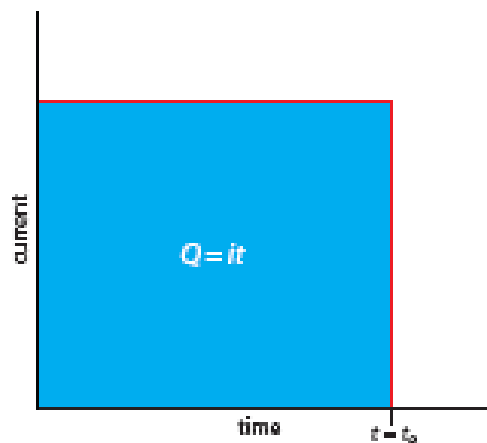
Current density: i/A



Constant potential or constant current electrolysis ?



Requires a setup with a reference electrode

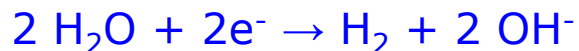


The potential is essentially constant during constant current electrolysis; thus a reference electrode is not needed



Electrode material

The potential limiting processes (in aqueous solution or water containing organic solvents) are



Overpotential for hydrogen evolution



Overpotential for oxygen evolution



Special electrode materials:

Glassy carbon, carbon rods, boron-doped diamond (BDD),

Dimensionally stable anodes (DSA, Ti covered with metal oxides) ---

Some metal electrodes may dissolve during oxidation (sacrificial anodes)



Solvent and supporting electrolyte

The solvent:

In addition to the usual solvent properties:
Medium to high dielectric constants

The supporting electrolyte

Well dissociated (\Rightarrow low resistance)

Both:

Applicable in the potential range +3V to -3V

Easy to remove during work-up

Preferably non-toxic

Non-nucleophilic and/or non-electrophilic

Recyclable and/or cheap for large-scale applications

Common solvents for oxidation:

MeCN, CH_2Cl_2 ,

Water, MeOH (methoxylations)

Common solvents for reduction:

Water, MeCN, DMF, DMSO

Common supporting electrolytes

for aprotic conditions:

R_4NBF_4 , R_4NPF_6

typically Bu_4NPF_6

(work-up may be difficult)

Substitutions/additions:

M^+ , Nu^- or R_4N^+ , Nu^-

Alkoxylation: KOH in ROH

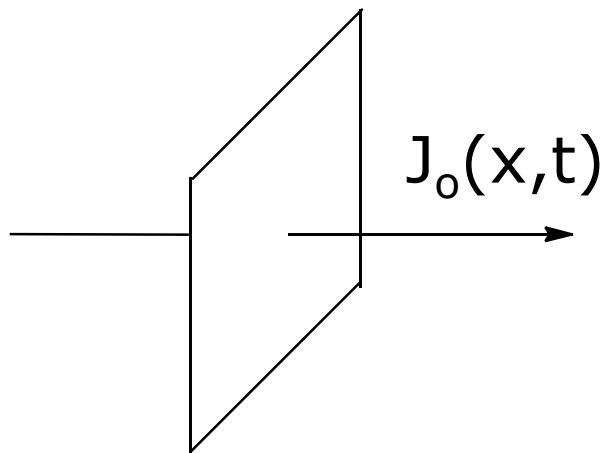


Mass transport and current (in one dimension)

Strategy for electroanalytical measurements:

Comparison of the experimental data and the theoretical response curves

The flux, $J_o(x,t)$, that is the rate of flow of a species per unit area (in a fluid medium), is the important parameter



Mass transport and current (in one dimension)

For the general case described in terms of the three components that constitute the **Nernst-Planck equation**

$$J_O(x,t) = -D_O \frac{\partial C_O(x,t)}{\partial x} - \frac{z_O F}{RT} D_O C_O(x,t) \left(\frac{\partial \Phi(x,t)}{\partial x} \right) + v(x,t) C_O(x,t)$$



The first term is the **diffusion component**

~~The second term is the **migration component**~~

The third term is the **convection component**

D_O is the diffusion coefficient of O

$C_O(x,t)$ is the concentration of the species O at the distance x and the time t

$\partial C_O(x,t)/\partial x$ is the concentration gradient

z_O is the charge of O

$\partial \Phi(x,t)/\partial x$ is the electrical potential gradient along the x -axis

$v(x,t)$ is the velocity of the fluid normal to the unit area

A high concentration of supporting electrolyte
1) makes the 2nd term negligible
2) lowers the solution resistance

Effective stirring or pumping increases the flux and thus the mass transport

Organic electrochemical synthesis in summary

Pros

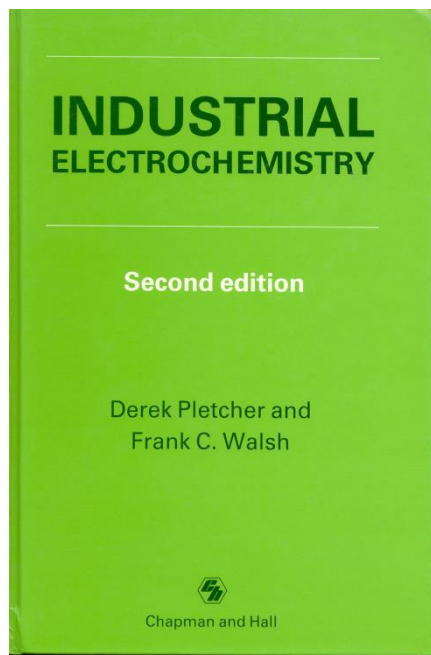
1. Replacement of inorganic redox reagents with electrochemical processes often reduces the total number of laboratory steps.
2. Electrode reactions are selective and present direct routes to products otherwise difficult to make (*via* 'umpolung').
3. Electrons are cheap and are easy to transport. Electricity can be made from many different natural resources.
4. Green and safe technology; no toxic wastes, no fire or explosion hazards, no storage/handling of aggressive reagents, mostly room temperature chemistry.
5. Electrochemical synthesis is easily scalable to the industrial level.

Cons

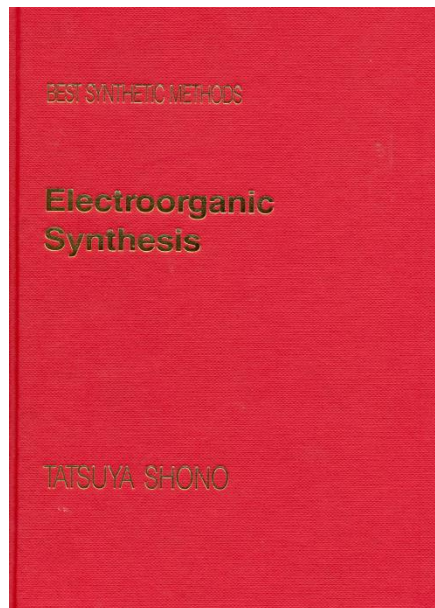
1. Organic electrochemistry is (still) considered a specialists topic and is usually not a part of the chemistry curriculum.
2. Reaction mechanisms are often complex and require insight into radical ion and radical chemistry. Products may be difficult to predict.
3. Requires equipment (electrodes, cells and current sources) that often is not available in an organic chemistry laboratory.
4. Electron transfer is a heterogeneous process and for that reason takes time ($1 \text{ mole of } e^- = 1F = 96485 \text{ C} = 96485 \text{ A}\cdot\text{s} = 26.8 \text{ A}\cdot\text{h}$).
5. Occasionally, electrode fouling occurs. Requires cleaning of electrodes and cells.



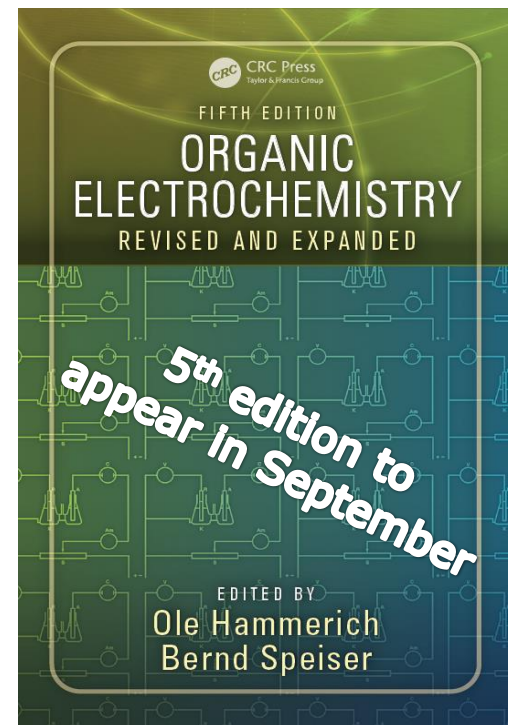
Recommended Literature



Pletcher/Walsh:
Industrial Electrochemistry,
Chapman & Hall, 1990.
not only organic



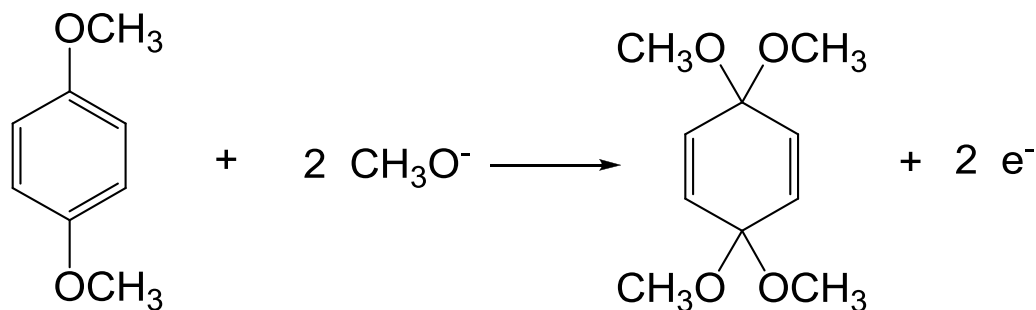
Shono:
Electroorganic synthesis,
Academic Press, 1991.
recipes included



Hammerich/Speiser, eds.:
Organic Electrochemistry, 5th ed.
CRC Press, 2015.

44 chapters written by 66 experts in the field covering
most aspects - except industrial processes

Recipe no 1

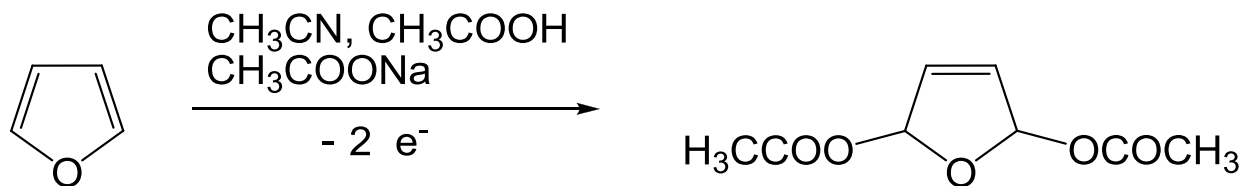


To a magnetically stirred solution of 1 g of KOH in 150 mL of methanol at $\sim 0^\circ\text{C}$ (ice-bath) is added 4.6 g (0.033 mol) of 1,4-dimethoxybenzene.

The solution is electrolyzed at a constant current of 1 A for 2 h in an undivided cell using a Pt gauze anode and a C cathode.

After oxidation, the solution is concentrated under reduced pressure. To the residue is added 100 mL of water that is extracted with three 50 mL portions of ether. After removal of solvent, the residue is recrystallized from light petroleum to give ~ 5 g of the product (m.p. $40\text{--}41^\circ\text{C}$).

Recipe no 2

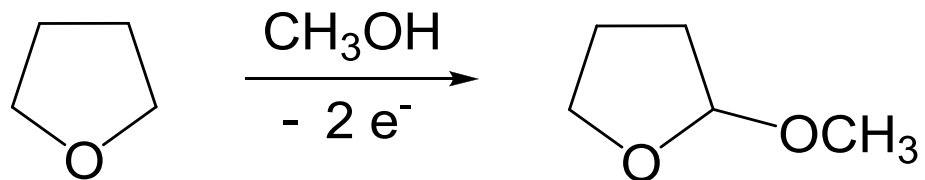


Into a cell equipped with a Pt anode and a C cathode is added a solution of furan (2 g) in a mixture of AcOH (120 mL) and MeCN (30 mL) containing AcONa (6 g).

The mixture is cooled to 3 - 7°C during the oxidation.

After 2.5 F ($\sim 1 A$ for 2h) of charge has passed, the reaction mixture is poured into water and extracted with CH_2Cl_2 . The extracts are dried with MgSO_4 and distilled to give the product.

Recipe no 3



A solution of tetrahydrofuran (7.4 mmol = 0.53 g) and Et₄NOTs (2 mmol = 0.6 g) in a mixed solvent of acetic acid (10 mL) and methanol (120 mL) is put into an undivided cell equipped with a platinum anode and a graphite rod cathode.

After 10 *F* (~1A for 4 h) of charge has passed, the product is obtained by distillation.