Reviews

Organic synthesis based on cathodic deprotonation of acids

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The results of studies on electrosynthesis involving carb- and heteroanions generated by cathodic deprotonation of acids (CDA), carried out in the laboratory headed by the author, are surveyed. These studies resulted in the elaboration of efficient electrochemical versions of the known Michaelis—Becker, Wittig—Horner, and Perkin reactions; electrochemical analogs of homolytic aromatic substitution, alkylation, heterocyclization, *etc.* were developed. Based on CDA, convenient and promising methods for preparing various *N*-, *O*-, *P*-, *S*-, and *C*-alkylated and arylated substances have been developed.

Key words: cathodic deprotonation of organic acids; carb- and heteroanions, electrochemical alkylation and arylation; paired electrolysis; ion association.

At present, judging from the great number of publications, interest in electroorganic synthesis as an efficient tool of synthetic organic chemistry has substantially increased. One of the most significant problems is the development of new approaches for the generation of organic anions, which are fundamental species of organic chemistry, widely used for synthetic purposes.

A typical electrochemical method for generating organic anions is two-electron cleavage of a σ-bond:

$$RX + 2e^- \rightarrow R^- + X^-.$$

However, the direct electrochemical deprotonation of relatively weak organic acids seems to be more attractive.

$$RH + e^- \rightarrow R^- + 1/2\ H_2.$$

In the 1970s, some examples of realization of processes of this sort in nonaqueous media have been reported (see, for example, Refs. 1—4). These works stimulated us to carry out a systematic study of synthetic applications of carb- and heteroanions generated by cathodic deprotonation of acids (CDA) under the conditions of cathodic electrolysis of relatively weak ($pK \sim 30$) organic acids. As a result, we have suggested efficient methods for *C*-, *O*-, *S*-, *N*-, and *P*-alkylation or arylation. Among these, electrochemical versions of a number of well known reactions, such as Michaelis—Becker, Wittig—Horner, and Perkin reactions have been developed. An important characteristic feature of these processes is that they occur under mild conditions, and the *in situ* electrochemical generation of organic anions makes it possible to avoid the use of chemical deprotonating reagents, which are often expensive and can be used only once. The purpose of the present work is to survey the results of these studies.

The examples of CDA-based electrosynthesis considered below have been realized, as a rule, using a Pt cathode in a diaphragm cell. Solutions of tetraalkylammonium salts in aprotic media (MeCN, CH_2Cl_2) served as

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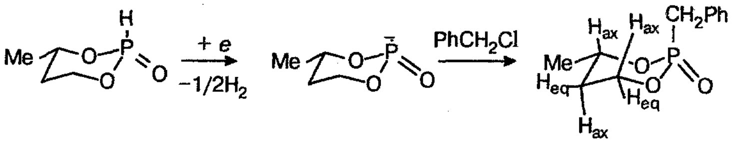
Scheme 1



1 1a 2

supporting electrolytes. The consumption of electricity normally did not exceed a theoretically required value of 1 F per mol of the starting acid, except for those cases where competing reactions occurred in parallel with cathodic deprotonation. The composition of the anolite or the material of the anode (normally Pt or graphite) had no substantial effects on the yields of the target products. With rare exception, all of the electrolyses were carried out under amperostatic conditions.

1. CDA-based alkylation processes

Synthesis of phosphonates. The cathodic generation of anions from available dialkyl phosphites, which was discovered by us for the first time, has become the key step of the method suggested[5] for the preparation of phosphonates (yield 60—80 %). This process can be considered to be an electrochemical version of the Michaelis—Becker reaction. To estimate the synthetic prospects of this reaction, it was necessary to determine the stereochemical stability of the phosphite anions under the experimental conditions. For this purpose, we studied electroreduction of stereohomogeneous *cis*-1,3-butylene phosphite (**1**) with equatorial methyl and phosphoryl groups. Based on the data of X-ray diffraction analysis,[6] it was found that the cathodic electrolysis of **1** at a Pt electrode in the presence of PHCH$_2$Cl in a 0.25 *N* solution of Et$_4$NBr in MeCN leads to stereodirected alkylation of the phosphite anion generated in the system, with retention of the configuration of the hydrophosphoryl center, and affords stereoindividual phosphonate (**2**) in a 60—70 % yield (Scheme 1).

Synthesis of olefins from phosphonates or dialkyl phosphinates. The generation of anions proved to be also possible during electroreduction of phosphonates. This allowed us[7] to accomplish an electrochemical version of the Wittig—Horner reaction, a classical method for preparing olefins, in which the yields of the target products were 60—85 % and the *E*-isomer usually predominated.

The idea of combining the Michaelis—Becker and Wittig—Horner reactions into one process led us to the development of a fundamentally new method for preparing olefins[8] (Scheme 2).

The procedure of this synthesis, carried out as a one-pot reaction, is very simple: a mixture of alkyl halide and dialkyl phosphite is subject to amperostatic electrolysis to give successively dialkyl phosphonate and its anion. When 2 F mol^{-1} of electricity is passed, a carbonyl compound is added to the solution being electrolyzed, and after stirring for ~30 min, the target product is isolated.

Alkylation of amines, dialkyl phosphites, and CH acids with dichloromethane. One rather poorly elaborated possibility of electroorganic synthesis is using the medium as a reactant. The examples presented below demonstrate the ability of normally inert CH$_2$Cl$_2$ to act as a methylating agent under the conditions of CDA, in particular, during cathodic electrolysis of NH acids.[9]

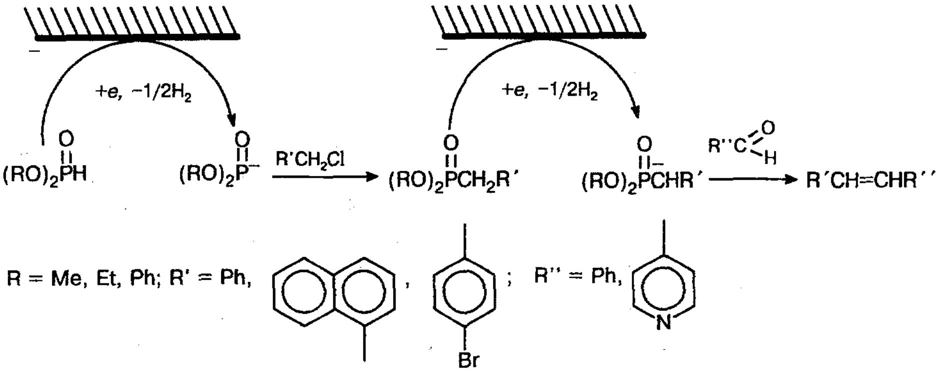
$$\mathrm{RR'N{-}H} \xrightarrow[(3\ \mathrm{F})]{\mathrm{H_2CCl_2}} \mathrm{RR'N{-}Me}$$

40—80 %

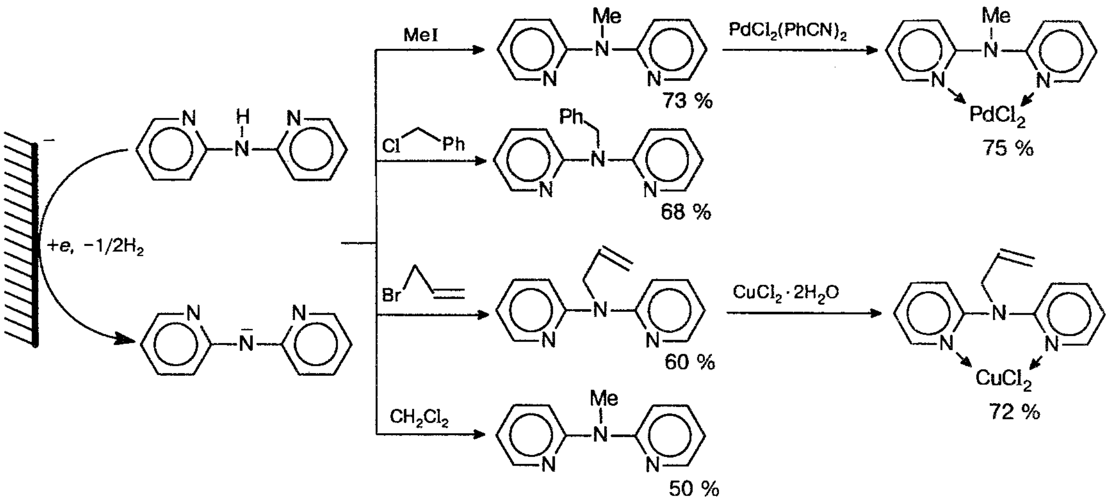
R = R' = Ph
R = R' = $-(CH_2)_5-$
R' = Ph; R = CN

N-Alkylation of ambident systems such as di(2-pyridyl)amine, where the N atoms of the pyridine ring and the amino group can act as reaction centers, is a somewhat special case (Scheme 3). The electroreduction of di(2-pyridyl)amine is accompanied by the

Scheme 2



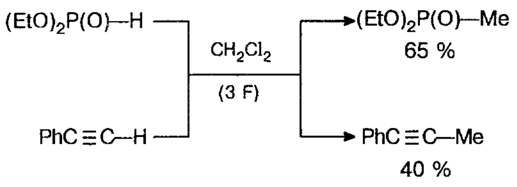
Scheme 3



generation of the N-anion at the extra-cyclic nitrogen, therefore, in the presence of CH_2Cl_2 or other alkylating agents, alkylation occurs regiospecifically.[10] Notice that the alkylation products formed behave as bidentate ligands in the reactions of complex formation with salts of divalent metals (Pd^{2+} and Cu^{2+}).

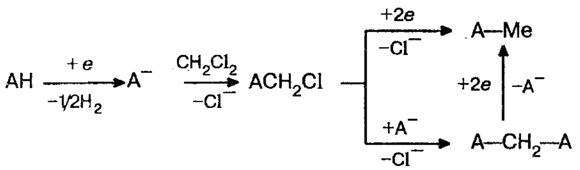
Electrolysis of PH and CH acids[11] under similar conditions yielded methylated products (Scheme 4).

Scheme 4



Alkylation of alcohols and thiols with dichloromethane. Conversely, the course of the cathodic electrolysis of OH and SH acids depends on the quantity of electricity passed, and the reaction can yield either acetals (1 F mol^{-1}) or products of their further reduction, *viz.*, the corresponding methyl derivatives ($\geq$ 3 F mol^{-1}). The combination of these results allowed us to describe the mechanism of the processes under consideration by the following general scheme[11] (Scheme 5).

Scheme 5



The electrolysis of OH or SH acids, whose anions are sufficiently nucleophilic, occurs according to the lower branch of Scheme 5.

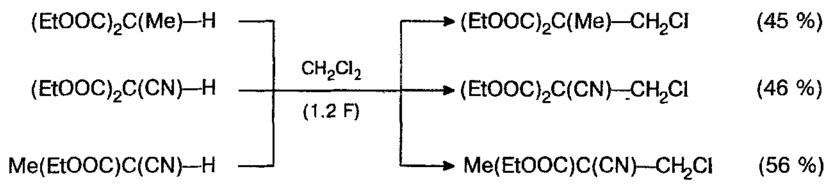
The intermediate formation of ACH_2Cl has been confirmed by the data on the cathodic electrolysis of monosubstituted derivatives of alkyl malonates[12] (Scheme 6).

This process, which affords chloromethylated products, may be regarded as a convenient route to polyfunctional multipurpose synthons. Notice that with more prolonged electrolysis (~3 F mol^{-1}) the corresponding methyl derivatives are produced, in conformity with the process described by the upper branch of Scheme 5.

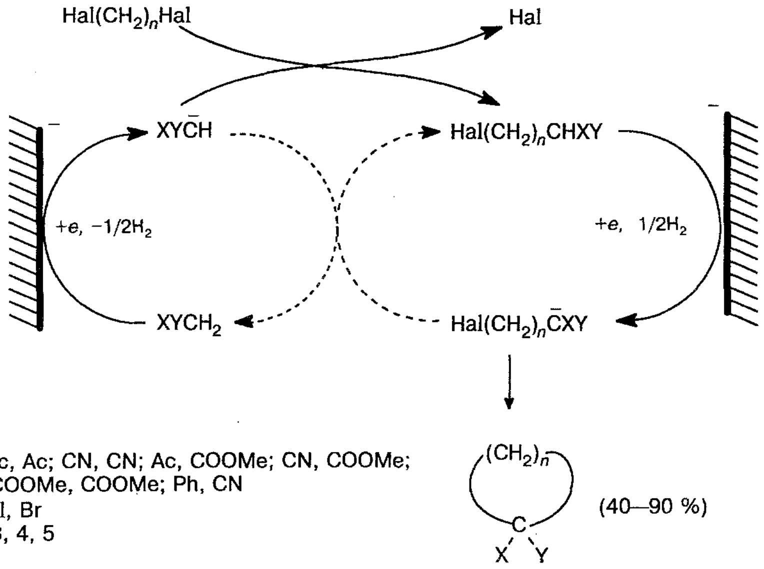
Double alkylation of CH acids. Let us consider one more example of electrosynthesis based on CDA that leads to generation of carbanions. This is the realization of an electrochemical version of the synthesis of carbocyclic compounds according to Perkin reaction, which gives rise to functionally substituted alicyclic compounds (Scheme 7). Methylene-active compounds of type CH_2XY are used in this process as the starting substances.

In a series of studies,[13–17] it has been shown that the electrochemical generation of carbanions in the first and third steps of the process shown in Scheme 7 is the driving force of the whole process. These steps, and also the intermediate step, alkylation, and the final step, intramolecular cyclization, are carried out as a one-pot reaction. The yields of the target products decrease (see, for example, Ref. 17), when either relatively strong or relatively weak CH acids are used as the starting compounds (Fig. 1). In the former case, this is obviously due to the low nucleophilicity of the carbanion generated. In the latter case, this is caused by the progressive increase in the reduction potential of the CH acid. Consequently, the reduction of dihaloalkanes competes with the cathode cleavage of the C—H bond. The yields of the target products can be substantially increased by

Scheme 6



Scheme 7

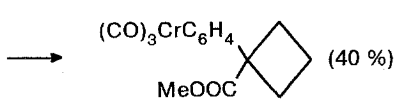


X,Y = Ac, Ac; CN, CN; Ac, COOMe; CN, COOMe; COOMe, COOMe; Ph, CN
Hal = Cl, Br
n = 2, 3, 4, 5

using electrogenerated bases[17] or by increasing the duration of the electrolysis (see Fig. 1).

One more possibility is to increase the mobility of the hydrogen atoms of the methylene unit in one way or another (for example, the mobility of benzylic hydrogen atoms is increased when electrolysis of the corresponding tricarbonylchromium complexes is carried out[18—20]). In fact, methyl phenylacetate is not alkylated under conditions of cathodic electrolysis, but alkylation of its tricarbonylchromium complex gave the corresponding cyclobutane derivative in 40 % yield.

$$(CO)_3CrC_6H_4{-}CH_2{-}COOMe + Br(CH_2)_3Br \xrightarrow[-2H,\ -2Br^-]{+2e}$$



However, the acidity of the tricarbonylchromium complex of toluene is still insufficient for alkylation to occur; during the electrolysis, competing reduction of alkyl halide apparently proceeds. Unlike electrochemically inactive benzotrimethylsilane, its complex is electrolyzed in the presence of dibromopropane with elimination of the trimethylsilyl group; this can serve as a convenient method for desilylation of systems of this sort under mild conditions:

$$(CO)_3CrC_6H_4{-}CH_2{-}SiMe_3 \xrightarrow{+2e,\ +DH} (CO)_3CrC_6H_4{-}Me\ .$$

Unexpected results were obtained in the cathode electrolysis of ethyl mono- and dibromomalonates (**3** and **4**) (Scheme 8), which, along with the dimeric products (**5** and **6**, respectively), gave tetracarbethoxyoxirane (**7**). With the overall yield of products being nearly quantitative,[21] the proportion of epoxide was 50—60 %, however, when the quantity of ester **3** taken was increased, epoxide proved to be practically the only reaction product.*

Alkylation of cyanamide. As a development of these studies, we have shown recently[22] that electrosynthesis of *N*-cyano substituted heterocyclic systems by cathodic electrolysis of NH_2CN in the presence of alkylene di-

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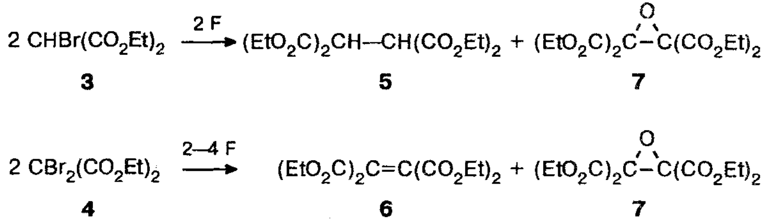
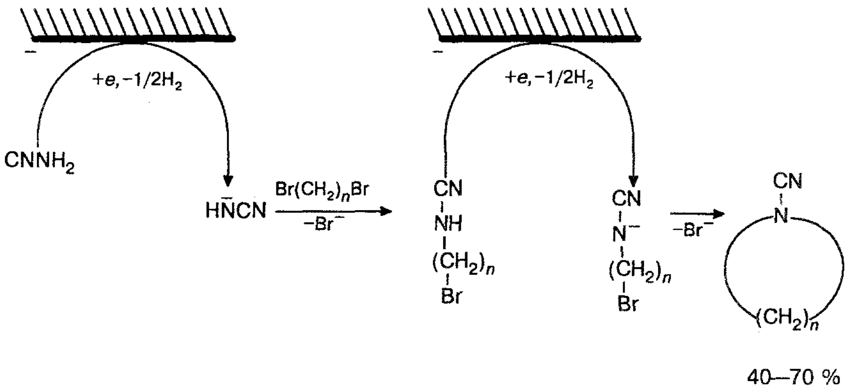
* In principle, the oxygen atom incorporated in molecule **7** could have come from traces of water or atmospheric oxygen. However, additional experiments did not lead to unambiguous conclusions, and this problem requires a special study. Nevertheless, it was shown that epoxide **7** does not result from products **5** and **6**.

Scheme 8



Scheme 9



bromides of the general formula $Br(CH_2)_nBr$, where n is 3 to 6, is possible (Scheme 9).

The regularities of this process are similar to those described above for cycloalkylation of methylene-active compounds.

Alkylation of N-nitramines. One of unexpected aspects of the development of the method of CDA in nonaqueous media is the fact that the selective cleavage of the R—H bond may occur even in the case where the molecule of the acid contains readily reducible functions such as a nitro group. This can be exemplified by cathodic alkylation of *N*-nitramines.[23]

$$RNHNO_2 \xrightarrow[-1/2H_2]{+e} R\bar{N}NO_2 \xrightarrow{CH_3I} RN(Alk)NO_2$$

$R = Et, Pr^i, o\text{-}Py$

Synthesis of sulfides. Thiolate anions are well known nucleophilic agents. Generation of these species under the conditions of cathodic electrolysis of mercaptans would make it possible to avoid the use of bases, whose presence during the synthesis of polyfunctional compounds, including sulfur-containing compounds, is usually undesirable. These considerations have been confirmed by the data obtained in the elaboration of a general method for the synthesis[24] of a variety of sulfides by the simultaneous electrolysis of mercaptans and organyl halides* according to Scheme 10.

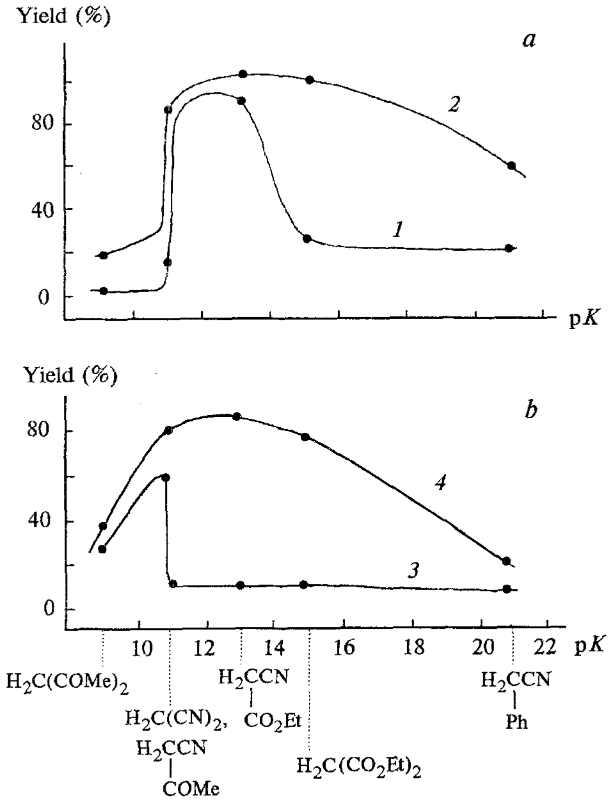


Fig. 1. Yields of cyclopropane derivatives in cathodic electrolyses of methylene-active compounds in $Cl(CH_2)_2Cl$ (*a*) and in a 1 *M* solution of $Br(CH_2)_2Br$ in MeCN (*b*) on passing 2 (*1, 3, 4*) or 4 (*2*) F mol^{-1} of electricity and with addition of benzene (*4*).

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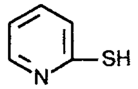
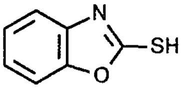
* An example of cathodic alkylation of mercaptans with methylene chloride has already been considered above.

Table 1. Formation of sulfides (R'SR) in the cathodic deprotonation of thiols (R'SH) in the presence of organyl halides (RX)[24]

R'SH	RX	Yield R'SR (%)	R'SH	RX	Yield R'SR (%)
Bu^nSH	Bu^nBr	86	Bu^nSH	CH_2Cl_2	91
$H_2N(CH_2)_2SH$	Bu^nBr	72	n-$C_{12}H_{25}SH$	CH_2Cl_2	90
Bu^nSH	$ClCH_2CN$	81	Bu^nSH	$Bu^nS(CH_2)_2Cl$	92
Bu^nSH	$ClCH_2C{\equiv}CH$	71	Bu^nSH	$ClCH_2CO_2Et$	95
n-$C_8H_{17}SH$	$BrCH_2CH{=}CH_2$	97	n-$C_6H_{13}SH$	$ClCH_2CO_2Me$	94
n-$C_8H_{17}SH$	EtBr	85		$ClCH_2CO_2Et$	97
PhSH	$ClNO_2C_6H_4$	84		$ClCH_2CO_2Et$	97

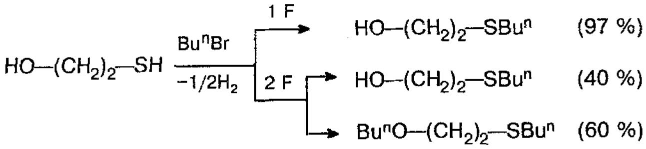
Scheme 10

$$R'SH \xrightarrow[-1/2H_2]{+e} R'S^- \xrightarrow[-X^-]{RX} R'SR$$

From the results presented in Table 1, it follows that sulfides containing such functional groups as ester, heteroaryl, vinyl, nitro, nitrile, *etc.* can be obtained according to this route under mild conditions and that high yields of the target compounds can be achieved.

An additional advantage of the method suggested is the possibility of selective alkylation of systems that, along with a mercapto group, incorporate other acidic functions, for example, as shown in Scheme 11.

Scheme 11



More prolonged electrolysis gives the completely alkylated product.

Dealkylation of onium compounds. The high nucleophilicity of the electrically generated thiolate anion made it possible to carry out efficient dealkylation of onium compounds that are present in the supporting electrolyte.

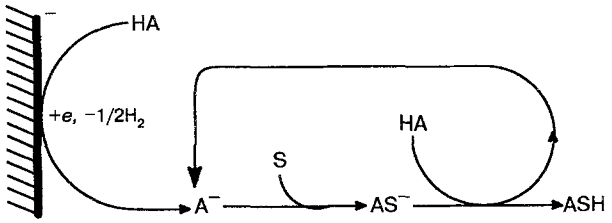
$$RSH \xrightarrow[-1/2H_2]{+e} RS^- \xrightarrow{Me\overset{+}{N}R_3} RSMe + R_3N\ .$$

The process occurring according to this scheme affords the corresponding trialkylamines and sulfides in 80—90 % yields and may be useful, for example, for removing an onium protection in the synthesis of natural compounds.

It has been found[25] that the ease of the abstraction of alkyl groups decreases on going from the methyl substituent to butyl, and the reactivity of the anions increases on going from C_{12}- or C_8-thioalkoxides to thiophenoxide. Notice that alternative chemical procedures for nucleophilic dealkylation involve prolonged boiling in a solvent in the presence of sodium telluride[26] or specially prepared alkali metal thiophenoxides.

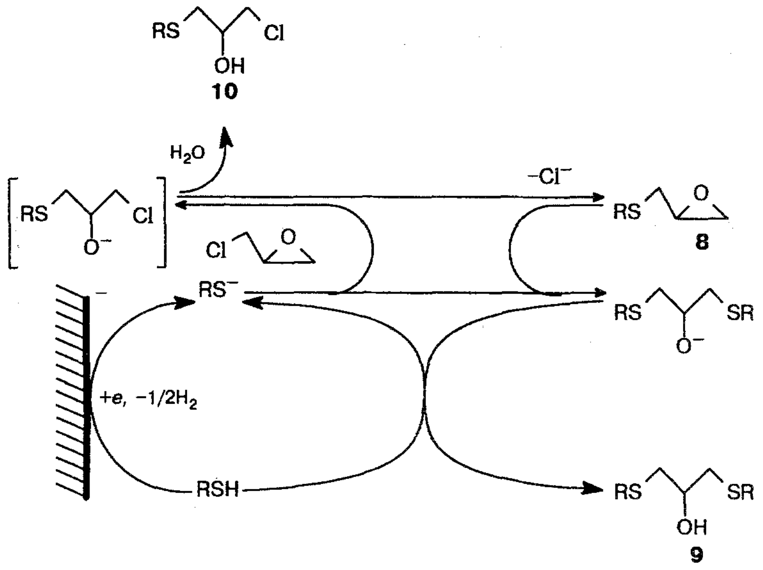
Homogeneous electrocatalysis under the conditions of CDA. In recent years, examples of homogeneous electrocatalysis, which can be conventionally named "electrosynthesis without current," since the current yields in these processes are sometimes as high as tens of thousands percent, have been found in the literature in increasing frequency.[27] These processes can occur, for example, during generation of an organic anion (A^-) from the conjugated acid (HA) in the presence of an electrophile (S). A necessary condition is that the basicity of the adduct (AS^-) should be higher than that of A^- (Scheme 12).

Scheme 12



For example, electrochemical addition of thiols (RSH, R = n-S_8H_{17}, n-$C_{12}H_{25}$, $HOCH_2CH_2$, Ph) to activated olefins[28] in which the substance yields of adducts were 90—98 % and the current yields were

Scheme 13



R = Bu^n; *n*-C_3H_{17}; *n*-$C_{10}H_{21}$

800—120,000 %; isomerization of epoxysulfoxides and sulfones to the corresponding allylic alcohols[29] in which proportions of the *E*-isomers were ~95 %; and thioalkylation of epichlorohydrin[30,31] have been accomplished according to this mechanism. The latter compound exhibits ambident properties and can be used in the synthesis of both hydroxy and epoxy compounds.

It was found[30,31] that the cathodic electrolysis of an equimolar mixture of thiol with epichlorohydrin gives epoxy sulfide (**8**) in 60 % yield and hydroxy sulfide (**9**) in 30—35 % yield, whereas electrolysis of a twofold excess of thiol (with respect to epichlorohydrin) gives only compound **9** in 95 % yield (Scheme 13). When water is added to the starting solution, electrolysis can be arrested at that step, giving hydroxy chloride (**10**), whose yield was 90—95 %.

2. Double inversion of the polarity of the starting reactant. Paired electrolysis

One of the basic ideas of organic synthesis is that the formation of a covalent bond requires interaction of species of various polarities. Nevertheless, practical implementation of this condition is generally associated with certain difficulties. In this respect, the electrochemical method can serve as a unique tool of organic synthesis, since inversion of the polarity (Umpolung) of organic molecules or ions readily occurs at an electrode.

The examples considered so far involved transformation of a neutral molecule of an RH acid to a nucleophilic anion. However, in an anode reaction, the polarity of this species can be readily inverted due to the transformation of the anion to the neutral radical.

Let us consider the conversion of weakly nucleophilic polynitrocarbanions into the corresponding highly electrophilic radicals as an example. We suggested the first model of this process based on combination of the previously developed cathode denitration of tetranitromethane[32] and anode polynitroalkylation of arenes.[33] However, CDA leading to the generation of polynitrocarbanions[34] also can be used as the cathodic reaction (Scheme 14).

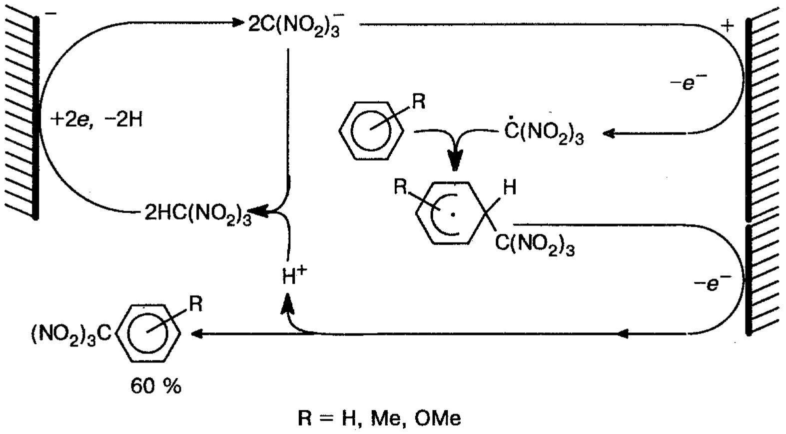
It is noteworthy that it is the formation of highly electrophilic radicals that made it possible to accomplish efficient alkylation of arenes by a mechanism of homolytic aromatic substitution, though it has been believed previously[35] that alkylation according to this mechanism is of no preparative value.

For the development of these studies, the use of not only carbanions, but also heteroanions proved to be promising. For example, it was found that the cathodic reaction of azoles involves deprotonation to give N-anion, which either is oxidized at the anode and reacts with an appropriate arene by a mechanism of homolytic aromatic substitution, or reacts with the radical cation resulting from oxidation of the arene by the same mechanism.[34] The products of arylation of azoles were obtained[36,37] by this route in 60—80 % yields.

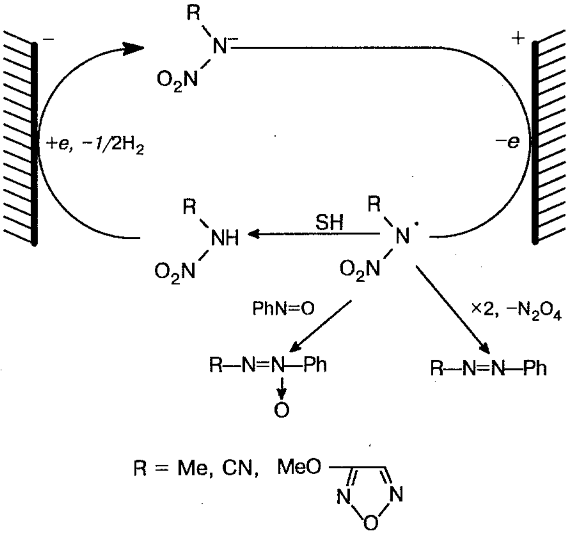
The possibility of cathodic deprotonation of *N*-nitramines established (see above)[23] made it possible to carry out undivided electrolysis in which the nitramine anion generated at the cathode is subsequently oxidized at the anode to give the corresponding radical and then azo derivative as the main product[38] (Scheme 15).

When nitrobenzene (an acceptor of radicals) is added to the solution electrolyzed, azoxybenzene becomes the main reaction product.

Scheme 14



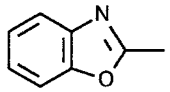
Scheme 15



Examples of undivided electrolysis that illustrate the two last schemes are characterized by one more significant point: processes that are useful (and not just inevitable) for the preparation of the target product occur at both electrodes. This paired electrolysis dramatically increases the efficiency of the energy consumption, which is of particular importance for industrial application. As one more example of paired electrolysis, we consider a general method of the electrosynthesis of disulfides[39] (Scheme 16, Table 2).

In this case, two possibilities are realized. The first of these (system *I*) involves the cathodic generation of the thiolate anion and its reaction with the Br_2, which is produced at the anode and acts as a mediator. However, when thiols, that are difficult to reduce, are used, the yield of disulfide decreases owing to its competing reduction. The process realized in the water—benzene two-phase system (system *II*), in which the disulfide formed is efficiently extracted with benzene, is free from this shortcoming.

Table 2. Results of electrosynthesis of disulfides RSSR by various methods

R	Yield RSSR (%)	
	I	*II*
C_8H_{17}	98	98
$C_{12}H_{25}$	97	99
Ph	95	96
4-ClC_6H_4	88	95
2-Py	94	96
	30	91

3. Relationship between the reactivity of electrogenerated anions and the nature of the supporting electrolytes

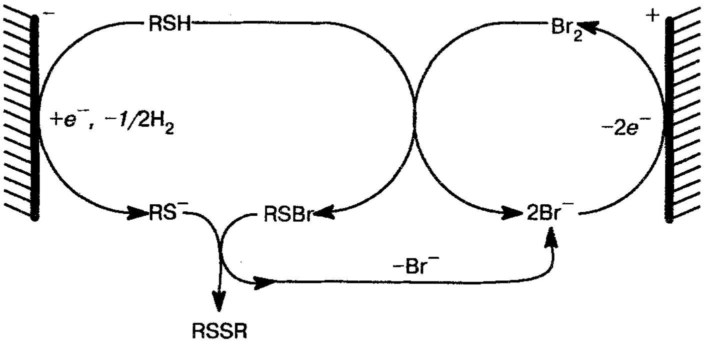
The reactivities of organic anions in nonaqueous media are known to depend on the nature of the counterion, due to the efficient ion association. However, most of the literature data deals with the chemical behavior of anions having alkali metal cations, more prone to ion association than onium cations, as counterions. This is caused to a large measure by the fact that the procedures for synthesizing onium salts are usually inconvenient multistep processes.

Notice in this respect that the cathode electrolysis of organic acids in nonaqueous media with tetraalkylammonium salts as supporting electrolytes directly affords onium salts of the corresponding carb- and heteroanions. This characteristic feature of electrochemical processes makes it possible to easily obtain additional information on the reactivities of anionic species and affects substantially the efficiency of processes involving electrogenerated anions.

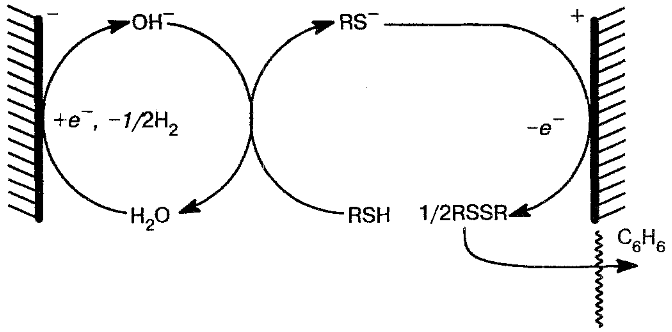
For example, when Bu_4NBr in the supporting electrolyte is replaced by $NaClO_4$,[6] the rate of alkylation of dialkyl phosphite **1** (see Scheme 1) decreases by almost an order of magnitude.

Scheme 16

***I.* NaBr/MeOH system**



***II.* $H_2O/C_6H_6/NaBr/Bu_4NBr$ system**



Unlike analogous chemical processes, efficient alkylation of electrically generated thiolate ions with onium counterions occurs even at room temperature.[24] Judging by the literature data,[40] thioacetals can be efficiently prepared from mercaptans and dihalomethanes only when CH_2I_2 is used, whereas electrochemically generated thiolate ions with onium counterions are alkylated by the considerably less electrophilic CH_2Cl_2 (see Table 1).

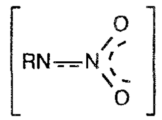
Effect of the nature of the counterion on the reactivities of ambident anions. Without dwelling on the discussion of this problem (since it deserves special consideration), we shall try to illustrate it by examples of processes that involve electrochemically generated anions derived from nitramines or mercaptans.

An analysis of the results obtained in a study of electrophilic alkylation of *N*-nitramines showed[23] that the efficiency of this process is determined by both the nature of the supporting electrolyte and ambident properties of the generated anions.

The existence of tautomeric forms of primary *N*-nitramines is of no doubt:

$$RNHNO_2 \rightleftharpoons RN{=}NO_2H\ ;$$

however, the actual structure of salts of these compounds has long been the subject of discussion (see, for example, Ref. 41). The averaged structure of the *N*-nitramine anion in which the charge is somewhat delocalized over the oxygen atoms of the nitro group is not inconsistent with the data available.



One may assume that alkali metal cations are coordinated to the oxygen atoms thus increasing the electron density at the functionally substituted nitrogen. In this context, the fact that the electrolysis of methylnitramine in the presence of 0.1 *N* $NaClO_4$ leads to *N*-alkylation products,[23] whereas electrolysis in the presence of tetraalkylammonium salts, whose tendency to form ionic associates is lower, gave no unambiguous results, becomes explicable. The latter observation is apparently accounted for by the instability of the intermediate *O*-methylated adducts. The results of the paired electrolysis of primary *N*-nitramines (see Scheme 15) presented in Table 3 can be interpreted in a similar way.[38]

In conformity with the foregoing, the use of alkali metal salts as supporting electrolytes favors the formation of N-anions and the formation of N-centered radicals in oxidation of the anions (see Scheme 15), whereas in the presence of tetraalkylammonium salts, the corre-

Table 3. Effects of the nature of the supporting electrolyte and the substituent in primary *N*-nitramines (R—$NHNO_3$) during their electrolysis in the presence of PhN=O on the yields of the corresponding azoxy derivatives of the general formula RN=N(O)Ph (undivided electrolysis in MeCN)[38]

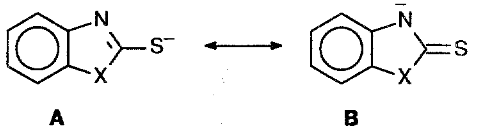
Entry	R	Yield (%)	
		0.1 *N* $NaClO_4$	0.1 *N* Bu_4NClO_4
1	Me	70	—
2	Et	*	—
3	CN	62	50

* Na-salt of nitramine is insoluble in MeCN.

sponding O-centered anions and radicals are obviously formed. This is in agreement with the results of entries *1* and *2* (see Table 3), which indicate that the electrolysis with tetraalkylammonium salts gives no azoxy derivatives even as traces. The foregoing is additionally supported by the results of entry *3* (see Table 3). The presence of an electron-withdrawing substituent in the *N*-nitramine molecule changes the electron density of the anionic intermediate in such a way that an N-centered anion structure and the corresponding N-centered radical structure are realized even in the presence of tetraalkylammonium salts. Consequently, the electrolysis with this supporting electrolyte gave the azoxy derivative (which has not been detected in entries *1* and *2*) in 50 % yield.

The allowance for the effects of ion association makes it possible to interpret the results of cathodic alkylation of heterocyclic mercaptans. These compounds are ambident due to the existence of two tautomeric forms, the equilibrium between which is shifted toward the thione form.[42] The corresponding anions can be described by two contributing structures (Scheme 17).

Scheme 17



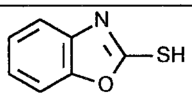
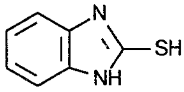
X = O, S, NH

One may believe that the effects of tetraalkylammonium cations on the contribution of one or the other form would be insignificant and would decrease with an increase in the size of the alkyl substituent.

The data presented in Table 4 obviously reflect the reactivities of the ambident systems considered under those conditions where the effects of ion association are weak. It turned out that in this case, highly electrophilic reagents (see entries *1—4*) react selectively at the S atom, despite the fact that the contribution of the thione form (**B**) predominates. Nevertheless, the latter factor is manifested in the Michael addition of electrochemically generated anions of heteroaromatic mercaptans (entries *8—11*). This process (see Table 4) occurs exclusively at the less nucleophilic N-center of the molecule. Therefore, it is easy to conclude that the direction of the alkylation of ambident heteroaromatic anions depends on the nature (strength) of the electrophilic reagent, all other factors being the same.

Note that the low yields of *N*-alkylated adducts in the reactions with the participation of olefins (see Table 4, entries *9* and *11*) are most likely due to the fact that $RNCH_2{}^-CH_2SO_2C_8H_{12}$ type carbanions are not basic enough for the catalytic cycle to be realized (see Scheme 12). For this reason, a quantity of electricity larger than that consumed in this case (0.4 F mol^{-1}) is needed to complete the process. In fact, consumption of

Table 4. Yields (%) and compositions of the products of electrochemical alkylation of heteroaromatic mercaptans[31] in anhydrous MeCN with 0.3 *N* Et_4NBr as the supporting electrolyte

Entry	Alkylating reagent	Q /F mol^{-1}				
			S-alkyl.	*N*-alkyl.	*S*-alkyl.	*N*-alkyl.
1	$ClCH_2Ph$	1—1.25	97	—		
2	$ClCH_2COOEt$	The same	97	—	90	—
3	$ClCH_2CH=CH_2$	»»	91	—	77	—
4	$ClCH_2CN$	»»	82	—	—	—
5	$ClCH_2CH_2COOEt$	»»	88	12	*	*
6	$ClCH_2CH_2SO_2Bu^n$	»»	—	—	—	—
7	$ClCH_2CH_2SO_2C_8H_{17}$-*n*	»»	2	**	—	—
8	$CH_2=CHC(O)OMe$	0.4	—	72	—	—
9	$CH_2=CHC(O)OEt$	0.4	—	49	—	—
10	$CH_2=CHSO_2Bu^n$	1.2	—		—	86
11	$CH_2=CHSO_2C_8H_{12}$-*n*	0.5	—	49	—	—

* Only $Bu^nSO_2CH=CH_2$ (75 %) and $(BuSO_2CH_2CH_2)_2$ (10 %) were isolated. ** *n*-$C_8H_{17}SO_2CH=CH_2$ (98 %) was formed as the second product.

1.2 F $\mathrm{mol^{-1}}$ of electricity (entry *10*) increases the overall yield of mono- and di-*N*-alkylated adducts to 86 % (see Table 4).

The processes of alkylation involving reagents that are simultaneously electrophiles and methylene-active compounds (see entries *5—7*) have some special features. Under the conditions of cathodic electrolysis they are able to undergo either chemical (through the action of N-centered heteroanion) or electrochemical dehydrochlorination. These processes compete with the generation of anions derived from mercaptans:

$$\mathrm{ClCH_2CH_2SO_2C_8H_{17}} \xrightarrow[-1/2\mathrm{H_2}]{+e} \mathrm{ClCH_2\overset{-}{C}HSO_2C_8H_{17}} \longrightarrow$$

$$\xrightarrow[-\mathrm{Cl^-}]{} \mathrm{CH_2{=}CHSO_2C_8H_{17}}$$

This may account for the composition of the electrolysis products in entries *5—7*. In particular, we believe that the 12 % yield of the *N*-alkylated product in the reaction with ethyl chloroacetate (entry *5*) is caused by the Michael addition of the *N*-centered heteroanion to the intermediate olefin.

As has already been noted, in the absence of ion association, the contribution of form **B** predominates (see Scheme 16). However, we believe that alkali metal cations, which tend to form ion pairs, are coordinated to the N-anionic center and thus change the distribution of the electron density in the heteroaromatic system in such a way that the nucleophilicity of the S atom increases. As this take place, a structure intermediate between contributing forms **A** and **B** is apparently realized (see Scheme 16). As a consequence, the reactivities of the heteroanions under consideration should also alter. This conclusion can be illustrated by the reaction of 2-pyridinethiol with octylvinylsulfone under the conditions of cathodic electrolysis. Note that the nucleophilicity of the sulfur atom in 2-pyridinethiol is higher than that in the heteroaromatic mercaptans[43] given in Table 4. This is manifested by the fact that electrolysis even in the presence of $\mathrm{Et_4NBr}$ gives the products of both *N*- and *S*-alkylation in a ratio of 30 % to 70 %. Nevertheless, when this supporting electrolyte is replaced by $\mathrm{NaClO_4}$, the ratio changes to 8 % to 92 %. Similarly, the addition of alkali results in a dramatic increase in the yields of *S*-substituted derivatives of 2-pyridinethione in its reactions with activated olefins.[44]

***

The approach to the electrochemical generation of carb- and heteroanions developed in this review is actually a method of titration of protic organic acids (pK ~ 30), whose peculiarity consists in that deprotonation is accomplished by the cathode (which acts as a base), and the proton of the acid is removed from the system as gaseous hydrogen. The versatility of this approach demonstrated for a wide variety of examples proves that this method is quite general, and, in our opinion, the abbreviation suggested (CDA for cathodic deprotonation of acids) adequately characterizes its essence.

The principle ideas that provide the basis of the present work have been formulated by the author in a report[34] delivered at a conference of the International Electrochemical Society. Some of these have been considered in a review.[45]

It should be noted that in the 1980s, systematic studies on the method of CDA were carried out in parallel by a group of scientists who worked independently of us using a system with a soluble anode. In particular, they showed[46] that the processes of CDA occur at cathodes made of transition metals, and the system chosen allowed them to obtain various organometallic compounds. By the way, this is one of the possible directions of efficient application of the method of CDA. Among other applications of this method, note the prospects of using it for controlling the reactivities of organic anions and for the realization of paired electrolysis. The routes for the development of these applications have only been outlined in the corresponding sections of the present paper. However, we practically did not discuss the possibility of using CDA for mediatory processes in which the anions of protic organic acids would act as electrically generated bases. Individual examples[47] of these processes based on CDA have not yet been properly developed. It might be expected that the method of CDA would also be promising for $\mathrm{S_{RN}1}$ type reactions, where anions act as donors of electrons. The above-presented list of applications of the method of CDA indicates that there are broad possibilities of synthetic development of this method.

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