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Electrochemically Induced Aromatic Nucleophilic Substitution in Liquid Ammonia. Competition with Electron Transfer

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Abstract: Electrochemical inducement of aromatic nucleophilic substitution of ArX compounds is investigated for a number of substrate and nucleophile systems in liquid ammonia. Electron transfer to the Ar· radical resulting from the initial reductive cleavage is essentially the only reaction competing with substitution. The competition occurs under two different regimes involving either homogeneous or heterogeneous electron transfer leading to different kinds of kinetic control. Cyclic voltammetry is used both for a rapid estimate of the nucleophile reactivity and for a quantitative determination of the rate constants of the nucleophile addition on Ar·. The method is also applied to the determination of the kinetic stabilities of the substrate anion radicals which is not possible through the standard application of electrochemical techniques. The agreement of the predicted kinetics with the experimental data both under homogeneous and heterogeneous electron transfer conditions provides further support for the $S_{RN}1$ mechanism.

It has been shown recently that $S_{RN}1$ nucleophilic substitution (see ref 2 and references cited therein) of aromatic halides can be induced electrochemically involving the reaction sequence

$$\mathrm{ArX} + 1\mathrm{e}\ (\text{electrode}) \rightleftarrows \mathrm{ArX}^{-\cdot}\ (\text{standard potential: } E_1^\circ) \qquad (0)$$

$$\mathrm{ArX}^{-\cdot} \xrightarrow{k_1} \mathrm{Ar}\cdot + \mathrm{X}^- \qquad (1)$$

$$\mathrm{Ar}\cdot + \mathrm{Nu}^- \xrightarrow{k_2} \mathrm{ArNu}^{-\cdot} \qquad (2)$$

$$\mathrm{ArNu}^{-\cdot} - 1\mathrm{e}\ (\text{electrode}) \rightleftarrows \mathrm{ArNu}\ (\text{standard potential: } E_2^\circ) \qquad (3)$$

and/or

$$\mathrm{ArNu}^{-\cdot} + \mathrm{ArX} \overset{k_4}{\rightleftarrows} \mathrm{ArNu} + \mathrm{ArX}^{-\cdot} \qquad (4)$$

(equilibrium constant: $K_4 = \exp[(F/RT)(E_1^\circ - E_2^\circ)]$

The reaction is initiated by setting up the electrode potential at the level of the reduction wave of the substrate. When the substrate is easier to reduce than the substitution product ($E_1^\circ > E_2^\circ$), the electrochemical injection of electrons is catalytic since reaction 3 is in favor of the right-hand side at the working potential and reaction 4 is spontaneously in favor of the right-hand side as well. In the reverse case the $\mathrm{ArNu}^{-\cdot}$ anion radical may have to be reoxidized independently in order to complete the reaction.

So far, the electrochemical inducement of such aromatic nucleophilic substitution reactions has been carried out in organic solvents such as acetonitrile and dimethyl sulfoxide with tetraalkylammonium salts as supporting electrolyte.[3,4] In these media a competing reaction that may lower the substitution yield is then H-atom abstraction from the solvent by Ar·.

$$\mathrm{Ar}\cdot + \mathrm{SH} \rightarrow \mathrm{ArH} + \mathrm{S}\cdot \qquad (5)$$

with further electron transfer to S· leading to S^-.[4,5]

Another competing reaction that may occur in any solvent is the reduction of Ar· through electrode and/or solution electron transfer.

$$\mathrm{Ar}\cdot + 1\mathrm{e}\ (\text{electrode}) \rightarrow \mathrm{Ar}^- \qquad (6)$$

$$\mathrm{Ar}\cdot + \mathrm{ArX}^{-\cdot} \xrightarrow{k_7} \mathrm{Ar}^- + \mathrm{ArX} \qquad (7)$$

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$$Ar\cdot + ArNu^{-}\cdot \rightarrow Ar^{-} + ArNu \quad (8)$$

Ar^- is finally converted into ArH by proton abstraction from the solvent in the absence of added water:

$$Ar^{-} + NH_3 \rightarrow ArH + NH_2^{-} \quad (9)$$

Liquid ammonia is anticipated to be, as water, a poor H-atom donor.[6] The interference of reaction 5 should then be much less than in organic solvents, the main competition to substitution thus arising from electron transfers (6)-(8). It is the purpose of the work reported hereafter to investigate the electrochemical inducement of $S_{RN}1$ reactions in liquid ammonia and, more specifically, to analyze the competition with electron transfer.

The conditions of competition are different whether electron transfer mainly occurs either at the electrode (ECE-type process) or in the solution (disproportionation-type process). This will be discussed first mainly in the context of cyclic voltammetry. The results of a rapid survey of the $S_{RN}1$ reactivity of a number of substrates and nucleophiles in liquid ammonia will then be given. The competition between substitution and electron transfer will be analyzed in detail on the examples of 2-chloroquinoline (disproportionation-type electron transfer) and 2-iodoquinoline (ECE-type electron transfer) with benzenethiolates as nucleophiles. The temperature in all the experiments was −40 °C. All the potentials are referred to the Ag/Ag+ 0.01 M reference electrode.

General Aspects of the Competition between Substitution and Electron Transfer

In the absence of nucleophile, the aromatic halides considered in this work undergo an irreversible two-electron hydrogenolysis of the carbon-halogen bond along a reaction sequence involving reactions (0) + (1) + (6) + (7) + (9). The cyclic voltammograms then exhibit a first two-electron irreversible wave (H) followed by a one-electron reversible wave (D) corresponding to the reduction of ArH formed at the first wave into its anion radical:

$$ArH + 1e \rightleftarrows ArH^{-}\cdot \quad (10)$$

as represented schematically in Figure 1a. This behavior may change at high sweep rates if the time scale of the experiment reaches the same order of magnitude as the lifetime of the $ArX^-\cdot$ anion radical (reaction 1). The number of electrons at the first wave will then tend to decrease toward one. Accordingly the first wave will tend to become reversible and the second wave to disappear. When such conditions are met, the quantitative analysis of the modifications of the cyclic voltammograms as a function of sweep rate provides the value of the rate constant k_1. When k_1 is large, the Ar· radical is formed close to the electrode and has time to diffuse back to the electrode surface and be reduced according to reaction 6 (ECE-type hydrogenolysis) before being reduced in the solution through reaction 7 (disproportionation-type hydrogenolysis). The parameter governing the competition between ECE and DISP is[7]

$$k_7 C^\circ (Fv/RT)^{1/2} k_1^{3/2} < 1 \rightarrow \text{ECE} \quad (11a)$$
$$> 1 \rightarrow \text{DISP} \quad (11b)$$

C° is the initial concentration of ArX and v is the sweep rate. Since the standard potential of the $Ar\cdot/Ar^-$ couple is largely positive to that of the $ArX/ArX^-\cdot$ reaction 7 is likely to be diffusion controlled. When the parameter is larger than one, the DISP process predominates and vice versa. Several experiments carried out in liquid ammonia at −40 °C with various organic molecules have revealed that the diffusion coefficients are about five times larger than in organic solvents at room temperature. k_7 can therefore be taken as equal to 3×10^{10} M^{-1} L s^{-1} as an average[8] in evaluating which is the dominant path in the ECE-DISP competition. When determining k_1 from the peak-height variations at high sweep rates two different working curves must be used according to whether ECE or DISP is the dominant pathway.[9]

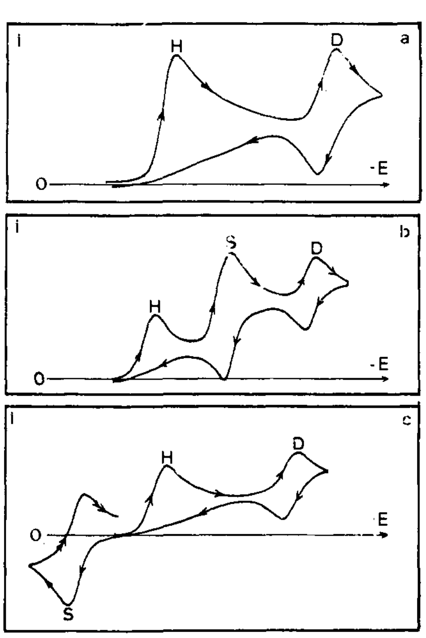


Figure 1. Schematic representation of the effects of nucleophilic substitution on the cyclic voltammograms of aromatic halides. (a) No nucleophile added. (b) Effect of the addition of a nucleophile when $E_1^\circ > E_2^\circ$. (c) Effect of the addition of a nucleophile when $E_1^\circ < E_2^\circ$. For definition of (H), (S), and (D) see text.

Upon addition of a nucleophile, changes will be observed in the slow sweep voltammograms. Their characteristics depend upon the relative values of the $ArX/ArX^-\cdot$ (E_1°) and $ArNu/ArNu^-\cdot$ (E_2°) standard potentials.

(1) If $E_1^\circ \gtrsim E_2^\circ$ (Figure 1b) addition of increasing amounts of the nucleophile results in a decrease of the first wave (H) and of the wave (D). At the same time a new wave (S) corresponding to the $ArNu/ArNu^-\cdot$ couple appears and increases. For a given nucleophile concentration, the changes are the more pronounced the larger the rate constant of reaction 2. A limiting situation is thus the complete disappearance of waves (H) and (D), the voltammogram involving then only wave (S). This does not reflect the complete conversion of ArX into ArNu in the bulk of the solution but merely the fact that substitution occurs efficiently in the vicinity of the electrode. Upon preparative-scale electrolysis at the potential of the first wave a mixture of ArNu and ArH will be obtained, the ratio of which reflects the competition between reactions (2) + (3) + (4) and reactions (6) + (7) + (8). The number of faradays per mole tends toward zero as the yield in ArNu tends toward 100%.

(2) If $E_1^\circ < E_2^\circ$ (Figure 1c), addition of increasing amounts of the nucleophile will again result in a decrease of waves (H) and (D). However, no (S) wave appears on the cathodic scan since at the level of wave (H) $ArNu^-\cdot$ is the reaction product; it is indeed not reoxidized into ArNu at the electrode. On the contrary, any ArNu formed through reactions 2 + 4 will be reduced into $ArNu^-\cdot$ at the electrode. Note that reaction 4 is endergonic in the present case but that its coupling with reaction 1 leads nevertheless to ArNu. The substitution product appears during the reverse scan as a reoxidation wave of $ArNu^-\cdot$ positive to wave (H).

Let us now analyze in some more detail the kinetics of the competition between substitution and electron transfer at the level of wave (H). Two limiting situations can be encountered depending on whether electron transfer mainly occurs at the electrode (ECE) or homogeneously (DISP). In the ECE case, i.e., for fast decomposition of the $ArX^{-}\cdot$ anion radical

$$k_1\ (\mathrm{s}^{-1}) > 3.5 \times 10^7 C^{\circ 2/3}\ (\mathrm{M\ L}^{-1})\ v^{1/3}\ (\mathrm{V\ s}^{-1}) \qquad (\text{at } -40\ ^\circ\mathrm{C}) \qquad (12)$$

The current function of $i_p/(i_p)_d$ [i_p is the observed peak current; $(i_p)_d$ is the peak current that would correspond to a one-electron reversible electron transfer

$$(i_p)_d = 0.446FSC^\circ D^{1/2}(Fv/RT)^{1/2}$$

with S = electrode surface area, D = diffusion coefficient. Without nucleophile the peak height of an irreversible two-electron wave obtained at low sweep rates is equal to $2.22(i_p)_d$] of peak (H) depends upon the parameter

$$\sigma = k_1/(k_2[\mathrm{Nu}^-])$$

Increasing the value of this parameter results in a decrease of the peak height from 2 to 0 electrons for $E_1^\circ > E_2^\circ$ and from 2 to 1 electrons for $E_1^\circ < E_2^\circ$. As anticipated from the first-order character of all reactions in this case (Nu^- is assumed to be in sufficient excess over ArNu for reaction 2 to be pseudo first order), the current function depends neither upon the initial concentration of the substrate, C°, nor upon the sweep rate. Its expression is simply

$$\begin{aligned} i_p/(i_p)_d &= 2.22\sigma^{1/2}/(1 + \sigma^{1/2}) \\ &= 2.22/(1 + k_1^{-1/2}k_2^{1/2}[\mathrm{Nu}^-]^{1/2}) \qquad (13) \end{aligned}$$

for the catalytic case.

Correspondingly, the substitution yield upon electrolysis beyond peak (H) does not depend upon C° and upon the stirring rate.

In the DISP case, i.e., for slower decomposition of $ArX^{-}\cdot$

$$k_1\ (\mathrm{s}^{-1}) < 3.5 \times 10^7 C^{\circ 2/3}\ (\mathrm{M\ L}^{-1})\ v^{1/3}(\mathrm{V\ s}^{-1}) \qquad (\text{at } -40\ ^\circ\mathrm{C}) \qquad (14)$$

the current function of peak (H) depends upon the parameter

$$\rho = k_7C^\circ(Fv/RT)^{1/2}/(k_1^{1/2}k_2[\mathrm{Nu}^-]) \qquad (15)$$

The peak height decreases, and accordingly the extent of substitution increases, upon diminishing the value of this parameter. They are now functions of initial concentration and sweep rate resulting from the second-order character of reaction 7 as opposed to reaction 2. The same trends will be observed in preparative-scale electrolysis, the yield of substitution increasing with $[\mathrm{Nu}^-]/C^\circ$ and with a lowering of the stirring rate. The expression of the competition parameter is then

$$\rho = k_7C^\circ D^{1/2}/(\delta k_1^{1/2}k_2[\mathrm{Nu}^-]) \qquad (16)$$

where δ is the thickness of the diffusion layer under the Nernst approximation.

The above distinction between the two kinds of competition with electron transfer is valid provided that one of the two parameters σ or ρ is small enough. For small σ's one will observe the substitution–DISP competition as a function of the single parameter ρ; conversely for small ρ's the substitution–ECE competitions will be obtained as a function of the single parameter σ.

For intermediary values of the parameters a mixed behavior will be observed. Starting, e.g., from a substitution–DISP situation, a decrease in C° and/or v will shift the system toward a substitution–ECE behavior.

The quantitative treatment of the kinetics leading to working curves which provide the variations of the current function with the pertinent parameter will be published elsewhere.[10]

Another interesting feature of the cyclic voltammograms resulting from the substitution reaction may be observed at wave (S). In the catalytic case ($E_1^\circ > E_2^\circ$) a dip is frequently observed at the foot of wave (S) for systems in which reaction 1 is fast, i.e., in which hydrogenolysis occurs through an ECE pathway.

Examples of such dips are shown in Figures 5a, 6, and 7b. The explication of this phenomenon is the following. At the level of wave (H) $Ar\cdot$ and then $ArNu^{-}\cdot$ are formed close to the electrode since reaction 1 is fast. Most of $ArNu^{-}\cdot$ is therefore reoxidized by the electrode itself (reaction 3) with negligible interference of reaction 4. However, as the electrode potential is made more negative, thus becoming closer to the standard potential of the $ArNu/ArNu^{-}\cdot$ couple, less and less $ArNu^{-}\cdot$ is oxidized by the electrode. The interference of reaction 4 is then more and more significant leading, through a chain mechanism, to a depletion of ArX and hence to a decrease of the current.

Survey of Substrates and Nucleophiles

Examples of electrochemically induced substitution were investigated starting from the following substrates: 2-chloro-, 2-bromo-, and 2-iodoquinoline, 1-chloro- and 1-iodonaphthalene, 4-chlorobenzonitrile, and 4-bromobenzophenone. Cyclic voltammetry was used to obtain a qualitative estimation of the reactivity of each substrate–nucleophile couple.

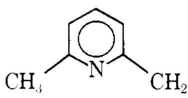
The behavior of these aromatic halides without added nucleophile is shown in Figure 2 for two typical examples, 2-chloroquinoline and 2-iodoquinoline. 2-Chloroquinoline (Figure 2a) exhibits an irreversible wave followed by a reversible wave. The ratio between the first and the second peak is close to 2. However, the waves are not strictly proportional to concentration (Figure 2b).

Proportionality is restored upon addition of water in concentration slightly larger than the concentration of the substrate (Figure 2b). As in the case of bromobenzophenone studied previously,[11] this phenomenon is related to the addition on the substrate of NH_2^- ions arising themselves from the neutralization of Ar^- by ammonia (reaction 9). 1-Chloronaphthalene and 4-chlorobenzonitrile exhibit very similar behavior.

2-Iodoquinoline shows an even more unusual behavior (Figure 2c), again most likely related to the interference of NH_2^- ions formed during the reduction process.

The canonical system of a two-electron irreversible wave followed by a one-electron wave is again restored upon addition of water, or of other proton donors. 2-Bromoquinoline and 1-iodonaphthalene show very similar behavior. The origin of these phenomena is currently under investigation. For the purposes of the present work it was sufficient in most cases to operate with a small amount of water added.

Among the various nucleophiles that were tested with 2-chloroquinoline as a substrate, the following compounds gave rise to no detectable modification of the cyclic voltammogram showing that they are practically unreactive (the figure in parentheses is the maximal nucleophile concentration in M L^{-1} that was used): CN^- (1.5×10^{-3}),[12] SCN^- (2.0), OH^- (5×10^{-3}), PhO^- (6×10^{-2}), $EtC^-(CO_2Et)_2$ (5×10^{-2}), $HC^-(CO_2Et)_2$ (0.1), $MeCON^-Me$ (0.1), $MeCONH^-$ (0.1). On the other hand, CH_2^-CN, i, and Ph_3C^- were observed to



i

react spontaneously or after a single voltammetric experiment on 2-chloroquinoline. The same result is obtained with the lutidine carbanion when 1-chloronaphthalene is used as substrate instead of 2-chloroquinoline. The other nucleophiles tested were benzenethiolate (PhS^-), 4-chlorobenzenethiolate ($ClPhS^-$), diethyl phosphite ($(EtO)_2PO^-$), and the enolates

Table I. Preparative-Scale Electrolysis of 2-Chloroquinoline in the Presence of Benzenethiolate at −1.43 V

2-ClQ concn, mM L^{-1}	$[Nu^-]/C^\circ$	n, faraday/mol	yield in 2-PhSQ, % measured	 from n	ρ	$k_7/k_1{}^{1/2}k_2$, $s^{-1/2}$
1.5	10	0.38	78	81	3.8	16
2.1	12	0.27	85	86.5	2.8	14
8.9	16	0.19	90	90.5	2.0	13
3.5	17	0.10	96	95	1.1	8

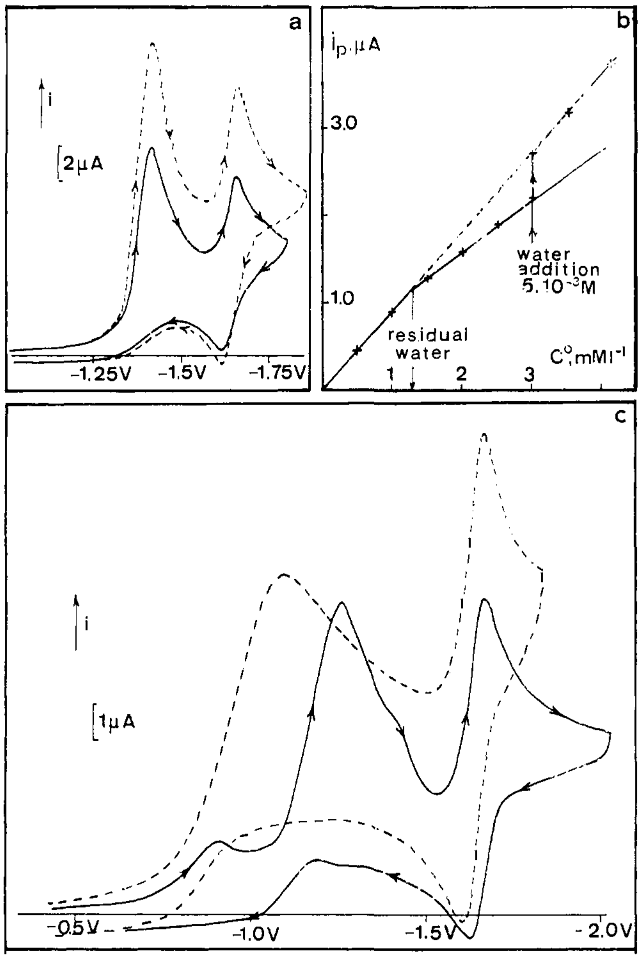


Figure 2. Cyclic voltammetry of chloro- and iodoquinoline in liquid NH_3 at −40 °C. (a) Chloroquinoline, 2×10^{-3} M, (——) without added water, (---) with 5×10^{-3} M H_2O. (b) Peak current of chloroquinoline as a function of concentration with and without addition of water. (c) Iodoquinoline, 1.4×10^{-3} M, (——) without added water, (---) with 10^{-2} M H_2O. Sweep rate: 0.2 V s^{-1}.

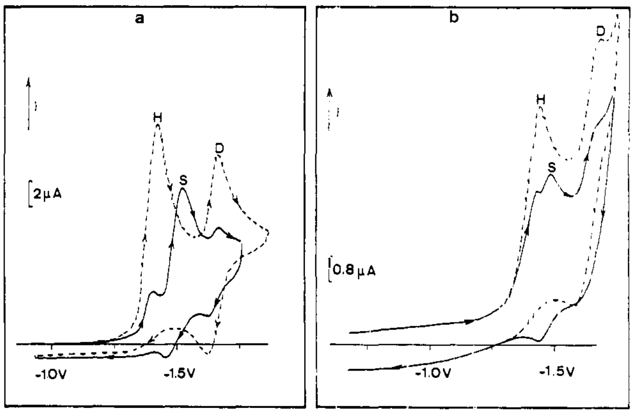


Figure 3. Cyclic voltammetry of 2-chloroquinoline: (a) 2.5×10^{-3} M without nucleophile added (---) or in the presence of benzenethiolate, 5.6×10^{-2} M (——). Scan rate: 0.2 V s^{-1}. (b) 7×10^{-4} M without nucleophile added (---) or in the presence of 4-chlorobenzenethiolate, 8.95×10^{-3} M. Scan rate: 0.2 V s^{-1}.

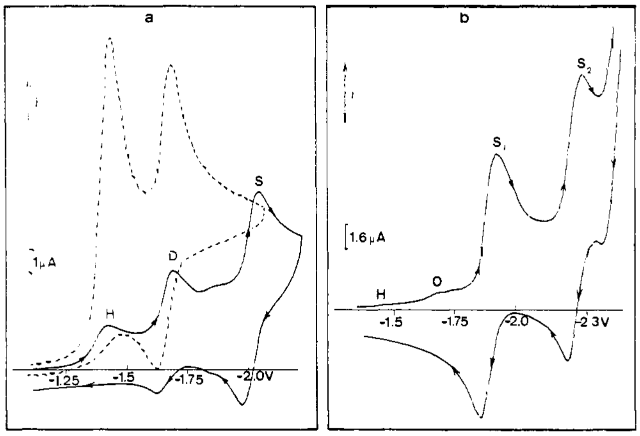


Figure 4. Cyclic voltammetry of 2-chloroquinoline: (a) 1.75×10^{-3} M without nucleophile added (---) or in the presence of $CH_3COCH_2^-$, 2.5×10^{-2} M (——). Scan rate: 0.2 V s^{-1}. (b) 2.7×10^{-3} M in the presence of $PhCOCH_2^-$, 0.1 M. Scan rate: 0.2 V s^{-1}.

of acetone ($CH_3COCH_2^-$) and of acetophenone ($PhCOCH_2^-$).

Figure 3a shows the reaction of PhS^- on 2-chloroquinoline. The decrease of waves (H) and (D) and the appearance of a new wave, (S), corresponding to the substituted compound are clearly seen. The extent of substitution increases when raising the nucleophile concentration for a given substrate concentration. Preparative-scale electrolysis give good yields of 2-(phenylthio)quinoline (Table I) increasing with the ratio of the nucleophile and substrate concentration. The yields in substitution and hydrogenolysis products were calculated from the heights of waves (S) and (D), respectively, on the cyclic voltammograms of the solution after exhaustive electrolysis. The nature and distribution of products were confirmed by gas-phase chromatography. The voltammogram of a solution containing an authentic sample of 2-(phenylthio)quinoline exhibits a single reversible wave located at the same potential as wave (S). It is noted that its standard potential (−1.48 V) is positive to the standard potential of quinoline itself (−1.64 V) as expected from the fact that the phenylthio derivative can accommodate a negative charge more easily than quinoline itself. The reaction of $ClPhS^-$ on the same substrate (Figure 3b) is very similar. The reactivity is, however, somewhat smaller than with PhS^- as anticipated from the electron-withdrawing effect of the para chlorine atom. For the same reason the wave of the substituted product is more positive, and hence closer to the substrate wave. Preparative-scale electrolysis of a solution containing 1.9×10^{-2} M L^{-1} QCl and 0.17 M L^{-1} $ClPhS^-$ gave a 80% yield of 2-(4′-chlorophenylthio)quinoline. This product would be difficult to obtain by solvated electron stimulation which would be likely to result in 4′-chlorine cleavage.

Other typical examples of catalytic electrochemical inducement ($E_1{}^\circ > E_2{}^\circ$) of substitution of 2-chloroquinoline are provided by the reaction of the acetone and acetophenone enolate (Figure 4). These systems have been investigated previ-

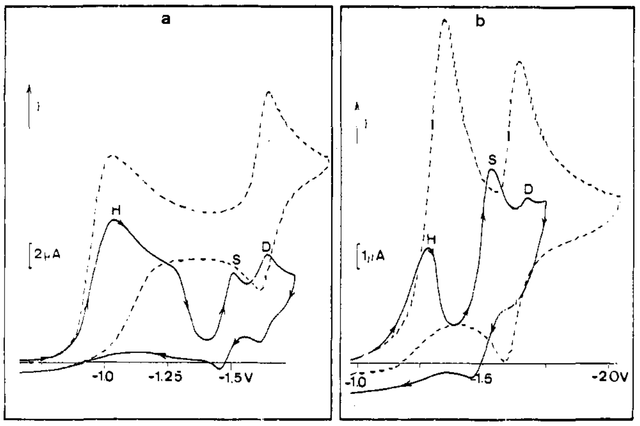


Figure 5. Cyclic voltammetry of (a) 2-iodoquinoline, 1.6×10^{-3} M (H_2O, 5×10^{-3} M) without nucleophile (- - -) or in the presence of PhS^-, 4.4×10^{-2} M, $v = 0.2$ V s^{-1}. (b) 2-Bromoquinoline, 1.5×10^{-3} M (H_2O, 5×10^{-3} M) without nucleophile (- - -) or in the presence of PhS^-, 5×10^{-2} M. Scan rate: 0.2 V s^{-1}.

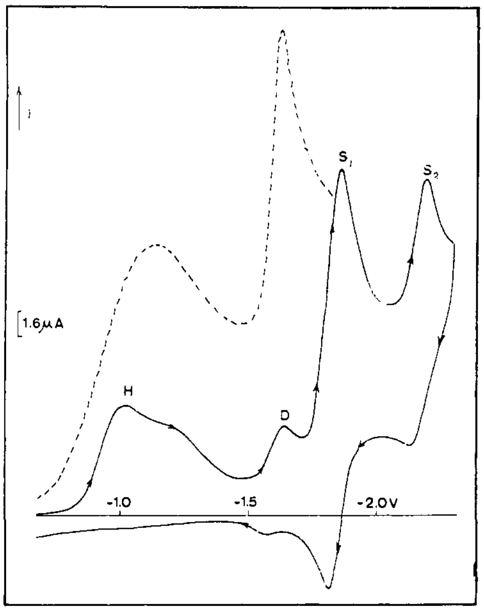


Figure 6. Cyclic voltammetry of 2-iodoquinoline, 4×10^{-3} M, without nucleophile added (- - -) or in the presence of $PhCOCH_2^-$, 0.1 M. Scan rate: 0.2 V s^{-1}.

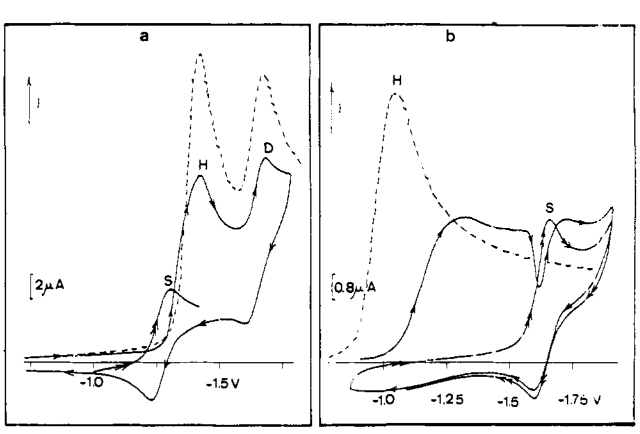


Figure 7. (a) Cyclic voltammetry of 2-chloroquinoline, 3.3×10^{-3} M, without nucleophile added (- - -) or in the presence of $(EtO)_2PO^-$, 9.4×10^{-2} M, (→) first cycle, (→→) tenth cycle. Scan rate: 0.2 V s^{-1}. (b) Cyclic voltammetry of 1-iodonaphthalene, 4×10^{-3} M, without nucleophile added (- - -) or in the presence of $(EtO)_2PO^-$ 0.1 M: (→) first cycle, (→→) second cycle. Scan rate: 0.2 V s^{-1}.

ously from a preparative point of view under photostimulation.[13] The substitution product gives rise to one reversible wave in the first case and to two reversible waves in the second. They are all located at potentials markedly negative to the wave of quinoline. This indicates that they are more likely to feature the reduction of the enolate anions rather than that of the corresponding ketones.[14]

The hydrogens on the α carbon are indeed likely to be more acidic than those in the reactants owing to the electron-withdrawing ability of the quinoline ring which is itself related to the imine-like character of the C–N bonds in the ring.

The reaction of PhS^- on 1-chloronaphthalene was found to be very similar to that on 2-chloroquinoline, being slightly more efficient. It gives rise to 1-(phenylthio)naphthalene, which exhibits a reversible one-electron wave at -1.77 V.

The reactions of PhS^- on 4-bromobenzophenone and 4-chlorobenzonitrile were found to be very efficient: for a nucleophile/substrate concentration ratio of 10, waves (H) and (D) are no longer present on the cyclic voltammograms, which shows only the waves of the substituted product. For an even larger concentration ratio, substitution was not complete in the case of 2-chloroquinoline (Figure 1a). This is related to the stronger electrophilic character of the Ar· radical owing to the electron-withdrawing ability of the carbonyl and the cyano groups.

The same substitution product as for 2-chloroquinoline appears (waves (S)) on the cyclic voltammogram of 2-iodo- and 2-bromoquinoline in the presence of PhS^- (Figure 5). The general aspect of the curves is, however, different. A large dip appears between waves (H) and (S). The decomposition of the substrate anion radical is faster for the iodo and bromo derivatives than for the chloro compound. The presence of the dip thus matches the tendency of shifting from a DISP to an ECE control of electron transfer when passing from the chloro to the bromo and iodo derivatives. It is also noted that substitution is more efficient with the bromo than with the iodo derivative. This again matches the ECE character of the kinetic control in the framework of which substitution competes with electron transfer the more efficiently the smaller the decomposition rate k_1. The latter observation can be made even more clearly in the case of the reaction of $PhCOCH_2^-$ on the same three substrates: with the bromo compound substitution is about complete as with the chloro compound (Figure 4b) whereas electron transfer still competes with substitution with the iodo derivative (Figure 6). In the latter case a dip is again observed after wave (H). The enhanced efficiency of the substitution reaction in this potential region is attested to by the disappearance of wave (H) on the second potential cycle. Reaction of $(EtO)_2PO^-$ on 2-chloroquinoline (Figure 7a) provides a typical example of a system in which the substitution product is easier to reduce than the substrate ($E_1° < E_2°$): wave (S) indeed appears only on the anodic and the second cathodic scans. With the same nucleophile but with 1-iodonaphthalene as substrate (Figure 7b) the reverse sequence of potential is observed giving rise to a catalytic system as with PhS^- and enolates. A dip is again observed at the foot of wave (S) corresponding to a high substitution efficiency as attested to by the absence of wave (H) on the second cycle.

All these observations match the $S_{RN}1$ character of the substitution reaction and the assumption that the main competing pathway is electron transfer to Ar·. The distinction between ECE and DISP control of electron transfer also clearly appears as a function of the decomposition rate of the substrate anion radical. In this framework, the efficiency of substitution is in good agreement with what can be qualitatively predicted about the nucleophilicity of the reagents and the electrophilicity of the Ar· radicals as function of the substrate structure. Let us now analyze in a more quantitative way typical exam-

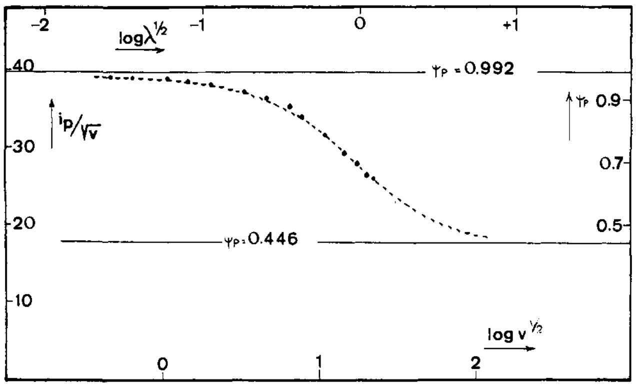


Figure 8. Determination of the rate constant for the cleavage of 2-chloroquinoline (2.72×10^{-3} M) radical anion. Variation of the normalized peak current in cyclic voltammetry vs. scan rate.

ples of the competition between substitution and electron transfer under either DISP or ECE control.

Competition between Substitution and Homogeneous Electron Transfer (DISP). Reaction of Benzene- and 4-Chlorobenzenethiolates on 2-Chloroquinoline

In the absence of nucleophile, the quantity $i_p v^{-1/2}$ characterizing wave (H) tends to decrease upon raising the sweep rate from 0.2 to 500 V s^{-1}, although no distinct reoxidation wave appears on the reverse scan. This is represented in Figure 8 under the form of a $(i_p)/(i_p)_d$ vs. $\log v$ plot. $(i_p)_d$ is not obtained directly since reversibility cannot be reached in the available range of sweep rates. It is obtained from the height of the peak at slow sweep rate which is equal to $2.22(i_p)_d$.[9] A good fit of these experimental data with the working curve corresponding to a DISP process is obtained for

$$k_1 = (1.7 \pm 0.2)10^4 \text{ s}^{-1}$$

Simulation of the whole cyclic voltammogram for such a DISP process[15] with this value of k_1 showed that no oxidation wave can indeed be detected at the highest sweep rate used here (500 V s^{-1}).

These observations do not, however, provide unequivocal evidence that hydrogenolysis actually occurs through a DISP process rather than through an ECE process since the shapes of the working curves are very similar in both cases.[9,16] If an ECE mechanism were assumed to hold the value of k_1 would be close to the above ($k_1 = 3.6 \times 10^4 \text{ s}^{-1}$). However, one can readily see that, with values of k_1 of this order of magnitude, condition 14 is fulfilled even at the lowest sweep rates (0.1 V s^{-1}) and concentrations (10^{-3} M L^{-1}) used in this study. In the following analysis of the competition between substitution and electron transfer it can therefore be assumed that we start from a DISP process and not from an ECE process.

The competition between electron transfer and substitution was quantitatively evaluated from the variations of the height of wave (H) with the nucleophile and substrate concentrations and with sweep rate. The results are shown in Figures 9 and 10 for PhS^- and $ClPhS^-$, respectively, under the form of a plot of the current function $i_p/(i_p)_d$ vs. the parameter $v^{1/2}C°/[Nu^-]$. It is immediately apparent that for a given value of $C°$ the efficiency of substitution increases upon raising $[Nu^-]$. The second-order character of the kinetics, however, appears from the observation that substitution efficiency decreases upon raising $C°$ for a given value of $[Nu^-]$. In the largest part of the diagram, i.e., when the current function is larger than about 0.2, the concentrations of nucleophile and substrate do not influence the competition independently. They actually act under the form of their ratio as predicted by the theory in the context of a competition between substitution and homogeneous electron transfer.

The prediction of the theory are also verified as regards the variation of the current function with sweep rate. The theoretical

$$[i_p/(i_p)_d] \sim \log \rho$$

working curve can indeed be fitted with the experimental

$$[i_p/(i_p)_d] \sim \log v^{1/2}C°/|Nu^-|$$

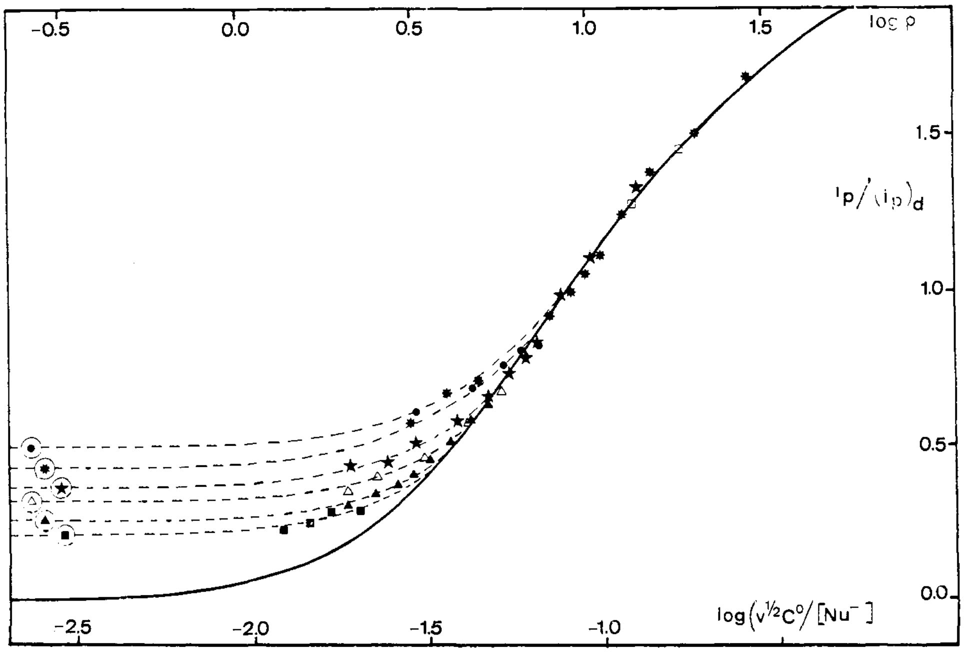


Figure 9. Cyclic voltammetry of the reaction of PhS^- on 2-chloroquinoline. Current function vs. the parameter $v^{1/2}C°[Nu^-]$ (experimental) and vs. the parameter ρ (theoretical see eq 14). The lines represent the theoretical predictions: the full line corresponds to the competition with homogeneous electron transfer (DISP) and the dashed ones to the influence of ECE control at high substitution efficiencies for each value of $[Nu^-]$ (same symbols as below). The points represents the experimental data for $C° = 1.5 \times 10^{-3}$ M ($[Nu^-] = 1.30 \times 10^{-2}$ M: □, 1.54×10^{-2} M (●) and $C° = 2.65 \times 10^{-3}$ M ($[Nu^-] = 2.12 \times 10^{-2}$ (✱), 3.18×10^{-2} (★), 4.08×10^{-2} (△), 6.62×10^{-2} (▲), 1.03×10^{-1} M (■)).

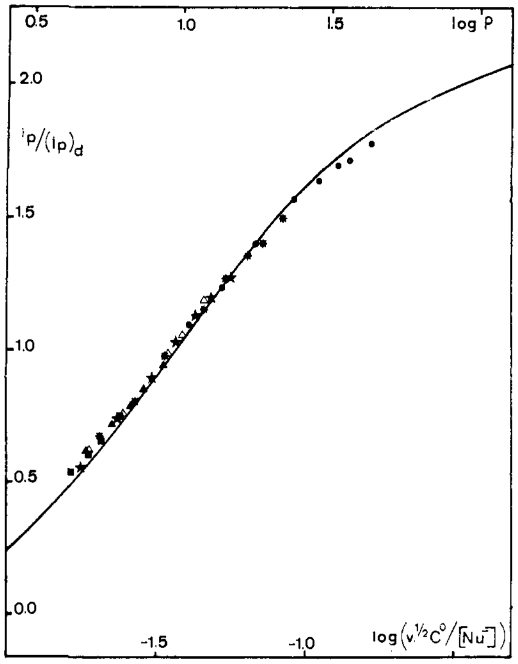
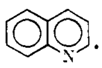
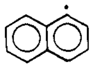


Figure 10. Cyclic voltammetry of the reaction of 4-ClPhS$^-$ on 2-chloroquinoline (2.65×10^{-3} M). Current function vs. the parameter $v^{1/2}C°/[Nu^-]$ (experimental) and vs. the parameter ρ (theoretical, see eq 14). The points represent the experimental data and the line the theoretical prediction ($[Nu^-] = 1.33 \times 10^{-2}$ (●), 2.67×10^{-2} (✱), 4×10^{-2} (★), 4.94×10^{-2} (△), 6.68×10^{-2} (▲), 9.34×10^{-2} M (■)).

Table II. Rate Constants of the Reaction $Ar\cdot + Nu^- \rightarrow ArNu^{-}\cdot$

system		k_2, M^{-1} L s^{-1}
	+ PhS$^-$	1.4×10^7
⋮	+ 4-ClPhS$^-$	6×10^6
⋮	+ (EtO)$_2$PO$^-$	1.8×10^7
⋮	+ CH$_3$COCH$_2{}^-$	7.5×10^6
⋮	+ PhCOCH$_2{}^-$	4.5×10^7
	+ PhS$^-$	2.3×10^7

plot by horizontal sliding of the abscissa axes. The distance between the origins of the abscissa axes immediately provides (eq 14) the value of the quantity

$$k_7/(k_1^{1/2}k_2)$$

which is found equal to 15.9 s$^{1/2}$ for PhS$^-$ and to 36.4 s$^{1/2}$ for ClPhS$^-$. Taking for k_1 the value found previously and $k_7 = 3 \times 10^{10}$ M^{-1} L s^{-1} it follows that the rate constants for the addition of the quinolyl radical on the two thiolates are those given in Table II.

Deviations from the theoretical behavior appear for small values of the current function, i.e., for high substitution efficiencies. They are more apparent in with PhS$^-$ than with ClPhS$^-$ since smaller values of the current function can be investigated in the first case than in the second. With ClPhS$^-$ indeed, waves (H) and (S) are too close[17] to be able to obtain meaningful results when wave (H) becomes small. These deviations are related to the shift of the system toward an ECE situation when substitution becomes more and more efficient as already discussed in the theoretical section. The predicted behavior corresponding to this phenomenon is shown in Figure 9. It is seen to fit satisfactorily the experimental data.

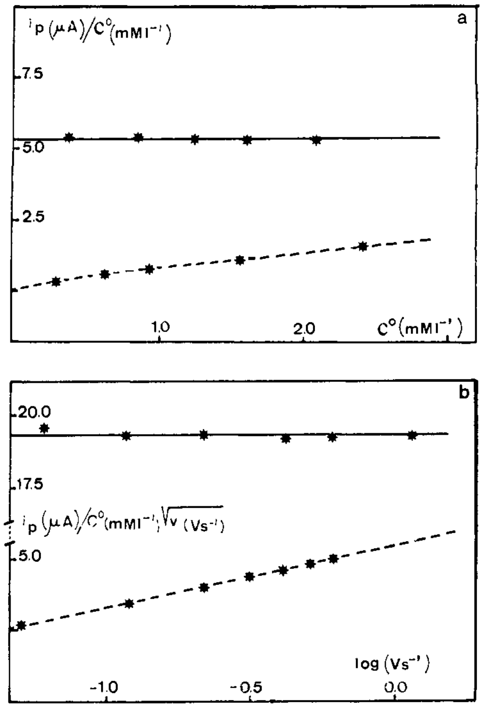


Figure 11. Cyclic voltammetry of the reaction of PhS$^-$ on 2-iodoquinoline. Peak current function vs. substrate concentration (a) ($v = 0.2$ V s) and (b) ($C° = 1.24 \times 10^{-2}$ M) for PhS$^- = 4.4 \times 10^{-2}$ M. Dashed lines: same plots for 2-chloroquinoline for $[PhS^-] = 2.2 \times 10^{-2}$ M and (a) $v = 0.2$ V s^{-1}, (b) $C° = 2.65 \times 10^{-3}$ M.

The results of preparative-scale experiments (Table I) can be rationalized in the same way. It is first noted that the coulometric data match the direct determination of the substitution yield. The yields evaluated from the number of faradays per mole, $100(1 - n/2)$ (fifth column), are indeed very close to the yields obtained from the analysis of the electrolyzed solutions (fourth column). This shows that all the charge passed through the cell has served to reduce QCl into QH without any other side reaction.

The value of the competition parameter, ρ, can be evaluated for each experiment from the theoretical working curve corresponding to the DISP-substitution kinetics in the framework of preparative-scale electrolysis (sixth column of Table I). The quantity $k_7/(k_1^{1/2} k_2)$ is then calculated (seventh column) using eq 15. The agreement is good between these values and those derived from cyclic voltammetry experiments. The slight decrease in the apparent values of $k_7/(k_1^{1/2}k_2)$ as $[Nu^-]/C°$ increases can again be explained as reflecting the interference of some ECE control as the substitution becomes more and more efficient.

Competition between Substitution and Heterogeneous Electron Transfer (ECE). Reaction of Benzenethiolate on 2-Iodoquinoline

Based on the observation of a current dip between waves (H) and (S) (Figure 5a), it has already been anticipated that the competition is under ECE control in the present case. On the other hand, the peak height decreases when [Nu$^-$] is raised. The ECE character of the process is confirmed by a systematic investigation of the peak height of wave (H) as a function of substrate concentration (Figure 11a) and sweep rate (Figure 11b). It is seen that the current function of peak (H) is strictly independent of both concentration of substrate and sweep rate in contrast with what happens with 2-chloroquinoline, which is represented on the same diagrams for comparison. These observations match the first-order character of the ECE control, more specifically, the fact that substitution efficiency is then a function of the parameter $\sigma = k_1/k_2[\mathrm{Nu}^-]$, which does not depend on either the sweep rate or the substrate concentration (eq 13). Application of eq 13 allows the determination of k_1/k_2 for the benzenethiolate–2-iodoquinoline system: $k_1/k_2 = 0.22$ M L^{-1}. Since k_2 is the same as for 2-chloroquinoline with benzenethiolate it follows that $k_1 \simeq 3 \times 10^6$ s^{-1} for the decomposition of the 2-iodoquinoline anion radical.

Determination of Additional Rate Constants

Assuming that competition is under ECE control for 2-bromoquinoline as in the preceding case, application of eq 13 to the data obtained for the reaction of this compound with benzenethiolate (Figure 5b) leads to $k_1/k_2 = 9 \times 10^{-3}$ M L^{-1} and therefore to $k_1 = 1.3 \times 10^5$ s^{-1}. Examination of conditions 12 and 14 shows that the system is at limit between the ECE and DISP controls under the concentration and sweep rate conditions corresponding to Figure 5b. It can, however, be proved that the ECE control prevails in the presence of the nucleophile since increasing substitution shifts the control from DISP to ECE as already discussed. Competition experiments between electron transfer and addition of a nucleophile thus provide a comparative evaluation of the stabilities of the anion radicals of the three haloquinolines:

$$k_{1,\mathrm{ClQ}} = 1.7 \times 10^4\ \mathrm{s}^{-1};\ k_{1,\mathrm{BrQ}} = 1.3 \times 10^5\ \mathrm{s}^{-1};\ k_{1,\mathrm{IQ}} = 3 \times 10^6\ \mathrm{s}^{-1}$$

that cannot be arrived at by the standard application of electrochemical techniques such as cyclic voltammetry. 2-Chloroquinoline was indeed close to the limit of applicability of the method; the bromo and the iodo derivatives are clearly beyond this limit.

As expected, the stability decreases from Cl to Br and I reflecting the increasing leaving-group ability of the halide ion. On the other hand, reactivity of nucleophiles on Ar· radicals can be estimated for the following additional systems: $CH_3COCH_2^-$ + 2-chloroquinoline, PhS$^-$ + 1-chloronaphthalene (catalytic DISP control, k_1 was found equal to 1.5×10^4 s^{-1} using the same procedure as for 2-chloroquinoline), $(EtO)_2PO^-$ + 2-chloroquinoline (noncatalytic DISP control), $PhCOCH_2^-$ + 2-iodoquinoline (catalytic ECE control). The results of these estimations are given in Table II, showing that there are no large differences between the reactivities of ClPhS$^-$, $CH_3COCH_2^-$, PhS$^-$, and $(EtO)_2PO^-$ on the 2-quinolyl radical as well as between the reactivities of the 2-quinolyl and the 1-naphthyl radicals toward PhS$^-$. Larger range of k_2 may be investigated by extending the domain of variations of k_1, the sweep rate, and the concentrations.

It is noted that these evaluations as well as the previous determinations of k_1 hinge upon the value taken for the second-order diffusion limit which is not known with accuracy. This does not, however, affect the relative values of these various rate constants.

Conclusions

In summary, the main conclusions of this study are the following.

(1) Electrochemical electron injection at the reduction potential of the substrate appears as an effective and convenient route to S$_{\mathrm{RN}}$1 aromatic nucleophilic substitutions in liquid ammonia, thus extending the scope of this mode of inducement which was previously described in organic nonaqueous solvents. Cyclic voltammetry is a convenient tool for a rapid estimate of the reactivity of nucleophiles. The results confirm that soft nucleophiles are required in order for this kind of substitution to be effective.

(2) Electron transfer to the Ar· radical is essentially the only reaction competing with substitution in contrast with what occurs in organic solvents where H-atom transfer may play an important role in lowering the substitution yield.

(3) Competition between substitution and electron transfer may occur under two kinds of kinetic control, one involving homogeneous electron transfer (DISP control) and the other heterogeneous electron transfer (ECE control); in the former case, the substitution yield will be increased by operating under low diffusion rates and by using the lowest possible substrate over nucleophile concentration ratio.

(4) The very fact that the predicted kinetics match satisfactorily the experimental data under DISP control as well as under ECE control provides further evidence of the correctness of the S$_{\mathrm{RN}}$1 mechanism.

Experimental Section

The experimental setup, electrochemical cell, and procedures for purifying the solvent were the same as previously described.[18,19] The working electrode in cyclic voltammetry was a platinum disk of 1-mm diameter. It was polished on alumina before use. In coulometric and preparative-scale experiments the working electrode was a platinum grid of about 15 cm^2 surface area. The experiments were carried out at −40 °C. The supporting electrolyte was potassium bromide in 0.1 M concentration.

The reference electrode was an Ag/Ag$^+$ 0.01 N electrode in liquid ammonia.[18] A solid-state amplifier potentiostat with positive feedback resistance compensation[20] was used together with a function generator (Tacussel TPPRT) and a storage oscilloscope (Schlumberger OCM 581) or an X-Y chart recorder (Ifelec 2025C). Ohmic drop compensation was required in the cyclic voltammetry experiments since the resistance between reference and working electrode was currently of the order of 4000–5000 Ω. The substrate concentration was about 3×10^{-3} M in coulometric and preparative scale experiments. The water content of the solvent was about 2×10^{-3} M; in the case where PhS$^-$ and ClPhS$^-$ were used as nucleophiles an excess of water was added up to 0.5 M. The nucleophiles were prepared according to three different procedures: (1) by neutralization of an amide solution by the conjugate acid of the nucleophile (ClPhS$^-$, $PhCOCH_2^-$, $CH_3COCH_2^-$, CH_2CN^-, $CH_3PyCH_2^-$, Ph_3C^-, OH$^-$, $H\bar{C}(CO_2Et)_2$, $Et\bar{C}(CO_2Et)_2$), (2) by addition of the conjugate acid of the nucleophile in a potassium solution until the solution decolorizes ($(EtO)_2PO^-$, PhS$^-$, PhO$^-$ CH_3CONH^-, $CH_3CON(CH_3)^-$), (3) by addition of KOH in the case when the conjugate acid of the nucleophile is more acidic than water (PhS$^-$, ClPhS$^-$).

The products of preparative electrolysis were identified and titrated by gas chromatography (3% OV 17 column, flame ionization detector, Varian 1400) or by cyclic voltammetry through comparison with authentic samples. The chemicals used were from commercial origin except 2-bromo-[21] and 2-iodoquinoline[22] and 2-(phenylthio)quinoline,[23] which were prepared according to known procedures. 2-(4′-Chlorophenylthio)quinoline, mp 82 °C, was identified through its mass spectrum (*m/e* 273 (20), 272 (34), 271 (60), 270 (100), 128 (35), 101 (25), 77 (15), 75 (15)) and its elemental analysis.

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Nucleophilic Catalysis by Polyethylenimines with Covalently Attached 4-Dialkylaminopyridine

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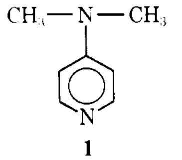
Abstract: A dialkylated pyridine, 3-[(*N*-methyl-*N*-4-pyridyl)amino]propionic acid, was attached covalently to laurylated poly(ethylenimine)s. It showed marked catalytic effects in the hydrolysis of nitrophenyl acylates. Spectrophotometric observations in the near-ultraviolet established that the hydrolysis proceeds through a nucleophilic pathway.

Polyethylenimine provides a versatile macromolecular matrix for the assembly of molecular environments that can accelerate a variety of chemical reactions.[1] Since the original discovery of the catalytic effects of imidazole per se,[2,3] this residue has been widely used in the polymeric state[4-8] to accelerate hydrolytic reactions. Alternatively, the hydroxamate group attached to polymers has been tried as a nucleophilic polymer catalyst.[8,9] There is still much scope, however, for development of more effective nucleophilic polymers.

In bulk solution pyridine has also been shown to catalyze the hydrolysis of esters[10] and acylpyridinium ion has been identified as a reaction intermediate.[11] Nevertheless, we have found no catalysis of cleavage of activated esters by pyridine attached to polyethylenimines (through a reduced Schiff base linkage). Evidently, in the polymer environment, the pK_a and nucleophilicity of the pyridine nitrogen are reduced substantially. On the other hand, Steglich and Höfle[12,13] have reported that 4-*N*,*N*-dialkylaminopyridines are acylation catalysts far superior to pyridine. Furthermore, acylation reactions with these dialkylaminopyridines are faster in apolar than in polar solvents.[15] Thus a 4-dialkylaminopyridine seemed to be a promising candidate for attachment to a modified polyethylenimine with apolar substituents to create a superior macromolecular nucleophilic catalyst.

Experimental Section

4-Dimethylaminopyridine (**1**) was purchased from Aldrich Chemical Co. and recrystallized from chloroform/ethyl acetate (9:1), mp 109–110 °C (lit.[13,14] 112–113 °C, 109–111 °C). 3-[*N*-Methyl-*N*-(4-pyridyl)amino]propionic acid (**2**) (mp 190–195 °C) was obtained from Dr. H. Vorbrüggen. *p*-Nitrophenyl caproate was purchased from Sigma Chemical Co. and acetic anhydride was a spectrophotometrically pure, analytical grade sample.



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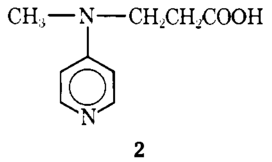

2

Laurylated polyethylenimines, containing $C_{12}H_{25}$ adducts, were prepared by procedures described previously.[8,16,17] Compound **2** was coupled to a laurylated polyethylenimine from polyethylenimine 600 (Dow Chemical Co.), molecular weight 60 000, by the following method. An equimolar amount of **2** and a water-soluble carbodiimide [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride] (obtained from Sigma) was added to a four-fold residue-molar excess of laurylated polyethylenimine in H_2O. The pH was adjusted to 5.7 with 1.0 N HCl, and the reaction mixture was stirred at room temperature for 10 days. The solution was then placed in an Amicon ultrafiltration vessel with a PM-10 membrane, diluted to about 200 mL total volume and ultrafiltered with 30 L of distilled H_2O. Thin-layer chromatography on silica gel plates (Eastman no. 6060) with methanol as eluent showed no free pyridine compound. Finally, the solution was concentrated, and the polymer was isolated by lyophilization.

Both proton magnetic resonance spectra and elemental analyses are consistent with the following stoichiometric formulas for the two samples prepared with covalently attached dialkylaminopyridine **2**:

$$(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.10m}$$

$$(C_2H_4N)_m(C_{12}H_{25})_{0.12m}(C_9H_{11}N_2O)_{0.17m}$$

The average molecular weight per monomer residue is 79 and 105, respectively.

Proton magnetic resonance measurements were made with a Hitachi Perkin-Elmer R-20B spectrometer operating at 60 MHz with a probe temperature of 35 °C. Samples were examined in D_2O (99.8%, Bio-Rad Co.) at a solute concentration of 5–10% by weight.

The hydrolysis of *p*-nitrophenyl caproate was followed by measurements, in a Cary 14 spectrophotometer, of the increase in absorbance at 400 nm due to released nitrophenolate ion. Below pH 9.0, 0.01 M tris(hydroxymethyl)aminomethane or 0.05 M bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane was used as a buffer, above pH 9.0, borate. Since *p*-nitrophenyl caproate was first dissolved in pure acetonitrile, the final aqueous solution contained 0.1% CH_3CN. Measurements of pH were made with an Orion Model 701A pH meter, at 25 °C. Pseudo-first-order rate constants were computed from semilogarithmic graphs of absorbance vs. time. Background rates were measured to assess the contribution from cleavage of activated ester in the presence of buffer and of each pyridine-free polymer in buffer and were subtracted to obtain corrected first-order constants, k_{obsd}, due to catalysis by the dialkylaminopyridine moiety. Below pH 9.7, background rates were less than 5% of k_{obsd}. Values of k_{obsd} were measured for a series of concentrations of dimethylaminopyridine (**1**) and for polymers with covalently attached 3-[*N*-methyl-*N*-(4-pyridyl)amino]propionic acid (**2**). From the linear dependence observed for k_{obsd} vs. concentration of pyridine moiety, second-order rate constants were calculated.

To reveal any acyldialkylaminopyridinium intermediate, the course of the acylation-deacylation reaction was followed spectrophotometrically with acetic anhydride as substrate, rather than *p*-nitro-

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