Oxidation potential as a measure of the reactivity of anionic nucleophiles. Behaviour of different classes of nucleophiles

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Anodic peak potentials for 42 anionic nucleophiles are reported along with the rate constants for the reactions of the anions with benzyl chloride. By comparing these rate constants with those of the reactions of outer-sphere electron-transfer reagents (radical anions), it has been demonstrated that the reactions of the anions with benzyl chloride are typical single-step S_N2 reactions as opposed to a two-step process comprising dissociative single electron transfer (SET) to benzyl chloride followed by radical combination. The data suggest that very electron-rich nucleophilic anions with potentials of − 1.5 to − 2.2 V (and more negative) with respect to the ferrocenium/ferrocene couple might participate in a SET reaction. The 42 anions studied included representatives of four classes of nucleophiles, *viz.* sulfur-, carbon-, oxygen- and nitrogen-centred anions. The previously observed correlation of rate constants and anodic peak potential was again found for these anions with the most reactive species having the most negative peak potentials. Correlations by class indicate that the sensitivity of the rate constants to changes in peak potential is greatest (and equivalent) for the sulfur-, carbon- and oxygen-anions and for representatives with the same peak potential, the rate constants by class follow the order sulfur > carbon > oxygen. The nitrogen nucleophiles show a significantly lower sensitivity of rate constant to changes in peak potential than do the other three classes.

Introduction

Many of the reactions of electrochemical synthesis involve direct transformations at the electrode, *e.g.* the conversion of one functional group to another. However, another very important use of electrochemistry in synthesis is the electrogeneration of reactive species which subsequently take part in purely chemical reactions leading to the desired products. There has been intense interest in the electrogeneration of reactive anions[1] which can, for example, be alkylated or catalyse Michael addition reactions, to name but two of a variety of applications. The anions can be generated by direct reduction of an element–hydrogen bond producing the anion and dihydrogen, *e.g.* $ROH + e^- \longrightarrow RO^- + \frac{1}{2} H_2$. Alternatively, some anions are best produced indirectly through the action of electrogenerated bases (EGB).

It is always of interest to have some knowledge of the nucleophilic reactivity of the electrogenerated anions in order to assess their potential usefulness in synthetic procedures. In particular, it would be most attractive to identify a single, easily determined property that would provide a measure of the nucleophilic reactivity of the anions. It has been found in earlier work that the anodic peak potential for the irreversible oxidation of neutral and anionic nucleophiles provides a good correlation with nucleophilic reactivity, with the most easily oxidized nucleophiles being the most active.[2] It has also been found that the reactivity of a given anion in different solution environments (solvent, counterion) correlates with the anodic peak potential (measured under the same conditions) for a number of anionic nucleophiles.[3] These results are appealing because the assessment of reactivity (anodic peak potential) can be carried out under precisely the same conditions used to produce the electrogenerated anion and with very similar equipment.

The basis of these observed correlations has been discussed previously[3] and will not be repeated here except to point out the qualitative fact that an anion with a rather negative anodic peak potential readily gives up an electron upon oxidation and thus it is not surprising that such an anion is a very reactive nucleophile because it can easily donate its electrons to form a new bond. However, it is unlikely that a single property such as oxidation potential can account for changes in reactivity of all anions under all conditions. Many other structural and environmental variables come into play. Thus, it is not expected that a master correlation of reactivity *vs.* oxidation potential for a wide variety of different classes of nucleophiles will be obtained, even when considering reactions with the same electrophile. In order to determine how good or bad such correlations might be, we have extended our studies to include families of carbon-, nitrogen-, oxygen- and sulfur-centred anionic nucleophiles, each reacting with the common electrophile, benzyl chloride. We have found that similar but separate correlations exist for each class of anion, have determined the approximate order of reactivity by class and have noted a statistically significant lower sensitivity of reactivity to changes in peak potential for the nitrogen-centred anions that were investigated. We also report the anodic peak potentials for 42 anions, which are of interest in their own right.

Results

Table 1 summarizes anodic peak potentials for the anions and rate constants for their reactions with benzyl chloride, each measured in acetonitrile containing 0.10 mol dm^{-3} of Bu_4NClO_4 at 22 ± 1 °C. The reproducibility of the peak potentials was generally ± 10 mV and that of the rate constants ± 20%. A few results for the reaction of nitrogen heterocyclic anions with ethyl 3-chloropropionate are included. In some cases, ethyl acrylate was detected as a product indicating that some dehydrochlorination was occurring as well as nucleophilic displacement. Therefore, these results were of less interest than those from reactions with benzyl chloride.

We also used homogeneous redox catalysis[4] to measure the rate of the electron transfer reactions of three radical anions, $A^{\bullet -}$, with benzyl chloride (BnCl). This process is an outer-sphere dissociative electron-transfer reaction,[5] eqn. (1).

Table 1 Anodic peak potentials and rate constants for reactions of anions

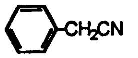
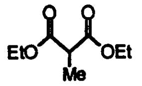
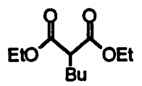
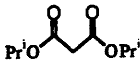
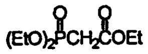
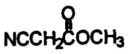
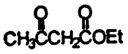
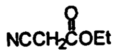
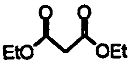
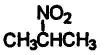
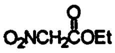
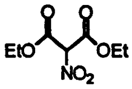
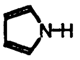
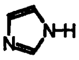
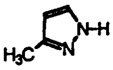
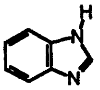
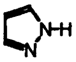
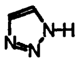
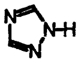
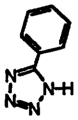
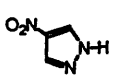
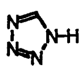
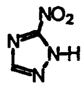
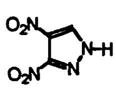
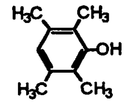
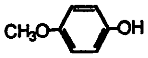
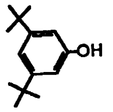
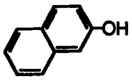
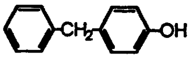
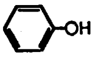
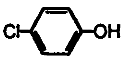
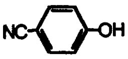
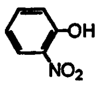
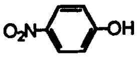
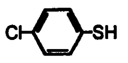
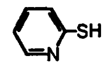
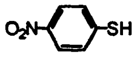
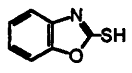
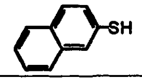
Entry	Precursor acid	$E_{p,a}$/V[a]	$\log(k_{BnCl})$[b]	$\log(k_{RCl})$[c]
1		−0.97	1.27	
2		−0.43	−0.40	
3		−0.41	−0.37	
4		−0.15	−1.37	
5	 $\mathrm{(EtO)_2\overset{O}{P}CH_2\overset{O}{C}OEt}$	−0.08	−1.86	
6	 $\mathrm{NCCH_2\overset{O}{C}OCH_3}$	−0.01	−1.58	
7	 $\mathrm{CH_3\overset{O}{C}CH_2\overset{O}{C}OEt}$	−0.00	−1.79	
8	 $\mathrm{NCCH_2\overset{O}{C}OEt}$	0.01	−1.50	
9	$\mathrm{NCCH_2CN}$	0.04	−1.98	
10		0.08	−1.60	
11	 $\mathrm{CH_3\overset{NO_2}{C}HCH_3}$	0.14	−2.80	
12	 $\mathrm{O_2NCH_2\overset{O}{C}OEt}$	0.43	−3.59	
13		0.66	−3.80	
14		−0.20	−0.49	
15		0.08	−1.39	
16		0.19	−0.56	
17		0.33	−1.65	0.74
18		0.34	−0.64	
19		0.71		−1.16
20		0.78		−1.34
21		1.04	−3.00	−2.56
22		1.12		−2.26
23		1.56	−3.44	−3.80
24		1.58		−3.65
25		1.65	−2.11	−4.10
26		−0.61	−1.58	
27		−0.45	−2.13	
28		−0.28	−1.89	
29		−0.24	−2.23	
30		−0.22	−2.08	
31		−0.21	−1.85	
32		−0.08	−3.32	
33		0.11	−3.49	
34		0.19	−3.80	
35		0.29	−4.15	

Table 1 (*contd.*)

Entry	Precursor acid	$E_{p,a}/V^a$	$\log(k_{BnCl})^b$	$\log(k_{RCl})^c$	Entry	Precursor acid	$E_{p,a}/V^a$	$\log(k_{BnCl})^b$	$\log(k_{RCl})^c$
36	$HOCH_2CH_2SH$	−0.77	1.24		40		−0.27		0.57
37		−0.44	0.28		41		−0.08		−0.89
38	$CH_3(CH_2)_7SH$	−0.34	1.40		42		0.12		−1.84
39		−0.31	0.97						

[a] Anodic peak potential with respect to the reversible ferrocenium/ferrocene couple measured at 0.20 V s^{-1} at a platinum electrode in acetonitrile containing 0.10 mol dm^{-3} Bu_4NClO_4. Numbers reported are averages of 2–5 determinations. The values are reproducible to about ± 10 mV. [b] Rate constant (dm^3 mol^{-1} s^{-1}) for reaction of the anion with benzyl chloride. [c] Rate constant (dm^3 mol^{-1} s^{-1}) for reaction of the anion with ethyl 3-chloropropionate.

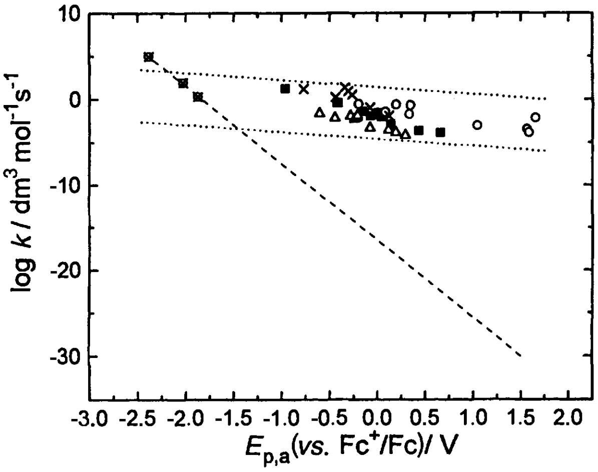


Fig. 1 Rate constants for reactions with benzyl chloride as a function of anodic peak potential. ⊗: Data for reactions (left to right) of the radical anions of anthracene, 1,4-dicyanobenzene and nitromesitylene. For these three points, the potentials are the reversible formal potentials. Other symbols (defined in Fig. 2): data for reactions of anionic nucleophiles.

$$A^{\bullet -} + R\text{-}Cl \longrightarrow A + R^{\bullet} + Cl^- \qquad (1)$$

The rate constants (reversible potentials *vs.* ferrocene) for anthracene, 1,4-dicyanobenzene and nitromesitylene were 9.5 × 10^4 (−2.384), 90 (−2.030) and 2.2 dm^3 mol^{-1} s^{-1} (−1.876 V), respectively, each determined in acetonitrile containing 0.10 mol dm^{-3} Bu_4NClO_4 at 22 ± 1 °C.

Discussion

First, it is of interest to identify the class of substitution reaction in which the anions studied here participate. The classical S_N2 reaction is a concerted process [reaction (2)], with bond-breaking and bond-making occurring together. There is no intermediate. Alternatively, when Nu^- is a very electron-rich species, a stepwise process can occur in which bond-breaking [reaction (3)] is followed by bond-making [reaction (4)]. It is at least possible that some of the anions studied in this work might react by reactions (3) and (4).

$$Nu^- + BnCl \longrightarrow BnNu + Cl^- \qquad (2)$$

$$Nu^- + BnCl \longrightarrow Nu^{\bullet} + Bn^{\bullet} + Cl^- \qquad (3)$$

$$Nu^{\bullet} + Bn \longrightarrow BnNu \qquad (4)$$

A simple way of characterizing the reactions is the 'kinetic advantage' method[6] wherein the rates of outer-sphere dissociative electron transfer from aromatic radical anions to the electrophile are measured. The rate constants of these reactions are governed almost entirely by the reversible potential of the aromatic neutral–radical anion couples with the largest rate constants associated with the couples having the most negative potentials. The linear log *k*–potential relationship can be extrapolated to the region of the reversible potentials of the nucleophiles being examined to predict the maximum possible rate constant that would be observed if the reactions follow the two-step process of reactions (3) and (4), dissociate electron transfer to benzyl chloride followed by radical combination. If, however, the observed rate constants are larger than these maximum values, the processes are of the S_N2 type. The inner-sphere S_N2 process possesses a 'kinetic advantage' because its transition state is stabilized by bonding interactions not present in the outer-sphere process.

Fig. 1 shows data for three outer-sphere reactions of radical anions with benzyl chloride along with the rate constants for the reactions of all 42 electrogenerated anions. An acceptable linear relationship exists for the outer-sphere reactants and extrapolation (line of long dashes, Fig. 1) into the region of oxidation potentials occupied by the anions under study indicates that in all cases the observed rate constants are orders of magnitude larger than for hypothetical outer-sphere reagents with the same reversible potential. Thus, all of the displacement reactions studied here are S_N2 reactions.

Admittedly, the potentials plotted in Fig. 1 are the irreversible anodic peak potentials rather than the reversible potentials for the $Nu^-/Nu^{\bullet}$ couples. However, these two quantities are usually quite similar, often differing by 100 mV or less[7,8] so the qualitative conclusion that the concerted S_N2 process is followed remains valid.

It is interesting to consider an approximate extrapolation of the rate constants for the carbon-, nitrogen-, oxygen- and sulfur-centred nucleophilic anions to potentials where the rate constants would be comparable to those of outer-sphere reactions (lines of short dashes, Fig. 1). It seems likely that electron-rich anions with potentials in the range of −1.5 to −2.2 V would be good candidates for two-step as opposed to concerted S_N2 reactions with benzyl chloride, *i.e.* such anions might transfer one electron to benzyl chloride in a dissociative electron-transfer reaction followed by radical combination, reaction (4).

Now let us turn to the correlations of the rate constants for

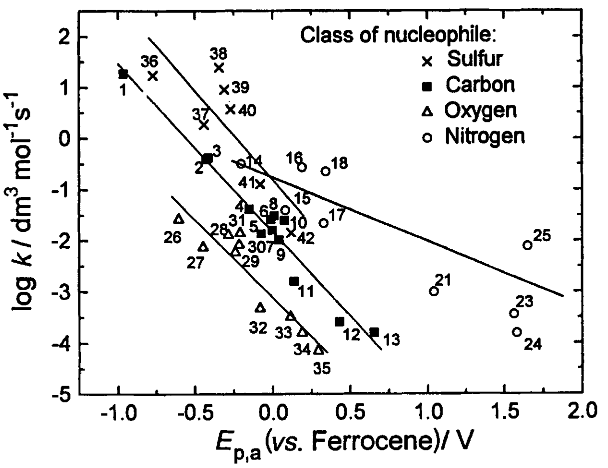


Fig. 2 Rate constants for reactions of 42 electrogenerated anions with benzyl chloride as a function of the anodic peak potential of the anions

the S_N2 reactions of the anions and their anodic peak potentials. Fig. 2 shows an expanded view of the data in Fig. 1 with the points labelled according to the entries in Table 1 and designated as to nucleophile class by the symbols indicated. It is clear that the previously noted correlation[2,3] is generally valid, *i.e.* the easily oxidized anions are also the most active as nucleophiles in their reaction with benzyl chloride.

When each class is considered separately, the following linear correlations (correlation coefficient) are found: sulfur anions, $\log k = -0.80 - 3.50E_{p,a}$ $(r = -0.818)$; carbon anions, $\log k = -1.82 - 3.29E_{p,a}$ $(r = -0.978)$; oxygen anions, $\log k = -3.11 - 3.06E_{p,a}$ $(r = -0.923)$; nitrogen anions, $\log k = -0.83 - 1.33E_{p,a}$ $(r = -0.828)$.

The quality of these correlations varies from poor to good but is adequate to reach two conclusions. First, for the sulfur, carbon and oxygen anions having a given $E_{p,a}$ in the range studied (−1.0 to +1.0 V), the sulfur nucleophiles are the most active, followed by carbon and oxygen. Secondly, the sensitivity of log k to changes in $E_{p,a}$ (slope of correlation line) is lower for the nitrogen anions than for the other three classes, the slopes of which are indistinguishable. That is, a larger shift of $E_{p,a}$ in the negative direction is needed to effect a given increase in rate constant for the nitrogen nucleophiles.

The first conclusion (reactivity of S > C > O) is certainly consonant with conventional wisdom though we know of no other experimental comparison among classes of nucleophiles having a given oxidation potential.

We do not have a compelling explanation for the second conclusion but believe that it must be related to the fact that the nitrogen nucleophiles were all anions derived from nitrogen heterocycles. We noted in AM1 calculations for the anion of pyrrole that the HOMO (whose energy affects $E_{p,a}$) was a delocalized π-orbital whereas the orbital showing greatest σ-type electron density at nitrogen (which is probably implicated in its S_N2 reactivity) was the second orbital below the HOMO. Thus, the structural factors affecting $E_{p,a}$ and k may be fundamentally different in the nitrogen heterocycles compared with the other anions, which possibly could underlie the observed lowered slope.

Close examination of those entries in Fig. 2 that deviate most from the correlation lines might lead to possible explanations for the deviant behaviour. These explanations might invoke steric factors or special effects on HOMO energies. We have resisted engaging in such speculation partly because of the generally low quality of the correlations but also because our intent was to present empirical data that can serve as a guide in evaluating electrochemical synthetic schemes involving electrogenerated anions.

Experimental

Materials

Anhydrous acetonitrile was obtained from Burdick and Jackson and used as received. Tetrabutylammonium perchlorate (Kodak) was vacuum dried before use. The precursor acids, anthracene, 1,4-dicyanobenzene, nitromesitylene and ferrocene were all of commercial origin and were purified as necessary.

Instrumentation and methods

The cells and apparatus for voltammetry and controlled potential electrolysis were the same as reported earlier[3] with the following exceptions: experiments were performed at 22 ± 1 °C, the working electrodes were 0.3 or 0.15 cm diameter platinum disks for cyclic voltammetry, the electrolyte was always 0.10 mol dm^{-3} Bu_4NClO_4, the counter electrode was a magnesium rod and the reference electrode was a silver wire in contact with 0.01 mol dm^{-3} $AgNO_3$ in acetonitrile. Its potential was −0.070 V *vs.* the reversible ferrocenium/ferrocene couple in the same medium.

Solutions of the anions (5×10^{-3} mol dm^{-3}) were generated by controlled potential reduction of the precursor acids at the platinum gauze electrode. This was achieved by direct reduction of the acid at potentials in the vicinity of the cathodic peak potential except in the case of compounds **11–13**, **22**, **24**, **25**, **34**, **35** and **41** where the anion was produced by the action of the electrogenerated base, superoxide, as reported elsewhere.[9] The anodic peak potentials for the anions were measured from the CV (0.20 V s^{-1}) of the precursor acid in which the characteristic peak for anion oxidation appears on the second half-cycle. Ferrocene was added as an internal standard and all potentials are referred to its reversible potential.

Kinetic measurements were carried out in the electrochemical cell. For slow reactions (half-lives greater than about 10 s) the electrophile was injected (0.125 mol dm^{-3}) and the reaction was monitored by periodic recording of the anodic voltammetric peak for the anion. The rate constant was evaluated from plots of the diminishing anodic peak as a function of time. The reaction of the nitrogen nucleophiles with ethyl 3-chloropropionate was an exception. Here the growth of the reduction peak of the product was monitored. This change was made because of interference of chloride oxidation with the anodic peak for the anion.

For faster reactions, after injection of the electrophile the rate was monitored by measuring the steady-state anodic current for anion oxidation while stirring the solution. In some cases, it was necessary to correct the current for slow decay apparently due to deposition of oxidation products on the electrode. The electrode surface was polished (0.05 μm alumina) between experiments. This technique was suitable for half-lives down to a few tenths of a second.

For representative examples (compounds **12**,[9] **33**[3] and **42**[3]) the expected benzylated products have been isolated and identified confirming that the nucleophilic displacement reaction occurs. Other evidence for the expected reaction was the appearance and growth of a voltammetric peak for oxidation of chloride as the reaction proceeded. For several of the reactions of the nitrogen heterocycles with ethyl 3-chloropropionate, ethyl acrylate was detected as a product indicating that dehydrochlorination was competitive with the nucleophilic displacement reaction. For this reason, the remaining studies focused on the reactions of benzyl chloride with the nucleophilic anions.

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