Nucleophilicity and Basicity in Anode Processes

IV.[1] Steric Effects

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The reactivity of anodically generated cation-radicals was found to be highly sensitive to steric factors. The relative rate constants for the reaction of 9,10-diphenylanthracene cation-radical with 3,5-lutidine, 2,5-lutidine, and 2,6-lutidine were estimated to be equal to 37, 6.5, and 1.0, respectively. While reaction at carbon centers is subject to steric inhibition of reactivity, proton abstraction by the nucleophile was found to be unaffected by making the nucleophilic site hindered. Thus, 9,10-dimethylanthracene cation-radical reacts nearly as rapidly with 2,6-lutidine as with 3,5-lutidine. These observations were exploited in developing a cyclic voltammetric technique for determining whether a nucleophile reacts at a carbon center or as a base during reaction with an anodically generated intermediate.

The ECE mechanism, in which a homogeneous chemical reaction is coupled between two electron transfer steps, is of paramount importance in anodic oxidation processes.[2] It has recently been suggested that many anodic substitution reactions of aromatic hydrocarbons, such as hydroxylation, methoxylation, cyanation, and acetoxylation, follow this mechanism.[3]

The term, ECE, is not a complete description of the anodic substitution process, since the function of the nucleophile may be both that of nucleophile and base. In general, substances acting as nucleophiles toward carbon centers are also nucleophiles toward protons, *i.e.* they may act as bases.[4] Thus, during reactions of intermediates formed at the anode with nucleophiles, the possibility frequently exists that the function of the nucleophile is actually that of a base. We can illustrate this situation by considering the case of anodic substitution on an anodically generated cation-radical which has both carbon sites and protons available for reaction (eqn. 1). The initially formed cation-radical may undergo nucleophilic attack on carbon to give *3*, or at a methyl proton to give *5*. The two mechanisms leading to *3* and *5* may be described as EC_NE (when the homogeneous chemical reaction between the two electron transfer steps involves interaction of the nucleophile with a carbon center) or EC_BE (when proton abstraction by the nucleophile is the homogeneous step).

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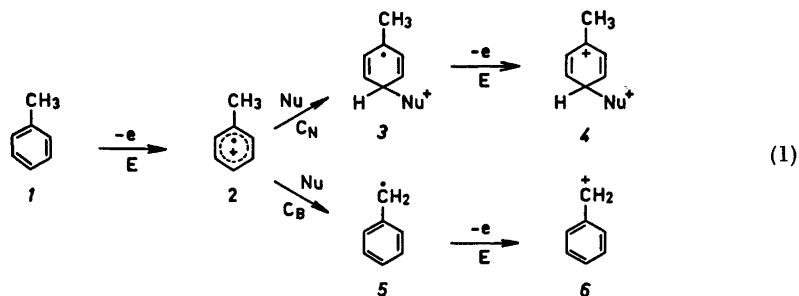
In order to have a complete understanding of the anodic substitution process, it is necessary to have a means of following the reaction from substrate to reactive intermediate to products. It is the purpose of this work to develop methods of studying these processes and, once having the means, apply them to the study of specific cases of anodic substitution reactions. This paper deals primarily with anthracene derivatives and is concerned with the steric aspects of the ECE mechanism.

RESULTS AND DISCUSSION

A. Steric requirements of the anodic substitution process. First of all it was necessary to show that the reactions of anodically generated intermediates are subject to steric factors. The approach used was to study the effect on the reactivity toward cation-radicals, of making the nucleophilic center sterically hindered toward a carbon center without diminishing its basicity towards the proton. This approach has been described in a preliminary communication.[5] The lutidines, *7, 8,* and *9,* provide a series of increasing steric hindrance to nucleophilic reactions of the nitrogen. 3,5-Lutidine, *7,* having no methyl
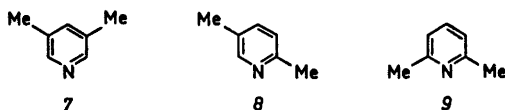
groups in the α-position, is not hindered, while 2,6-lutidine, *9,* substituted at both α-positions, is severely hindered. The reaction chosen as a standard, the anodic pyridination of anthracene derivatives, was reported several years ago.[6]

The substrates chosen were 9,10-diphenylanthracene (DPA, the pyridination of which has been studied[3]), 9,10-dimethylanthracene, DMA, and 1,4-dimethoxybenzene, DMB. DPA forms a cation-radical which is stable in acetonitrile.[7] DMA[8] and DMB[9] form cation-radicals of limited stability which are, however, stable during the time-scale of cyclic voltammetry. The technique employed to determine relative reactivities was to determine the dependence of the concentration of the nucleophile on the magnitude of the reduction

current for the cation-radical during cyclic voltammetry. Since the concentration of the cation-radical formed at the anode depends only on the concentration of the substrate (independent of the nucleophile), the relative concentrations of the nucleophiles necessary to eliminate the reduction current is related to the rate constant for the reaction of the nucleophile with the cation-radical. The data for the three substrates are summarized in Table 1.

Table 1. Relative dependence of the elimination of the cation-radical reduction current on nucleophile concentration.

Substrate	3,5-Lutidine	2,5-Lutidine	2,6-Lutidine
9,10-Diphenylanthracene	1.0	6.5	37
1,4-Dimethoxybenzene	2.1	35	64
9,10-Dimethylanthracene	0.75	1.0	1.25

The data show (Table 1) that the slightly hindered nucleophile, *8*, is 6.5 times less reactive toward the DPA cation-radical than unhindered *7*, while *7* is 37 times as reactive as the hindered nucleophile, *9*. The reaction of DPA cation-radical with the nucleophiles has to involve attack at a carbon center since no other sites are available. This system very nicely demonstrates the importance of steric effects in the anodic substitution process. DMB shows similar behavior with *7* being 32 times as reactive as *9*. However, DPA cation-radical is about 2 times as reactive toward the unhindered nucleophile, *7*, as is the cation-radical from DMB. Both DPA and DMB only have carbon centers available for reaction to occur, and the reactivity differences observed are a reflection of the effect on the rate of the reaction of making the nucleophile hindered toward the carbon center.

The reactions of the DMA cation-radical offer a real test of the method. In this case, both carbon centers and methyl protons are available for reaction. This factor was overlooked in a discussion of the effect of blocking groups on cation-radical stability. [8] DMA cation-radical shows very little difference in reactivity toward the three nucleophiles, all reacting in nearly stoichiometric fashion. In view of the steric requirements observed when a carbon center is attacked as discussed above, this is compelling evidence that the site of reaction of the DMA cation-radical with a nucleophile is on a methyl proton (eqn. 2). This hypothesis is strongly supported by the isolation of the dimer, *12*, from the anodic oxidation of DMA in the presence of 2,6-lutidine. A similar dimerization was observed during cupric chloride oxidation of 9-methoxy-10-methylanthracene.[10]
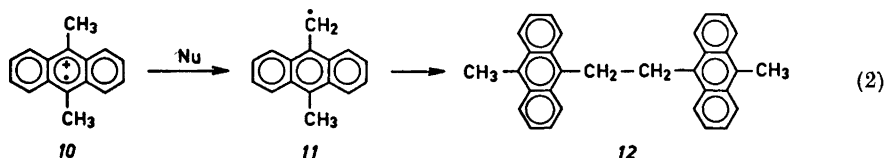

(2)

10   *11*   *12*

Fig. 1 illustrates the method as applied to the reaction of DPA cation-radical with *7*, and Fig. 2 shows the cyclic voltammograms of DPA in the presence of *9*. Fig. 3 illustrates the reactivity of DMA cation-radical with the hindered nucleophile, *9*.
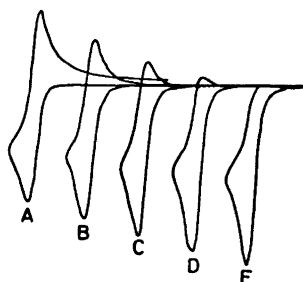

Fig. 1. Cyclic voltammograms of 9,10-diphenylanthracene in the presence of 3,5-lutidine. A (lut)=0.0; B (lut)=0.25 mM; C (lut)=0.50 mM; D (lut)=0.75 mM; E (lut)=1.00 mM.
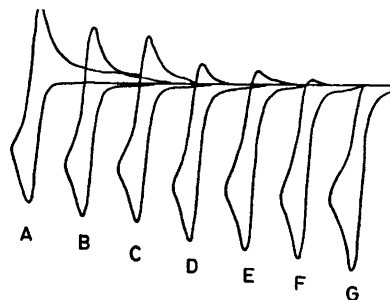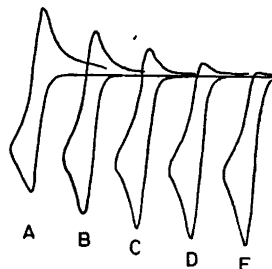
Fig. 2. Cyclic voltammograms of 9,10-diphenylanthracene in the presence of 2,6-lutidine. A (lut)=0.0; B (lut)=5.0 mM; C (lut)=10.0 mM; D (lut)=20.0 mM; E (lut)=30.0 mM; F (lut)=40.0 mM; G (lut)=50.0 mM.

Fig. 3. Cyclic voltammograms of 9,10-dimethylanthracene in the presence of 2,6-lutidine. A (lut)=0,0; B (lut)=0.25 mM; C (lut)=0.50 mM; D (lut)=0.75 mM; E (lut)=1.00 mM.

B. The $EC_N EC_{N(B)}$ mechanism. In the preceding section we made the statement that the term, ECE, is not a complete description of the anodic substitution process. Likewise, the designation, $EC_{N(B)}E$, does not describe the process from substrate to product, but rather describes the reaction leading to the intermediate involved in the product forming step.

The $EC_N E$ mechanism for the reaction of 9-phenylanthracene (PA) with a nucleophile is illustrated in eqn. 3. Examination of the structure of the intermediate after the $EC_N E$ process, *15*, reveals that there are now two possible sites for reaction with the nucleophile, the positive carbon center at the 9-position or the proton at the 10-position.
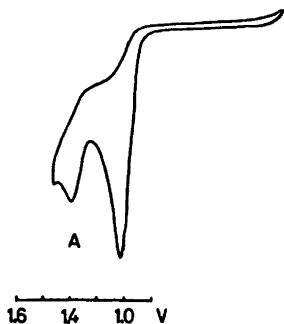
$$\text{(3)}$$

13   14   15
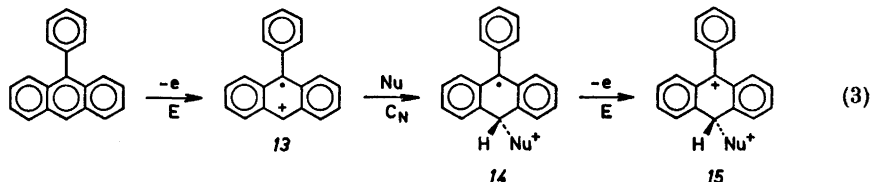
Fig. 4. Cyclic voltammogram of 9-phenyl-anthracene in the presence of 3,5-lutidine.
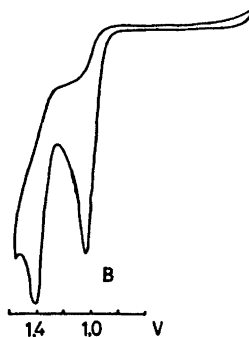
Fig. 5. Cyclic voltammogram of 9-phenyl-anthracene in the presence of 2,5-lutidine (10 mM).

The voltammogram of PA in acetonitrile in the presence of 7 (Fig. 4) shows a two electron oxidation peak at +1.0 V (all potentials refer to the aqueous saturated calomel electrode, and the supporting electrolyte was lithium perchlorate in all cases) and a smaller peak at +1.4 V. The voltammograms in the presence of the more hindered bases, 8 and 9, (Fig. 5), show two electron oxidation peaks at +1.0 V and secondly two electron peaks at +1.4 V. Controlled potential coulometry of PA in the presence of any of the three nucleophiles (at +1.1 V) resulted in the consumption of two Faradays per mole of substrate. The voltammograms of the three solutions all showed an oxidation peak at +1.4 V. The height of the oxidation peak for the solutions containing the hindered nucleophiles was precisely the same as the original peak at +1.0 V of the solutions before coulometry. However, the solution obtained from controlled potential coulometry of PA in the presence of 7 exhibited a voltammetric oxidation peak at +1.4 V only 0.38 times as great as that of the original solution at +1.0 V. After heating the solution to the boiling point for 1 h and allowing to cool, voltammetric analysis showed the oxidation peak at +1.4 V to be as large as that of the other two solutions indicating that a chemical reaction had taken place to produce the oxidizable intermediate. The product of this reaction was isolated and the structure shown to be 17a (eqn. 4). Thus, the chemical reaction occurring after electrolysis is the conversion of 16a to 17a. The rate of this reaction was found to be much too low to account for the production of 17a during the time-scale of cyclic voltammetry (the half-life of 16a in the electrolysis medium was found to be about 6 h at 27°C). The conversion of the 9.10-dipyridinium salt from anthracene to the 9-pyridylanthracene salt by the action of base has been reported.[6]

We can conclude from our data that $k_B \gg k_N$ for the reaction of 15 with 8 and 9. When the nucleophile is 7, $k_B = 0.6 \ k_N$ (determined by measurement of the peak heights for the oxidation at +1.0 V and +1.4 V of the solution of PA and 7, or by measurement of the peak height at +1.0 V before coulometry as compared to that at +1.4 V after coulometry, both methods giving the same value). Thus, nucleophilic attack at the carbon center at the 9-position

Nu, k_N
C_N

16

15

(4)

Nu, k_B
C_B

17

a Nu = 3,5-lutidine
b Nu = 2,5-lutidine
c Nu = 2,6-lutidine
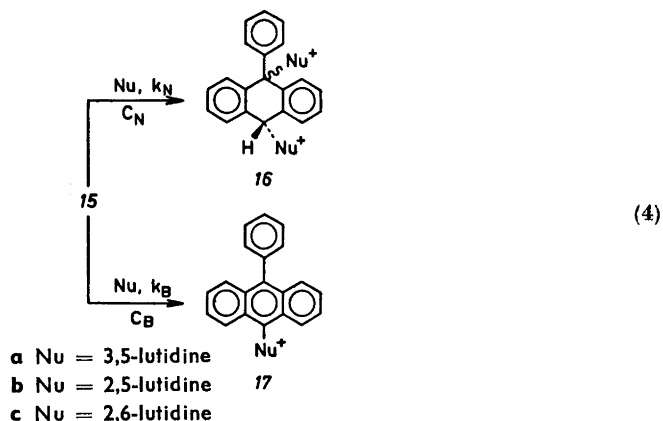
is favored with *7* and severely inhibited with either *8* or *9*. This effect is illustrated by the voltammograms in the presence of *7* (Fig. 4) and *8* (Fig. 5). The lutidination of PA was described in a preliminary communication.[11]

The EC_NE reaction of anthracene with a nucleophile produces *18*. The carbon center at C_{10} would be expected to be relatively insensitive to steric factors. The voltammograms of anthracene in the presence of either *7*, *8*, or *9*

H Nu$^+$

H Nu$^+$

H

H Nu$^+$

18

19
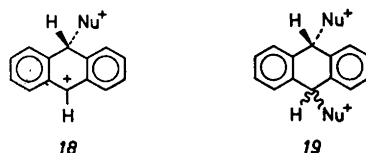
all show a single oxidation peak at $+1.08$ V corresponding to the transfer of two electrons and a very small peak at $+1.42$ V. The unhindered carbon site (C_{10}) is the position of almost exclusive nucleophilic attack for all three of the nucleophiles producing the dilutidinium salts, *19*. The monopyridinium salt has been observed to form by the action of base on the dipyridinium salt and is oxidized at $+1.50$ V (in the absence of nucleophile).[6] Therefore, if the mono-lutidinium salt were formed during cyclic voltammetric oxidation of anthracene in the presence of lutidine, it would be detected. The peak at $+1.42$ V is most likely due to the monolutidinium salts, but is so small that the direct formation during cyclic voltammetry must be considered as a negligible reaction pathway in this case.

The method for determining whether a nucleophile reacts at a carbon center or as a base on hydrogen (discussed in Section A) required that the substrate form a cation-radical of great enough stability to show reduction current during cyclic voltammetry. The voltammetry of anthracene (which forms a very reactive cation-radical that can only be detected at very high voltage sweep rate during cyclic voltammetry [7]) in the presence of *7*, *8*, and *9*

Table 2. Peak currents for the oxidation of anthracene in the presence of the lutidines.

Nucleophile	Peak current at various nucleophile concentrations						
	0^a	0.5	1.0	1.5	4.0	8.0	20.0
3,5-Lutidine	285	242	208	144	157	153	155
2,5-Lutidine	290	254	220	165	156	154	156
2,6-Lutidine	282	278	275	262	230	200	164

a Current in $\mu A.^{12}$

illustrates a variation of the method. Table 2 is a summary of peak currents (recorded at 10 V/min) observed for the oxidation of 1.0 mM solutions of anthracene in acetonitrile in the presence of varying concentrations of the nucleophiles. A plot of the peak currents *versus* nucleophile concentration (Fig. 6) shows that the peak current of anthracene in the presence of *7* and *8* decreases linearly with concentration of the nucleophile with a maximum effect observed near the stoichiometric concentration for reaction to the dilutidinium salt. That *8* is as reactive as *7* reflects that the reactivity of anthracene cation-radical is not sufficiently influenced by steric factors to differentiate between the unhindered *7* and moderately hindered *8*. However, the severely hindered lutidine, *9*, does not produce the maximum effect unless present at a concentration of about 50 mM. Therefore, *9* is at least 25 times less reactive than *7* and *8* toward the anthracene cation-radical.

Thus, formation of a cation-radical stable during the time-scale of cyclic voltammetry is not a requirement for application of the method to determine
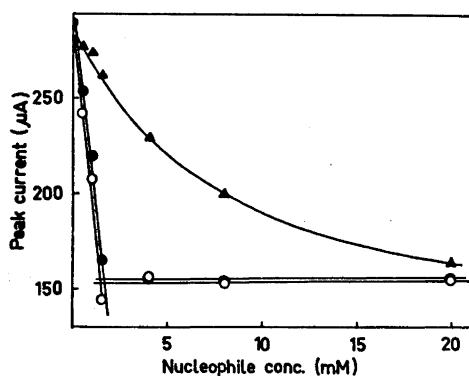

Fig. 6. Dependence of peak current on nucleophile concentration for the voltammetric oxidation of anthracene. Empty circles, 3,5-lutidine; filled circles, 2,5-lutidine; triangles, 2,6-lutidine.
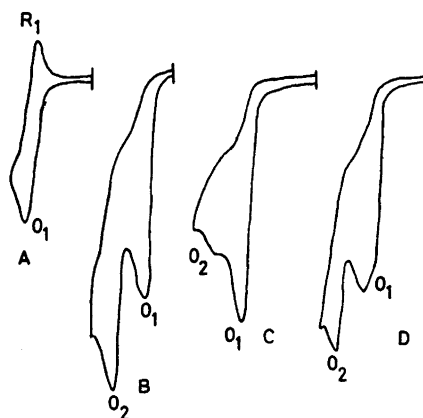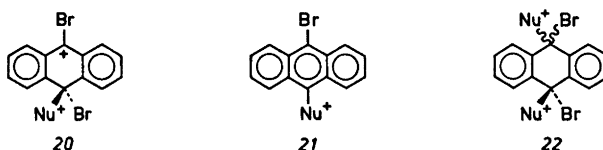
Fig. 7. Cyclic voltammograms of 9,10-dibromoanthracene in acetonitrile containing lithium perchlorate. Sweep rate 10 V/min. A, no added nucleophile; B, 10 mM in 3,5-lutidine; C, 10 mM in 2,5-lutidine; D, 10 mM in 2,6-lutidine.

whether the nucleophile acts as a base or as a nucleophile toward a carbon center. As long as a change in the peak current is observed when voltammetry is carried out in the presence of a nucleophile, the method is of potential use.

C. *Anodic nucleophilic displacement on bromine.* The EC_NE mechanism for the reaction of 9,10-dibromoanthracene with a nucleophile produces *20* analogous to *15* for 9-phenylanthracene. In this case, the intermediate contains

two possible sites for reaction with a nucleophile to occur, either on bromine to give the monolutidinium ion, *21*, or on carbon to give the dilutidinium salt, *22*.

Fig. 7A is the cyclic voltammogram of 9,10-dibromoanthracene in acetonitrile containing lithium perchlorate as supporting electrolyte. An oxidation peak, O_1, is observed at $+1.42$ V, and on reversing the direction of the scan, a cathodic peak is observed at $+1.34$ V, which is due reduction of the cation-radical formed at the first oxidation peak. In Figs. 7B, 7C and 7D the concentrations are for the same solution made 10 mM in 3,5-lutidine or 2,5-lutidine, or 50 mM in 2,6-lutidine, respectively. The first oxidation peak in the latter three cases now corresponds to the transfer of two electrons, and no reduction current is observed on the reverse scan. A second oxidation peak, O_2, is observed in all three cases. The height of this peak, however, is dependent on the nucleophile.* The solution containing 3,5-lutidine produces a second oxidation peak of nearly the same height as O_1, while the solution containing 2,5-lutidine gives a voltammetric peak, O_2, which is barely visible, and 2,6-

Table 3. Voltammetry of bromoanthracenes in the presence of lutidines.

Substrate	Nucleophile	$O_1{}^a$	$O_2{}^a$	$i_{O_1}/i_{O_2}{}^b$
9,10-Dibromoanthracene	7	$+1.24$	$+1.48$	1.17
	8	$+1.34$	$+1.50$	35
	9	$+1.36$	$+1.56$	2.0
9-Bromoanthracene	7	$+1.12$	$+1.47$	2.65
	8	$+1.20$	$+1.53$	1.45
	9	$+1.27$	$+1.60$	1.52

^{a} V *vs.* SCE.
^{b} Measured at a voltage sweep rate of 10 V/min in acetonitrile containing lithium perchlorate (0.1 M).

* The positions of both O_1 and O_2 are dependent on the nucleophile. The voltammetry in the presence of the lutidines is summarized in Table 3.

lutidine gives a voltammogram with O_2 intermediate in height between the other two cases.

Controlled potential coulometry of 9,10-dibromoanthracene in the presence of 3,5-lutidine at the voltage of the first peak verified the transfer of two electrons. The voltammogram of the resulting solution showed the presence of a single oxidation peak identical in position to O_2. The height of the oxidation peak was very nearly the same as O_1 of the solution before coulometry, showing that the substrate is quantitatively converted to an oxidation product, which undergoes voltammetric oxidation at the potential of O_2.

Coulometry in the presence of 2,5-lutidine or 2,6-lutidine was accompanied by the consumption of two Faradays per mole of substrate. Voltammetry of the resulting solutions showed single oxidation peaks, O_2, in either case considerably smaller than O_1 of the solutions before coulometry. However, upon heating the solutions at the boiling point for 1 h, the oxidation peaks increased in height to about the same heights as O_1 of the original solutions. This shows that a homogeneous chemical reaction can occur to form the oxidizable product. However, this reaction occurs at a rate much too low to account for the observation of O_2 during the time-scale of cyclic voltammetry.

Controlled potential electrolysis was conducted on a solution of 9,10-dibromoanthracene in acetonitrile containing 3,5-lutidine (10 mM). The product was isolated and the structure shown to be *21*, in which Nu represents 3,5-lutidine. Voltammetry shows that *21* is oxidized at the potential of O_2. Similarly, Lund [6] isolated and identified the monopyridinium salt from oxidation of 9,10-dibromoanthracene in acetonitrile containing pyridine. However, he assumed that the initial product was the unstable dipyridinium salt which decomposed to the monopyridinium salt during work-up. Our results show that this reaction indeed does occur but is slow during the time-scale of both voltammetry and coulometry and thus cannot account for the direct observation of *21* during voltammetric oxidation of 9,10-dibromoanthracene.

The reactions leading to the two products, *21* and *22*, are summarized in eqn. 5. For the unhindered nucleophile, *7*, $k_{Br} \gg k_C$ (eqn. 5), since voltammetry shows that *21* is the only product. In the case of the more hindered nucleophile, *8*, $k_C \gg k_{Br}$ as shown by voltammetry, with only a small degree of attack occurring on bromine. Voltammetry indicates that $k_{Br} \simeq k_C$ for the severely hindered nucleophile, *9*.

$$(5)$$
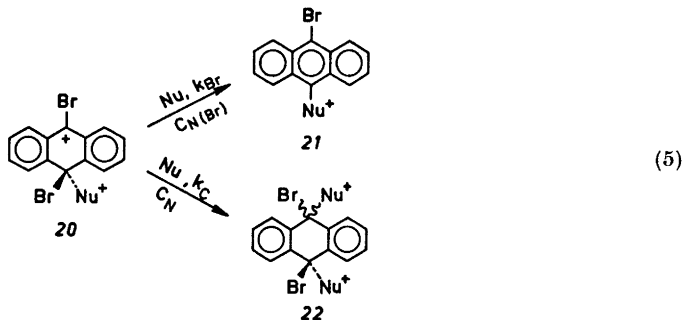
9-Bromoanthracene could give either *23* or *24* as an intermediate from the EC_NE reaction in the presence of the lutidines. Attack by the nucleophile on hydrogen or bromine would produce *21* or *25*, respectively (eqn. 6). The cyclic voltammograms of 9-bromoanthracene in the presence of *7*, *8*, and

$$(6)$$
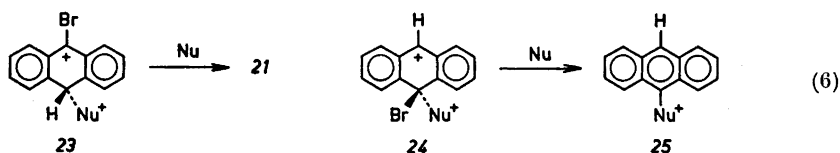
9 are illustrated in Fig. 8. Data obtained from voltammetry are summarized in Table 3. The ratio, i_{O_1}/i_{O_2}, in the presence of *7*, *8*, and *9* parallels that observed for 9-phenylanthracene in that O_2 is larger for the more hindered nucleophiles.
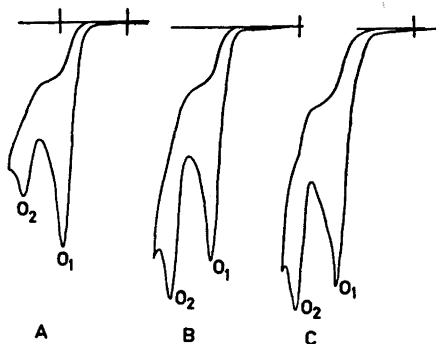

Fig. 8. Cyclic voltammograms of 9-bromo-anthracene in the presence of 3,5-lutidine (A), 2,5-lutidine (B), and 2,6-lutidine (C).

The position of O_2 in the presence of *7*, *8*, and *9* matches O_2 for 9,10-dibromoanthracene quite closely (Table 3). If *25* were the intermediate, O_2 would be due to the oxidation of *24*. However, *25* is considerably more easily oxidized than *21*[6] and O_2 would appear at less anodic potentials. The fact that a single peak, O_2, is observed indicates that the intermediate is not a mixture of *23* and *24*. We thus conclude that *23* is the exclusive product of the EC_NE reaction.

<div align="center">EXPERIMENTAL</div>

All reagents were reagent grade and used without further purification. Acetonitrile was distilled twice from phosphorus pentoxide in which only the middle 60 % fraction was collected. Acetic acid was purified by crystallization.

Voltammetry. Both single sweep (at a rotating platinum electrode) and cyclic voltammetry (at a Beckman platinum button No. 39273) were carried out with a Heath EUW 19B operational amplifier with polarography module EUA-19-2. All potentials are expressed in volts relative to the aqueous saturated calomel electrode (SCE).

Coulometry. Controlled potential coulometry was conducted on 1.0 mM solutions. Coulometric *n* values were determined by integration of the current-time curves. The

potential of the working electrode was controlled by an Amel (Model 555) potentiostat. The anode was a platinum gauze electrode and the cathode a carbon rod. Anode and cathode compartments were separated by a fritted glass disk.

Preparative electrolyses. The preparative experiments were conducted in the same apparatus as used for coulometry. The substrate (1.0 mmol, 20 mM solutions) was exhaustively oxidized until the current dropped to residual levels. The electrolysis mixture was poured into a separatory funnel containing chloroform (100 ml). The chloroform phase was extracted with several equi-volume portions of water. After drying over anhydrous magnesium sulfate, the chloroform was removed under the aspirator. The lutidinium salts were redissolved in a minimum amount of chloroform and then precipitated with a generous amount of anhydrous ether. After filtering, the solid was thoroughly washed with more anhydrous ether. The lutidinium salts obtained in this manner were quite pure. Assignment of structure was based on NMR and elemental analysis. The preparative aspects and complete product characterization of reactions described in this paper will be reported later. The following example is typical.

9-Phenyl-10-(3,5-lutidinium)-anthracene perchlorate. The product obtained by oxidation of 9-phenylanthracene in the presence of 3,5-lutidine was isolated according to the procedure outlined above after heating the electrolysis mixture at reflux for 1 h. The solid salt was dissolved in chloroform and precipitated with anhydrous ether and collected by filtration. This procedure was carried out two more times before submitting for NMR and elemental analysis. The NMR spectrum consisted of singlets at 2.41 (6H), 8.10 (2H) and 8.32 ppm (1H) due to the lutidinium protons and a broad signal centered at about 7.20 ppm (13H) due to the aromatic protons. (Found: O 13.9; N 3.00. Calc. for $C_{27}H_{22}ClNO_4$: O 13.91; N 3.04.).

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12. In the absence of an added nucleophile, anthracene undergoes four electron oxidation (Parker, V. D. *Acta Chem. Scand.* **24** (1970) 2757), while in the presence of the lutidines a two electron oxidation is observed.