

# Substituent, Solvent and Steric Effects on the Electrochemical Reduction of Aziridinium Salts

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The polarographic behavior of a series of *N,N*-dimethyl-2-arylaziridinium fluorosulfonates was investigated as another example of ring-opening reactions of this important class of compounds. Half-wave potentials showed that in water reduction was *facilitated* by electron-donating groups. This unusual result was explained in terms of electron transfer to an aminocarbonium ion-like species. In methylene chloride, however, two one-electron waves were observed, with the first showing a normal substituent effect ( $\rho = 0.17 \pm 0.03$  V). This result indicated direct electron transfer to the aziridinium ion itself to form a radical species which was detected by cyclic voltammetry. Reasons for the change in mechanism are presented, and  $E_{1/2}$  values for selected aziridinium salts illustrate the importance of steric effects on the reduction process.

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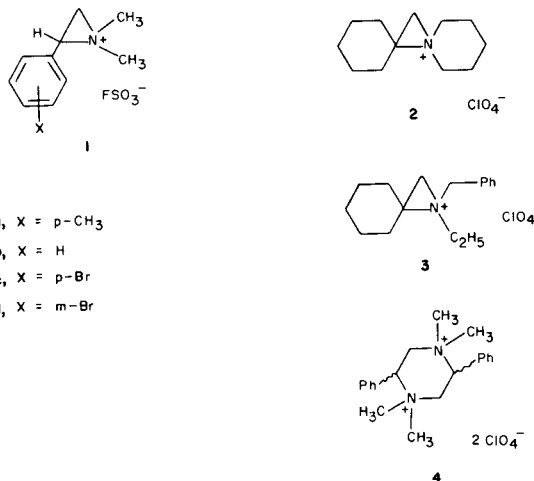
Aziridinium ions, the three-membered ring species generated from nitrogen mustards and responsible for their physiological activity, undergo a wide range of ring-opening and ring-expanding reactions in the presence of various nucleophiles (1). Because of their high degree of ring strain, aziridinium ions are also readily cleaved in electrochemical reductions, as can be seen by more positive half-wave potentials through the series tetrabutylammonium bromide ( $-2.57$  V SCE) (2), benzyltriethylammonium salts ( $-2.2$  V) (3), benzyl-dimethylanilinium bromide ( $-2.2$  V) (4), *N,N*-diethylaziridinium perchlorate (*ca.*  $-1.5$  V) (5), and 2-arylaziridinium salts (*ca.*  $-0.5$  V) (6).

Although polarography has been used primarily for quantitation purposes (7), the details of the reduction process for two alkylaziridinium salts have been investigated (5).

In the first systematic study of the substituent effect on electrochemical ring-opening reactions, we reported that dispiro-2-arylaziridinium salts exhibited unusual polarographic behavior (6). Unlike the vast majority of benzene derivatives (8, 9, 10), reduction was favored by electron-donating groups which suggested aminocarbonium-like species in the electrode process. It would be of interest to see if this trend was maintained with stronger electron-withdrawing groups and also if separate one-electron waves could be observed in aprotic solvents (5) with only the first showing an "abnormal" substituent effect. We now report our results for the polarographic reduction of these salts in water and methylene chloride as well as cyclic voltammetry data to clarify the mechanism of the electrode process.

## Results and Discussion.

A series of 2-arylaziridinium salts **1** was prepared by the alkylation of the corresponding aziridines with methyl fluorosulfonate (11), while two examples of alkyl substituted salts **2** and **3** were made by the diazomethane insertion method of Leonard (2, 12).



For comparison purposes, the piperizinium dimer **4**, which was reported as a decomposition product of *N,N*-dimethyl-2-phenylaziridinium perchlorate (13), was prepared from *N,N*-dimethyl-2-chloro-2-phenethylamine hydrochloride.

Table I

Polarographic Data for Reduction of Aziridinium Salts (a)

Salt	In Water (b)		In Dichloromethane (e)	
	$E_{1/2}$ , V(SCE)	n(c)	$E_{1/2}$ , V(f) first wave	$E_{1/2}$ , V(f) second wave
<b>1a</b>	-0.34	1.3 ± 0.1	-0.36	-0.73
<b>1b</b>	-0.40	2.2 ± 0.2	-0.31	-0.67
<b>1c</b>	-0.47	2.5 ± 0.1	-0.29	-0.79
<b>1d</b>	-0.43	1.4 ± 0.1	-0.26	-0.64
<b>2(d)</b>	-1.32	2.4 ± 0.2		
<b>3</b>	-0.99	1.3 ± 0.1		

(a) All salts 0.5M initial concentration. (b) Boric acid-borate buffer at pH 6.92 as supporting electrolyte. (c) Uncertainties represent average deviation. However, errors caused by assuming an average diffusion constant of  $6 \times 10^{-6}$  cm<sup>2</sup>/sec (18b) or by other factors (see text) may be substantially larger. (d) In the presence of Triton X-100. (e) With 0.1M tetrabutylammonium perchlorate as supporting electrolyte. (f) With respect to Ag/AgI electrode (see Experimental).

## Aqueous Polarographic Studies.

All aziridinium salts gave well-defined polarographic waves in a boric acid-borate buffer (pH 6.92) supporting electrolyte (7b) in the 0.0 to  $-1.5$  V (SCE) range (Table I). These waves did not correspond to reduction of piperazinium salts, since **4** did not show a wave below  $-1.5$  V. Also, the observed waves cannot be due to benzyl alcohol hydrolysis products (14) or, in the case of aryl bromides to reduction of the bromo group, since both types of compounds are not reduced in the range of potentials studied (15).

As shown in Figure 1 for **1c**, some of the salts (**1a**, **1c** and **1d**) exhibited a small pre-wave which could be due to adsorption (1, 16). The irreversible waves ( $E_{1/4} - E_{3/4}$  values of 175 to 250 mV) (17) were found to be diffusion controlled by the linear dependence of  $i_1$  on  $\sqrt{h}$ , where  $h$  is the uncorrected mercury height. Values of  $n$  calculated by the Ilkovic equation (18) (see Table I) can be regarded as evidence for a two-electron reduction consistent with the observations of Tyssee and Baizer for alkylaziridinium salts (5) in aqueous solution. Values of  $n$  less than two may reflect lower concentration of the aziridinium salt due to hydrolysis (14), an error in the choice of diffusion coefficient (18b), or side reactions of the benzyl radicals produced after one electron transfer (4, 5). Hydrolysis precluded coulometric determination of  $n$  and controlled potential electrolysis studies.

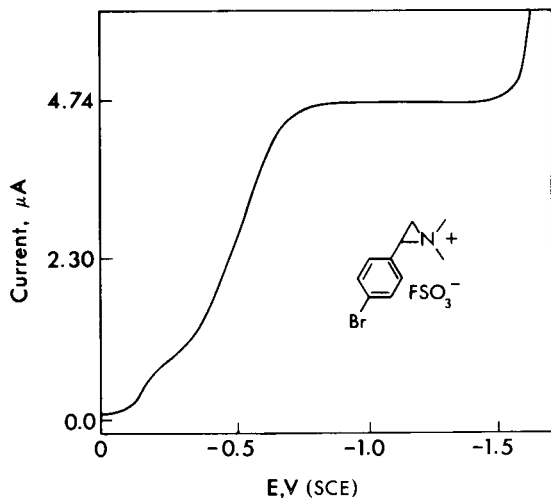


Figure 1. Polarogram of 0.5mM **1c** in aqueous boric acid-borate buffer, pH 6.92.

Steric effects on the ease of reduction can be seen in the trends of half-wave potentials in Table I. It was found that alkyl substituents on the ring carbon lowered  $E_{1/2}$  from  $-1.5$  for *N,N*-diethylaziridinium perchlorate (5) to  $-1.32$  for *N*-pyrrolidinyl salt **2** to  $-0.99$  V for the *N*-benzyl salt **3**. The data suggest that  $E_{1/2}$  values are a very sensitive

measure of the structural and steric effects in these compounds.

Similar effects have been noted in the solvolysis of aziridinium ion intermediates (14). Rates were rationalized in terms of a balance between inductive stabilization by alkyl groups and labilization of the ion by relief of steric strain. These effects undoubtedly play a role in electrochemical reduction. An important additional consideration is the structural orientation aspects of these salts at the electrode surface (19).

Results for the 2-arylaziridinium salts, which were most easily reduced, provide a series in which steric effects are relatively constant. Half-wave potentials plotted *vs.* Hammett  $\sigma$  values (20) showed that electron-donating groups favor reduction with a negative  $\rho$  value of  $-0.32 \pm 0.02$  V (Figure 2), with the *m*-bromo derivative falling off the correlation line. For comparison, values for 1-aryl-3-azoniaspiro[2.4]heptane fluoroborates (6) with more electron-donating substituents are also given in Figure 2.

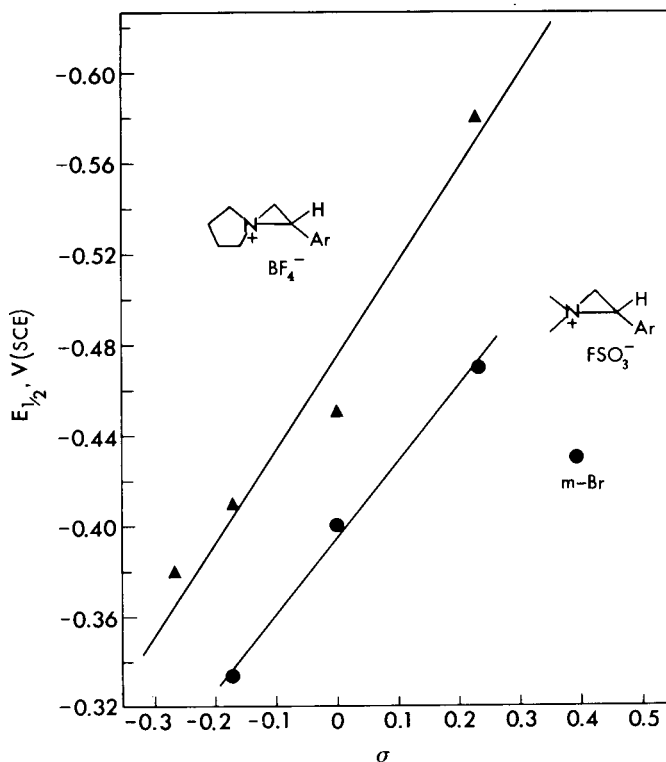
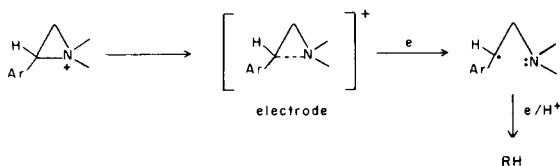


Figure 2. Dependence of half-wave potentials of arylaziridinium salts on  $\sigma$  values; 1-aryl-3-azoniaspiro[2.4]heptane fluoroborates (▲) from Ref. 6; *N,N*-dimethyl-2-arylaziridinium fluorosulfonates (●).

Although the slope is the same within experimental error ( $-0.39 \pm 0.06$  V), there is a constant shift to more negative potentials which is probably due to steric effects discussed above.

Only a few well-substantiated examples of reduction of benzene derivatives having negative reaction constants have been reported (21). These cases, which include reduction of nitrobenzenes in sulfuric acid (21b, 22) and, for electron-releasing groups, reduction of benzyl bromides (23a) and benzenediazonium ions (23b), can be explained by formation of a net positive charge in proceeding from the ground state to the electron transfer step. In the present case a slope of  $-0.32$  V corresponds (24) to a  $\rho$  value of  $-1.4$ . This abnormal substituent effect suggests considerable positive charge buildup at the benzylic carbon before electron transfer, as represented in Scheme I. In water, reduction of an amino radical occurs at more positive potentials than the ring opening reduction (5) so that a single two-electron wave is observed (25a).

Scheme I



An alternate process involving formation of an aminocarbenium ion in a fast prior equilibrium step in bulk solution can also be imagined. Such a process, however, would be expected to give a *positive* reaction constant for electron transfer to the fully developed carbonium ion and to give a better correlation of  $E_{1/2}$  values with  $\sigma$ , rather than  $\sigma_+$ . Also, one would expect a kinetic wave for such a process (25b) with  $i_1$  independent of mercury height, contrary to what was observed.

One explanation for the deviation of the *m*-bromo derivative is that there is less benzylic carbonium ion character at the electron transfer stage than one would predict from electron-donating groups. Comparison of the *p*- and *m*-bromo substituents shows that for the *m*-bromo derivative (26), to some degree the normal substituent effect has become operative, namely that electron withdrawal favors reduction. For the reduction of benzyl bromides, which is probably a similar case, a curved Hammett plot was in fact observed (23, 27).

#### Reduction in Methylene Chloride.

Polarographic reduction of 2-arylaziridinium salts in methylene chloride gave two waves in agreement with Scheme I and is shown in Figure 3 for **1a**. Although half-wave potentials for the second wave (see Table I) gave no correlation with  $\sigma$  or  $\sigma_+$ , those for the first correlated well with  $\sigma$  giving a  $\rho$  value of  $+0.17 \pm 0.03$  V (Figure 4).

In methylene chloride electron donating groups appear to hinder reduction, an effect opposite to that observed in water for which the formation of a partial aminocarbenium ion was postulated. In methylene chloride it would

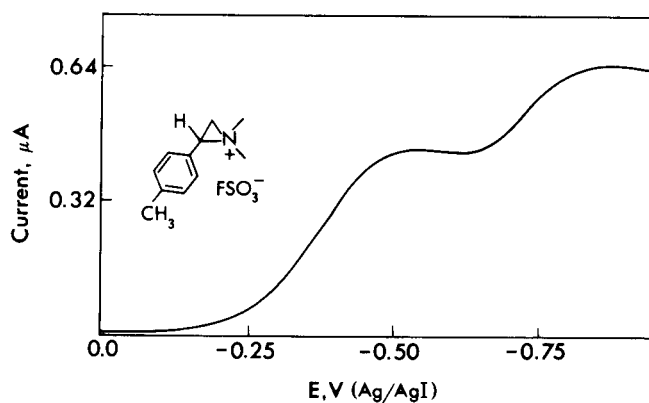


Figure 3. Polarogram of nonaqueous (dichloromethane) reduction of  $0.5$  mM **1a** containing  $0.1$  M tetrabutylammonium perchlorate supporting electrolyte.

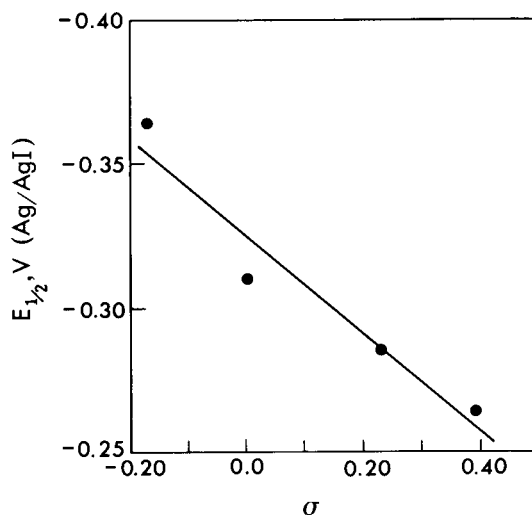


Figure 4. Dependence of half-wave potentials on substituent for arylaziridinium fluorosulfonates **1** in dichloromethane containing  $0.1$  M tetrabutylammonium perchlorate supporting electrolyte.

appear from the normal substituent effect that reduction occurs *via* electron transfer to the aziridinium ion itself without involving aminocarbenium ion (*cf.* the tendency for a similar process for reduction of the *m*-bromo salt in water).

One possible explanation for this dramatic solvent effect is that in methylene chloride, aziridinium salts exist as ion pairs, as reported for the supporting electrolyte (28) or even as ion clusters (29a). Ring opening to give a partially dispersed positive charge (*i.e.*, a change toward nonpolar character) would be disfavored in such a highly polar environment (29, 30) and the carbonium ion-type mechanism becomes disfavored.

Cyclic voltammetry was used to investigate the details of the reduction process in methylene chloride, specifically to test reversibility of the first wave and to determine the lack of substituent correlations for the second. As shown in Figure 5 for **1a**, two unequal reduction peaks were observed (peaks A and B). Peak-clipping of A at a sweep rate of

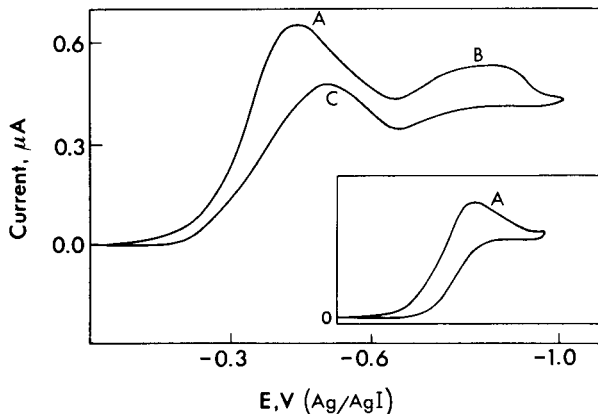
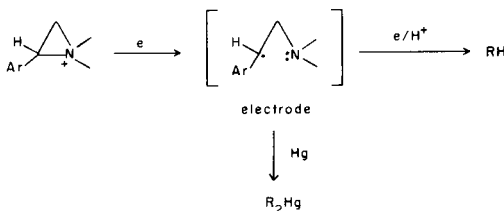


Figure 5. Cyclic voltammogram for reduction of 0.5mM **1a** in methylene chloride containing 0.1M tetrabutylammonium perchlorate supporting electrolyte, scan rate 300 mV/sec: insert, first wave clipped at  $-0.73$  V (offset with different scales).

300 mV/sec showed that this first reduction step was irreversible, since a mirror image anodic peak was not observed. More importantly, a reverse sweep after peak B gave a different cathodic peak C. This unusual result (31, 32) had been observed in the reduction of alkylaziridinium salts (5) and was attributed to the reduction of organomercurials formed from radical intermediates.

The various observations for electrochemical reduction of arylaziridinium salts in methylene chloride can be rationalized by the mechanism shown in Scheme II.

Scheme II



The aziridinium salt is irreversibly reduced on the electrode surface to give an intermediate radical corresponding to the first wave. At a more negative potential, this radical is further reduced to a carbanion which on proton abstraction is converted to an amine (5). The radical can also undergo reaction with mercury to give an organomercurial, thus lowering the height of the second wave as

observed. The organomercurial, formed after the time represented by sweeping through peak B, can also be reduced, as evidenced by the inverted peak. The present data do not rule out the possibility of additional non-reductive reactions of the radical such as dimerization or disproportionation (5).

### Conclusions.

The present results show that electrochemical reduction of aziridinium salts is sensitive to steric, substituent and solvent effects. In water, the abnormal substituent dependence of the half-wave potential for the two-electron, irreversible wave suggests that an aminocarbonium-like species is reduced in the potential-determining step. In methylene chloride the usual substituent dependence of the first wave suggests direct electron transfer to the aziridinium ion. Stepwise reduction was indicated by the presence of a second wave and cyclic voltammetry evidence for radical intermediates.

An explanation for the marked solvent effect on the mechanism is that reduction *via* aminocarbonium ion-type species may occur only when the carbonium ion is stabilized, as with *para*-directing substituents in water. Under conditions that destabilize carbonium ions, reduction occurs preferentially by electron transfer to the aziridinium ion itself. From the present work, this appears to be the case for the *m*-bromo derivative in water and all 2-aryl salts **1** in methylene chloride, possibly due to a highly polar, local environment.

### EXPERIMENTAL

#### Materials.

Methylene chloride (spectroquality), tetrabutylammonium perchlorate (polarographic grade), tetrabutylammonium iodide (polarographic grade), and acetonitrile (spectroquality) were obtained from Matheson, Coleman and Bell. Arylaziridinium salts **1a-d** were prepared as described by Borsetti and Crist (11). 5-Azoniadispiro[4.0.5.1]dodecane perchlorate **2** (12) and 1-benzyl-1-ethyl-1-azoniaspiro[2.5]octane perchlorate **3** (33) were prepared by the diazomethane insertion method of Leonard (1).

#### Aqueous Polarographic Studies.

A Sargent Polarograph Model XV, equipped with a dropping mercury electrode and H-type polarographic cell containing a saturated calomel reference electrode (SCE), was used and standardized with a reference solution of 0.1mM thallium nitrate in 0.1M potassium chloride. The cell was Lingane-Laitinen type, modified for easy cell drainage. The height of the mercury throughout all runs was constant at 63.0 cm, giving capillary characteristics of  $t = 4.0$  sec and  $m = 1.86$  mg/sec. Oxygen was removed from the test solution with tank nitrogen. The electrolyte consisted of a borate buffer with pH 6.92, prepared as 10 ml mixtures of 9.7 ml of 0.2M boric acid and 0.3 ml of 0.05M Borax ( $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ ) (34).

For measurements of  $E_{1/2}$ , 4 ml of the buffer solution was introduced into the cell and degassed with nitrogen for three minutes. To a previously weighed sample was added by pipette a 1:1 solution of buffer:acetonitrile (spectroquality). An aliquot of this sample solution, the amount required for a  $5 \times 10^{-4}$ M cell concentration (15-50  $\lambda$ ), was quickly transferred into the cell by syringe and an additional 20 seconds of degassing followed. The potential was then scanned over a range of 0.0 to  $-2.0$  V vs. SCE with the half-wave potential recorded ca. 2.5 minutes

after injection of the sample. Blank experiments with the buffer and the usual amounts of acetonitrile did not give waves in the region of interest. Values of  $E_{1/2}$  were concentration dependent for some of the arylaziridinium salts, with shifts of 50 to 100 mV as the concentration decreased by a factor of 5. Consequently, all  $E_{1/2}$  values were measured at the same initial concentration and before significant hydrolysis.

#### Nonaqueous Studies.

Nonaqueous polarography and cyclic voltammetry were carried out using a Heathkit Polarograph Model EUA-19-2 containing a Heath Model UUA-19-4 stabilizing unit. Polarograms were recorded on a Hewlett-Packard 7035B X, Y Recorder. Cyclic voltammograms were obtained using a Wavetek Model 110 Function Generator. Recording of current-voltage curves was accomplished with a Hewlett-Packard 7035B, X, Y Recorder (0.33 V/min sweep rate).

A three-electrode configuration was used with a platinum wire auxiliary electrode coiled around a hanging drop mercury working electrode in the sample compartment of the cell. The Ag/AgI reference electrode (35, 36) was prepared by shaking freshly prepared silver iodide with 10 ml of a dry methylene chloride solution 0.42M in tetrabutylammonium perchlorate and 0.05M in tetrabutylammonium iodide. This heterogeneous mixture was placed in a glass tube equipped at one end with a silver wire for external contact and at the other end with an asbestos fiber for contact with the supporting electrolyte. The reference electrode was allowed to equilibrate for 72 hours before use. The reference compartment was connected to the sample compartment by a tube with fine porosity glass frits at each end and containing the supporting electrolyte. A stopcock drain and ground glass joint on this connecting tube permitted convenient replacement of the supporting electrolyte between consecutive polarograms. The supporting electrolyte consisted of 0.1M solution of tetrabutylammonium perchlorate in methylene chloride.

Solutions were degassed *via* a bubbler at the base of the sample compartment for *ca.* 10 minutes with nitrogen which had been passed first through Linde molecular sieves, type 4A, then over hot copper pellets, and finally through a methylene chloride bubbler. Throughout the duration of all measurements, nitrogen was passed over the solution. The cell was standardized by calibration with respect to the ferrocene-ferricinium perchlorate couple as described by Coutagne (35). Half-wave potentials were measured as described above, scanning over a range of 0.0 to -2.0 V *vs.* Ag/AgI.

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