THE OXIDATION MECHANISM OF SOME PSYCHOTROPIC SUBSTANCES WITH SEVEN-MEMBERED RINGS AT PLATINUM ELECTRODES

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A voltammetric study of some psychotropic substances with seven-membered rings and an attempt to follow the reaction mechanism of their oxidation at platinum rotated disk electrode is presented. An E.C.E. mechanism has been confirmed for this group of compounds and on the basis of the obtained experimental data a reaction scheme is suggested.

In a previous communication[1], the authors have shown the possibility of anodic oxidation at rotated platinum disk electrode of some psychotropic substances with a seven-membered ring, and the analytical usefulness of the obtained anodic waves, especially for the substances derived from dibenzocycloheptane or of their heterocyclic analogues, *e.g.* 5-(3-dimethylaminopropylidene)--10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (amitriptyline, *I*) 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b,e*]thiepine (prothiaden, *II*) and 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3]benzothiepine (dithiaden, *III*).

An interpretation of the anodic behaviour of this last group of compounds is the aim of this communication. We have carried out experiments using classical dc. and cyclic voltammetric measurements, coulometric determinations, preparative electrolysis and have presented a spectrophotometric proof of the products.

EXPERIMENTAL

In general, the same experimental conditions as described before[1], were ensured. Lithium perchlorate was used instead of tetrabutylammonium perchlorate as supporting electrolyte in anhydrous acetonitrile. Coulometric measurements were performed with an Amel 558 electronic current integrator (Aparecchiature di misure elettroniche, Milano). The number of electrons *n*, consumed per molecule, was obtained by coulometry at a rotated platinum disk electrode, either of $r = 1.05$ mm (area $= 3.45$ mm^2), or $r = 1.63$ mm (area $= 8.34$ mm^2), following the change in the wave-height at intervals after the consumption of a measured charge and plotting the percentage of the original wave-height *versus* the consumed charge. For isolation of the product of amitriptyline (*I*) oxidation a large area platinum electrode ($r = 5.1$ mm, area $= 81.67$ mm^2) was used with a potentiostatic control of applied electrolysis potential (in the case of amitriptyline (*I*) $+1.3$ V *vs* s.c.e.).

For both coulometric and preparative electrolysis experiments, the working platinum electrode was always polished only at the beginning of the experiment; when during electrolysis the electrode surface was blocked (as indicated by a strong decrease of current passing during electrolysis),

the electrode surface was electrochemically regenerated by applying to it a potential equal to zero. This process of electrical regeneration of electrode surface was carried out at intervals of about 7 minutes during electrolysis and before recording the polarograms for measuring the wave-height at certain consumed amount of charge. The whole procedure was carried out after deaeration but without passing inert gas through the solution, as the presence of oxygen was found not to affect the anodic oxidation. The auxiliary platinum sheet electrode in $0.1M$-$LiClO_4$ in aceto-nitrile has to be separated from the acetonitrile solution by a sintered glass. This solution in the electrode has to be changed after each determination. In preparative electrolysis it was not possible to separate the auxiliary electrode because of the high resistance that will result.

The speed of rotation of the electrode was measured with the help of a manual speed-meter H 6 (Meßgerätewerk, Beierfeld). For spectral measurements in the ultraviolet region a Unicam SP 800 spectrophotometer was used. EPR spectra were followed using a Varian E 4 EPR spectrometer.

RESULTS AND DISCUSSION

From the relationship between structure and the ease of electrooxidation, and as it has been stated before[1], we assume that the active site of these molecules is related to a common grouping possessed by all these compounds (in essence all derived from trimethylamine) and that the electrode process is an attack on the amino group. It could be a fission of the double bond between the exocyclic chain and the seven-membered ring[2] or an oxidation of the nitrogen atom to the N-oxide state[3]. A further possibility for such a structure is its oxidability as an amine (with nitrogen atom having an electron lone-pair).

The first of these three possibilities has been first considered, and it has been shown that the presence of the double bond between the aromatic moiety and the aliphatic chain is not necessary for an oxidation at the RDE, as follows from the oxidation wave (at $E_{1/2} = +1.05$ V vs s.c.e.) obtained with 7-chloro-1-(2-diethylamino-ethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (fluorazepam).

Important is the anodic behaviour of the structurally more similar compound 5-(3--dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine (imipramine); the only difference between amitriptyline (I) and imipramine is the presence of the double bond in the structure of the first compound. Imipramine also showed a well-defined anodic wave at the rotated platinum disk electrode at an $E_{1/2}$ of $+1.15$ V vs s.c.e.

This is considered as a sufficient evidence that the active site in these groups of compounds is related only to the aliphatic amine side chain, $i.e.$ only the third possibility must be considered.

The coulometric determination of n, the number of electrons for amitryptyline has been performed and n has been found to be close to 2. Corresponding values for prothiaden (II) and dithiaden (III) were 3 and 4, respectively.

As regards the coulometric determination of n for amitriptyline (I), it is worth mentioning here that when a large size platinum working electrode $(r = 1.36$ mm$)$

is used, the recorded polarogram showed a double anodic wave. The second wave disappeared after the consumption of certain amount of charge (about 10% of the total necessary amount of charge). Whether the coulometric determination was performed in every case at one stated potential ($+1\cdot3$ V) or using different potential values ($+1\cdot6$ and then $+1\cdot3$ V, for fear of interference of decomposition potential of the suppositing electrolyte) a value very near to two was always obtained.

Waves of prothiaden (*II*) and dithiaden (*III*) are shown to be of a composite nature. Attempts to determine *n*-values at potentials less positive than that corresponding to the total anodic wave height, were not successful because of the difficult wave-height measurement, especially after consumption of a certain amount of charge where the wave becomes less clear-cut, and a separation of the individual steps is impossible.

Controlled potential electrolysis at $+1\cdot3$ C *vs* S.C.E. was carried out with a $5 \cdot 10^{-2}$M ($\sim$340 mg quantities) solution of hydrochloride of *I* as well as with its free base, in 20 ml of acetonitrile.

Unfortunately, no defined product has been identified after column chromatographic or solvent extraction procedure separations. Only some of the starting material has been identified by IR and mass spectra. This, at least will exclude the oxidation to an N-oxide, as much as no such type of product could be detected.

A valuable diagnostic test for follow-up chemical reactions is the variation of $I_L/\omega^{1/2}C$ with $\omega^{1/2}$ (I_L is the limiting current, ω is the rotation rate and C the bulk concentration of electroactive species)[4,5]. If follow-up reactions are present $i_p/\omega^{1/2}C$ will decrease with increasing rotating rate. If not, the plot will be a horizontal straight line. The former behaviour has been found with *I* and, in a similar manner with the two other compounds.

$$(A)$$

$$(B)$$
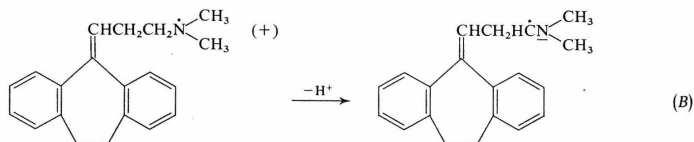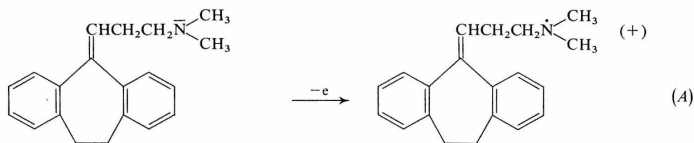
In cyclic voltammetry, a complete change between the first and all subsequent sweeps sometimes occurs[6]. This behaviour has been also found in cyclic voltammograms of I (with $0.1M$-$LiClO_4$ in acetonitrile at a platinum electrode of $3.45 mm^2$ area). The sweep was started from zero volts in an anodic direction. An oxidation peak A can be seen at about $+1.15$ V. The sweep is reversed at $+2.0$ V and in the reverse cycle there is no evidence of a reversible process corresponding to the anodic oxidation. A marked cathodic peak B appears, however, at about -0.3 V. In the second and all subsequent cycles the anodic peak is changed into a double wave with a higher anodic peak A' (at the same potential as A) with an additional small peak C at about $+1.35$ V. The increase from the original anodic peak A to the peak A' and the new peak C which both appear only after an initial electrode oxidation of I, mark the system as one where the electron-transfer is followed by a chemical reaction[6]. A similar situation was also found with II and III; here, more than one cathodic peak result in the cathodic region.

$$(C)$$
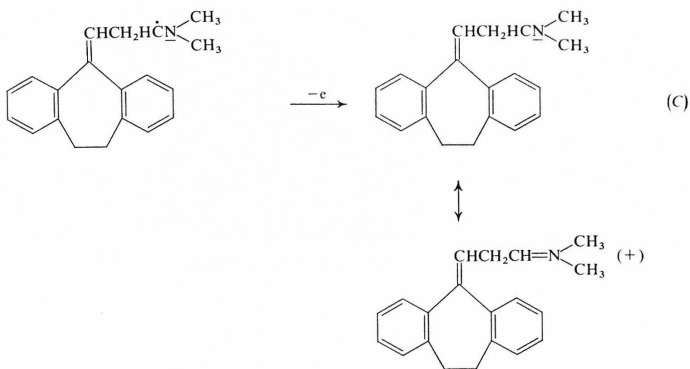
The whole group of compounds has been essentially derived from an aliphatic amine; one can find in the literature different ideas as regards the oxidation mechanism in this group of organic compounds[7-12]. Several reaction pathways have been suggested for a variety of different reactions.

Oxidation of tertiary amines was initiated by a detailed investigation of a model system, tri-n-propylamine at a platinum anode in acetonitrile[13]. Reactions of other amines and behaviour in other solvents were compared with the model system. Stable cation radicals and dications have been observed from anodic oxidation of aromatic amines and have been studied by electrochemical and spectral techniques[14].

Basing upon the evidence of a 2-electron process (coulometric determination of n), and upon the evidence of an E.C.E. electrode process ($I_L/\omega^{1/2}C$ vs $\omega^{1/2}$ — relationship together with the behaviour in the cyclic voltammograms), and in spite of the lack of data as regards the reaction product isolation, our suggested mechanism for anodic oxidation of I is described by equations (A), (B) and (C).

After the first electron loss (A), a rapid follow-up chemical reaction follows (B), resulting in a neutral cation, which undergoes only a further oxidation in the next step (C), but is not able to disproportionate[13]. The chemical follow-up reaction is rapid and E_1 and E_2 are near; (only one transition time is observable[15]).

The stability of the cation radical under the given conditions is insufficient to allow its observation by EPR spectroscopy.

The electrochemical behaviour of a variety of types of compounds containing the carbon–sulfur bond has been investigated[16]. A lot of work is present in the field of heterocyclic sulfur compounds[17–22]. One can find in literature cases where heterocyclic sulfur compounds showed irreversible oxidation steps, with no indication of appreciable life-time of any radical[23]. The present case of II could only be compared with the anodic oxidation of phenothiazine[24] with detectable radical intermediates if one considers a conjugation of the sulfur atom with the aromatic system through an exocyclic π-bond.

With our studied sulfur-containing compounds, II showed a further one-electron step which could be described in the following way if one considers a conjugation with the sulfur atom *via* an exocyclic π-bond. As yet, no experimental proof of this mechanism has been obtained (reaction D).
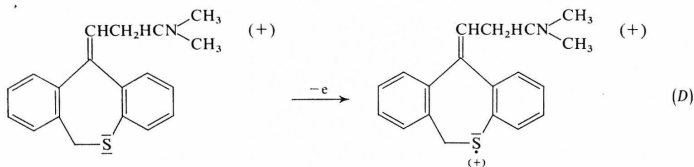
II, containing two sulfur atoms, will follow the same E.C.C. pathway as that suggested for I, and will further lose two electrons (reaction (E)).

Studies of the voltammetric oxidation to dications have been reported recently[25], and the last cation radical of III will have the possibility of forming 6 tautomers.

The stability of the cation radicals of both II and III were insufficient to allow their observation by EPR spectroscopy. One can find in literature that the life-times of anodically generated cation radicals from aromatic sulfur containing compounds appear to be even shorter than those of the corresponding amines[26].
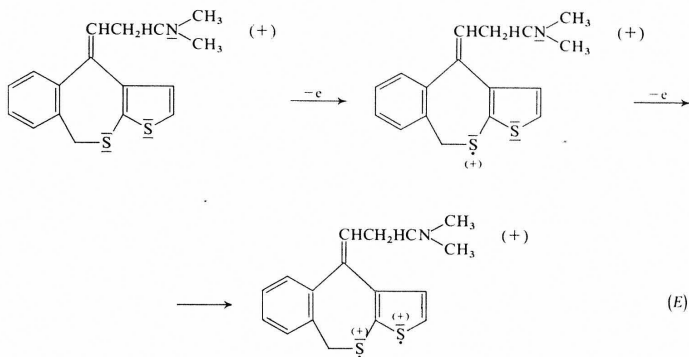
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