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SHORT COMMUNICATION

PRELIMINARY VOLTAMMETRIC DATA FOR THE OXIDATION OF 4-METHYLAMINOPHENETHYLAMINE DERIVATIVES IN BUFFER AND IN APROTIC SOLVENTS

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SUMMARY

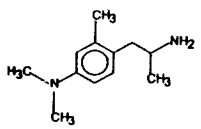
The electrochemistry of a series of monoamine oxidase-inhibitory 4-*N*-methyl and *N,N*-dimethylaminophenethylamines was studied using cyclic voltammetry. Electron transfer was irreversible both in aqueous buffer (pH = 7.4) and in aprotic solvents. The peak potentials in buffer solution lie between 0.59 and 0.63 V, and increase only slightly upon addition of up to 20% (v/v) acetonitrile. These potentials are low enough for these phenethylamine derivatives to be detected electrochemically under standard conditions used for HPLC analysis of catecholamines, serotonin, and their metabolites.

RESUMEN

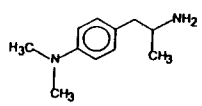
Se estudió la electroquímica de una serie de 4-*N*-metil y *N,N*-dimetilaminofeniletilaminas inhibidoras de monoaminooxidasas usando voltametría cíclica. La transferencia de electrones fue irreversible tanto en solución acuosa tamponada (pH = 7,4) como en solventes apróticos. Los potenciales de pico en solución acuosa se encuentran entre 0,59 y 0,63 V y aumentan muy poco al agregar hasta 20% (v/v) de acetoniitrilo. Tales potenciales son lo suficientemente bajos como para que estos derivados de feniletilamina sean detectables electroquímicamente bajo condiciones estándar empleadas para el análisis por CLAE de catecolaminas, serotonina y sus metabolitos.

INTRODUCTION

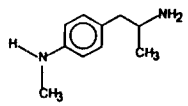
Over the last fifteen years many phenylalkylamine derivatives bearing amino groups on the aromatic ring have been evaluated as selective, reversible inhibitors of the enzyme monoamine oxidase A (MAO-A) for the treatment of depression[1-3]. Of these, amiflamine (**1**) [(+)-1-(4-dimethylamino-2-methylphenyl)-2-aminopropane] was developed to a stage in which it was shown that, administered to depressed patients, it led to clinical improvement[4-7] without causing the side effect ("cheese effect") most commonly associated with the use of non-selective MAO inhibitors[8].



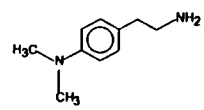
1. Amiflamine



2. DMAA



3. MAA



4. DMAPEA

A recent reassessment of the MAO inhibitory effects of some of these compounds led to the serendipitous finding that 4-alkylaminophenethylamines, following HPLC separation, can be detected electrochemically at a potential of 0.85 V [9]. Such a property in experimental or clinically useful drugs could be of great value for analytical purposes, e.g. in pharmacokinetic studies or in monitoring plasma levels. Moreover, the parent compound 4-dimethylaminophenethylamine proved to be a good substrate for MAO-B [9] which, together with the possibility of following its concentration by HPLC/ED, could presumably lead to the development of a simple and inexpensive assay for MAO-B inhibitors. We felt therefore that further study of the electrochemistry of 4-alkylaminophenethylamines was warranted. In this paper we report some electrochemical properties of a series of phenethylamines with N-methyl or N,N-dimethylamino groups at position 4 of the benzene ring, in aqueous solution and in polar aprotic organic solvents, using cyclic voltammetry.

RESULTS AND DISCUSSION

Fig. 1 depicts the cyclic voltammogram of DMAA in buffer solution. The voltammogram shows that this compound is oxidized in a single irreversible wave (the peak potential separation ΔE is 0.10 V and the peak current ratio ip_a/ip_c is different from unity) while $ip_a/v^{1/2}$ is constant, indicating that the oxidation process is diffusion-controlled. Similar behavior is seen for the other substances.

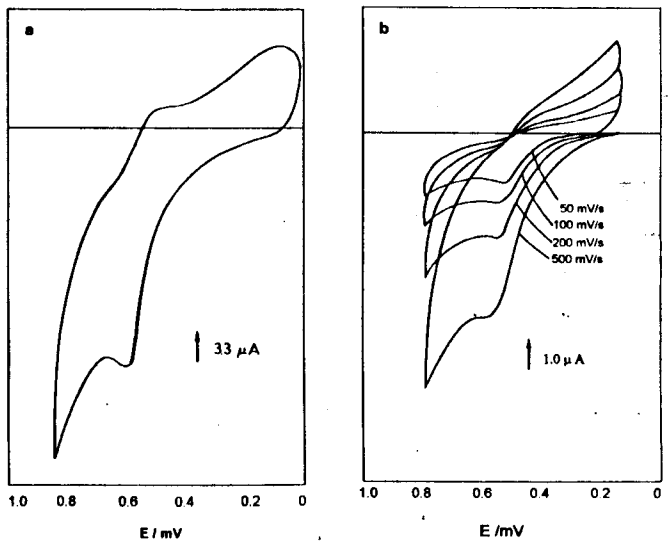


FIGURE 1. (a) Cyclic voltammogram of DMAA in buffer (pH=7.4), sweep rate = 0.20 V/s. (b) Cyclic voltammogram of DMAA in buffer (pH=7.4), at different sweep rates.

Table I lists values for the anodic and cathodic voltammetric peaks and the anodic and cathodic currents for all compounds. Increasing the sweep rate displaces the anodic peak towards more positive potentials with no cathodic response, showing that the oxidation process is irreversible. The ease of oxidation of the compounds appears to decrease in the order amiflamine > DMAA = DMAPEA > MAA, from 0.59 to 0.63 V, but the differences may not be significant.

TABLE I. Cyclic voltammetric parameters of 10^{-3} M 4-aminophenethylamine derivatives in phosphate buffer (pH = 7.4), sweep rate = 0.20 V/s.

Compound	E_{pa}/V	E_{pc}/V	ΔE/V	ip_a/mA	ip_c/mA	ip_a/ip_c
DMAA	0.61	0.51	0.10	6.60	1.09	6.25
DMAPEA	0.61	0.50	0.11	12.98	0.85	15.27
MAA	0.63	0.45	0.18	9.15	0.74	12.36
amiflamine	0.59	0.49	0.10	8.57	0.97	8.83

The HPLC conditions used to analyze neurotransmitters and their metabolites which led to the unexpected electrochemical detection of 4-aminophenylalkylamines involved mobile phases consisting of buffer solutions containing variable amounts of acetonitrile (ACN, up to 4.5% v/v) and tetrahydrofuran (THF, up to 5.0% v/v), with the least polar mobile phase, which was used for amiflamine, containing 4.0% ACN and 5.0 % THF [9]. In order to assess the effect of an organic modifier on the peak potentials, the anodic oxidation of DMAA was studied in the presence of 10 and 20% (v/v) ACN (Table II), which led to increases in E_{pa} from 0.61 to 0.65 and 0.70 V, respectively. The peak intensity also increased with increasing ACN concentrations, in line with the greater intensities observed in DMSO and DMF (Tables III and IV).

TABLE II. Cyclic voltammetric parameters of 10^{-3}M 4-dimethylamino-α-methylphenethylamine in phosphate buffer (pH = 7.4) with added acetonitrile, sweep rate = 0.20 V/s.

Acetonitrile concentration	E_{pa}/V	E_{pc}/V	ΔE/V	ip_a/mA	ip_c/mA	ip_a/ip_c
0% (v/v)	0.61	0.51	0.10	6.60	1.09	6.25
10% (v/v)	0.65			8.84		
20% (v/v)	0.70			13.09		

Cyclic voltammograms of DMAA in DMF and amiflamine in DMSO are given in Figs. 2 and 3, respectively. With the exception of amiflamine, no cathodic peak could be observed, suggesting that

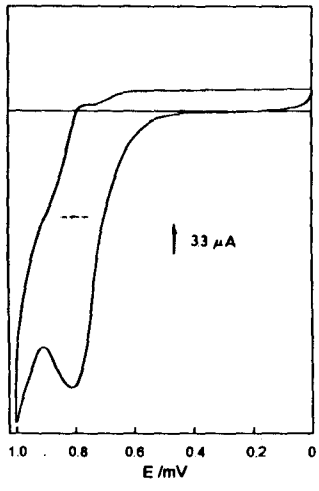


FIGURE 2. Cyclic voltammogram of DMAA in DMF, sweep rate=0.20 V/s.

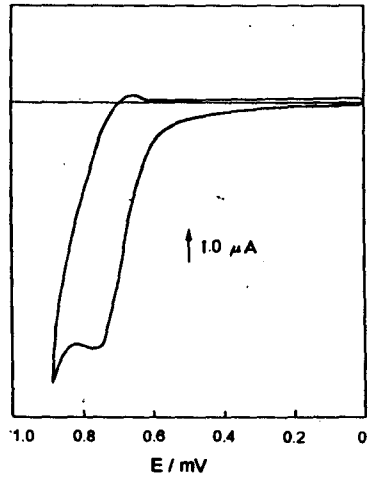


FIGURE 3. Cyclic voltammogram of amiflamine in DMSO, sweep rate=0.20 V/s.

the redox couple is irreversible. Furthermore, the position of the anodic peak was displaced to more positive potentials with increasing sweep rate v, also indicating that the oxidation is irreversible. Table III contains the values for the potential and current peaks of amiflamine, with the anodic potentials of the other compounds for comparison. Table IV shows that the behavior of all four substances in DMF is similar to that found in DMSO.

TABLE III. Cyclic voltammetric parameters of 10^{-3} M 4-aminophenethylamine derivatives in dimethyl sulfoxide, sweep rate = 0.20 V/s.

Compound	E_{pa}/V	E_{pc}/V	ΔE/V	ip_a/mA	ip_c/mA	ip_a/ip_c
DMAA	0.73				32.01	
DMAPEA	0.80				43.00	
MAA	0.77				23.45	
Amiflamine	0.76	0.72	0.04	81.39	0.14	581.36

TABLE IV. Cyclic voltammetric parameters of 10^{-3}M 4-aminophenethylamine derivatives in dimethylformamide, sweep rate = 0.20 V/s.

Compound	E_{pa}/V	ip_a/mA
DMAA	0.80	23.58
DMAPEA	0.86	40.49
MAA	0.88	82.28
Amiflamine	0.83	35.03

The voltammetric analysis of the oxidation step for all 4-aminophenethylamine derivatives in both aprotic solvents and in buffer indicated that electron transfer is irreversible. The compounds are presumably oxidized in a single step to give the corresponding benzylium radical cation, as has been shown for substituted anilines[10] and methoxylated amphetamine derivatives[11]. It has been shown[11] that the oxidation potentials of arylakylamines fall considerably when the benzene ring bears two methoxy groups, and that in the 4-X-2,5-dimethoxy series E_{pa} is correlated with σ^+ parameter of substituent X. This phenomenon is presumably due to an increase in the HOMO energy related to the presence of electron-donating substituents on the aromatic ring. Considering that amino and alkylamino groups are very good electron donors, the observed electrochemical detection of amiflamine and analogues at low anodic potentials is not surprising. The hypothesis that the side chain amino group may be oxidized to a radical cation can be rejected on the basis of the great sensitivity of the peak potentials to changes in the electron donor ability of ring substituents[10,11] and their insensitivity to methyl substitution in the side chain.

The anodic peaks of the 4-aminophenethylamines in solutions with compositions resembling those used for the HPLC analysis of catecholamines, serotonin and their metabolites lie in the 0.60-0.70 V range. As the neurotransmitters and their products of *O*-methylation and oxidative deamination are generally detected at 0.85 V, this means that the concentrations of drugs such as amiflamine, bearing an arylamine functionality, may be monitored by HPLC/ED simultaneously with the endogenous compounds whose concentrations they are expected to alter[9].

While studying the influence of 4DMAPEA on biogenic amine and metabolite concentrations[9], a reproducible peak was seen which eluted earlier than the drug, with a retention time resembling those of the MAO and COMT products 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). In view of the insensitivity of the anodic peak potentials to changes in the aliphatic side chain, it now seems reasonable to assign the unexplained signal to the hypothetical 4DMAPEA metabolite 4-dimethylaminophenylacetic acid. Moreover, it may be expected that in general not only drugs bearing the arylamine functionality, but also drug metabolites in which this structural feature remains intact, will be quantifiable electrochemically in the same low potential range as biogenic monoamines and their metabolites.

EXPERIMENTAL

Reagents

All chemicals used were of analytical grade unless stated otherwise. The 4-aminophenethylamine derivatives used in this work were 1-(4-dimethylamino-2-methylphenyl)-2-aminopropane (amiflamine, **1**), 1-(4-dimethylaminophenyl)-2-aminopropane (**2**, DMAA), 1-(4-methylaminophenyl)-2-aminopropane (**3**, MAA), and 1-(4-dimethylaminophenyl)-2-aminoethane (**4**, DMPEA), all as the acid tartrate salts, and were either obtained from Astra A.B. (amiflamine), or synthesized following published sequences[1,3]. Briefly, 4-dimethylaminobenzaldehyde was condensed with nitroethane or nitromethane, and the corresponding β-nitrostyrenes obtained were reduced for several days with $LiAlH_4$, using dry THF as solvent. 4-Methylamino-α-methylphenethylamine (MAA, **3**) was prepared by an indirect route according to Florvall *et al.* [5].

Apparatus

A three electrode cell was used, with a platinum disk as the working electrode. The counter-electrode was a platinum wire separated from the rest of the cell by a glass frit. All potentials are reported with reference to a saturated calomel electrode. Phosphate buffer, pH = 7.4 (NaH_2PO_4/Na_2HPO_4), dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were used as solvents, with tetraethylammonium perchlorate (TEAP) as supporting electrolyte. The aprotic solvents

contained less than 0.04% water, as determined by Karl Fischer titration. All electroanalytical experiments were carried out in the usual way, varying the sweep rate between 0.050 and 0.50 V/s on a Bank-Werking pos 73 instrument with a Linseis LX 17100 X-Y recorder.

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