Electrochemical study of some 2,5-dimethoxyamphetamine derivatives

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ABSTRACT

A set of 2,5-dimethoxyamphetamines differing in their substitution at C4 was studied by differential pulse voltammetry and linear scan cyclic voltammetry in aqueous media. These experiments showed a single oxydation peak for each of the compounds studied. This peak is attributed to oxidation of the aromatic ring with formation of a radical cation stabilized by the methoxy group bonded to the benzene ring.

RESUME

Un ensemble de cinq 2,5-dimethoxyamphetamines qui differaient au substitution du C4 été etudiees par moyen de la voltamétrie de pouls differentiel et de la voltamétrie cyclique au milieu aqeux. Cettes expériences on montré, pour chacun de composés éstudiés un seul pic d'oxydation d'anneau aromatique avec la formation d'un radical cation stabilisé par le groupe méthoxy adossé au anneau du benzene.

INTRODUCTION

The psychomotor stimulant action of 2-amino-1-phenylpropane is well known since the late 1920's. This drug was rapidly introduced into the clinic and is now designated by the generic name amphetamine[1]. Many ring substituted amphetamine derivatives are known to be hallucinogenic and the study of the structure-activity relationships in these one-ring psychotomimetics has centered on the substitution pattern of the aromatic ring[2]. A simple generalization based on the rather limited spread of functionalities examined in this group of compounds is that 2,5-dimethoxy substitution is associated with greater potency and that C4

substituent increases hallucinogenic activity some way[3].

A number of attemps have been made to explain the influence of the C4 substituent on the pharmacology of these drugs. It was suggested quite early that the introduction at this position of an appropiate atom or group able to withstand enzyme action might retard the metabolism of a substance[2]. This could be expected to prolong a drug's action, but would not necessarily increase potency. A positive correlation was shown to exist between the lipophilicity of the C4 substituent in a number of 2,5-DMA analogs and the magnitude of a compound's effect[3,4]. Nevertheless, studies on a more extensive series of compounds and in particular the observations that the analogue bearing the highly hydrophilic nitro group para-substituted regard to the amine chain is active of low doses in a rat behavioral assay of psychotomimetics potencies[5] and is an unusually potent hallucinogen in humans[6], showed that the lipophilic nature of the C-4 substituent is relatively unimportant. It has therefore been postulated on the basis of quantum-chemical calculations that the overall electronic structure of the molecule rather than the lipophilic contribution of a particular substituent is a crucial determinat of pharmacologic activity[6].

There appears to be good agreement between activation of 5-HT$_2$ (or S$_2$) serotonin receptors and hallucinogenic acyivity in humans, and several 4-substitued 2,5-dimethoxyamphetamines show high affinity for these receptors[7]. Although the electronic structure, largely determined by the substitution pattern, may well be of crucial importance for the recognition of a drug molecule, it has been suggested that the role of the C-4 substituent might include direct interaction with the receptor[3,8]. A more elaborate proposal is that the receptor recognizes a non-bonding electron pair on the C-5 methoxyl group and that any C-4 substituent larger than hidrogen forces this group into a more favorable conformation for drug-receptor binding[9].

Due to the foregoing discussion we felt that it would be useful to identify a physical-chemical parameter able to quantify the influence of the C-4 substituent on the benzene ring of 2,5-dimethoxyamphetamines. In this regard we considered electrochemical techniques as a potentially fruitful approach to the problem, as the electrochemistry of this kind of compounds has barely been touched. To the best of our knowledge, there is only one paper on this subject[10], concerning the polarographic reduction of 2,5-dimethoxy-4nitroamphetamine (DON). Nothing has been published regarding the oxidative behavior of these substances. In this contribution we

have studied the electrochemistry of 2,5-dimethoxyamphetamine (2,5 - DMA) and four of its 4-substitued derivates (Figure 1), with a view to analizing the influence of the C-4 substituent on their anodic reactivity.

EXPERIMENTAL

Chemicals:

Amphetamine sulfate from Sigma. The substitued amphetamine derivates ware synthesized following published procedures, altough in one case a previously undescribed salt was prepared to make purification easier.

Melting points are uncorrected[1]. H n m.r spectra were recorded at 60 MHz in D_2O (standard TMSPA-d sodium salt).

(±)-1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-DMA) hydrochloride.

m.p. 106 - 107 °C (from i-PrOH-et$_2$O) ; δ_H 1.33 (3H , d, J 6.5 Hz, Me) 2.90 (2H, d, J 6.5 Hz, CH_2), 3.68 (1H , m , CH), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 7.0 (3H, s, ArH).

(±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) hydrochloride.

m.p. 189 - 190 °C (from i-PrOH) ; δ_H 1.33 (3H, d, J 6.5 Hz, Me), 2.93 (2H, d, J 6.5 Hz, CH_2), 3.63 (1H, m, CH), 3.83 (6H, s, OMe), 6.87 (1H, s, ArH), 6.93 (1H,s , ArH).

(±)-1-(2,4,5-trimethoxyphenyl)-2-aminopropane (TMA-2) hydrocloride.

m.p. 190 - 192 °C (from i-PrOH) ; δ_H 1.30 (3H, d, J 6.5 Hz, Me), 2.86 (2H, d, J 6.5Hz , CH_2), 3.7 (1H, m, CH), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 3.89 (3H, s, OCH), 6.73 (1H, s, ArH), 6.86 (1H, s, ArH).

(±)-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB) hydrochloride.

m.p. 201 - 202 °C (from i-PrOH-et$_2$O) ; δ_H 1.33 (3H, d, J 6.5 Hz, Me), 2.94 (2H, d, J 6.5Hz, CH_2), 3.65 (1H, m, CH), 3.83 (3H, s, Me), 3.88 (3H, s, OMe), 6.95 (1H, s, ArH), 7.23 (1H, s, ArH).

(±)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (DON) nitrate.

m.p. 154 - 155.5 °C (from i-PrOH-et$_2$O); δ_H 1.32 (3H, d , J 6.5 Hz, Me), 3.00 (2H, d, J 6.5 Hz, CH_2), 3.7 (1H, m, CH), 3.88 (3H, s, OMe), 3.95 (3H, s , OMe), 7.17 (1H, s, ArH), 7.55 (1H, s, ArH) (Found : C , 43.39; H , 5.71 ; N 13.54 ; $C_{11}H_{17}N_3O_7$ requires C, 43.56; H, 5.65; N, 13.86).

(±)-1-(2-methoxyphenyl)-2-aminopropane (2-MA) hydrochloride.

m.p. 110 - 112.C (from i-PrOH); δ_H 1.29 (3H, d, J 6.5 Hz, Me), 2.29 (2H, d, J 6.5 Hz, CH$_2$), 3.7 (1H, m, CH), 3.85 (3H, s, OMe), 7.15 (4H, m, ArH).

All other reagents were p.a grade. Electrolyses were carried out in buffered aqueous solutions in 0.02 M phosphoric acid with 0.02 M acetic acid for pHs 1 - 8.5 or 0.02 M Na$_2$CO$_3$ for pHs 8.5 - 12. The pH was adjusted using HCl or NaOH and the ionic strength was raised to 0.3 M with NaNO$_3$. The solid electrodes were routinely cleaned with chromic acid solution.

APPARATUS:

A TACUSSEL CPRA thermostatic cell with three different working electrodes (platinum, glassy carbon and carbon paste) was employed.

A TACUSSEL model EDI rotating electrode assembly was used with platinum and glassy carbon electrodes. These electrodes are interchangeable on the electrode assembly. The diameter of the disk ware 2 mm and 3 mm for platinum and glassy carbon respectively. A METROHM carbon paste electrode with a geometric area of 38.5 mm^2 also was used. A platinum wire and a saturated calomel electrode were used as auxiliary and reference electrodes.

Electrochemical measurements were performed with , and INELECSA assembly equipped with the following elements:

a) a generator - potentiostat type PDC-210 with a built-in compensator for the ohmic drop.

.b) an interface containing 12-bit A/D and D/A converters, connected to a microprocessor with suitable software for fully automated control of the experiments and data acquisition. A Multitech, Apple II Plus-compatible microcomputer was used for data control, acquisition and treatment.

U.V-vis spectra were recorded using a SHIMADZU U.V-160 A Spectrophotometer with 1 cm quartz cells.

Operating conditions:

a) Differential pulse voltammetry: Pulse of 50 mV and 40 ms were applied with a delay of 1000 ms.

b) Cyclic Voltammetry: Sweep rates between 0.05 and 5 v/s were used.

RESULTS AND DISCUSSION

We have found that working in aqueous solution 2,5-DMA and its 4-substituted derivatives can be oxydized at platinum, glassy carbon and carbon paste electrodes (PE, GCE. and CPE. respectively) within a broad pH range, producing an anodic peak which is best resolved using differential pulse voltammetry. Figure 2 shows the voltammograms for one of the compounds with all three electrodes. We carried out most of our work with the GCE due to greater experimental ease and good resolution and sensitivity.

For the sake of comparison, we also examined the electrochemical behavior of unsubstituted amphetamine and 2-methoxhyamphetamine (2-MA) . No oxydation peak was obtained for these compounds , suggesting that the anodic process observed with the other analogs does not involve the NH_2-substituted side chain but rather the 2,5-dimethoxy-substituted benzene ring.

All 2,5-DMA analogs exhibited a single voltammetric peak over the pH range studied, extending from pH 1 to 8.5 or higher. The peak potential Ep vs. pH graphs (Figure 3) show two linear segments for each compound, indicating that in the acid range the electrode process is pH-independent. In the basic range, and depending on the compound studied, Ep decreases linearly with pH, therefore, these compounds are oxydized more easily in more alkaline solutions.

Examination of the peak current (i_p) values indicates that these fall slightly , and the peak broadens, as the pH rises. This may be due to a decrease in the heterogeneous rate constant, affected by proton transfer[11] . In Figure 4 we show the behavior of i.p. as a function of pH for one of the compounds studied by us.

As differential pulse voltammetry might be a convenient analytical technique for the quantification of these compounds, we also examined the concentration dependence of i.p. On the basis of data obtained earlier in this study , we chose to work at pH 4 with 2,5-DMA, TMA-2 and DOM , and at pH 3 with DOB and DON . All these experimentals were carried out with the carbon paste electrode which gave more reproducible results and proved to be more sensitive, e.g. for ten independent runs on the same solution we have obtained a variation coefficient of 2.06 % in the peak current value . Under these conditions we observed a linear relationship between i.p. and drug concentration in a range going fron 5×10^{-6} M to 1×10^{-4} M. Within this range, the Ep values remained constant showing that adsorption phenomena or second

order reactions are not significant. These results point to the usefulness of differential pulse voltammetry in the quantitative analysis of 2,5-DMA derivatives. They also allowed us to study the stability of aqueous solutions of these compounds, which ramained unchanged after 30 days at room temperature under normal laboratory lighting.

Linear sweep cyclic voltammetry experiments showed a single oxydation peak for all five 2,5-DMA derivatives, recording the voltammograms at sweep rates (v) between 50 mV/sec and 5 V/sec. Figure 5 shows the cyclic voltammograms of each of the compounds studied at two different sweep rates. From this study it can be seen that:

a) the i.p. increases linearly with the sweep rate.

b) i.p. /$V^{0.5}$ is virtually constant in the v range observed, and

c) The Ep shifts anodically by about 30 mV for each tenfold increase in v. These results agree with an EC mechanism[12] with a one-electron transfer in the electrochemical step and a subsequent chemical reaction, e.g. the electrochemical formation of a cation radical with a subsequent chemical reaction of this specie. The formation of cation radicals in related compounds such as p-alkylarylethers in non-aqueous media have been reported previously[13-16].

As can be seen in Figure 5 d and 5 e , a return peak seems to develop at high sweep rates, suggesting that under these conditions the chemical reaction is sufficiently incomplete for the presence of some reducible intermediate to be observed in the return sweep. Unfortunately , work with the glassy carbon electrode does not permit clearcut cyclic voltammograms to be obtained at sweep rates in excess of 5 v/sec due to the increase in charge current. It was therefore not possible to find i.p,c/i.p,a ratios which would have allowed the rate of the coupled chemical reaction to be calculated. Nevertheless, the appearance of a return peak supports and EC type mechanism.

One of the main purposes of this work was to evaluate the incidence of the C-4 substituent on the electrochemical behavior of this series of drugs. The experimental evidence shown here clearly indicates that the electron acceptor or donor character of this substituent is directly related to the greater or lesser of oxydation of these compounds. A simple explanation is that electron-donating substituents increase the electron density of the aromatic ring system making it easier to remove an electron, thus producing a cation radical which is stabilized by the methoxyl groups at C-2 and C-5 . This is reflected in voltammetric peaks with lower Ep's in the cases of DOM and TMA-2, which bear a methyl and methoxyl group, respectively, at C-4 .

Conversely, DOB and DON, with the electron-attracting substituents bromine and nitro, present higher Ep values. Here the oxidation of the ring system is presumably more difficult due to decreased relative stability of the resulting cation. Figure 3, where it can be seen that at all pH values the Ep's follow the order TMA-2 < DOM < 2,5-DMA < DOB < DON, illustrates this effects.

In view of the foregoing results, it seems obvious that a direct oxydation of the aromatic ring, influenced by the C-4 substituent, is occurring. Although the postulate of a carbocation forming in an aqueous medium is arguable, it is quite justified in this case due to the well-known stabilizing effect of the methoxyl groups[17] which share the positive charge . The dependence of Ep on pH (Figure 3) requires more detailed interpretation. A slope close to 30 mV/pH and a transition point dependent on the ring substituent is interpreted assuming a kinetic control of the electrochemical oxydation by a first order reaction of the cation radical. The breaks in the curve could arise , from competing mechanisms for reaction of the cation radical in the aqueous media. Certainly at high pH the slopes seem to point to attack of OH on the cation radical in the chemical step.

Finally , to confirm the ralationship between Ep and the effect of the C-4 substituent on the oxydation moiety, we considered σ_p^+ as an extrathermodynamic parameter combining the reductive and resonance effects of substituents on the benzene ring. This factor can be applied to oxydation reactions involving resonance stabilization of a positive charge on an aromatic ring[18]. As can be seen in Figure 6 , there is a linear relationship between the σ_p^+ factors of the C-4 substituents and the Ep's obtained experimentally by differential pulse voltammetry. This behavior is described by the following equations obtained by least square linear regression:

$$Ep \ (mV) = 262.2 \ \sigma_p^+ \ + \ 1001.8 \qquad (1)$$
$$r = 0.996, \ n = 5 \ , \ pH = 7.0, \ t = 25 \ °C$$
$$Ep \ (mV) \ = \ 292.3 \ \sigma_p^+ \ + \ 1042.7 \qquad (2)$$
$$r = 0.990, \ n = 5 \ , \ pH = 3.0 \ , \ t = 25 \ °C$$

These correlations should predict the Ep of any 2,5-DMA derivative which is oxydized by the same general mechanism . Moreover, they provide an experimental parameter (Ep) which quantifies the effect of the C-4 substituent in 2,5-DMA derivatives and may be a useful tool in the development of empirical quantitative structure-activity relationships for this type of drugs.
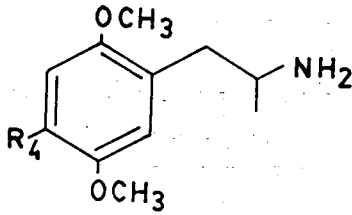
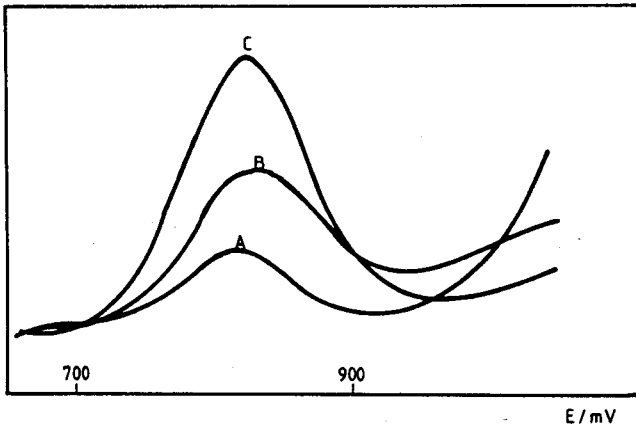Figura 1: Molecular structure of the 2,5-dimethoxyamphetamine derivatives.

Figure 2:Differential pulse voltammograms of 0.1 mM TMA-2 solution, pH 4 in three different working electrodes:

A) Platinum electrode (PE) ip= 0.93 uA

B) Glassy carbon electrode (GCE) ip= 2.54 uA
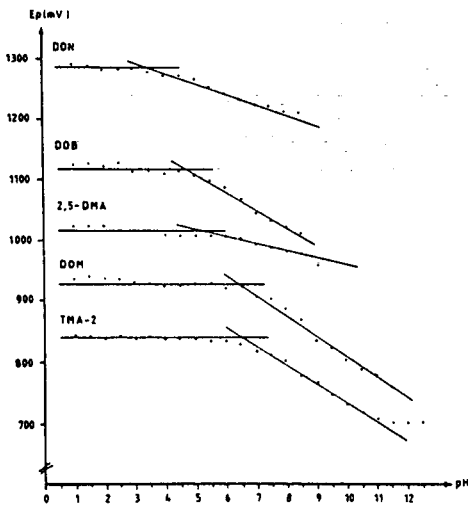
C) Carbon paste electrode (CPE) ip= 8 uA

Figure 3: Variation of the peak potential Ep with pH for the differential pulse voltammetric oxidation of the 2,5-dimethoxyamphetamine derivatives. Concentration 0.1 mM. GCE.
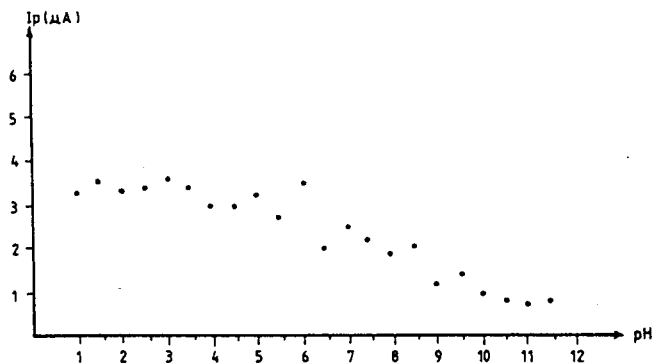

Figura 4: Variation of the peak current ip with pH for the differential pulse voltammetric oxidation of DOM in GCE.
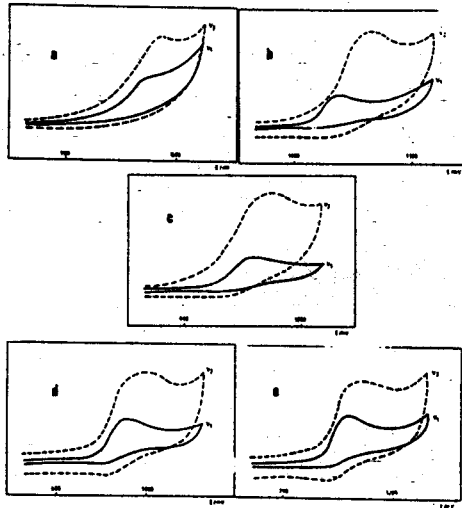
Figure 5: Cyclic voltammograms obtained for : a) DON; b) DOB; c) 2,5-DMA; d) TMA-2 and e) DOM at two different sweep rates v_1 = 0.01 v/seg and v_2 = 1.0 v/seg.
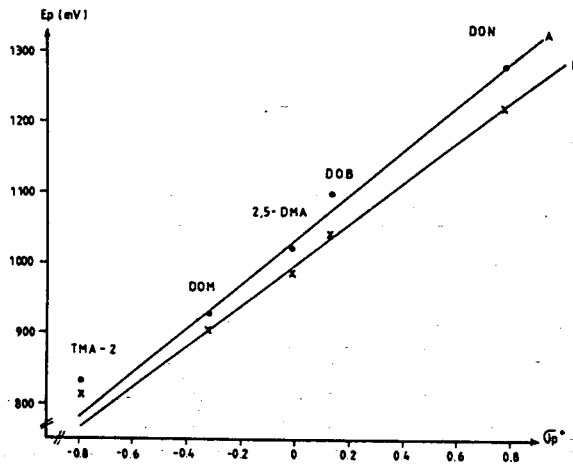

Figure 6: Dependence of the peak potential for the oxidations of 2,5-dimethoxyamphetamines derivatives on the electrophilic substituent constants (σ_p^+).

A) pH= 3, B) pH= 7, 25 °C.

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