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Cyclic Voltammetry with Cyclic Iminium Ions: Implications for Charge Transfer with Biomolecules (Metabolites of Nicotine, Phencyclidine, and Spermine)[1]

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Recently, the theory was advanced that the iminium species plays a widespread role in living systems as a charge transfer agent. Cyclic voltammetry was applied to model compounds, 3,4-dihydro-1,5-dimethyl-2H-pyrrolium perchlorate **2** and 3,4-dihydro-1-methyl-5-phenyl-2H-pyrrolium chloride **3**, in order to provide reference data. Compounds **2** and **3** gave reductions with $E_p = -1.11$ and -0.98 V, respectively, vs SCE (DMF). Reactions were also carried out in water and benzonitrile. Resonance and inductive effects are used to rationalize the data. Iminium ions **5**, **12**, and **18** are intermediary oxidative metabolites of nicotine **6**, the hallucinogenic drug phencyclidine **8**, and spermine **17a**, respectively. Reduction potentials are -1.04, -0.93, and -1.10 V, respectively. It is suggested that electon transfer mediated by iminium moieties may be related to biological activity. Examples are presented of electrochemically reducible iminium compounds which exhibit physiological activity in a variety of areas.

1. INTRODUCTION

Recently the theory was advanced that iminium species play a widespread role in living systems (*1*). Some illustrations are the following: herbicides (diquat), redox enzymes (NAD^+), chlorophyll iminium, vitamins (retinal iminium), carcinogens, and drugs, e.g., cyanines and triphenylmethane dyes. We have provided experimental support for this concept from studies on carcinogens (purine iminium) (*2*) and antibacterial heterocyclic di-*N*-oxides (phenazines and quinoxalines) (*3*). In general, the iminium ion is believed to be generated metabolically *in vivo* (*1*). The principal function is participation in charge transfer (CT) processes: beneficial transformations, interference with normal electron transfer, or genera-

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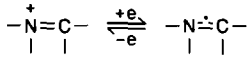
tion of toxic oxy radicals. CT is postulated to occur in many cases via the iminium entity **1** (*1–3*):



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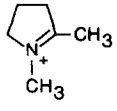
The positive charge enhances the potential for electron abstraction from cellular material. In some cases the ions may exert their effect by electrophilic alkylation, e.g., of DNA (*4, 5*).

Since there is increasing evidence that iminium ions may be widely involved in a variety of redox processes in vivo, we decided to apply cyclic voltammetry in the study of some relatively simple cyclic types in order to provide reference data. In this connection, compound **2** was selected as one of the standards for comparison.



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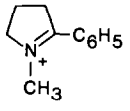
Iminium **3**, which contains phenyl in place of methyl at C-5, presents an opportu-



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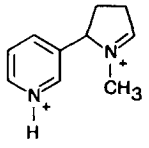
nity for investigating resonance and inductive effects. The dication **4** incorporates



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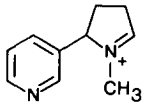
iminium and pyridinium in the same molecule in a nonconjugative relationship. The species **5**, **12**, and **18** are of interest since there is evidence for their formation



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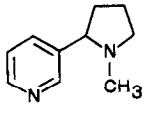
during metabolism of nicotine **6**, phencyclidine **8**, and spermine **17a**, respectively.



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2. EXPERIMENTAL PROCEDURES

Compounds **2** (*6*), **3** (*6*), **4** (*7*), **12** (*8*), and **19** (*9*) were prepared by literature methods.

Cyclic voltammetry was performed on an ECO Model 550 potentiostat with a PARC Model 175 waveform generator. All solutions were degassed for 15 min with prepurified dinitrogen that was passed through an oxygen-scrubbing system. A platinum flag (7 × 9 mm) and a mercury drop (HMDE) were the working electrodes for the cyclic voltammetry done in organic and aqueous solvents, with a platinum wire as the counterelectrode. The reference for all solvents was a Sargent-Welch saturated calomel electrode. The supporting electrolyte was tetraethylammonium perchlorate (G. F. Smith Chemical Co.). The organic solvents, *N*,*N*-dimethylformamide (DMF), acetonitrile and benzonitrile were obtained from Aldrich Chemical Company in the highest available purity. Buffer solutions of pH 1.2 (0.2 M HCl/0.2 M Cl^-), pH 3.5 ($H_3PO_4/H_2PO_4^-$ from 0.2 M H_3PO_4 and 6 M NaOH), and pH 6.1 (0.05 M KHP/0.04 M HCl) were used for the cyclic voltammetry of compounds **4**, **12**, and **19**. Acid solutions, prepared with water as solvent, were added to the test solutions during individual runs to make the desired concentrations.

3. RESULTS AND DISCUSSION

3.1. Model Iminium Ions

Compound **2** yielded a single wave with E_p of −1.11 V (DMF) and −1.45 V (C_6H_5CN) with the absence of any reoxidation peak with the platinum electrode (Table 1). A linear plot passing through the origin of the peak current versus the square root of the sweep rate was observed in DMF. $E_{pp}/2$ sp. ($E_p - E_p/2$) values were constant (140 mV) at all sweep rates. Comparison of the current function, CF (Eq. [2]) with that obtained for benzil, a compound known to undergo reversible one electron reduction (*10*) ($CF/CF_{benzil} = 0.92$) (Table 1) indicated the transfer of one electron. Also E_p was independent of the concentration, and changed by 20 mV upon a 10-fold increase in scan rate, indicating fast electron transfer followed by a rapid chemical reaction. An unexpected result was observed when the

$$CF = \frac{i_p}{V^{1/2} \times C} \qquad [2]$$

platinum electrode was replaced by mercury. Waves were observed in both DMF (Fig. 1) and H_2O at E_p of −1.70 V. Usually only minor changes in reduction potential are observed following switching of these two electrodes (*11*). $E_{pp}/2$ was 50 mV and E_p was independent of concentration in the organic media and changed 20 mV per decade in V change. As in the case of the Pt electrode a one-electron process was indicated.

Single waves were observed for **3** in DMF and C_6H_5CN at E_{p_c}, −0.98 and −1.20 V, respectively, with the platinum electrode (Fig. 2). The ΔE_p values for each

TABLE 1

CYCLIC VOLTAMMETRY OF IMINIUM CATIONS[a]

Iminium cation	Anion	$-E_p$ (V)			CF_{ratio}[j]
		H_2O	DMF	C_6H_5CN	
2	ClO_4^-	1.70(Hg)	1.70(Hg)[b]	—	1.25
			1.11(Pt)	1.45(Pt)	0.92
3	Cl^-	1.18(Hg), 1.34(Hg)	1.04(Hg), 1.16(Hg)[c]	—	—
		—	0.98(Pt)	1.20(Pt)	0.63
4 or 5	ClO_4^-	1.28(Hg, pH 6.1)	1.11(Hg), 1.29(Hg)	—	0.87, 0.98
		1.14(Hg, pH 3.2)[d]	1.06(Pt)[e]	—	—
		1.06(Hg, pH 1.2)	—	—	—
Pyridinium	I^-	—	1.29[f]	—	—
N-Methylpyridinium	ClO_4^-, I^-	—	1.28[g,h]	—	—
12	ClO_4^-	1.46(Hg, pH 6.5)[d]	1.53(Hg)	—	0.43
		1.31(Hg, pH 3.5)	0.93(Hg)[i]	—	—
		1.01(Hg, pH 1.2)	1.03(Pt)	—	0.61
19	$2ClO_4^-$	1.10(Hg, pH 1.2)	1.20(Hg)[b]	—	0.77

[a] 100 mV/s, tetraethylammonium perchlorate (0.1 M), substrate (0.5 mM) (0.25 mM for **12**), vs SCE, irreversible.

[b] No change with added acid, $[HClO_4]$ = 1.3 mM; adsorption on electrode apparently occurs.

[c] Both peaks observed with and without acid, $[HClO_4]$ = 1.3 mM.

[d] Unbuffered solution.

[e] Also a peak at −0.52 V due to acid.

[f] Original value (−0.75 V) adjusted 516 mV cathodic for Hg vs SCE reference [Ref. (*61*)].

[g] Ref. (*23*).

[h] Ref. (*38*).

[i] $[HClO_4]$ = 1.3 mM.

[j] $CF_{ratio} = CF_{compound}/CF_{benzil}$; $CF_{benzil}\ A/(V/s)^{1/2}M$ = 13.77 (0.5 mM, Pt electrode); 0.292 (0.5 mM, Hg electrode); 0.333 (0.25 mM, Hg electrode); all values are in DMF.

media are about 600 mV, and i_{pc}/i_{pa} was about 2. $E_{pp}/2$ values were constant (133 mV) in DMF, with a linear plot of i_p versus the square root of the sweep rate passing through the origin and E_p independent of concentration changing 60 mV per decade change in sweep rate. The current function value of 8.7 indicates a slow electron transfer caused by a rapid chemical reaction. Again when the electrode was switched, the reduction values changed appreciably. In DMF (HMDE) multiple waves similar to Fig. 3 were observed with the most positive at −1.04 V. The second wave was observed at −1.16 V. Both gave linear plots of i_p versus the square root of the sweep rate with intercepts of 0.7 μA. $E_{pp}/2$ values for both peaks were in the range of 50–60 mV, with E_p independent of concentration changing about 20 mV per decade change in sweep rate. Since there is independence of E_p versus concentration for the representative compounds **2** and **3**, concentration dependence for the other compounds in this study was not examined due to the similarity of structures. In H_2O the E_p's were at −1.18 and −1.34 V. All of the values for **3** are more positive than for **2**. The results can be attributed

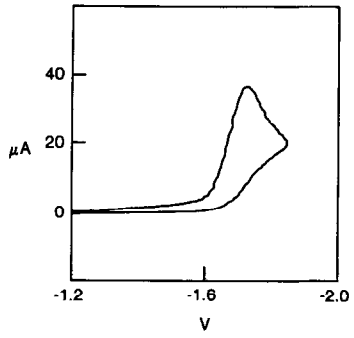


FIG. 1. Cyclic voltammogram of **2** in DMF, Hg electrode, scan rate 100 mV/s.

to inductive and resonance effects of phenyl vs. methyl, in agreement with prior findings when phenyl replaces alkyl (*12a*).

A rather extensive study of the electroreduction of open-chain iminium cations in acetonitrile and benzonitrile was reported in 1970 (*13*). The investigation addressed the aspects of $E_{1/2}$, reduction mechanism, reversibility, and reaction products. The effect of substituents on half-wave potential is shown in Table 2. Although the values from the two studies are quite negative in the nitrile media, our figures for comparable substrates are significantly more positive, e.g., **2** (−1.45 V) vs entry **1** (Table 2) (−1.95 V), and **3** (−1.20 V) vs entry **2** (Table 2) (−1.53 V). Also, substitution of phenyl for methyl produced a greater enhancement (0.42 V) (entry **1** vs entry **2**, Table 2) in the positive direction, in contrast with 0.25 V for **2** vs **3**. Studies have been carried out on the electroreduction of iminium ions derived from protonation of imines (*14a*). The cation is known to be a better electron acceptor than the uncharged precursor. There is evidence that the imine derived from acetone and ammonia is reduced at −1.6 V, pH 9.3 (*15*). The known susceptibility of open chain iminium ions to hydrolysis (*14b*) would be diminished for the cyclic types employed in this study.

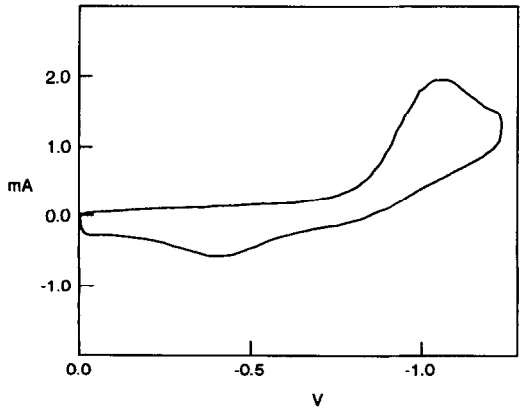


FIG. 2. Cyclic voltammogram of **3** in DMF, Pt electrode scan rate 200 mV/s.

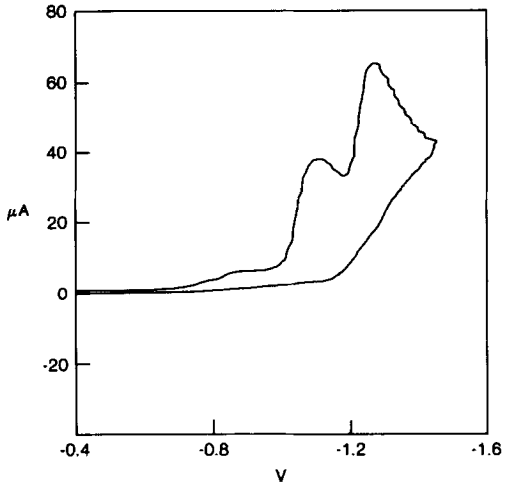


FIG. 3. Cyclic voltammogram of **4** in DMF, Hg electrode, scan rate 100 mV/s.

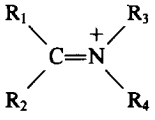
An equilibrium situation can exist between iminium and the conjugate base (Eq. [3]) (*16*): a situation which was observed with the iminium metabolite of phencyclidine (PCP) (vide infra). It was not evident that **2** or **3** dissociates in this fashion since the same reduction potentials were observed with and without added acid (Table 1). Acid did have an effect on the reduction potential of **4** as discussed in a following section.

3.2. Nicotine Metabolite

Compound **4** in DMF exhibits two waves at −1.11 and −1.29 V with the Hg electrode (Fig. 3). It is reasonable to assign the −1.11 V value to iminium and

TABLE 2

LITERATURE $E_{1/2}$ VALUES FOR OPEN-CHAIN IMINIUM CATIONS[a]

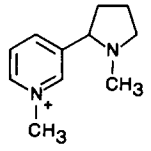


R_1	R_2	R_3	R_4	$-E_{1/2}$ (V)
Me	Me	$CH_2CH_2CH_2CH_2$		1.95
C_6H_5	Me	$CH_2CH_2CH_2CH_2$		1.53
C_6H_5	H	$CH_2CH_2CH_2CH_2$		1.21
C_6H_5	Me	Me	Me	1.49

[a] Ref. (*13*).

−1.29 V to pyridinium (Table 1). The aliphatic cation in **4** is expected to be reduced at a value slightly less than **2** based on the reduction potentials of propionaldehyde (−1.92 to −2.12 V) and methyl ethyl ketone (−2.25 V) (*17a*). The pyridine group should influence the reduction potential to a small extent in the positive direction by analogy to the *N*-benzyl substituent (*18*). The CF values are presented in Table 1. The $E_{pp}/2$ values for peak 1 and peak 2 are 68 and 52 mV, respectively. The E_p's for both peaks underwent about 40 mV change with a 10-fold change in sweep rate. Studies on solutions of **4** in water with the Hg electrode showed a variation with pH (Table 1). A pH 1.2 buffer solution incorporates two nonconjugated cationic entities each of which is capable of being reduced electrochemically. It is reasonable to assign the value of −1.06 V to both contributing ionic moieties at this pH. A solution of **4** alone, pH 3.2, gave a value of −1.14 V. Two possible sources for the acidity are pyridinium dissociation and enamine-iminium equilibrium (vide infra). At pH 6.1 a value of −1.28 V was observed. This potential arises solely from the iminium entity, since at this pH the pyridine ring is unprotonated while the five-membered ring in **5** remains intact. Supporting structural evidence was provided by the 400-MHz ^{1}H NMR spectrum of a 0.5 mM solution of **4** in D_2O (pD_c 5.7), which showed less than 5% contamination after 140 min at 22°C. More concentrated solutions were unstable at this pH indicating that the enamine–iminium equilibrium (Eq. [3]) may be operating as evidenced by the dimerization of **4** upon standing (*7*). By analogy, it is known that the reduction potential of purine bases is pH dependent, becoming more positive with decrease in pH (*19*).

Species **5** is of particular interest in relation to biological ramifications. There is good evidence (*7, 20*) that oxidative metabolism of nicotine **6** proceeds via **5**, including isolation of the corresponding α-cyano adduct from a liver microsomal incubation mixture containing nicotine, via trapping with the nucleophilic cyanide ion (*21*). Recently the *N*-methyl salt **7** was identified as a metabolite of nicotine



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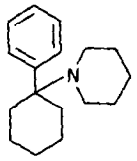
from liver, lung, spleen, and brain homogenates (*22*). The *N*-methylpyridinium ion is observed to undergo a one electron reduction (E_p = −1.28 V) in solution (*23*). In the context of the iminium thesis as applied to living systems, it is conceivable that some of the observed physiological properties of nicotine are a result of CT by the iminium metabolite **4**, the *N*-methyl analog or the free base **5**.

3.3. Phencyclidine Metabolite

The recent and dramatic increase in the abuse of phencyclidine [PCP, 1-(1-phenylcyclohexyl)piperidine] **8** has led to concern over long-term behavioral alter-



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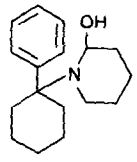
ations that may be associated with its extended use (*24*). Attempts to explain prolonged neurotoxic effects have prompted biodisposition and metabolism studies which have led to the identification of several polar metabolites in mammalian species (*25–29*). The cytochrome *P*-450 mediated metabolism of PCP appears to entail oxidation of the α-carbon in the piperidine ring. The resulting carbinolamine **9** could exist in equilibrium with the isomeric ring-opened aminoaldehyde **10a**.



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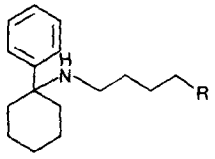

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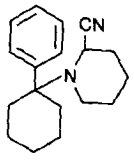
a) R=CHO
b) R=CH_2OH
c) R=CO_2H

The reduced (alcohol) **10b** and oxidized (acid) **10c** products of the aldehyde have been identified from *in vivo* investigations (*30a*). Other experiments have led to the isolation and characterization of the α-cyanoamine **11** which most likely is



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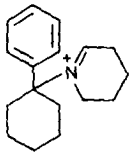
formed by cyanide trapping of the intermediate iminium species **12** (*24, 30a, 31*)



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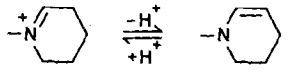
derived either directly from **8** or **9**. As part of the effort to elucidate further the biochemical characteristics of the iminium ion, studies were carried out on the consequences of covalent binding of PCP with specific biomolecules (*8*).

Discussion of results should be prefaced by a treatment of the behavior of iminium species **12** in aqueous solution. An equilibrium situation can exist between **12** and the conjugate enamine base **13** (Eq. [3]) (*16*):



[3]

12 **13**

Compound **12** appears to be stable below pH 2; at higher pH values it tends to decompose to a variety of products, similar to other iminium-enamines (*16*), including such metabolites derived from MPTP (*32*) and nicotine (*7*). The behavior of **12** as a proton acid (Eq. [3]) was evident from electroreduction studies involving an Hg electrode in which the pH was varied in aqueous and organic systems (Table 1). Thus, with no added acid (pH 6.5), E_p of -1.46 V was observed with no indication of a reoxidation peak. At pH 3.5 the value changed to -1.31 V and at pH 1 to -1.01 V (with adsorption characterized by an oxidation peak at -1.01 V). Similarly, in DMF with no added acid, the value was -1.53 V, with $E_{pp}/2$ of about 60 mV. A linear plot is obtained for i_p versus the square root of the sweep rate passing through the origin. E_p changed about 20 mV per 10-fold increase in sweep rate. Addition of $HClO_4$ increased E_p to -0.93 V. One electron reduction of **12** generates the carbon centered radical intermediate **15**. One electron oxidation of enamine **13** would be expected to form the carbon-centered iminium radical **16**. These two intermediates might also play important biological roles.

13 **14** **15** **16**

An intriguing result similar to that from **2** and **3** was observed when the mercury electrode was replaced by platinum. A quasireversible wave similar to Fig. 2 was observed with E_p -1.03 V (DMF), ΔE_p of 725 mV, ipc/ipa of about 1 and $E_{pp}/2$ of 240 mV. E_p became 105 mV more negative as the sweep rate underwent a 10-fold increase. A plot of i_p versus the square root of the sweep rate was linear with an intercept of zero.

Apparently, the mechanism of reduction is complex. However, the magnitude of E_p suggests that **12** or a closely related entity is undergoing reduction. The electrode surface may favor the dipolar iminium resonance form **14** or **13**.

Next, various factors will be considered which may influence the energetics and course of the electrochemical reactions. One possibility to account for the Hg vs Pt data is the occurrence of different processes at the two electrode surfaces. However, this seems unlikely on the basis of functionality since the only one present, other than the iminium or enamine species, is an aromatic nucleus. The reduction potential for benzene is reported to be very unfavorable, -3.29 to -3.31 V (indirect determination and calculated) (*33*), and the alkyl substituent is ex-

pected to produce a further move in the negative direction (*34*). Steric parameters also may influence the electrochemical behavior of this system. Zuman has discussed the effect of steric factors on half-wave potential (*12b*), which are most noticeable in extreme cases. The conclusion was drawn from prior reports that polarographic reduction potential is not sensitive to steric hindrance (*35*). However, interference with adsorption on the electrode, a factor previously suggested, would increase the energy barrier to addition of the electronic charge. Work with aliphatic halides has demonstrated the importance of the steric crowding element for both the reduction group and the electrode surface. Nevertheless, no simple connection can be discussed involving E_p, solvent, and type of electrode with steric requirements in the present work.

If one assumes that iminium ions may serve catalytically as biological CT agents, it is reasonable to speculate on the possible involvement of such species in neuronal processes. This could entail interference with normal electrical processes, e.g., shunting, blockage, or enhancement of nerve depolarization. In a study of PCP analogues, blocking of potassium ion channels in nerves was observed with those that exhibited behavioral activity (*30b*). Muscarinic receptors and ion channels of nicotinic receptors were similarly affected. The involvement of dopaminergic, cholinergic, and opiate receptors in behavior responses to PCP has been investigated (*30c*). Specificity in site binding also may play a key part. Alternatively, the critical biochemical lesion may arise from interaction of a metabolite with macromolecules (*8, 30, 36, 37*). Related oxidative metabolites have been reported for MPTP, and mechanistic implications discussed (*38*).

3.4. Spermine Metabolite

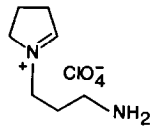
Spermine **17a** and spermidine **17b** are aliphatic polyamines having extensive

$NH_2(CH_2)_3NH(CH_2)_4NHR$

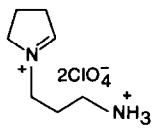
17 a) $R=(CH_2)_3NH_2$
b) $R=H$

distribution in bacteria, viruses, animals and plants. However, their specific role in cells and organisms is not clearly defined. They are known to play regulatory functions in DNA replication, cell division, and protein synthesis (*39, 40*). Enzymatic oxidation of **17** can give rise to metabolites similar to those from PCP **10a–c** (*9*). We will focus on the iminium form **19**. The oxidative products, cytotoxic to mammalian cells at very low concentration (*40*), inhibit the growth of Ehrlich ascites cells and various bacteria, and also inactivate bacterial and plant viruses (*41*).

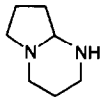
The reduction potentials of **19** are summarized in Table 1. The reductions were performed in the presence of added acid in order to minimize formation of the gem-diamine **20** which can arise from **18**. Thus, in DMF with no added acid, E_p was -1.20 V without any reoxidation peak. $E_{pp}/2$ was 70 mV. A plot of i_p versus the square root of the scan rate was linear with an intercept of 3.5 μA. E_p became 35 mV more negative with a 10-fold increase in sweep rate; addition of $HClO_4$ gave no change in potential, similar to **2** and **3**. At pH 1.2 (aqueous) the value was



18



19



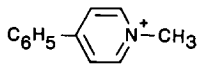
20

−1.10 V with no reoxidation peak. Again, it is conceivable that some of the observed physiological properties of spermine are a result of CT by the iminium metabolite **18**. Alternatively the cytotoxic effects have been attributed to the breakdown product, acrolein, derived from an aminoaldehyde intermediate (*40*).

3.5. Reversibility and Magnitude of Reduction Potential

According to the theory the ultimate form of many drugs operates *in vivo* as a charge transfer catalyst. In our study the reductions observed during voltammetry were irreversible. The reaction pathways in electrochemical processes are known to be dependent on the type of medium and scan rate (*17b, 42*). Many potentially reversible cases are characterized by fast followup chemistry in solution, e.g., dimerization. Immobilization at the active site could prevent such reactions.

Conditions are also known to influence reduction potential (*17b*). It has been pointed out that *in vivo* values may be more positive than *in vitro* due to beneficial factors operating in living systems (*43, 44*). The general consensus is that a reduction potential of about −1 V is too negative for the biological milieu. This view should be questioned since values in this range are reported for NAD^+ (−0.98 V) (*45*) and dioxidine (−1.06 V) (*3*). The antibacterial dioxidine is believed to function by oxy radical formation via CT. The most convincing example is 1-methyl-4-phenylpyridinium ion (cyperquat) **21**. It is reasonable to propose a commonality of mechanism within the class of pyridinium herbicides. Much evidence is consistent with the proposition that paraquat functions in plants and mammals by oxy radical generation via electron transfer (*46*). Cyperquat **21** (−1.09 V, DMF) (*38*) which



21

displays herbicidal activity (*47*), is also an oxidative metabolite of MPTP, a neurotoxin producing the Parkinsonian syndrome. Various investigators have suggested that the toxic manifestations of MPTP occur by oxidative stress brought about by the pyridinium derivative (*48*).

3.6. Source of Electrons in Charge Transfer

Several cellular biopolymers could reasonably serve as donors in electron transfer. The most likely source is protein which commonly participates in binding (*49*). The donor and acceptor need not be in intimate contact since it is well documented that charge transfer can take place via electron hopping (*49–51*).

TABLE 3

REDUCTION POTENTIALS FOR IMINIUM COMPOUNDS HAVING PHYSIOLOGICAL ACTIVITY

Iminium compound	Activity	Reduction potential (V)	Reference
Mepacrine.H^+	Antimalarial	−0.96	*52*
Pyocyanine	Antibiotic	−0.78	*53*
Paraquat	Herbicide	−0.64	*54, 55*
1,1',3,3'-Tetramethyl-2,2'-bibenzimidazolium salt	Herbicide	−0.84	*56, 57*
Diazepam.H^+	CNS	−0.74	*58*

3.7. Other Biologically Active Iminium Ions

Table 3 lists various classes of additional compounds (*52–58*) which incorporate the iminium functionality along with their reduction potentials and physiological responses. A recent review deals with potentially toxic iminium ions from oxidative metabolism of xenobiotics (*59*) and another describes these cations in the alkaloid domain (*60*). The iminium theory appears broadly applicable to agents involved in a wide variety of biological systems (*1–3, 52*): carcinogens, drugs, herbicides, insecticides, redox enzymes, and alkaloids.

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