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An electrochemical interpretation of the mechanism of the chemical decarboxylation of 6-carboxyperhydropyrimidin-4-ones

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Abstract—The present work analyzes the anodic oxidation of the tetrabutylammonium salt of 1-benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxyperhydropyrimidin-4-one, which is a useful starting material in the synthesis of enantiopure α-substituted β-amino acids. It was demonstrated that in CH_2Cl_2 solvent, the anodic oxidation reaction results in fast and complete decarboxylation, followed by proton elimination thereby leading to the same product of chemical (diacetoxyiodobenzene) oxidative decarboxylation. The electrochemical mechanism involves two electron transfer steps, but appears as a monoelectronic process owing to the release of one proton from the key acyliminium carbocation intermediate. The relative stability of this intermediate and the suppression of any solvolysis reaction in CH_2Cl_2 allow for the detection of the acyliminium intermediate by means of cyclic voltammetry experiments. By contrast, in the presence of a nucleophilic solvent such as acetonitrile, the acyliminium intermediate is trapped in a typical Ritter reaction.

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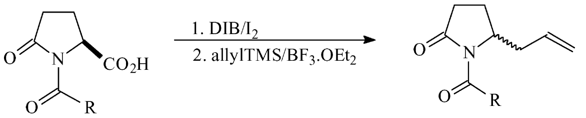
1. Introduction

Diacetoxyiodobenzene (DIB) is now a well recognized reagent with numerous applications in synthetic organic chemistry.[1] Particularly useful is the employment of diacetoxyiodobenzene/iodine as an effective mixture of reagents in the oxidative decarboxylation of carboxylic acids (Eq. 1).[2]

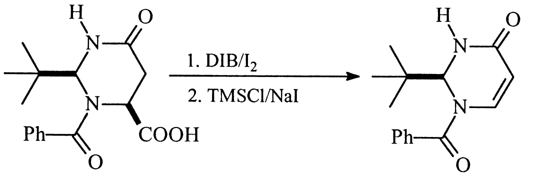
$$\text{R-CO}_2\text{H} \xrightarrow{\text{DIB/I}} \text{R-CO}_2\text{I} \xrightarrow{-\text{CO}_2} \text{R-I} \qquad (1)$$

In this context, Suárez and co-workers have recently demonstrated that DIB-mediated radical decarboxylation–oxidation of α-amino acids can be successfully complemented by nucleophilic trapping of the generated iminium ion (Eq. 2).[3]



(2)

By contrast, when 1-benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxyperhydropyrimidin-4-one, **1**, a useful intermediate for the enantioselective synthesis of α-substituted β-amino acids,[4,5] was treated with the DIB/I_2/TMSCl/NaI reagent mixture, heterocyclic enone **2** was formed in good yield (Eq. 3).[6,7]



1 **2**, 71% (3)

The formation of enone **2** was accounted for in terms of a three-step radical decarboxylation–oxidation–β-elimination sequence, as outlined in Scheme 1.[6]

The proposal advanced in Scheme 1 is based on reasonable mechanistic considerations,[2,3] and it is supported by recent reports concerning the anodic oxidation of benzylic and aliphatic carboxylic acid salts,[8–11] indicating the intervention of both radical and carbocation intermediates (Scheme 2).

The present report describes the results of a voltammetric study of the decarboxylation process for the tetrabutylammonium salt of the carboxylic acid **1**. The main goal in this study was to establish the participation of radical **3** and/or iminium ion **4** as intermediates in the formation of enone **2**.

Keywords: Oxidative decarboxylation; Non-Kolbe electrochemical reaction; Ritter reaction; Pyrimidinone carboxylic acid.

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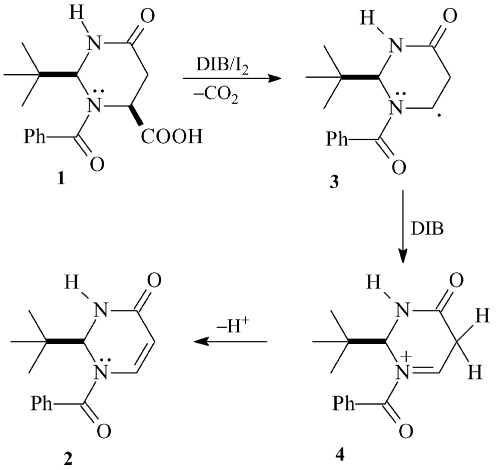
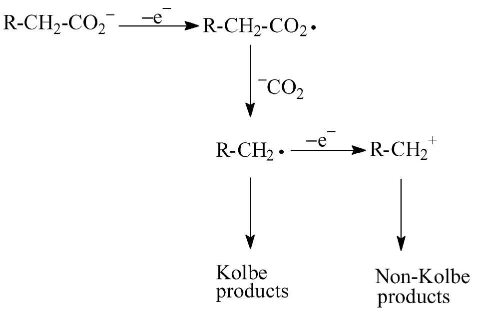


Scheme 1. Proposed mechanism for the DIB-induced decarboxylation of **1**.[6]

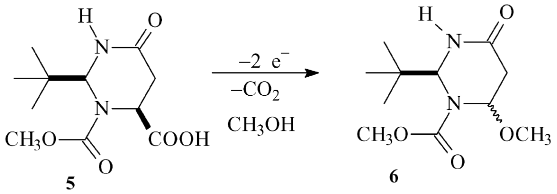


Scheme 2. Electrochemical decarboxylation of carboxylate salts.[8–11]

2. Results and discussion

2.1. Electrochemical oxidation of the tetrabutylammonium salt of carboxylic acid 1 in CH_2Cl_2

Several years ago, Konopelski and co-workers[12] reported the electrolysis of pyrimidinone carboxylic acid **5** in methanol, at very high potential conditions. The non-Kolbe type product **6** obtained, was the result of nucleophilic solvent (methanol) addition to the intermediate[13] (Eq. 4).



(4)

Nevertheless, recent developments in the electrochemical oxidative decarboxylation protocol have demonstrated that carboxylic acid salts decarboxylate under milder electrolytic conditions, relative to those required with the corresponding carboxylic acids. The use of tetrabutylammonium carboxylate salts has proven particularly convenient.[8–11]

Figure 1(a) shows the voltammetric behavior of the oxidative electrochemical process of the tetrabutylammonium carboxylate **7** in CH_2Cl_2, using glassy carbon electrodes. Two chemically irreversible waves are observed, corresponding to the oxidation of the starting salt at E_p=1.07 V/Ag/Ag$^+$ and to the oxidation of the electrolysis product at E_p=1.88 V/Ag/Ag$^+$. That the product of the initial anodic oxidation corresponds to enone **2** was demonstrated by separate electrochemical oxidation of this previously reported[4b,h,6] heterocyclic enone (Fig. 1(b)).

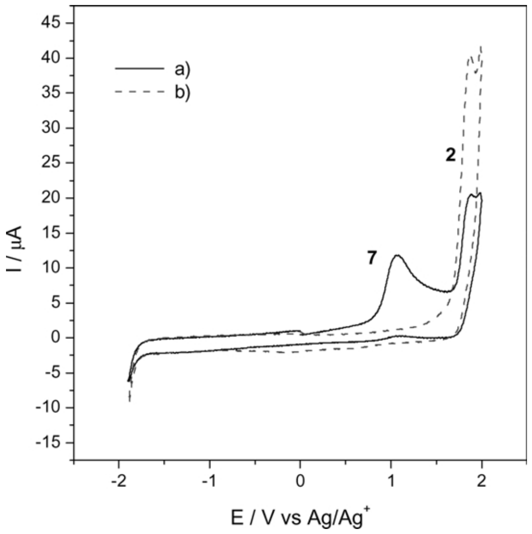
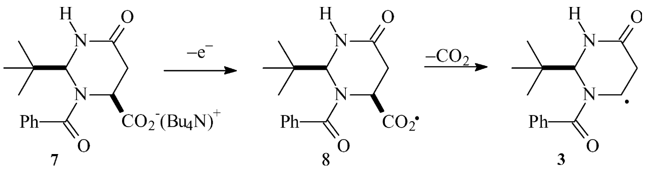


Figure 1. Cyclic voltammetry of (a) 0.82 mM of tetrabutylammonium carboxylate **7** and (b) 1.63 mM of compound **2** in CH_2Cl_2+0.2 M n-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1}.

Based on literature precedent,[8,9a] it can be proposed that one-electron anodic oxidation of carboxylate **7** affords the *O*-radical **8** that immediately loses CO_2[14,15] to give the *C*-radical **3** (Scheme 3).[9b]



Scheme 3. Mechanistic pathway for the one-electron oxidative decarboxylation of carboxylate **7** to give *C*-radical **3**.

Owing to the anticipated lability of the resulting aminoketal **9**, no attempts to trap this intermediate were made.

2.2. Electrochemical oxidation of tetrabutylammonium carboxylate 7 in CH_2Cl_2 and CH_3CN

By comparison with data reported for the oxidation potentials of common radicals,[16,17] the one assigned to the oxidation peak potential of carboxylate **7** is substantially higher (>500 mV), and this observation can be interpreted in terms of a rapid oxidation of radical **3** to delocalized carbocation **4**. Indeed, the reversible wave observed at 0.227 V/Ag/Ag$^+$ in Figure 2(a), which shows the voltammetric behavior of **7** at the more rapid scan rate of 10 V s^{-1}, may correspond to the redox couple $R^{\cdot}/R^+$. Generally, the reactivity of such intermediates is so high that their voltammetric detection is difficult even at higher scan rates. However, the participation of the electron pair of the vicinal nitrogen contributes to the greater stability of

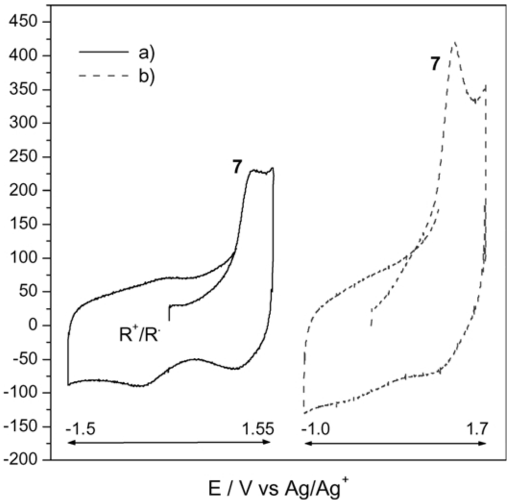
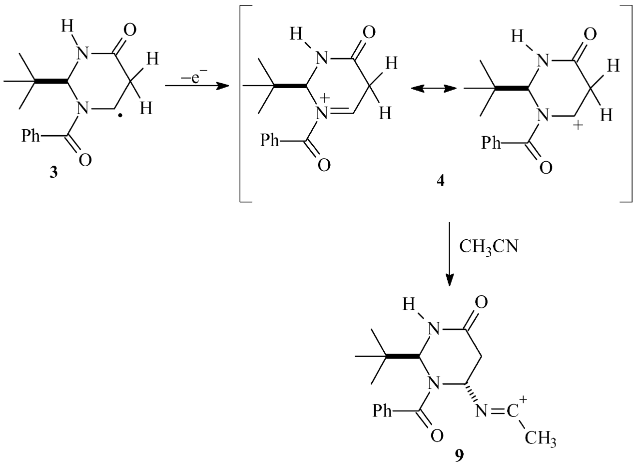


Figure 2. Cyclic voltammetry of carboxylate **7** on glassy carbon electrode (3 mm ϕ) at 10 V s^{-1}. (a) 1.13 mM in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6. (b) 1.69 mM in CH_3CN+0.2 M *n*-Bu_4NPF_6.

acyliminium cation **4**, allowing for its detection. The fact that the addition of acetonitrile causes the disappearance of this reversible signal (Fig. 2(b)), suggests that this acyliminium carbocation is trapped in a Ritter type solvolytic reaction[18] to give intermediate **9** (Scheme 4).



Scheme 4. Radical oxidation and carbocation nucleophilic trapping.

Furthermore, cyclic voltammograms in CH_2Cl_2 conducted in the presence of increasing amounts of acetonitrile (Fig. 3(a)–(c)) show that the concentration of the reaction product decreases with the increase of the concentration of acetonitrile, suggesting that the product of the electrolysis of the carboxylate salt **7** in CH_2Cl_2 is indeed a substrate amenable to nucleophilic trapping.

2.3. Constant potential electrolysis experiment

The previous experiments indicate that in pure CH_2Cl_2 the solvolysis of the cation **4** is precluded. Therefore, the efficient formation of enone **2** in these conditions (Section 2.1) may be interpreted in terms of intermolecular transfer of a proton at C(5) in iminium ion **4** to carboxylate **7** (Scheme 5).

The mechanistic proposal advanced in Scheme 5, and in particular the formation of carboxylic acid **1** during the proton-elimination step (**4**→**2**) are supported by the results of a constant potential electrolysis experiment. The imposed potential of electrolysis was selected to be 150 mV more anodic than the peak potential value measured at 0.1 V s^{-1}. Figure 4(a) shows the voltammogram of **7** before the constant potential electrolysis. Following complete electrolysis (Fig. 4(b)), the signal corresponding to the oxidation of enone **2** is the only one observed. Addition of tetrabutylammonium hydroxide produces the recovery of the oxidation signal of the carboxylate **7** now with half of the initial current intensity (Fig. 4(c)). The value of the total charge consumed in the electrolysis corresponds to an apparent electron number close to one (n_{app}=0.96 e$^-$), which indicates that the mechanism is globally monoelectronic. This is consistent with the global stoichiometry derived from the sequence of reactions proposed here; although the mechanism comprises the transference of two electrons, it appears monoelectronic due to the proton elimination step, which results in the neutralization of half the initial concentration of carboxylate **7**.

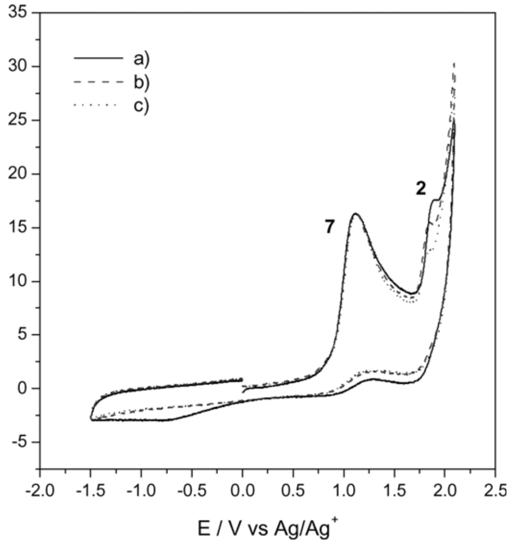
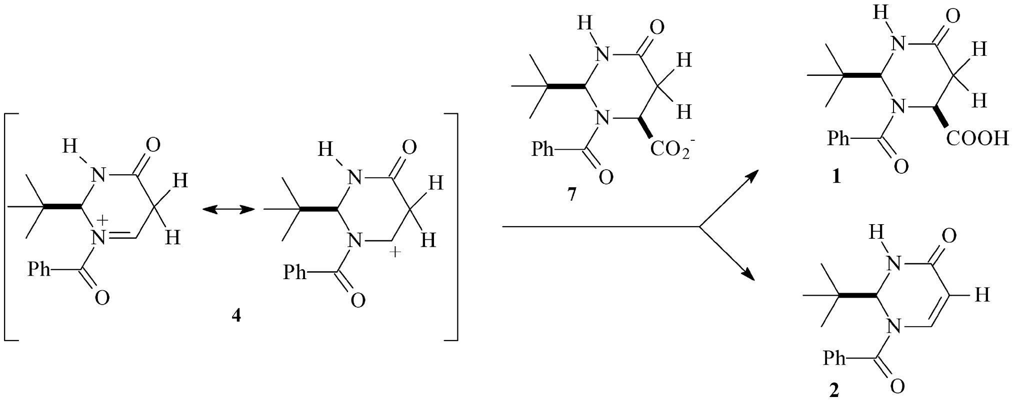


Figure 3. Cyclic voltammetry of 1.13 mM of carboxylate salt **7** in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1} at different concentrations of CH_3CN (a) 0 mM, (b) 1.9 mM, (c) 3.8 mM.

2.4. Electrochemical evidence for intermolecular hydrogen bonding

As it can be noticed in Figure 4(b), following complete electrolysis, the signal corresponding to the enone **2** is slightly shifted toward more anodic potential, taking as reference the corresponding signal obtained before the electrolysis (Fig. 4(a)). Furthermore, the peak potential of the regenerated carboxylate **7** shows the same tendency.

In order to explain both peak displacements, additional experiments were carried out. Considering that after the total electrolysis of carboxylate **7** both the carboxylic acid **1** and enone **2** coexist, the oxidation process of **2** in the presence of the carboxylic acid **1** was conducted. Consistent with the electrolysis experiment, it is observed that the oxidation wave of **2** is displaced toward more anodic



Scheme 5. Mechanistic hypothesis for the in situ formation of enone **2** during anodic oxidation of carboxylate salt **7**.

potentials. This result can be explained in terms of intermolecular association between both products of reaction, through hydrogen bond formation. Consideration of the structures of **1** and **2**, suggests that an interaction could be established between the carbonyl oxygen of ring amide **2** and the hydroxyl group of **1** (see Scheme 6(a)). In this interaction, it is expected that a decrease of the partial negative charge on the carbonyl of **2** results in its more difficult oxidation.

By the same token, the neutralization of the carboxylic acid **1** obtained in the electrolysis experiment (Fig. 4(c)) results in the coexistence of the carboxylate **7** and the enone **2**. Thus, the oxidation process of **7** in the presence of the enone **2** was carried out. The shift of the oxidation signal of the carboxylate **7** toward more anodic potentials (35 mV), can be attributed to hydrogen bond interaction between the NH group of **2** and the negative oxygen of **7**. Accordingly, the negative charge of the carboxylate **7** is stabilized with the NH group of **2** (see Scheme 6(b)), resulting in its more difficult oxidation.

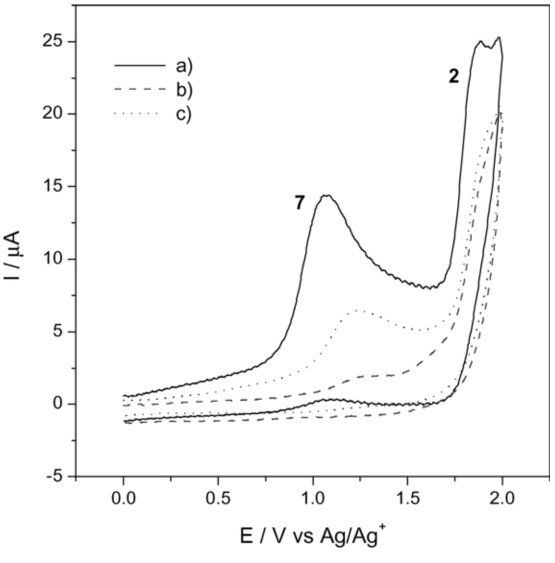


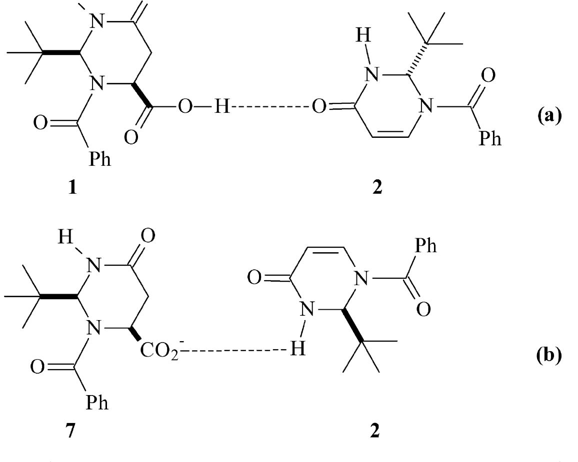
Figure 4. Cyclic voltammetry of 1.0 mM of tetrabutylammonium carboxylate **7** in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1}. (a) Before the electrolysis. (b) After complete electrolysis. (c) After complete electrolysis and following addition of 0.5 mM *n*-Bu_4NOH.

3. Conclusions

The efficient decarboxylation of pyrimidinone carboxylic acid **1** was achieved under mild oxidative electrolytic conditions via the tetrabutylammonium carboxylate **7**, in the non-nucleophilic solvent CH_2Cl_2.

The accumulated evidence supports an initial one-electron loss, followed by rapid decarboxylation, so that carboxylate **7** is converted to radical **3**. A second electron transfer produces the nitrogen-stabilized cationic species **4** that eliminates a β-proton by intermolecular proton transfer to the available carboxylate **7**. Thus, enone **2** is produced in a process that involves two electron-transfer steps that appears, nevertheless, monoelectronic owing to such release of a proton from acyliminium cation **4**.

The suppression of any solvolysis reaction in CH_2Cl_2 solvent allows for the detection of cationic intermediate **4** in the cyclic voltammetry experiments, at 10 V s^{-1}. By contrast, in the presence of a nucleophilic solvent such as



Scheme 6. Intermolecular hydrogen bond associations (a) between **1** and enone **2** and (b) between carboxylate **7** and enone **2**.

acetonitrile, intermediate **4** is trapped in a typical Ritter reaction.

The present report shows the great potential that electrochemical techniques have in the study or verification of organic reaction mechanisms.

4. Experimental

CH_2Cl_2 and CH_3CN (spectrophotometric grade) were used as solvents. Tetrabutylammonium hexafluorophosphate (99%) was the supporting electrolyte. The tetrabutylammonium pyrimidine-carboxylate **7** was prepared by mixing stoichiometric amounts of the corresponding carboxylic acid and tetrabutylammonium hydroxide in anhydrous methanol, which was then removed under reduced pressure. The obtained glassy solid was dried in a vacuum pump for several hours to provide the solid salt. An authentic sample of the expected decarboxylation product, enone **2**, was obtained following our recently reported tandem chemical decarboxylation protocol.[6,7]

The electrochemical apparatus consisted of a potentiostat DEA-332 (Radiometer, Copenhagen) with positive feedback compensation. A conventional three-electrode cell was used to carry out the voltammetric experiments. The work electrode was a 3 mm diameter glassy carbon disk. This electrode was carefully polished with 1 μm alumina powder and ultrasonically rinsed with ethanol before each run. The counter electrode was a platinum screen and the reference electrode was an aqueous saturated Ag/Ag^+ electrode. A salt bridge, containing 0.2 M $n\text{-}Bu_4NPF_6+CH_2Cl_2$, connected the cell with the reference electrode.

4.1. Voltammetric and electrolysis experiments

Cyclic voltammetry experiments were carried out by using a carboxylate solution which was deoxygenated by dry argon bubbling. After this, an argon atmosphere was maintained over the solutions during each experimental run. All electrochemical experiments were performed at room temperature. The electrolysis of the carboxylate **7** (20 mM), was carried out in a 10 mL divided cell. The working electrode was a 5 mm diameter glassy carbon rod. The electrolysis potential was selected to be 150 mV more positive than the peak potential of the carboxylate **7**.

Acknowledgements

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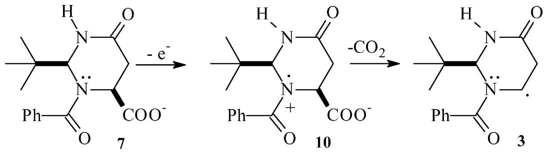

This alternative mechanism may be discarded owing to the fact that the parent amide moiety in enone **2** is more difficult to oxidize than the carboxylate group in substrate **7**, that is approximately 800 mV more anodic. Furthermore, the transfer coefficient (α=0.501) obtained from the variation of the peak potential with the scan rate ($\partial E_P/\partial \log \nu$=58.1 mV/dec) indicates that the electron transfer is not intrinsically slow and it should be followed by a very fast chemical step as the decarboxylation of the acyloxy radical here proposed. Contrasting with this, in pathways involving zwitterionic radicals, the variation of the peak potential with the scan rate ($\partial E_P/\partial \log \nu$) is expected to be smaller than the observed value, which approaches those reported for an electrochemical–chemical mechanism where the chemical step corresponds totally or partially to the rate determining step (Ref. 9a).

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