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Electrochemical behaviour of 9-methylcaffeinium iodide and in situ electrochemical synthesis of hymeniacidin☆

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ABSTRACT

9-Methylcaffeinium iodide, a bio-based salt obtained by reaction of caffeine with methyl iodide, is an imidazolium salt. The electrochemical behaviour of 9-methylcaffeinium iodide was studied by means of cyclic voltammetry, differential pulse voltammetry and electrolysis. Its behaviour revealed to be very similar to that of common imidazolium salts. In fact, its cathodic reduction yielded the corresponding N-heterocyclic carbene, which was evidenced by its reaction products with dioxygen and with sulfur, although in low amounts. In fact, this electrogenerated carbene was very unstable and prone to add water, yielding a ring opening product (hymeniacidin) in high yield. Hymeniacidin is a natural product from the marine sponge *Hymeniacidon* sp. The voltammetric behaviour of isolated hymeniacidin confirmed the in situ formation of this ring opening product, by comparison of the voltammetric peak potentials of starting caffeinium salt and hymeniacidin. This study allowed to determine that hymeniacidin derives from NHC, and not by hydrolysis of the caffeinium salt.

1. Introduction

Caffeine (1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione, Scheme 1) is a widespread natural product found in seeds, nuts, leaves of plants from South America and East Asia [1]. Among them, the most famous are coffee, tea, cocoa plants. Caffeine is thus a bio-based, renewable reagent and its use as starting material in chemical synthesis is highly recommended. Caffeine structure can be divided into two substructures, a pyrimidinedione ring and an imidazole ring. In particular, we envisaged in the presence of the imidazole ring the possibility of transforming caffeine in a bio-based imidazolium salt, which could be used in organic synthesis as N-heterocyclic carbene (NHC) precursor (Scheme 1). In fact, the deprotonation (chemical or electrochemical) of the C–H between the two nitrogen atoms in the imidazole ring of an imidazolium salt leads to the formation of the corresponding carbene [2,3]. The reactivity (as nucleophile or base) of this NHC is strongly influenced by the substituents of the imidazole ring, and thus the presence of the amide moiety of the caffeine structure could give this molecule a particular reactivity [4,5].

Although the electrochemical behaviour of caffeine has been extensively studied [6] due to the importance of this molecule, no paper on the electrochemical behaviour of the corresponding caffeinium salt is present in the literature. Nevertheless, caffeinium salts are molecules known for decades and sparingly used as chemical synthons [7–9], but mainly as precursors of ligands in Pd [10–12], Pt [13], Ru [14], Ag [15,16], Au [17] complexes, in some cases yielding complexes with biological activity.

In no case the free NHC derived from caffeinium salts has been evidenced. Scope of this paper is the study of the electrochemical behaviour of 9-methylcaffeinium iodide (1,3,7,9-tetramethyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-7-ium iodide, Scheme 1) by voltammetric techniques and electrolysis, in order to establish the possibility to obtain the corresponding NHC by cathodic reduction.

2. Experimental

9-Methylcaffeinium iodide (1,3,7,9-tetramethyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-7-ium iodide) was synthesized by the

☆ Although 9-methylcaffeinium iodide, caffeine, hymeniacidin and theacrine are not IUPAC names, we decided to use them throughout the paper due to their widespread and common use. In any case, the corresponding IUPAC names are reported in the paper.

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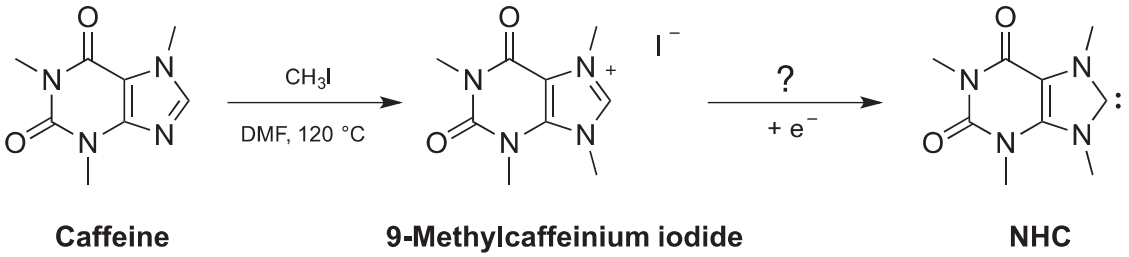


Scheme 1. Synthesis of 9-methylcaffeinium iodide from caffeine, and possible NHC formation.

method reported in the literature [15]. Voltammetric measurements were performed as previously described [18], using a 492/GC/3 (glassy carbon) Amel microelectrode. Differential pulse voltammetric (DPV) analysis was carried out using an AMEL 2551 potentiostat galvanostat, using a 492/GC/3 Amel microelectrode and elaborating data with VApeak 2016. Constant potential electrolyses were performed under a nitrogen atmosphere, at 25 °C, using an Amel 2053 potentiostat-galvanostat equipped with an Amel 731 integrator. The cell was a divided glass one separated through a porous glass plug filled up with a layer of gel (i.e., methyl cellulose 0.5% vol dissolved in DMF-Et_4NBF_4 1.0 mol dm^{-3}); Pt spirals (apparent area 0.8 cm^2) were used as both cathode and anode. Catholyte: 10 mL of DMF-0.1 M Et_4NBF_4 containing 0.5 mmol of 9-methylcaffeinium iodide. Anolyte: 2 mL of DMF-0.1 M Et_4NBF_4. The constant potential was kept at −2.0 V vs Ag/AgCl. At the end of the electrolysis (98 C, 2.0 F), the solvent of the catholyte was evaporated under reduced pressure. Flash column chromatography (eluent: ethyl acetate-methanol 80:20) gave purified hymeniacidin (*N*-(1,3-dimethyl-6-(methylamino)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-*N*-methylformamide) in 88% yield (with respect to starting 9-methylcaffeinium iodide). Its spectral data were in accordance with those reported in the literature [19].

When, after the electrolysis, the catholyte was treated with elemental sulfur and oxygen under ultrasound irradiation [20], 1,3,7,9-tetramethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione (Theacrine, NHCO [21], Fig. 3) and 1,3,7,9-tetramethyl-8-thioxo-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione (NHCS [22], Fig. 3) were isolated in low amount along with hymeniacidin. Their spectral data were in accordance with those reported in the literature.

Hymeniacidin (*N*-(1,3-dimethyl-6-(methylamino)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-*N*-methylformamide), mixture of rotamers: yellow oil. ^{1}H NMR (200 MHz, CD_3CN) δ, *major rotamer*: 7.93 (s, 1H, C*H*O), 5.6 (bs, 1H, 4-N*H*Me), 3.37 (s, 3H, 3-N*Me*), 3.19 (s, 3H, 1-N*Me*), 2.89 (s, 3H, 5-N*Me*), 2.87 (d, $J = 5.0$ Hz, 3H, 4-NH*Me*); *minor rotamer*: 8.16 (s, 1H, C*H*O), 5.4 (bs, 1H, 4-N*H*Me), 3.36 (s, 3H, 3-N*Me*), 3.18 (s, 3H, 1-N*Me*), 2.89 (s, 3H, 5-N*Me*), 2.83 (d, $J = 5.0$ Hz, 3H, 4-NH*Me*). ^{13}C NMR (50.3 MHz, CD_3CN) δ, *major rotamer*: 166.6 (CHO), 161.8 (C6), 153.2 (C4), 150.9 (C2), 94.8 (C5), 33.0 (5-NMe), 31.2 (4-NMe), 30.4 (3-NMe), 27.5 (1-NMe); *minor rotamer*: 165.1 (CHO), 159.9 (C6), 152.5 (C4), 150.9 (C2), 92.2 (C5), 36.6 (5-NMe), 31.2 (4-NMe), 30.5 (3-NMe), 27.5 (1-NMe). MS (ESI), *m*/*z* ($M + Na^+$): 248.53.

1,3,7,9-tetramethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione (Theacrine, NHCO) and 1,3,7,9-tetramethyl-8-thioxo-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione (NHCS), in ≈8:1 mixture:

NHCO: ^{1}H NMR (200 MHz, $CDCl_3$) δ, 3.74 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 3.39 (s, 3H). MS (EI), m/e (relative intensity): 224 (65%, $M^{+\cdot}$), 166 (16%), 139 (19%), 82 (79%), 67 (100%), 42 (49%).

NHCS: ^{1}H NMR (200 MHz, $CDCl_3$) δ, 3.82 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 3.24 (s, 3H). MS (EI), m/e (relative intensity): 240 (45%, $M^{+\cdot}$), 166 (7%), 128 (19%), 82 (62%), 67 (100%), 42 (51%).

3. Results and discussion

The cyclic voltammetry (CV) of a DMF- 0.1 M Et_4NBF_4 solution of 9-methylcaffeinium iodide on a GC electrode shows a cathodic peak at - 1,76 V vs Ag/AgCl (Fig. 1A), while there is no anodic peak attributable to the cation (Fig. 1B), only the anodic peaks relative to iodide anion at + 0.66 and + 0.92 V vs Ag/AgCl [23].

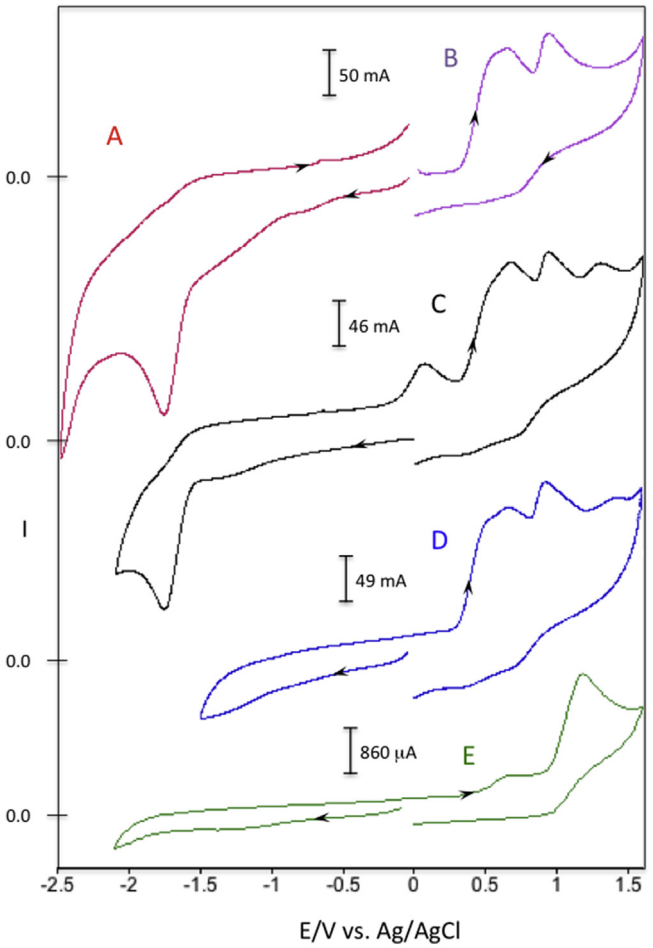


Fig. 1. CV of a DMF- 0.1 M Et_4NBF_4 solution of **A** (red): 9-methylcaffeinium iodide (5×10^{-3} M), potential scan: 0.0 to −2.5 to 0.0 V; **B** (violet): 0.0 to +1.6 to 0.0 V. **C** (black): 0.0 to −2.2 to +1.6 to 0.0 V; D (blue): 0.0 to −1.5 to +1.6 to 0.0 V. **E** (green): Hymeniacidin 1×10^{-3} M. Potential scan: 0.0 to −2.1 to +1.6 to 0.0 V. GC working electrode, Ag/AgCl reference electrode; $\nu = 0.2$ V s^{-1}; RT, N_2 atmosphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The electrodic process at −1.76 V generates a product which is oxidised at +0.05 V, as can be seen in Fig. 1C–D, in which the negative potential limit is shifted from −1.5 V to −2.2 V; no oxidation peak is present when the reversal potential is more positive than the reduction peak potential of caffeinium salt. Moreover, when caffeinium salt is reduced, a second oxidation peak appears at + 1.20 V (vide infra).

The electrochemical behaviour of 9-methylcaffeinium iodide is very similar to the one of other imidazolium salts [3], for which the cathodic reduction generates the corresponding N-heterocyclic carbene (NHC) which, in turn, is oxidised at a potential near 0 V. Following this hypothesis, in order to better understand the electrochemical behaviour of 9-methylcaffeinium iodide, we carried out the cathodic reduction of 9-methylcaffeinium iodide in DMF-0.1 M Et_4NBF_4 solution, at the potential of −2.0 V on a Pt cathode. At the end of the electrolysis (2.0 F), a ring opening product, hymeniacidin, was isolated in 88% yield (Scheme 2), whose oxidation peak potential is +1.20 V (Fig. 1E).

Hymeniacidin is a natural product, isolated for the first time by Capon and coworkers [19] from the Southern Australian marine sponge *Hymeniacidon* sp. Although this sponge metabolite revealed not active against nematocides (the object of Capon study), its biological activity is still under study.

The formation of hymeniacidin from the cathodic reduction of 9-methylcaffeinium iodide seems to be an indirect confirmation of the formation of NHC during the electrolysis. In fact, Capon [19] reported the chemical synthesis of hymeniacidin by reaction of 9-methylcaffeinium iodide with a base (ammonium hydroxide). The action of the base should be the deprotonation of the C–H between the two nitrogen atoms (in the imidazolium ring) and formation of the corresponding NHC. NHC reaction with H_2O yields the ring opening and hymeniacidin formation. In order to exclude that the formation of hymeniacidin derives from mere hydrolysis of the caffeinium salt, we studied the stability of 9-methylcaffeinium iodide in water: after 1 week in D_2O at RT, no decomposition product was evidenced.

Another hint on the strict correlation between NHC and hymeniacidin formation was obtained by carrying out the cyclic voltammetries of 9-methylcaffeinium iodide in the presence of carbon dioxide. As seen before (Fig. 1C), when 9-methylcaffeinium iodide is reduced (negative scan of the CV), a product is formed which is oxidised at +0.05 V (which we attribute to NHC) and a second oxidation peak is evident at +1.20 V (hymeniacidin). If CO_2 is added to the solution, the CV alters considerably (Fig. 2). In fact, if the reversal potential is less negative than CO_2 reduction (so that carbon dioxide is not electrochemically reduced), a new peak is formed during the positive scan at −0.22 V and no peak attributable to hymeniacidin is present.

In analogy with the electrochemical behaviour of other imidazolium cations [24], it can be hypothesized that the cathodic reduction of caffeinium salt leads to the formation of the

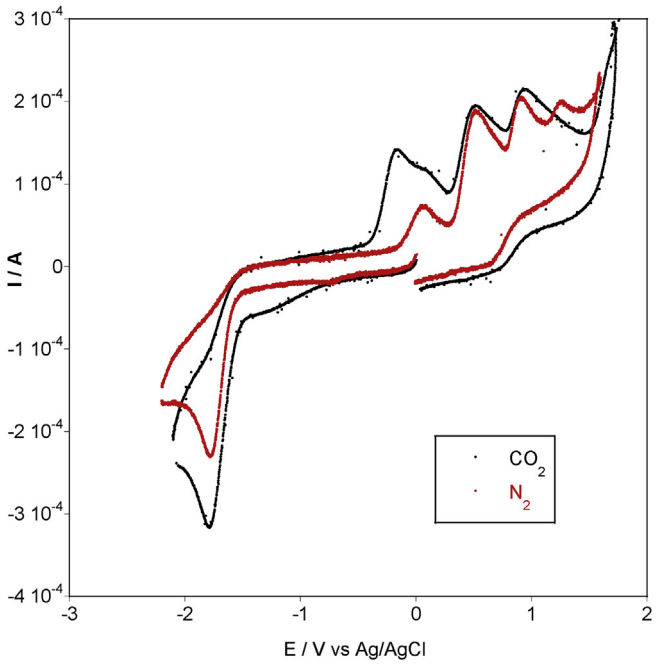


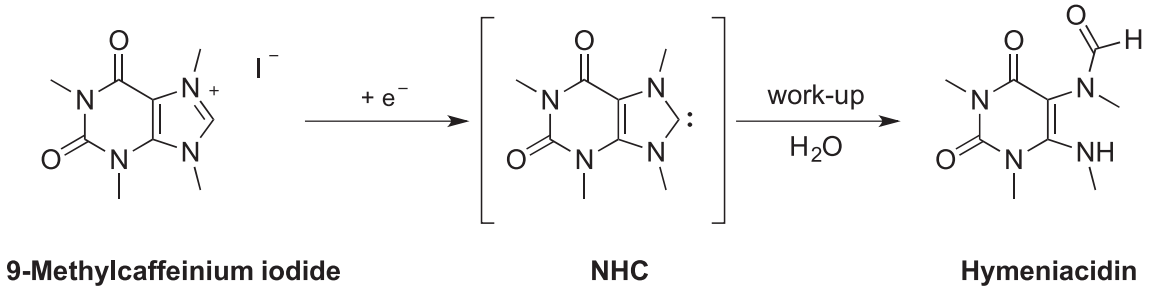
Fig. 2. CV of a DMF- 0.1 M Et_4NBF_4 solution of 9-methylcaffeinium iodide (5×10^{-3} M) under N_2 (red) or CO_2 (black) atmosphere. Potential scan: 0.0 to −2.1 to 1.8 to 0.0 V. GC working electrode, Ag/AgCl reference electrode; $\nu = 0.2$ V s^{-1}. RT. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

corresponding NHC (Scheme 2). This NHC in the presence of CO_2 forms an adduct NHC–CO_2 which subtracts NHC from the oxidation and from the reaction to hymeniacidin (Scheme 3).

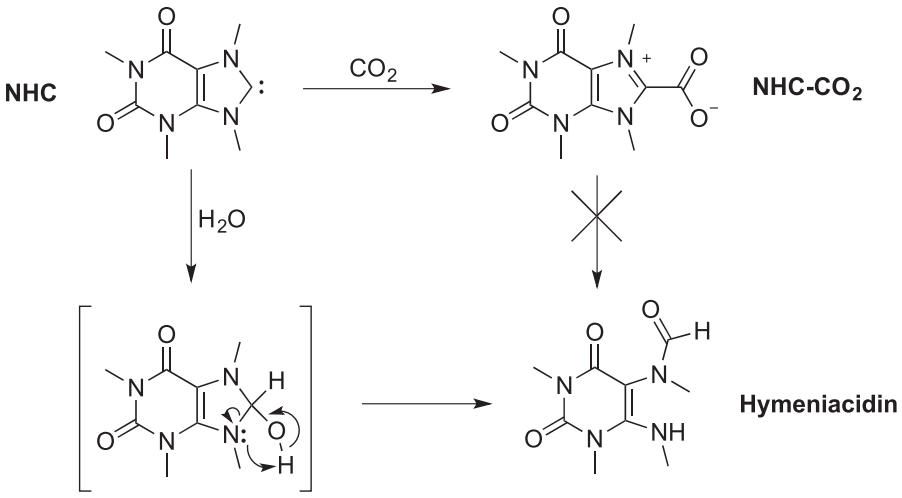
A further confirmation of a NHC intermediate in this electrolysis derives from a paper of Bredereck and coworkers [25] dated 1959, in which the reaction between water and this NHC (represented with a triple bond between an imidazole nitrogen atom and the carbene carbon atom) led to the formation of hymeniacidin.

Last, the formation of NHC by electrochemical reduction of the caffeinium salt was confirmed by the isolation of 1,3,7,9-tetramethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione (NHCO, Theacrine -a biologically active compound- Fig. 3) and 1,3,7,9-tetramethyl-8-thioxo-3,7,8,9-tetrahydro-1*H*-purine-2,6-dione (NHCS, Fig. 3) by reaction of electrochemically reduced 9-methylcaffeinium iodide and sulfur and dioxygen. These two compounds should derive from the corresponding NHC by reaction with dioxygen and sulfur, as reported in the literature for other imidazole carbenes [20].

It is thus possible to infer that the reduction of 9-methylcaffeinium iodide leads to the formation of the corresponding carbene, whose oxidation peak potential is +0.05 V



Scheme 2. Electrochemical reduction of 9-methylcaffeinium iodide yielding hymeniacidin.



Scheme 3. Electrochemical reduction of 9-methylcaffeinium iodide in the presence of carbon dioxide. Hypothesis of reactivity.

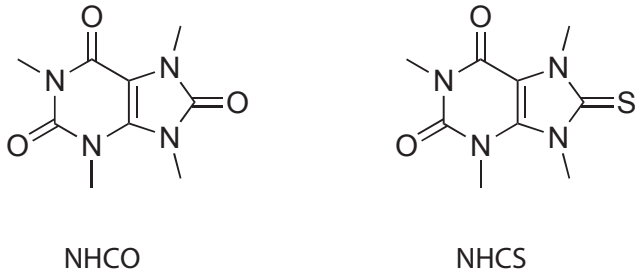


Fig. 3. Products obtained by reaction of electrochemically reduced 9-methylcaffeinium iodide and elemental sulfur and dioxygen.

(Fig. 1b, black curve, first oxidation peak). This carbene evolves towards the formation of hymeniacidin, whose oxidation peak potential is +1.20 V (Fig. 1C, black curve, fourth oxidation peak, and Fig. 1E).

Any attempt to carry out the benzoin condensation starting from benzaldehyde and cathodically reduced 9-methylcaffeinium iodide failed, confirming the unstability of the corresponding NHC (or the too weak nucleophilicity of the carbene site).

In order to better understand and identify the oxidation peaks appearing during the CV anodic sweep, differential pulse voltammetric analysis (DPV) was carried out. In this case, sharper peaks (with respect to CV ones) were obtained.

In Fig. 4, the DPV sweeps for caffeinium salt (■) and hymeniacidin (●) (from −2.1 V to 1.6 V vs Ag/AgCl) are reported.

Peak I of caffeinium salt (−1.72 V) is attributable to its reduction reaction, as showed in Scheme 2, leading to the carbene formation. The oxidation of the NHC, as already discussed, produces a sharp peak (II) centered at ~0 V. In the next region of potential (III) a series of peaks related of the iodide oxidation is well evident [23]. Finally the comparison between the scan of caffeinium salt and hymeniacidin for peak IV (1.10 V) provides confirmation of hymeniacidin as a product from caffeinium salt.

The confirmation that the peak I indicates the reduction process of caffeinium ion is found in the voltammetry in Fig. 5, where the negative current occurring during the anodic sweep from −2.1 V is maintained till −1.4 V, value of potential corresponding to the sign inversion of current in DPV scan.

In Fig. 6, the DPV curve for caffeinium iodide (■) is reported along with the DPV obtained after a pre-electrolysis at −2.1 V for

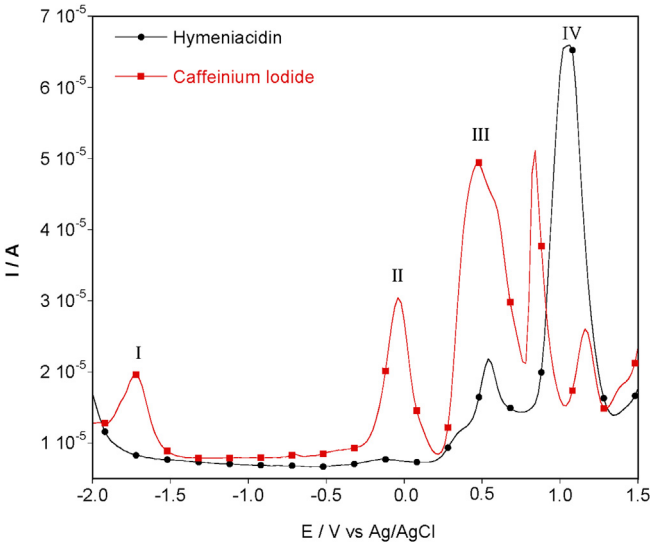


Fig. 4. DPV scan for caffeinium iodide (■) and hymeniacidin (●). DMF-0.1 M Et_4NBF_4, solute: 5×10^{-3} M; GC working electrode. Scan rate: 100 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere.

10 s (●). A direct correlation between the time at the reductive potential of −2.1 V and peak II and IV heights is evident, confirming that the products corresponding to oxidation peaks II and IV derive from the reduction of caffeinium salt.

The study of the effect of the sweep rate on the faradaic current intensity and corresponding peak height is reported in Fig. 7. Although peak I seems to be independent of the scan rate, for peak II (highlighted in Fig. 8a) it is evident that there is variation with the sweep rate, while for peak IV (highlighted in Fig. 8b) no correlation is found, probably due to the presence, close to the electrode surface, of species resulting from iodide oxidation process.

Analyzing the carbene oxidation peak (highlighted in Fig. 8a), a good linear dependence (confirmed by a correlation value close to 1) between the current intensity and the square root of the scan rate was found (Fig. 9), indicating the formation of NHC as a process under diffusion control in the range 10–100 mV s^{-1}. It is worth mentioning that for 10 mV s^{-1} only a very small signal is observed, while for scan rates exceeding 100 mV s^{-1} no correlation was found.

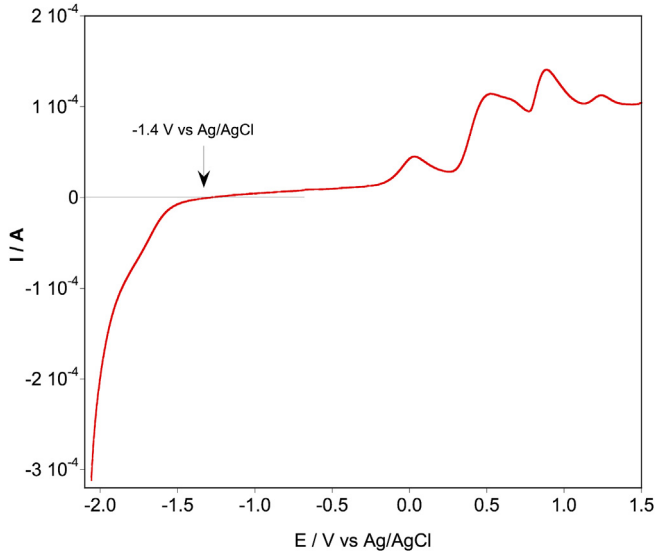


Fig. 5. Linear Scan Voltammetry for caffeinium iodide (5×10^{-3} M). DMF-0.1 M Et_4NBF_4, GC working electrode. Scan rate: 100 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere.

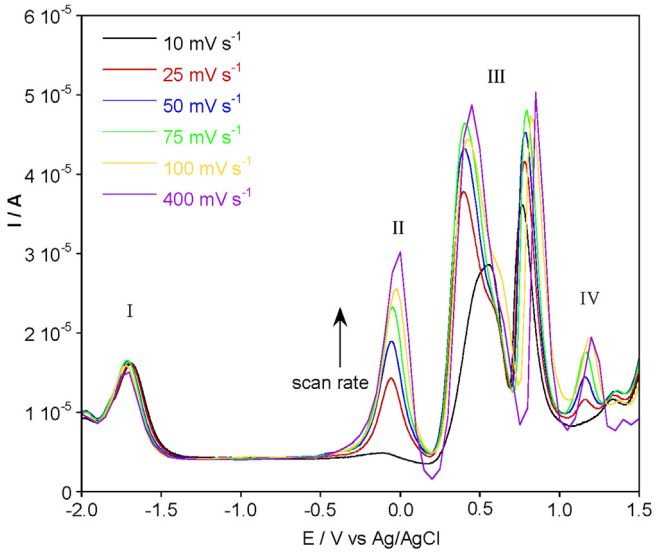


Fig. 7. Effect of scan rate on DPV for caffeinium iodide (5×10^{-3} M) with 10 s pre-electrolysis at −2.1 V. DMF-0.1 M Et_4NBF_4, GC working electrode. Scan rate: from 10 to 400 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere.

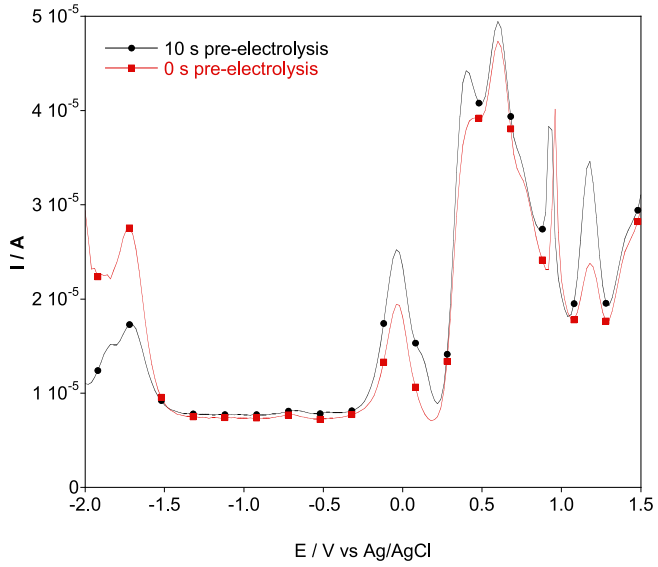


Fig. 6. DPV scan for caffeinium iodide (5×10^{-3} M) without pre-electrolysis (■) and with 10 s pre-electrolysis at −2.1 V (●). DMF-0.1 M Et_4NBF_4, GC working electrode. Scan rate: 100 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere.

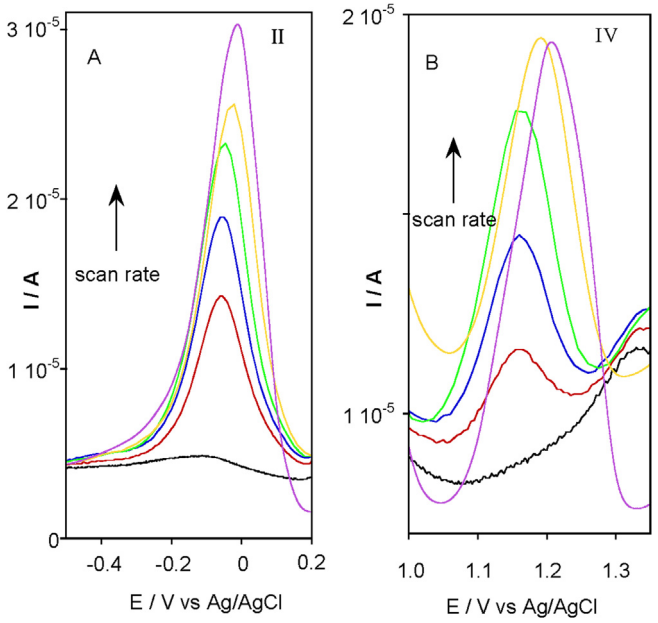


Fig. 8. Effect of scan rate on DPV for caffeinium iodide (5×10^{-3} M) with 10 s pre-electrolysis at −2.1 V. DMF-0.1 M Et_4NBF_4, GC working electrode. Scan rate: from 10 to 400 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere. Selected potential ranges from Fig. 7, corresponding to peak II (graph A, left) and peak IV (graph B, right).

4. Conclusions

Caffeine, a natural product, can be easily transformed into the corresponding imidazolium salt (9-methylcaffeinium iodide) by reaction with methyl iodide. Scope of this work was the study of the electrochemical behaviour of 9-methylcaffeinium iodide (never reported in the literature) by means of cyclic voltammetry, differential pulse voltammetry and electrolysis.

The interpretation of the voltammetric peaks and their interrelation allowed to describe the cathodic process for 9-methylcaffeinium iodide. Confirmation came from isolated products after electrolysis.

In fact, the cathodic reduction of the caffeinium iodide yielded the corresponding carbene, whose presence was confirmed by its reaction products with elemental sulfur and dioxygen. Moreover, the cathodic reduction of the caffeinium iodide gave a ring opening product, hymeniacidin (a natural product), in high yield. This work proved that hymeniacidin derives from hydrolysis of electrogenerated carbene and not from hydrolysis of caffeinium salt.

Hymeniacidin was obtained in high yield (88%) by simple electrolysis of 9-methylcaffeinium iodide in DMF solution. This is the first electrochemical synthesis of this natural product (previously isolated from a marine sponge). Although the cathodic reduction of 9-methylcaffeinium iodide leads to the formation of the corresponding carbene (in analogy with the behaviour of other

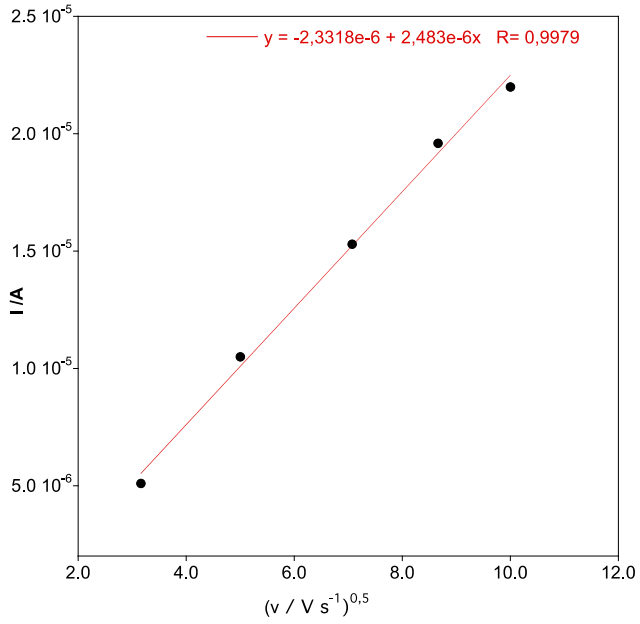


Fig. 9. DPV for caffeinium iodide (5×10^{-3} M) with 10 s pre-electrolysis at −2.1 V. DMF-0.1 M Et_4NBF_4, GC working electrode. Scan rate: from 10 to 400 mV s^{-1}; potential range: −2.1 V to +1.5 V vs Ag/AgCl, RT, N_2 atmosphere. Linear dependence of the current intensity of peak II upon the square root of the scan rate. Data from Fig. 7.

imidazolium salts), this NHC seems to be either too unstable or too weak nucleophile to catalyse the benzoin condensation (a classical NHC-catalysed organic reaction). Further work is currently underway in our laboratory to verify the possibility to use this NHC in other organocatalysed reactions.

Declarations of interest

None.

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