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

Fabiana Pandolfi [a], Leonardo Mattiello [a], Daniela Zane [b, **], Marta Feroci [a, *]

[a] Dept. Basic and Applied Sciences for Engineering (SBAI), Sapienza University of Rome, via Castro Laurenziano, 7, 00161, Rome, Italy
[b] CNR ISMN Istituto per lo Studio dei Materiali Nanostrutturati, UOS Sapienza, Via del Castro Laurenziano 7, 00161 Roma, Italy

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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

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[☆] 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.

* Corresponding author.

** Corresponding author.

E-mail addresses: daniela.zane@ismn.cnr.it (D. Zane), marta.feroci@uniroma1.it (M. Feroci).

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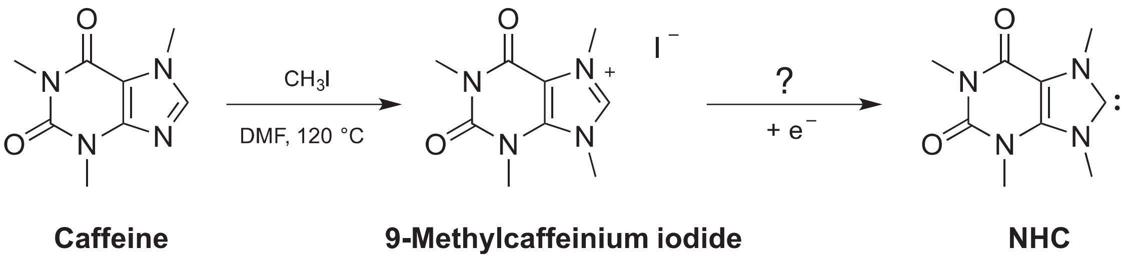

Scheme 1. Synthesis of 9-methylcaffeinium iodide from caffeine, and possible NHC formation.

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].

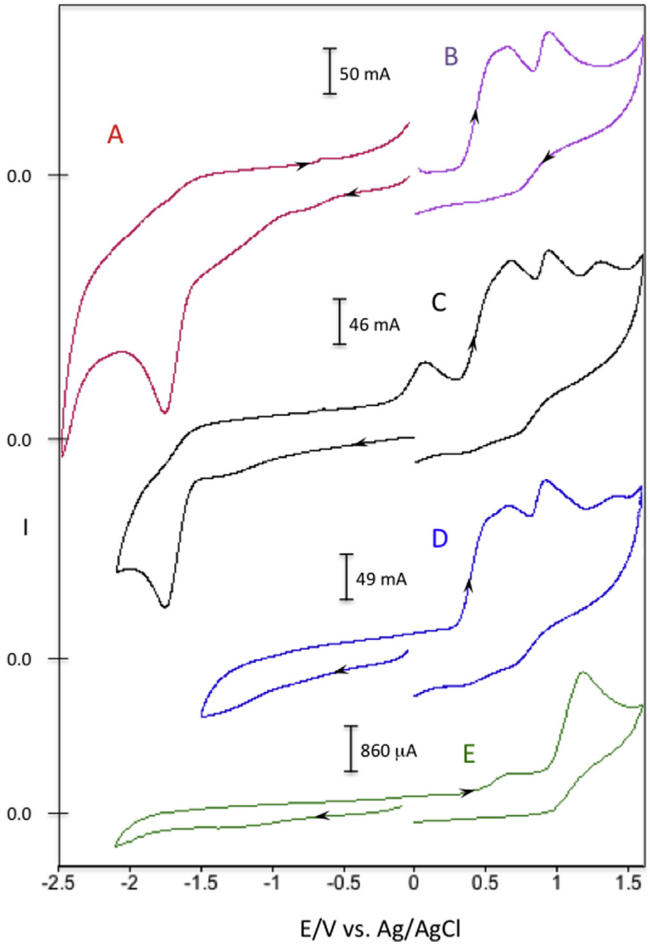

Fig. 1. CV of a DMF- 0.1 M Et_4NBF_4 solution of **A** (red): 9-methylcaffeinium iodide (5×10^{-3} M), potential scan: 0.0 to −2.5 to 0.0 V; **B** (violet): 0.0 to +1.6 to 0.0 V. **C** (black): 0.0 to −2.2 to +1.6 to 0.0 V; D (blue): 0.0 to −1.5 to +1.6 to 0.0 V. **E** (green): Hymeniacidin 1×10^{-3} M. Potential scan: 0.0 to −2.1 to +1.6 to 0.0 V. GC working electrode, Ag/AgCl reference electrode; ν = 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.)