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Thiophene-based electrochemically active probes for selective calcium detection

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ABSTRACT

Electrochemically active probes containing a tetraalkylated p-phenylenediamine redox responsive moiety and thiophene ligands were found to be sensitive to calcium ions. The electrochemical studies revealed that these compounds were able to bind Ca^{2+} ions. The redox properties of the transducer underwent dramatic changes upon calcium chelation provoking large oxidation potential shifts comprised between 549 and 911 mV. A high selectivity towards Ca^{2+} over Zn^{2+} was observed. The zinc complex was found to spontaneously undergo metal ion exchange in presence of Ca^{2+} yielding $[Ca(\mathbf{L})_2]^{2+}$.

1. Introduction

In the human body, calcium is very abundant. This element is mostly stored in the bones where it is responsible for their strength [1]. Ionized calcium plays also an important role in cells proper functioning because of its ability to bind proteins reversibly and activate their catalytic and mechanical properties [2]. Many biological processes are dependent on this mineral such as muscle contraction, exocytosis, neurotransmitter release and steady heartbeat [3,4]. Excess as well as calcium deficiency can be the origin of severe diseases [5,6]. It is therefore very important to be able to monitor calcium fluxes in biological media.

In analogy with biological systems that require specific sites for selective calcium binding, chemosensors are used to detect and eventually to deliver calcium ions [7]. The chemosensors contain multidentate ligands able to coordinate the Ca^{2+} ions and thus modifying the physicochemical properties of the transducers [8].

In the last two decades, chemosensors based on a redox-active moiety were widely investigated. In the last years, mainly ferrocene [9,10], cobaltocene [11] and phenylenediamine [12] moiety were employed as electrochemical transducers. Crown ethers were particularly used as a receptor for the detection of calcium [13] and alkaline ions [14]. In contrast, thiocrown ethers, developed by Sibert et al., present a good affinity for heavy metals ions such as mercury (II) and platinum (II) [15,16].

Herein, we report the electrochemical investigation of a series of electroactive tetraalkylated p-phenylenediamine (TAPD) chemosensors **1** and **2** relying on thiophene ligands as calcium receptor site (Fig. 1). The electrochemical properties in the presence of Ca^{2+} and Zn^{2+} were studied using cyclic (CV) and differential pulse voltammetry (DPV).

2. Experimental

2.1. Materials

All reagents and solvents were purchased from Sigma–Aldrich and Acros (France) and used without further purification unless otherwise indicated. Tetrabutylammonium tetrafluoroborate ($TBABF_4$) supporting electrolyte had been recrystallized from methanol/water mixture (50/50, v/v) and dried at 60 °C for 12 h. AnhydroScan® acetonitrile was freshly distilled before use.

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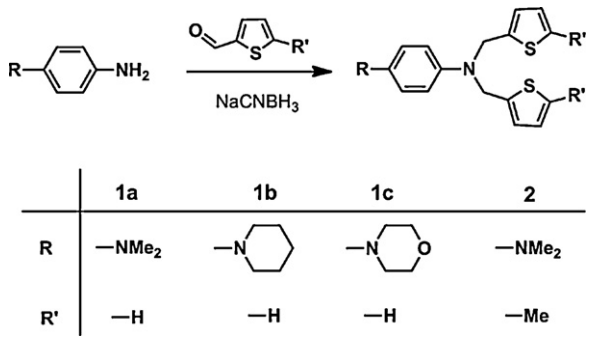

Fig. 1. General route to tetraalkylated p-phenylenediamine-based probes.

2.2. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 MHz apparatus in deuterated solvents. Chemical shifts values were given in ppm relative to tetramethylsilane as internal reference. IR spectra were measured on a Perkin-Elmer Alpha ATR spectrophotometer. The electrochemical experiments were conducted, at ambient temperature and at a potential sweep rate of 100 mV s^{-1}, in 0.1 M tetrabutylammonium tetrafluoroborate acetonitrile solution in a three-electrode glass cell controlled by a Radiometer Analytical potentiostat (Voltalab PST050) equipped a HBV-100 booster (for cyclic voltammetry) and Radiometer Analytical POL 150 with MED 150 stand (for differential pulse voltammetry). The cell was fitted with a glassy carbon disk as a working electrode (3-mm-diameter), with a platinum wire as a counter electrode. $Ag|Ag^{+}$ 0.01 M in acetonitrile (for CV) and Ag|AgCl (3 M KCl) (for DPV) electrodes were used as reference electrodes. Data acquisition and treatment were performed, respectively, with VoltaMaster 4.07 and TraceMaster 5 software for CV and DPV experiments. The working electrode was polished prior to each experiment. Differential pulse voltammetry (DPV) scanning was performed from −0.2 to 1.5 V with a potential increment of 10 mV, pulse amplitude and width, respectively, of 50 mV and 40 ms and a frequency of 10 Hz under the optimized conditions.

2.3. Synthesis

The target molecules **1** and **2** were prepared according to a previously published procedure [17]. The reaction was performed under argon atmosphere at room temperature and shielded from the light by an aluminium foil. To a solution of 2.0 mmol of the primary aromatic amine in methanol (50 mL), 8.0 mmol of aldehyde and 10.0 mmol of acetic acid were added and the mixture was stirred for 12 h. Sodium cyanoborohydride (2.0 mmol) was added and stirring was kept for further 4 h. The mixture was neutralized with 50 mL of saturated ammonium chloride solution and extracted twice with 20 mL of dichloromethane. The organic phase was washed twice with 10 mL of distilled water, dried over magnesium sulfate and evaporated to dryness. The oily brownish residue was chromatographed on silica gel and eluted with 20:80 ethyl acetate–petroleum ether mixture to afford the desired products.

N,N-Dimethyl-N′,N′-di((5-methylthiophen-2-yl)methyl)-p-phenyldiamine **2** ($C_{20}H_{24}N_2S_2$). Yield: 75%; mp 95–97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm 2.41 (s, 6H, CH_3), 2.84 (s, 6H, CH_3), 4.43 (s, 4H, CH_2), 6.55 (mu, 4H, thiophene), 6.74–6.85 (d, 4H, $^{3}J_{H-H}$ = 7.5 Hz, CHarom.); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ/ppm 15.4, 41.7, 50.4, 114.7, 124.4, 125.2, 138.9, 140.0, 141.0, 144.8. MS (EI^{+}): *m*/*z* (%): 356 (100) [M^{+}.]; 245 (98) [$M-C_6H_7S]^{+}$. IR ν_{max}/cm^{-1} 3065 (CH), 2847 (CH), 1516 (C=N), 1251, 703.

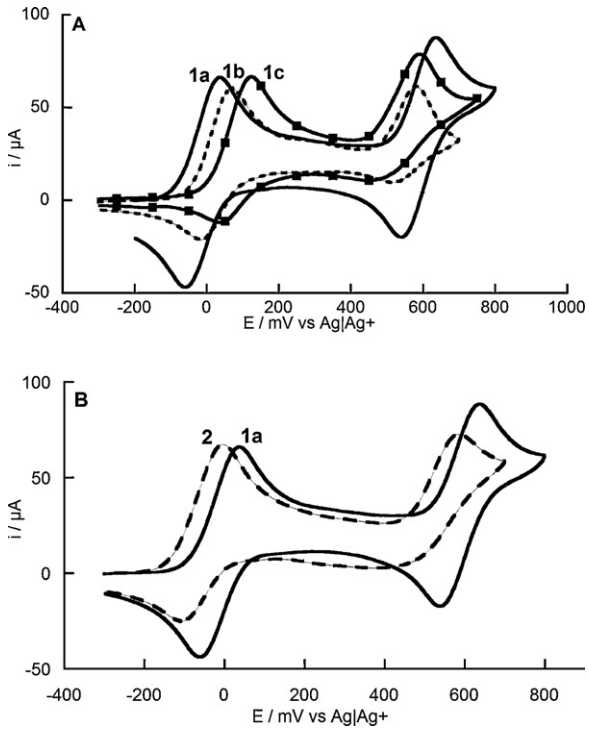

Fig. 2. (A) Cyclic voltammograms of 4.0 mM solutions of **1a** (—), **1b** (- - -) and **1c** (–■–). (B) Voltammetric curves of 4.0 mM solutions of **1a** (—) and **2** (- - -) showing the effect of introduction of the methyl group on α-position to the sulfur atom, in 0.1 M $TBABF_4$ acetonitrile solution. Scan rate: 0.1 V s^{-1}.

3. Results and discussion

3.1. Electrochemistry of the free ligands

The cyclic voltammograms (CV) of all compounds **1** and **2** (Fig. 1) were similar to tetramethylated *p*-phenylenediamine [18–20] and showed two oxidation peaks attributed to the formation of the radical-cation and the dication (Fig. 2). The replacement of the dimethylamino group in compound **1a** with piperidinyl (**1b**) and morpholinyl (**1c**) groups had only little effect on the oxidation potentials.

The i_{pa}-to-i_{pc} currents ratio was close to unity indicating a reversible electron transfer [17]. The peak current was found to be linearly dependant on the square root of scan rate indicating a diffusion-controlled electrochemical process [21] (see Fig. A.1 in Electronic Supplementary Materials). The second oxidation process was reversible only in the case of **1a**, whereas only partial reversibility was observed for **1b** and **1c**, attesting a chemical reaction following the electron transfer (Fig. 2A) [17,22].

In compound **2** the α positions of the thiophenyl groups were protected by methyl groups in order to check whether the irreversible wave was not due to thiophene dimerization or polymerization [23]. However, Fig. 2B shows that the second oxidation wave of **2** is irreversible (whereas reversible for **1a**), thus discarding the possibility of thiophenyl dimerization in the observed potential window. The electrochemical characteristics **1a**–**1c** and **2** were summarized in Table 1.

3.2. Calcium detection

The CV studies revealed that all prepared compounds were able to bind Ca^{2+}. As shown in Fig. 3 (and in Fig. A2 supplementary materials), the calcium chelation by **1a**–**1c** and **2** provoked large anodic shifts. Indeed, upon progressive addition of Ca^{2+}, the two oxidation