



Electrochemical behavior of 2-aminodiphenylamine and efficient factors on the site-selectivity of sulfonylation reaction: Experimental and theoretical studies



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ARTICLE INFO

Article history:

Received 9 September 2016

Received in revised form 7 November 2016

Accepted 8 November 2016

Available online 14 November 2016

Keywords:

2-Aminodiphenylamine
Regioselective sulfonylation
Natural charge
NBO analysis
Cyclic voltammetry
Antibacterial activity
EDA analysis

ABSTRACT

The electrochemical dimerization of 2-aminodiphenylamine (**2ADPA**) has been studied. The data indicate that electrochemically generated (*Z*)-*N*-(6-iminocyclohexa-2,4-dien-1-ylidene) aniline (**2ADPA_{ox}**) can serve as a Michael acceptor in the reaction with starting molecular (**2ADPA**) form and converts to the corresponding dimer. The mechanism of dimerization has been studied using both controlled-potential coulometry and cyclic voltammetry. The anodic dimerization of 2-aminodiphenylamine has been successfully performed under constant current condition in good yield and purity in an undivided cell. Furthermore, electrochemical oxidation of **2ADPA** has been studied both experimentally and theoretically to provide insight into the influence of some factors on the type of chemical reaction which follows **2ADPA_{ox}**. The effect of natural charge of **2ADPA_{ox}** on the reaction site was calculated using PBE/def2-SVP level of theory to identify regioselective sulfonylation of **2ADPA**. The results indicate that the natural charge of Michael acceptor **2ADPA_{ox}** and thermodynamic stability of products lead to site-selectivity sulfonylation of **2ADPA**. In addition, the sulfone products were evaluated for their in vitro antibacterial activity against two bacterial ATCC strains (*Staphylococcus aureus*, and *Escherichia coli*).

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1. Introduction

Electrochemical synthesis of main organic compounds has been extensively employed as a synthetic method in a variety of chemical transformations due to its unique properties such as eco-friendly nature, direct and short-cut synthetic route, high current efficiency values, high selectivity and sustainability of the reactions [1–9]. Phenylamine derivatives such as carbazole and triphenylamine are important compound for organic electronics [10,11]. Moreover, sulfonated phenylamine display a wide variety of biological properties such as: antibacterial [12], antifungal [13], antimalarial [14], anti-cancer [15], thyroid receptor antagonist [16], or inhibitor of several enzymes such as cysteine protease [17], protein phosphatase methylesterase-1 [18], cyclooxygenase-2 (COX-2) [19] and HIV-1 reverse transcriptase [20], γ -secretase [21] and gelatinase [22] inhibitor. Therefore, the regioselective synthesis of these valuable

compounds is a relevant and interesting reaction, which leads to sulfonylation under kinetically and thermodynamically controlled situation. Selective synthesis of desired compounds has been a challenging goal for synthetic chemists [23]. On the other hand, understanding the mechanism of these reactions has been a main and attractive area of computational organic chemistry and close cooperation between experimentalists and theorists demonstrate a growing trend [24]. With new advances in theoretical methods and increasing in power of computational chemistry, applications of it as a powerful tool are becoming practical in many fields of chemistry. Computational chemistry plays an important role in elucidating reaction mechanisms and the selectivity of various organic reactions, such as chemo, regio and stereoselectivities [25]. The aim of this research is a complementary study of electrochemical behavior of 2-aminodiphenylamine (**2ADPA**) and discussion about the details of the mechanism of a recently reported regioselective sulfonylation reaction of it [26]. In this paper, firstly the electrochemical behavior of **2ADPA** in various conditions (such as various pH, concentration, scan rate, and in the absence or presence of nucleophiles) was investigated and using the data obtained, a unique dimer of **2ADPA** is synthesized. In this work, we also

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discussed the mechanism of the regioselective sulfonylation of **2ADPA** using computational chemistry methods. In addition, we discussed about the parameters which influence on the reaction mechanism of regioselective formation of 1-*N*-phenyl-4-(sulfonyl)-benzene-1,2-diamines, and thermodynamic stability of them. Finally, the antibacterial properties of the synthesized sulfones were evaluated.

2. Experimental

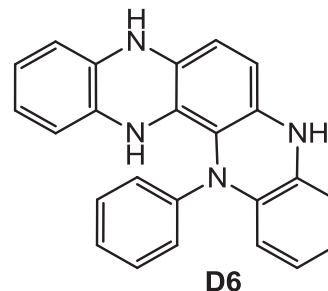
2.1. Apparatus, reagents and general remarks

Cyclic voltammetry was carried out using an Autolab model PGSTAT 20 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm² area) and platinum wire was used as counter electrode. The working electrode potentials were measured versus 3.0 M Ag/AgCl (all electrodes from AZAR electrode). **2ADPA**, phosphate salts and EtOH were obtained from commercial sources. These chemicals were used without further purification. The glassy carbon electrode was polished using alumina slurry (from Iran Alumina Co.). Melting points were measured using an Electrothermal 9100 apparatus (Rochford, UK). IR spectra (KBr) were recorded as KBr pellets on a Perkin–Elmer GX FT-IR spectrometer. NMR spectra were recorded using Bruker DRX-400 AVANCE (Rheinstetten, Germany) instruments (500 MHz for ¹H and 125 MHz for ¹³C). Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constants, *J*, are reported in Hz. Mass spectra were recorded on an Agilent-5975C inert XL MSD mass spectrometer (USA) operating at an ionization potential of 70 eV. Elemental analysis was recorded using CHNS-O Elemental Analyzer (Vario EL III, ELEMENTAR, Hanau-Germany).

The geometries of all species in the gas phase were fully optimized at PBE/def2-SVP [27] level of theory using Gaussian 03 [28]. Vibrational frequency analysis, calculated at the same level of theory, indicates that optimized structures are at the stationary points corresponding to local minima without any imaginary frequency. Also, NBO analyses were carried out at the mentioned levels of theory [29]. The geometry of the compound **3c** as determined by the X-ray crystal structure analysis [24], was fully optimized at above mentioned level of theory. A starting molecular-mechanics structure for the DFT calculations was obtained using the HyperChem 5.02 program for other compounds. Bonding analyses in the terms of energy-decomposition analysis, were carried out at BP86/TZ2P(ZORA)//PBE/def2-SVPP with C1 symmetry. The basis sets for all elements have triple- ζ quality augmented by one set of polarization functions (ADF basis set TZ2P(ZORA)) with the program package ADF2009.01. EDA calculations were carried out in order to analyze the nature of the bonding. In the EDA, bond formation between the interacting fragments is divided into four steps, which can be interpreted in a plausible way. In the first step, the fragments, which are calculated with the frozen geometry of the entire molecule, are superimposed without electronic relaxation to yield the quasi classical electrostatic attraction ΔE_{elstat} . In the second step, renormalization of the anti-symmetry product wave function gives the Pauli repulsion ΔE_{Pauli} . In the third step, the molecular orbitals relax to their final form to yield the stabilizing orbital interaction ΔE_{Orb} . The latter term can be divided into contributions of orbitals that have different symmetry (in the EDA) or into contributions of NOCV orbital pairs (EDA-NOCV). This step is crucial for the present study, because we focus on the different types of orbital interactions. The sum of the four terms $\Delta E_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{Orb}} + \Delta E_{\text{Disp}}$ gives the total interaction energy ΔE_{Int} .

2.2. Electroorganic synthesis of **2ADPA** dimer (**D6**)

A mixture of water (phosphate buffer, *c* = 0.2 M, pH 2.0)/ethanol (60/40, v/v), containing **2ADPA** (1.0 mmol) was electrolyzed in an undivided cell under controlled potential condition at 0.50 V versus 3.0 M Ag/AgCl or galvanostatic method with current density 0.9 mA cm⁻¹. In controlled potential method, the synthesis was terminated when the decay of the current became more than 95%, and in galvanostatic method the synthesis was finished when the consumed charge was 300 C. The process was interrupted during the electrolysis, and the carbon rod anodes were washed in acetone for reactivation. At the end of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration, washed copiously with distilled water and recrystallized from EtOH.



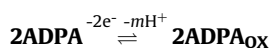
D6

Pink solid; mp 162–164 °C; Isolated yield: 95%; FT-IR (KBr) (cm⁻¹): 3363–3370 (medium, stretching N-H); ¹H NMR, δ ppm (500 MHz in CDCl₃): 5.33 (brs, 3H, NH, disappeared by addition of D₂O), 6.54 (s, 2H, Ar-H), 6.75 (s, 2H, Ar-H), 6.89 (s, 1H, Ar-H), 7.13–7.25 (m, 6H, Ar-H), 7.46–7.53 (m, 3H, Ar-H) 7.74 (s, 1H, Ar-H); ¹³C NMR, δ ppm (125 MHz in CDCl₃): 115.9, 118.1, 119.3, 120.3, 122.5, 127.7, 129.6, 129.9, 133.2, 134.2, 136.9, 138.3, 142.3, 142.9; Anal. Calcd. for C₂₄H₁₈N₄ (362.15): C, 79.54; H, 5.01; N, 15.46. Found: C, 79.51; H, 5.11; N, 15.57; MS (EI) *m/z* (%): 361 [(M-1), 100].

3. Results and discussion

3.1. Electrochemical study of **2ADPA**

Since the majority of organic electrochemical reactions involve proton transfer, there is need to study the effects of pH on the electrochemical oxidation behavior of **2ADPA**. Cyclic voltammogram of **2ADPA** (1.0 mM) in a water (with various pH values)/ethanol (70/30, v/v) mixture are shown in Fig. 1P1. It was found that by increasing pH, the anodic peak potential (E'_{pA1}) shifts to the negative values. This is expected due to the participation of protons in the oxidation of **2ADPA** to **2ADPA_{ox}**.



Where *m* is the number of protons involved in the reaction. The oxidation peak potential (E'_{pA1}) is given by:

$$E'_{\text{pA1}} = E'_{\text{pA1}(\text{pH}=0)} - (2.303 mRT/2F) \text{pH}$$

Where $E'_{\text{pA1}(\text{pH}=0)}$ is the oxidation peak potential at pH = 0.0, and *R*, *T* and *F* have their usual meanings. A potential-pH diagram (Pourbaix diagram) is constructed for **2ADPA** by plotting the E'_{pA1} values as a function of pH (Fig. 1P2). As can be seen, E'_{pA1} was shifted to negative potentials with the slope of about 51 mV/pH which is in agreement with the theoretical slope ($2.303 mRT/2F$) of 59 mV/pH with *m* about 2 (*m* = 1.8) (Fig. 1P2).

It is well known that, in an EC mechanism with a reversible electrochemical process, the peak current ratio ($I_{\text{pC1}}/I_{\text{pA1}}$) is a criterion for the stability of **2ADPA_{ox}**, so that, **2ADPA_{ox}** is unstable in the time scale of CV experiment, when $I_{\text{pC1}}/I_{\text{pA1}}$ is zero or small [30].

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