

Synthesis and DFT characterisation of 2-arylamino-1,4-benzoquinone derivatives as potential electron transfer mediators

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A series of new potential electron transfer mediators, 2-substituted 1,4-benzoquinone derivatives bearing an arylamino group with various substituents in *o*-, *m*- and *p*-positions of an aromatic ring were synthesised by adding a solution of aniline derivatives in aqueous acetic acid to an aqueous solution of 1,4-benzoquinone. The structure and properties of synthesised compounds were investigated by NMR spectroscopy methods in detail. The redox ability of 2-arylamino-1,4-benzoquinone derivatives has been estimated by calculations of quantum chemical structure–activity relationship (QSAR) descriptors within the framework of density functional theory.

Keywords: 1,4-benzoquinone, aromatic amine, 2-arylamino-1,4-benzoquinone, NMR spectroscopy, quantum chemical structure–activity relationship (QSAR) descriptors, electron transfer mediator

INTRODUCTION

In the context of ‘life quality improvement’ in different fields, such as medicine, food, environmental or safety control, the development of new technologies operating on a base of bioelectrocatalysis is applied more and more. Employment

of enzymes as biocatalysts in these processes offers the benefits for sustainable green methodologies concerning biosensorics, bioconversion reactors or fuel cells. The bioelectrocatalytic system combines a biological element and a suitable transducer converting the response from interaction with the target analyte into a quantifiable signal [1]. However, an effective electron transfer in bioelectrocatalysis requires the presence of an

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intermediary compound, the so-called mediator. The mediator shuttles redox equivalents between a bio-element (enzyme) and a transducer (electrode), and this supplementary step usually results in an increased effectivity of the system in terms of selectivity and sensitivity. In fact, a good mediator must fulfil a number of requisites such as: it should be absorbed on the surface of the electrode, be retained active on it, react rapidly with the reduced enzyme, be stable in the reduced and oxidised forms and, finally, be non-toxic [2]. In this context, a number of electron acceptors and complexes as well as various methodologies involved in the mediated systems have been created and still in focus nowadays [3]. Due to fast and reversible redox-reactions quinone derivatives have attracted a special attention as potential mediators. Recently, the influence of electron donating substituents on the electrochemical oxidation behaviour of methyl substituted 1,4-benzoquinone derivatives was discussed with the help of quantum chemical calculations [4]. Also, aminated quinoidal compounds have been examined as redox mediators applicable for bioelectrocatalytic systems using two types of pyrroloquinoline quinone-dependent alcohol dehydrogenases as well as the determined molecular characters by *ab initio* quantum chemical calculation have been suggested as a useful instrument for predicting of potential mediators in the biosensors based on different oxidoreductases [5]. Thus, in our opinion, 2-arylamino-substituted 1,4-benzoquinone derivatives having two oxygen atoms of different activity and, therefore, modified redox properties compared to quinone are of interest as potential electron transfer mediators.

The aim of our work was to synthesise a series of 2-substituted 1,4-benzoquinone derivatives bearing an arylamino group with various substituents in *o*-, *m*- and *p*-positions of an aromatic ring, and a detail study of the structure and properties of the obtained products using NMR spectroscopy. According to the literature, 2-arylamino-1,4-benzoquinones are readily formed as the main product by treatment of *p*-benzoquinone with aromatic amines in the aqueous medium [6–9]. However, the authors give different reaction conditions and melting characteristics for the same compounds. For example, the melting point for 2-phenylamino-1,4-benzoquinone is indicated as

117–118°C [10], 131–133°C [9], 139–140°C [7] and, meanwhile, the reaction temperature ranges from cooling at 0°C [7] to heating at 50–70°C [9] for a similar process time. On the other hand, some researches note that this reaction usually gives a mixture of mono- and dianilino-1,4-benzoquinones [7, 11, 12]. Only by a suitable selection of the temperature, time and solvent the mono- or disubstituted derivatives of benzoquinone and primary aromatic amines can be synthesised [7]. In order to avoid the formation of disubstituted derivatives the reactions were carried out at low temperatures in dilute solutions [11]. Therefore in this work we thoroughly investigated a conjugate addition of aromatic amines: *N*-methylaniline, *m*-nitro-, *p*- and *o*-methoxy- or fluorosubstituted anilines to 1,4-benzoquinone (BQ) and established the optimal reaction conditions for the synthesis of sufficiently pure target products. We present a detailed description of the synthesis, purification procedures and structure evaluation of the obtained 2-arylamino-1,4-benzoquinones.

In a view of our special interest to synthesise new promising and potential electron transfer mediators in the range of 2-arylamino-1,4-benzoquinone derivatives, we have made an attempt to estimate their electron transfer (redox) ability by calculations of quantum chemical structure-activity relationship (QSAR) descriptors. The obtained results have been compared with those of the well-known standard electron transfer mediator BQ. The use of QSAR descriptors is of great importance for screening a series of compounds in order to select structures with the desired molecular properties, including those not yet synthesised [13–16]. The general idea of QSAR descriptors has been widely presented in the past [17]. It means the rules to transform searches of compounds with definite, desirable molecular properties into a computationally quantified mathematical form. The correlations between the structure and activity properties have been detected for important findings in bioelectrochemistry [18–20]. So, in this way, with the help of calculated QSAR descriptors, it becomes possible to examine the newly synthesised 2-arylamino-1,4-benzoquinone molecular structures, then find a relationship between molecular structures and desired electron transfer properties. This hereafter enables one to select the most promising electron transfer

compounds for bioelectrocatalytic systems and to synthesise them in the laboratory. Therefore, in this work we have made an attempt to define how the newly synthesised arylamino-1,4-benzoquinones benefit the characteristics of effective electron transfer mediators by calculation of their electron accepting and donating ability expressed by appropriate QSAR descriptor characters. A further experimental evaluation of the synthesised compounds in terms of electron transfer mediators in bioelectrocatalytic systems are in our closest plans.

EXPERIMENTAL

Chemistry

Materials. 3-Nitroaniline, N-methylaniline, 2-methoxyaniline and 4-methoxyaniline were obtained from Sigma Aldrich (Germany). 1,4-Benzoquinone, 2-fluoroaniline and 4-fluoroaniline were supplied by Alfa Aesar (Germany). Chloroform was from AppliChem (Germany). Bi-distilled water was made employing a local custom made distiller (Institute of Biochemistry, Life Sciences Center, Vilnius University, Lithuania).

General methods. Melting points were determined in open capillaries on a MEL-TEMP 1202D apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 operating in the Fourier transform mode and Bruker Ascendtm 400 at 302 K. Chemical shifts are given in δ units (ppm), relative to the TMS as the internal standard and referenced to the centre of the deuterated solvent signal: CDCl_3 (7.26, 77.0 ppm) and DMSO-d_6 (2.5, 39.5 ppm) for ^1H and ^{13}C spectra, respectively. ^{19}F spectra are given relative to CFCl_3 , and referenced to CF_3COOH (−76.5 ppm) as the internal standard. The values of chemical shifts are expressed in ppm and coupling constants (J) in Hz. The spectral data of the third composed aromatic ring of compound **4e** are marked in italic. Elemental analyses (C, H, N) were performed on an Elemental Analyser CE-440. The reactions were controlled by the TLC method and performed on a Merck precoated silica gel aluminum roll (60F₂₅₄) with chloroform-ethyl acetate (v/v, 14:7) as the eluent. Dry column vacuum chromatography was performed with silica gel 60 (0.015–0.040 mm, Merck).

General procedure for the synthesis of 1,4-benzoquinone derivatives 2a–f, 3b, e and

4e. BQ (10 or 20 mmol, see Table 1) was dissolved in hot distilled water (60°C), and the solution was clarified by filtration. The filtrate was cooled and a solution of the appropriate aniline **1a–f** (10 mmol) was added to it. The solution of aniline **1a–f** was prepared by adding 10 mmol of these compounds into water (50 ml) and then adding acetic acid under stirring until all amine dissolved. The resulting mixture was stirred at the required temperature for 15–20 min (see Table 1). The formed dark crystals were filtered off, washed with water and dried under reduced pressure.

2-(3-Nitrophenylamino)cyclohexa-2,5-dieno-1,4-dione (2a). Dark violet crystals, m. p. 250–260°C (lit. m. p. 290–300°C [21]). ^1H NMR (300 MHz, DMSO-d_6): δ = 6.08 (br. d., J = 1.9 Hz, 1H, 3-CH), 6.75 (br. d., J = 1.8 Hz, J = 10.0 Hz, 1H, 5-CH), 6.87 (br. d., J = 10.0 Hz, 1H, 6-CH), 7.67 (br. t, J = 7.7 Hz, 1H, 5'-CH), 7.81 (br. d., J = 7.4 Hz, 1H, 6'-CH), 7.98 (br. d., J = 7.7 Hz, 1H, 4'-CH), 8.18 (br. s., 1H, 2'-CH), 9.30 (br. s., 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 101.38 (C-3), 117.14 (C-22), 118.92 (C-42), 8.73 (C-5'), 130.61 (C-6'), 133.52 (C-5), 138.46 (C-6), 139.68 (C-1'), 143.63 (C-2), 148.32 (C-32), 183.34 (C-4), 186.36 (C-1).

2-[Methyl(phenyl)amino]cyclohexa-2,5-dieno-1,4-dione (2b). Dark brown crystals, m. p. 120–130°C (lit. m. p. 139–140°C [22], lit. m. p. 125–130°C [6]). ^1H NMR (300 MHz, CDCl_3): δ = 3.33 (s, 3H, N-CH₃), 5.84 (d, J = 2.3 Hz, 1H, 3-CH), 6.49 (d, J = 10.0 Hz, 1H, 6-CH), 6.63 (dd, J = 2.3 Hz, J = 10.0 Hz, 1H, 5-CH), 7.07 (d, J = 7.4 Hz, 2H, 2',6'-CH), 7.25 (t, J = 7.4 Hz, 1H, 4'-CH), 7.37 (t, J = 7.4 Hz, 2H, 3',5'-CH). ^{13}C NMR (75 MHz, CDCl_3): δ = 42.84 (NCH₃), 109.13 (C-3), 5.22 (C-2',6'), 6.45 (C-4'), 9.62 (C-3',5'), 134.67 (C-5), 137.35 (C-6), 147.37 (C-1'), 150.10 (C-2), 183.86 (C-4), 186.18 (C-1).

2,5-bis[Methyl(phenyl)amino]cyclohexa-2,5-dieno-1,4-dione (3b). Brown crystals, m. p. 200–210°C (lit. m. p. 205°C [6]). ^1H NMR (300 MHz, CDCl_3): δ = 3.39 (s, 6H, N-CH₃), 5.55 (s, 2H, 3,6-CH), 7.13 (d, J = 7.5 Hz, 4H, 2',6'-CH), 7.26 (t, 2H, J = 7.5 Hz, 4'-CH), 7.39 (t, 4H, J = 7.5 Hz, 3',5'-CH). ^{13}C NMR (75 MHz, CDCl_3): δ = 43.07 (2NCH₃), 106.99 (C-3,6), 5.27 (2(C-2',6')), 6.18 (2C-4'), 9.43 (2(C-3',5')), 147.89 (2(C-1')), 151.32 (C-2,5), 181.68 (C-1,4).

2-(2-Methoxyphenylamino)cyclohexa-2,5-dieno-1,4-dione (2c). Dark brown crystals,

m. p. 107–114°C (lit. m. p. 114°C [6]). ^1H NMR (300 MHz, DMSO- d_6): δ = 3.83 (s, 3H, 2'-OCH₃), 5.57 (br. s., 0.7H, 3-CH), 6.56 (br. s., 0.3H, 3-CH), 6.70 ((br. d., J = 9.9 Hz, 1H, 5-CH), 6.82 (br. d., J = 10.1 Hz, 1H, 6-CH), 6.99–7.32 (br. m., 4H, 3',4',5',6'-CH), 8.35 (br. s., 0.8H, NH), 8.61 (br. s., 0.2H, NH). ^{13}C NMR (75 MHz, DMSO- d_6): δ = 55.72 (OCH₃), 100.08 (C-3), 1.05 (C-3'), 0.80 (C-5'), 3.75 (C-6'), 6.07 (C-1'), 6.68 (C-42), 132.92 (C-5), 139.11 (C-6), 143.70 (C-2), 152.09 (C-2'), 183.60 (C-4), 185.66 (C-1).

2-(4-Methoxyphenylamino)cyclohexa-2,5-dieno-1,4-dione (2d). Dark violet crystals, m. p. 121–129°C (lit. m. p. 132–134°C [9], lit. m. p. 155–156°C [8]). ^1H NMR (300 MHz, CDCl₃): δ = 3.81 (s, 3H, 4'-OCH₃), 5.98 (br. s., 1H, 3-CH), 6.68 (br. s., 2H, 5,6-CH), 6.91 (br. m., 2H, 2',6'-CH), 7.13 (br. m., 2H, 3',5'-CH + NH).

2-(2-Fluorophenylamino)cyclohexa-2,5-dieno-1,4-dione, 2,5-bis(2-fluorophenylamino)cyclohexa-2,5-dieno-1,4-dione and 2,5-bis(2-fluorophenylamino)-4-(2-fluorophenylimino)cyclohexa-2,5-dien-1-one (2e, 3e, 4e). After filtration, the obtained product mixture was purified by dry column chromatography in the eluent system benzene-dichloroethane with a gradient from 10:0 to 0:10. The collected three fractions were subsequently concentrated under reduced pressure, the solid residues were filtered by using diethyl ether to give mono substituted **2e** (R_f 0.32), disubstituted **3e** (R_f 0.45) and trisubstituted **4e** (R_f 0.57) derivatives, yield 43, 18 and 15%, respectively.

2-(2-Fluorophenylamino)cyclohexa-2,5-dieno-1,4-dione (2e). Dark red crystals, m. p. 118–122°C. Anal. calcd. for C₁₂H₈FNO₂ (217.2): C 66.36; H 3.71; N 6.45. Found: C 66.47; H 3.59; N 6.61. ^1H NMR (300 MHz, DMSO- d_6): δ = 5.30 (br. m., 1H, 3-CH), 6.71 (dd, J = 2.1 Hz, J = 10.0 Hz, 1H, 5-CH), 6.82 (d, J = 10.0 Hz, 1H, 6-CH), 7.24–7.45 (m, 4H, 3',4',5',6'-CH), 8.90 (br. s., 1H, NH). ^{13}C NMR (75 MHz, DMSO- d_6): δ = 100.45 (C-3), 116.55 ($^2J_{\text{CF}}$ = 19.2 Hz, C-3'), 125.03 ($^2J_{\text{CF}}$ = 12.8 Hz, C-1'), 127.57 (C-5'), 128.20 ($^3J_{\text{CF}}$ = 7.8 Hz, C-4'), 133.16 (C-5), 138.77 (C-6), 145.02 (C-2), 156.01 ($^1J_{\text{CF}}$ = 249.0 Hz, C-2'), 183.36 (C-4), 185.77 (C-1). ^{19}F NMR (282 MHz, DMSO- d_6): δ = -66.92 (s, 1F, 2'-F).

2,5-bis(2-Fluorophenylamino)cyclohexa-2,5-dieno-1,4-dione (3e). Dark brown

crystals, m. p. 190–200°C. Anal. calcd. for C₁₈H₁₂F₂N₂O₂ (326.30): C 66.26; H 3.71; N 8.59. Found: C 66.40; H 3.59; N 8.73. ^1H NMR (400 MHz, DMSO- d_6): δ = 5.24 (br. d., J = 1.7 Hz, 2H, 3,5-CH), 7.25–7.45 (m, 8H, 3',4',5',6'-CH), 9.23 (br. s., 2H, NH). ^{13}C NMR (75 MHz, DMSO- d_6): δ = 95.92 (C-3,6), 116.54 ($^2J_{\text{CF}}$ = 19.3 Hz, 2C-3'), 125.02 ($^2J_{\text{CF}}$ = 12.0 Hz, 2C-1'), 125.14 ($^3J_{\text{CF}}$ = 3.7 Hz, C-6'), 127.64 (C-5'), 128.56 ($^3J_{\text{CF}}$ = 7.8 Hz, C-4'), 148.22 (C-2), 156.00 ($^1J_{\text{CF}}$ = 249.1 Hz, C-2'), 179.34 (C-1,4). ^{19}F NMR (282 MHz, DMSO- d_6): δ = -67.54 (s, 1F, 2'-F).

2,5-bis(2-Fluorophenylamino)-4-(2-fluorophenylimino)cyclohexa-2,5-dien-1-one (4e). Dark red crystals, m. p. 124–127°C. Anal. calcd. for C₂₄H₁₆F₃N₃O (419.40): C 68.73; H 3.85; N 10.02. Found: C 68.51; H 3.71; N 10.16. ^1H NMR (400 MHz, CDCl₃): 5.98 (br. d., J = 2.0 Hz, 1H, 3-CH), 6.06 (d, J = 0.8 Hz, 1H, 6-CH), 7.00–7.23 (m, 11H, CH_{ar}), 7.48–7.53 (m, 1H, 6'-CH), 7.70 (s, 1H, NH), 8.70 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl₃): δ = 91.67 (6-CH), 98.03 (3-CH), 116.14 (d, $^2J_{\text{CF}}$ = 19.8 Hz, 3'-CH), 116.16 (d, $^2J_{\text{CF}}$ = 19.4 Hz, 3'-CH), 116.38 (d, $^2J_{\text{CF}}$ = 19.5 Hz, 3'-CH), 121.68 (5'-CH), 123.21 (5'-CH), 124.31 (5'-CH), 124.31 (d, $^3J_{\text{CF}}$ = 4.6 Hz, 6'-CH), 124.38 (d, $^3J_{\text{CF}}$ = 4.0 Hz, 6'-CH), 124.63 (d, $^3J_{\text{CF}}$ = 4.0 Hz, 6'-CH), 125.12 (d, $^3J_{\text{CF}}$ = 7.5 Hz, 4'-CH), 126.23 (d, $^3J_{\text{CF}}$ = 7.4 Hz, 4'-CH), 126.54 (d, $^3J_{\text{CF}}$ = 7.5 Hz, 4'-CH), 126.00 (d, $^2J_{\text{CF}}$ = 11.6 Hz, 1'-CH), 126.59 (d, $^2J_{\text{CF}}$ = 11.5 Hz, 1'-CH), 136.33 (d, $^2J_{\text{CF}}$ = 11.7 Hz, 1'-CH), 140.73 (2-CH), 148.77 (5-CH), 152.84 (d, $^1J_{\text{CF}}$ = 247.7 Hz, 2'-CH), 154.74 (d, $^1J_{\text{CF}}$ = 247.8 Hz, 2'-CH), 155.25 (C = N), 155.67 (d, $^1J_{\text{CF}}$ = 248.6 Hz, 2'-CH), 180.58 (CO). ^{19}F NMR (282 MHz, CDCl₃): δ = -73.19, -73.36, -74.14 (s, 3F, 2'-F). The spectral data of the third composed aromatic ring of compound **4e** are marked in italic.

2-(4-Fluorophenylamino)cyclohexa-2,5-dieno-1,4-dione (2f). Brown-black crystals, m. p. 135–140°C. Anal. calcd. for C₁₂H₈FNO₂ (217.2): C 66.36; H 3.71; N 6.45. Found: C 66.19; H 3.60; N 6.62. ^1H NMR (300 MHz, CDCl₃): δ = 6.00 (d, J = 1.7 Hz, 1H, 3-CH), 6.73 (br. m., 2H, 5,6-CH), 7.08–7.20 (br. m., 4H, 2',3',5',6'-CH + 1H, NH). ^{13}C NMR (75 MHz, CDCl₃): δ = 100.61 (C-3), 116.62 ($^2J_{\text{CF}}$ = 23.0 Hz, C-3',5'), 124.68 ($^3J_{\text{CF}}$ = 8.4 Hz, C-2',6'), 132.39 (C-5), 133.05 ($^4J_{\text{CF}}$ = 2.9 Hz, C-1'), 139.70 (C-6), 143.52 (C-2), 160.29 ($^1J_{\text{CF}}$ = 246.7 Hz, C-4'), 183.52 (C-4), 186.46

(C-1). ^{19}F NMR (282 MHz, CDCl_3): $\delta = -68.15$ (s, 1F, 4'-F).

Computational background and methods/calculations

The DFT calculations were performed with the B3LYP and 6-311+g(d,p) basis set using the Gaussian 09 program package [23] for BQ and **2a–f**, **3b** of quinones (Q) and hydroquinones (QH_2) (+2e⁻ and +2H⁺). The use of the B3LYP hybrid functional at the DFT level is the most popular choice for treatment of heteroaromatic derivatives which matches well with the experimental observations [24–27]. The use of 6-311G, 6-31G basis sets accomplished with additional diffuse and polarized functions for the aromatic heterocycles also provided comparable results [28–31]. In this investigation, the search of a reasonable basis set has been explored for BQ and compounds **2a–f**, **3b**. Thus, the electronic parameters and the optimal geometries of compound **2a** in the form of Q and QH_2 have been calculated by means of 6-311+g(d,p) and 6-311++g(d,p) basis sets. The calculated values of the electronic parameters revealed negligible differences for both basis sets. Therefore, we chose the 6-311+g(d,p) basis set for the other BQ and **2a–f**, **3b** calculations. Ionic structures having neutral molecule geometry were also calculated to obtain vertical ionization energies and electron affinities. Initial structures were modelled and prepared for calculation with GaussView 5 [32]. The following electronic parameters were calculated and analysed: vertical ionization energy I_v – energy needed to remove one electron from a neutral molecule without changing its geometry (measure of electron donating power)

$$I_v = E(M_n^{+1}) - E(M_n^0); \quad (1)$$

vertical electron affinity A_v – gain (or loss if negative) of energy after one electron addition to a molecule (electron accepting power)

$$A_v = E(M_n^0) - E(M_n^{-1}); \quad (2)$$

chemical potential μ_v (negative electronegativity χ [33])

$$\mu_v = \frac{\partial E}{\partial N} = -\chi \approx -(I_v + A_v) / 2; \quad (3)$$

chemical hardness η_v (resistance to the change number of electrons in a molecule [33–35])

$$\eta_v = \frac{\partial^2 E}{\partial N^2} \approx I_v - A_v, \quad (4)$$

the fractional number of electrons to be added to the molecule to get its minimal energy without changing the geometry ΔN_{max} :

$$\Delta N_{\text{max}} = -\mu/\eta. \quad (5)$$

Here $E(M_n^{+1})$ stands for the total energy of the molecule M being a cation (net charge equal to +1), and having neutral (subscript n) molecule geometry, N is the number of electrons in the molecule. Energy of HOMO–LUMO gap ($\Delta E_{\text{H-L}}$) was calculated from the differences of LUMO and HOMO energies of neutral Q or QH_2

$$\Delta E_{\text{H-L}} = E_{\text{LUMO}} - E_{\text{HOMO}} = \eta_K, \quad (6)$$

and it is equal to the hardness calculated using the Koopman's theorem [36, 37].

The concepts of chemical potential μ_v and chemical hardness η_v arise from the Taylor series expansion of molecule energy dependence on the electron number $E = E(N)$ when geometry is fixed and leaving only first two series terms

$$\Delta E = \mu_v (\Delta N) + \frac{1}{2} \eta_v (\Delta N)^2, \quad (7)$$

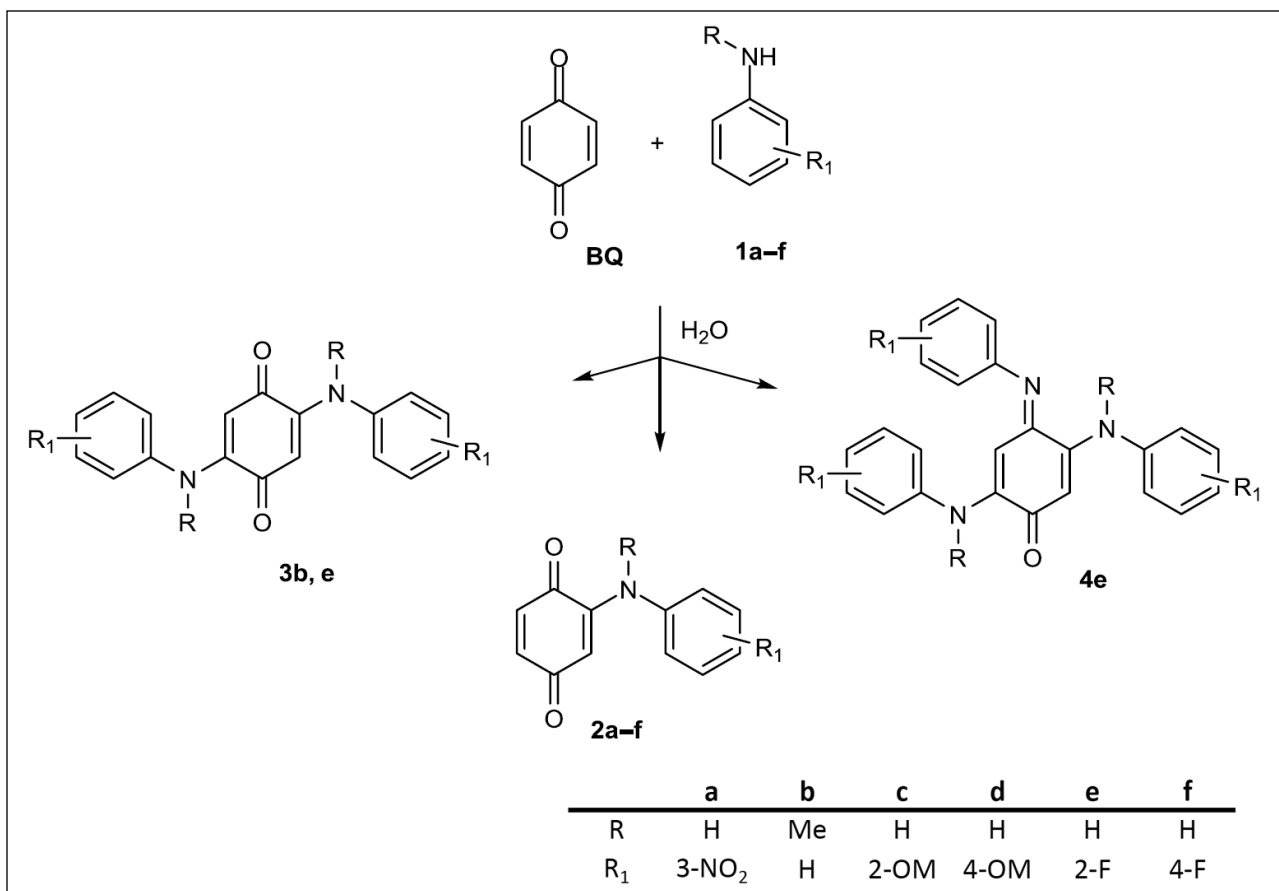
where according to formulas (3) and (4) the first order derivative (slope) is μ_v and the second one (curvature) is η_v .

RESULTS AND DISCUSSION

Chemistry

A synthesis of the studied 2-aryl amino substituted 1,4-benzoquinone derivatives is presented in the Scheme.

Target 2-substituted compounds **2a–f** were obtained by the reaction of BQ with the corresponding aromatic amine **1a–f** in an aqueous acetic acid solution. The first attempt to synthesise 2-substituted derivatives **2c**, **d** by the treatment of BQ with *o*- and *p*-methoxyanilines (**1c**, **d**) at the described conditions [6] was unsuccessful, we did not succeed to separate and purify purposive compounds. The main reasons for this failure were the



Scheme. The general scheme of the synthesis of 1,4-benzoquinone derivatives 2a–f, 3b, e and 4e

formation of the considerable amount of 2,5-disubstituted products in these reaction conditions. With the aim to minimise its amount, the reaction temperature, time, dilution and ratio of reacting components were varied to optimise the synthesis conditions of the target 2-arylamino-1,4-benzoquinones **2a–f** and **3b**. The results of this investigation are presented in Table 1.

The yield of compounds **2a–f** and **3b** was moderate because the reaction process was stopped at the start of formation of the first crystals. If the re-

action mixture is kept till the end of crystallisation, the mixtures of several products are always obtained. Product purification and isolation from the mixture is complicated.

Since *m*-nitro-, *o*- and *p*-methoxyanilino-1,4-benzoquinones **2a**, **c**, **d** were described previously [6, 8, 9, 21], we focused on the investigation of interactions of *o*- and *p*-fluoroaniline (**1e**, **f**) with BQ. It was established that the reaction of *o*-fluoroaniline with quinone even at 0°C temperature and the high dilution gave the mixture

Table 1. Optimal synthesis conditions for 2- and 2,5-arylamino- 1,4-benzoquinone derivatives **2a–f** and **3b**

Compound	<i>t</i> , min	<i>T</i> , °C	BQ/amine, mmol/mmol	BQ/H ₂ O, mmol/ ml	Yield, %
2a	20	60	1 : 1	20/40	61
2b	15	5	2 : 1	20/200	43
3b	20	60	1 : 1	20/40	54
2c	15	5	2 : 1	20/200	54
2d	15	5	2 : 1	20/200	48
2e	15	0	2 : 1	20/300	43
2f	15	5	2 : 1	20/200	37

of three products – mono-, di- and trisubstituted benzoquinone derivatives **2e**, **3e** and **4e**, yield 43, 18 and 15%, respectively. The formation of the trisubstituted derivative was unexpected, since some authors accent that the carbonyl group of benzoquinone does not react with aromatic amines under these conditions [7]. It should be noted that in the case when *o*-fluoroaniline **1e** was used, we did not succeed to establish the correct version of the reaction conditions leading to one product – monosubstituted derivative **2e**. Compound **2e** was isolated from the mixture by column chromatography. Meanwhile, in the reaction with *p*-fluoroaniline **1f**, only one compound **2f** was isolated.

In addition, it is imperative to note that the melting point of some synthesised compounds does not correspond to the literature data (see Experimental). The main reason for this may be a dark intense colour of the synthesised compounds, which becomes completely black during the melting decomposition of the material. The melting range of these dark products is difficult to determine. Consequently, the structure of the synthesised compounds was investigated in detail by NMR spectroscopy.

The structure of all newly synthesised 1,4-benzoquinone derivatives was identified by the ^1H , ^{13}C , $^1\text{H}/^{13}\text{C}$ 2D (HETCOR and HMBC) NMR spectra [38]. The resonances were assigned on the basis of arguments of chemical shift theory, signal intensity, and by the consideration of spin-spin coupling multiplets. The title compounds are formed of 1,4-benzoquinone and substituted aniline moieties, and observed by characteristic patterns in the NMR spectra. 2-Monosubstituted 1,4-quinones **2a–f** are presented by the proper spin-spin ABX multiplet, determined by the interaction of 3, 5 and 6 hydrogens in the ^1H NMR spectra, and by 6 separate resonances in the ^{13}C NMR spectra. In the case of 2,5-substitution, 1,4-benzoquinones **3b**, **3e** alone resonance of hydrogens 3, 6 and three resonances of C-1/C-4, C-2/C-5, C-3/C6 were detected in ^1H and ^{13}C NMR, respectively.

The studied compounds **2e**, **f** and **3e**, **4e** possess a fluorine atom at the *o*- or *p*-position of the aromatic ring. Due to the specific magnetic properties of the fluorine atom, spin-spin coupling (up to 4 bonds) multiplets were observed in

the ^1H and ^{13}C NMR spectra [39]. The splitting, arising from the fluorine, complicates the analysis of the aromatic region of the NMR spectra. The multiplets of the aromatic resonances in the ^1H NMR spectra overlap and are insufficiently informative, whereas in the case of the ^{13}C NMR spectra the multiplets are resolved. The difference of $^2J_{\text{CP}}$, $^3J_{\text{CF}}$ values observed in the ^{13}C NMR spectra for the same aromatic ring can be rationalised in terms of the substituent effects [40, 41]. Taking into account the investigated compounds **4e** bearing 3 *o*-fluorine substituted aromatic rings, 3 sets of the corresponding aromatic ring chemical shifts and *J* values were observed in the ^{13}C NMR spectra. The formation of compounds **4e** was proved by the presence of resonance at about 155 ppm (C = N) and 180 ppm (C = O) and 3 signals in the ^{19}F resonance spectrum integrated to one fluorine atom. Two signals of fluorine are broadened and one is sharp due to a different interconnection between benzoquinone and aromatic moieties. The spectral data of the third aromatic ring in compound **4e** are marked in italic, to indicate the dissimilarity of other two aromatic rings.

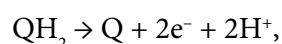
The presence and location of substituents of the aniline moiety were proved by the analysis of NMR data and ascertaining a characteristic influence on the chemical shifts and spin-spin coupling constants of study compounds.

The obtained NMR data are listed in the Experimental section.

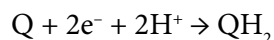
Theoretical studies

The title study has been further extended aiming to indicate the possible oxidative (for dihydro-1,4-benzoquinones) and reductive (for 1,4-benzoquinones) ability of the newly synthesised aryl-amino-1,4-benzoquinones **2a–f**, **3b** by means of calculation appropriate QSAR descriptors. Aiming to select the most promising redox mediator candidates the obtained computational results have been compared with those of the well-known standard mediator 1,4-benzoquinone (BQ).

The electrochemical oxidation reaction of dihydro-1,4-benzoquinone derivatives (QH_2) proceeded with the two electron and two proton transfer yielding benzoquinones (Q)



and the reversible reduction process [42, 43]



was broadly described in the past based on cyclic FT-IR spectroelectrochemistry and cyclic voltabsorptometry [4, 42–45]. In this context, it is important to find descriptors revealing the oxidative and reductive activity of **2a–f**, **3b** in the forms of QH_2 and Q, respectively.

A lot of work has been done in the field of theoretical chemistry in the prediction of the reactivity and definition of molecular meaningful QSAR descriptors [15, 17, 46–50]. In particular, density functional theory (DFT) has provided formal definitions for many descriptors [33, 51] and a part of them have been used as a tool to study the electrochemical redox reaction [4, 52–54]. In the present work definitions presented in the Computational

Background Section like η , the energy gap ΔE_{H-L} between LUMO and HOMO, I_v , A_v , the HOMO energy (E_H) and ΔN_{max} have been used to express the oxidative (for QH_2) and reductive (for Q) ability of arylamino-1,4-benzoquinones **2a–f**, **3b** and BQ. The calculated quantum chemical indices are presented in Table 2.

So, to find a theoretical relationship between QH_2 structural and oxidative properties, the E_H and I_v quantities have been considered. The ionisation potential means the amount of energy needed to remove an electron from an isolated gaseous atom or a molecule. So, it can be a meaningful measure of molecular oxidative ability. Another way to calculate the ionisation potential is the Koopman's theorem [36, 37]. According to it the ionisation potential is equal to the negative value of the energy of the HOMO orbital. Low ionization energy infers an easy removal of an

Table 2. QSAR descriptors of 2- and 2,5-arylamino- 1,4-benzoquinone derivatives **2a–f**, **3b** and benzoquinone (BQ). Calculated in the form of quinones (Q) and hydroquinones (QH_2)

Compound	I_v , eV	A_v , eV	E_H , eV	μ_v , eV	η_v , eV	ΔN_{max}	ΔE_{H-L} , eV
BQ							
Q	9.972	1.895	-7.809	-5.933	8.077	0.735	3.859
QH_2	7.972	-1.207	-5.885	-3.383	9.180	0.368	5.196
2a							
Q	8.409	2.184	-6.808	-5.424	5.971	0.908	2.936
QH_2	7.283	0.831	-5.714	-4.057	6.452	0.629	3.018
2b							
Q	7.890	1.516	-6.234	-4.703	6.374	0.738	2.914
QH_2	6.852	-0.578	-5.321	-3.090	7.526	0.411	4.435
3b							
Q	7.187	1.084	-5.712	-4.098	6.178	0.663	3.152
QH_2	6.407	-0.323	-5.138	-3.042	6.730	0.452	4.155
2c							
Q	7.579	1.704	-6.011	-4.641	5.875	0.790	2.571
QH_2	6.586	-0.654	-5.064	-2.966	7.241	0.410	4.435
2d							
Q	7.562	1.699	-6.00	-4.631	5.862	0.790	2.536
QH_2	6.597	-0.625	-5.073	-2.986	7.222	0.413	4.553
2e							
Q	8.074	1.892	-6.445	-4.983	6.181	0.806	2.783
QH_2	6.972	-0.506	-5.397	-3.233	7.478	0.432	4.526
2f							
Q	8.056	1.878	-6.422	-4.967	6.178	0.804	2.757
QH_2	6.947	-0.508	-5.358	-3.220	7.455	0.432	4.551

electron and the molecule undergoes oxidation easily. As well, the HOMO energy of QH_2 can also disclose the oxidative power of QH_2 . The higher HOMO energy the easier to remove electrons from the molecule.

The oxidative ability of the newly synthesised QH_2 compounds **2a–f**, **3b** expressed as I_v varied in a range from 6.41 eV for **3b** to 7.28 eV for **2a**. The E_H varied from -5.06 eV for **2c** to -5.71 eV for **2a**. This evidently points that QH_2 **2a–f**, **3b** can act as electron transfer mediators and most of them can participate more efficiently in the oxidation process as compared to that of the standard BQH_2 characterised by the higher I_v of 7.97 eV and the lower E_H value of -5.89 eV. The electron donating ability revealing oxidation trends of QH_2 calculated for I_v decreases in the order $\text{BQH}_2 > \mathbf{2a} > \mathbf{2e} > \mathbf{2f} > \mathbf{2b} > \mathbf{2d} > \mathbf{2c} > \mathbf{3b}$, similar decreases in the order $\mathbf{2c} > \mathbf{2d} > \mathbf{3b} > \mathbf{2b} > \mathbf{2a} > \text{BQH}_2$ were obtained for HOMO's of QH_2 . So, the electron donating (oxidative) power of all QH_2 compounds **2a–f**, **3b** is higher than that of BQH_2 . This phenomenon can be explained due to the presence of electron donating arylamino moieties, which are directly bonded to the quinone ring through the amino group.

Unlike the oxidative ability, the reductive ability of many mediators is sometimes weakly pronounced in the experiment, due to the difficulty to clearly express cathodic peaks. Despite the complexity of cathodic processes in an experiment, there are some theoretical QSAR descriptors used to estimate the electron accepting of mediators.

In our case the fractional number of electrons (ΔN_{max}) clearly implies the electron accepting nature of mediators. This parameter characterises how many electrons should be added to a molecule to reach the minimum energy and testifies about the electron accepting ability of mediators.

The Q and QH_2 of compound **2a** have the highest possible saturation with electrons ($\Delta N_{\text{max}} = 0.908$ and 0.629 for Q and QH_2 , respectively). ΔN_{max} quantity for other compounds **2b–f** was somewhat smaller than for **2a**. However, it is evident that the newly synthesised mediators **2a–f** express a higher ability to accept electrons than that of BQ ($\Delta N_{\text{max}} = 0.735$ and 0.368 for Q and QH_2 , respectively).

The electron affinity A_v is the meaningful measure for evaluation of electron accepting (reduc-

tive) power. This characteristic means the energy lowering (or rising) after an electron addition to a neutral molecule. A high positive electron affinity value implies the molecule tends to accept an additional electron easily with the energy lowering while the negative value indicates molecule resistance to that (energetically unfavourable process).

As it was indicated above, all QH_2 of **2a–f**, **3b** exhibit an enhanced electron donating (oxidative) power due to the presence of the electron donating arylamino moiety as compared to BQ. Therefore, it was expected that the Q of **2a–f**, **3b** should be characterised by reduced electron accepting power with respect to BQ. However, A_v and μ_v values which are responsible for the characterisation of electron accepting potency testify a more complicated picture. For example, the highest value of A_v has the Q of **2a** bearing a 3- NO_2 group bonded to the arylamino moiety as compared to other Q **2b–f**, **3b** and BQ. The NO_2 group is well known as an excellent electron acceptor characterised by negative inductive and mesomeric ($-I$ and $-M$) effects. Meanwhile, compounds **2e** and **2f** substituted with a methoxy group ($+I$, $+M$) and fluorine groups ($-I$, $+M$) have A_v values almost equal to that of BQ. Considering this, an expected result of the reduced electron accepting power was observed for Q of **2b** and **3b** compounds with the methyl group directly added to the N atom of the amine group. The calculation results in this case testify that the reduced electron addition power is possibly influenced by the electron donating methyl group ($+I$). Also, it is worth mentioning the results that we have got for the electron accepting power of QH_2 . It is well known that hydroquinones are bad electron acceptors and this was shown by our calculations which provided negative values of A_v for all QH_2 except compound **2a**. The A_v value for **2a** is positive and equal to 0.831 eV showing that QH_2 **2a** can be a good electron acceptor.

Aiming to properly establish an insight into the electrochemical oxidation of hydroquinones and the reduction of quinones it is important to point out other definitions of molecular stability and reactivity. One of them is the absolute chemical hardness η_v which reveals the power of a molecule both to accept and to remove electrons. The hardness measures the resistance of a chemical system to change in the number of electrons [36, 37]. This means that η_v can support

the concept describing oxidative and reductive strengths of a mediator. The higher η_v value corresponds to the higher resistance of the mediator to change in the number of electrons that means to be reduced or oxidised. The most accurate method to get hardness is formula (4), but there is another way to calculate η_v . In accordance to the Koopman's theorem [36, 37] and within the HF framework of molecular orbital theory, the absolute hardness can be calculated also as the energy gap between LUMO and HOMO orbitals. Thus, in this case the hardness corresponds to the gap between the HOMO and LUMO orbitals. The larger the HOMO–LUMO energy gap the harder, more resistant the mediator is. Even more, the hardness correlates quite well with the chemical reactivity of the molecule [16]. Thereby, this quantity can predict the effectiveness of the mediated system in the reaction process, that is the acceptance and donation of electrons.

The calculated hardness of all hydroquinones QH₂ **2a–f** and **3b** was found to be gradually decreasing in the order of BQH₂ > **2b** > **2e** > **2f** > **2c** > **2d** > **3b** > **2a**. Similarly, the hardness of Q **2a–f** and **3b** is gradually lowering in the order BQ > **2b** > **2e** > **2f** > **3b** > **2a** > **2c** > **2d**, which testifies the increased reductive or oxidative ability of **2a–f** and **3b** as compared to BQ or BQH₂, respectively. Compound **2a** is characterised by the highest reactivity to donate and accept electrons and the lowest η_v values. BQ and BQH₂ show the highest η_v values and the highest resistance to participate in redox reactions than that of new **2a–f**, **3b** hydroquinones and quinones. It indicates that **2a–f** and **3b** can more easily participate in redox reactions than BQ and BQH₂. The results of the HOMO–LUMO energy gap calculation presented in Table 2 confirm the redox regularities obtained by the analysis of η_v values.

CONCLUSIONS

In summary, we have presented the synthesis study of a conjugate addition of aromatic amines: N-methylaniline, *o*-, *m*- and *p*-nitro-, methoxy- and fluorosubstituted anilines to 1,4-benzoquinone. A series of new generation electron transfer mediators 2-arylamino-substituted 1,4-benzoquinone derivatives with various substituents in the *o*-, *m*- and *p*-positions of the aromatic ring have been

synthesised and optimal reaction conditions for the synthesis of each of them have been established.

The oxidative and reductive properties of the newly synthesised 2-arylamino-1,4-benzoquinones expressed by QSAR descriptors evidently point to that they can act as electron transfer mediators. The electron donating (oxidative) power of all arylamino-substituted 1,4-dihydrobenzoquinones is higher than that of 1,4-dihydrobenzoquinone. However, the calculated electron affinity testifies that the electron accepting potency of arylamino-substituted 1,4-benzoquinone correlates well with the ability of substitutes to withdraw or donate electrons. Moreover, most of them should enhance the redox process as compared to the known standard 1,4-benzoquinone mediator. The experimental validation of these findings is the subject of our further work.

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**POTENCIALIŲ ELEKTRONŲ PERNAŠOS
MEDIATORIŲ 2-ARILAMINO-1,4-
BENZOCHINONO DARINIŲ SINTEZĖ IR
TEORINIS TYRIMAS**

S a n t r a u k a

Medžiagos, pasižyminčios redokso savybėmis ir gebančios reoksiduoti fermentus, yra kuriamos ir tiriamos jau kelis dešimtmečius. Chinoidinės struktūros junginiai yra vieni iš perspektyvių redokso savybėmis pasižyminčių mediatorių. 2-Arilamino-1,4-benzochinono dariniai, turintys du skirtingo aktyvumo deguonies atomus ir dėl to modifikuotas redokso savybes, palyginti su nepakeistu chinonu, yra potencialūs elektronų pernašos mediatoriai. Taip buvo ištirta 1,4-benzochinono ir aromatinių aminių: N-metilanilino, *o*-, *m*- ir *p*-nitro, metoksi- ir fluoropakeistų anilinių sąveika ir sintezuota eilė 2-arilamino-1,4-benzochinonų, turinčių įvairius pakaitus benzeno žiedo *o*-, *m*- ir *p*-padėtyse. Nustatytos optimalios kiekvieno anilino prisijungimo reakcijos sąlygos: reakcijos laikas, temperatūra, reagentų bei tirpiklio (vanduo) santykiai. Sintezuotų junginių struktūra buvo patvirtinta BMR spektroskopijos metodais. 2-Arilamino-1,4-benzochinono darinių oksidacinės ir redukcinės savybės įvertintos remiantis apskaičiuotais kvantinės chemijos reaktivity indeksais. Skaičiavimų rezultatai parodė, kad naujai sintezuoti 2-arilamino-1,4-benzochinonai turėtų efektyviau spartinti oksidacinę redukcinių procesą, lyginant su žinomu standartu – 1,4-benzochinonu.