ortho-Substituted (Aryl)(3-nitrobenzo[*b*]thiophen-2-yl)amines: Study of the Electrochemical Behavior

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The reduction potentials of the title compounds **4** have been measured by cyclic voltammetry. The effect of the substituents has been evaluated by using a linear free energy relationship treatment, thus evidencing that the present *ortho*-substituents affect the E_{pc} values basically by electronic effects. A comparison with data previously collected on *ortho*-substituted (aryl)(2-nitrobenzo[*b*]thiophen-3-yl)amines **3** has provided some interesting information. Different electrochemical behaviors are observed during the reduction (a reversible process and an irreversible process are operating in **3** and **4**, respectively): to elucidate the reasons for this different behavior, the "reversible" reduction potentials of **5** and of **6** have been measured. Moreover, higher susceptibility constants have been calculated for compounds of series **4** with respect to those of series **3** ($\rho_4 = 329$ and $\rho_3 = 182$, respectively). A rationale for all of these findings has been offered.

Introduction

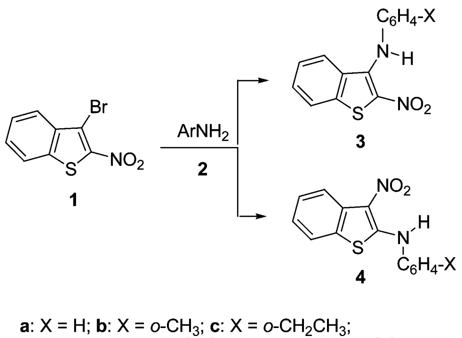
In the framework of our interest in the study of reactions of nitrothiophenes and -benzo[*b*]thiophenes with nucleophiles and with the aim of gaining information on their general reactivity as well as on their synthetic applications,[1] we have deeply investigated the behavior of 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) with amines, discovering a "novel" aromatic nucleophilic substitution with rearrangement.[2]

As a matter of fact, **1** reacts with anionic and neutral nucleophiles in different solvents, giving the "expected" substitution products deriving from an *ipso*-substitution, presumably occurring via the usual S_NAr (aromatic nucleophilic substitution) pathway.[3]

On the contrary, **1** could give the "expected" products of the nucleophilic *ipso*-substitution (**3**) together with the "unexpected" **4**,[2] e.g., in DMF (dimethyl formamide) with feeble nucleophiles (e.g., **2**: anilines *ortho*-substituted or *meta*- and *para*-substituted, but in the second instance not containing electron-donating substituents) and in the presence of some non-nucleophilic bases (tertiary amines as well as potassium carbonate) (Scheme 1).

Compounds **4** seem to derive from some rearrangement of the nitro group at the level of the formed intermediates, as confirmed by a deep investigation on ^{13}C-labeled **1**.[2b] A study on the effect of the nature of the used anilines together with an accurate examination of different experimental conditions (e.g., the effects of the solvents used, of the reaction temperature, and of the nature and/or quantity of the bases used have been evaluated) as well as DFT (density functional theory) computations[2c,d] has furnished information allowing the proposal of a mechanism for the studied reaction.

SCHEME 1



a: X = H; **b**: X = *o*-CH$_3$; **c**: X = *o*-CH$_2$CH$_3$; **d**: X = *o*-F; **e**: X = *o*-Cl; **f**: X = *o*-Br; **g**: X = *o*-OCH$_3$

Interestingly enough, some **3**-type compounds showed pharmacological properties (antiexudative and analgesic responses),[4] which as nonacid and nonsteroidal compounds meet some interest considering the heavy problems associated with the gastrointestinal tolerance of anti-inflammatory drugs.[5] Moreover, by using the Ames test,[6] it has been observed that several compounds of series **3** show low or no mutagenicity, despite the presence of the nitro group (a group generally leading to genotoxicity).[7] Therefore, the electrochemical reduction of nitro compounds appears of interest from a biological point of view as it, in some way, mimics the action of nitroreductase in living systems. This fact has attracted our attention because the nitro group represents an interesting pharmacophore.[4] Moreover, it must be remembered that also thienyl and benzo[*b*]thienyl residues enter into the structure of several drugs or of interesting hits.[4a−c,8] In this line and considering the above recalled pharmacological activity of some compounds of series **3**,[4a−c] we have enlarged the investigation of the electrochemical behavior to compounds **4**−**6**.

Thus, considering the role of bacterial nitroreductase (as well as of nitrosoreductase and of *O*-acetyltransferase) in the biological reduction process of the nitro group, we have carried out

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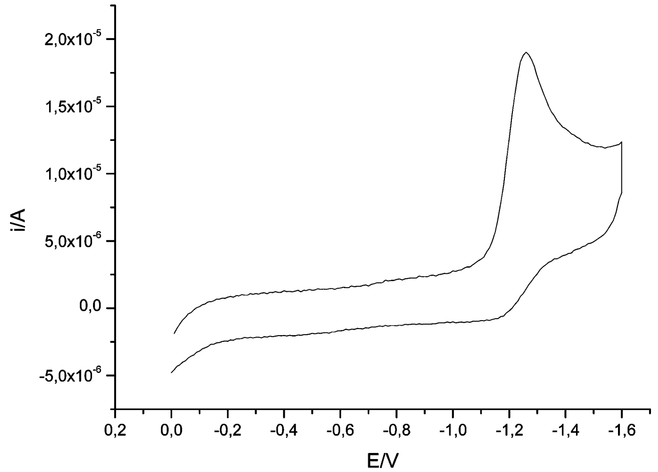


Figure 1. Cyclic voltammogram obtained for **4a** in DMSO solution with 0.1 M $N(Et)_4BF_4$ as the supporting electrolyte ($\nu = 1.2$ V/s).

the electrochemical reduction of some *ortho*-, *meta*-, and *para*-substituted (aryl)(2-nitrobenzo[*b*]thiophen-3-yl)amines **3**.[9] The investigation of the substituent effect by using LFERs (linear free energy relationships) has provided interesting information.[9]

Moreover, the special effect exerted by the *o*-hydroxy substituent on the voltammetric behavior has been enlightened by a deep computational study.[9b] Interestingly, *ortho*-substituted **3** gave a good LFER simply using the relevant *para*-substituent constants (σ_p). Indeed, a parallel examination of the SCS (substituent chemical shift) of ^{13}C NMR data had been carried out, allowing a nice investigation of the substituent effects on the different skeleton carbon atoms of **3**.[10]

DFT computations in the gas phase[11] were carried out on **3a** and **4a**, and an examination of their most stable conformers puts in evidence some interesting differences in their geometries and stabilities.[2d] As a matter of a fact, the unexpected **4a** is "completely planar" and is stabilized by a strong $>NH\cdots O_2N-$ hydrogen bond (1.784 Å). In contrast, in **3a** the relevant hydrogen bond is quite feeble (1.922 Å), and **3a** on the whole is not planar [with respect to the benzo[*b*]thienyl ring the phenylamino group is rotated about 35° to minimize the repulsive interactions between C−4(H) and C−2′(H) protons]. As a consequence, **4a** is significantly more stable than **3a** ($\Delta E = 16.8$ kJ mol^{-1}).

These observations suggest that in the compounds of series **4** the transmission of electronic effects should be more and more effective than in those of series **3**, and therefore, the dependence of the standard redox potential on the electronic effects of the substituent should be stronger.

On the basis of this hypothesis, we have now enlarged our study of the electrochemical behavior to a series of *ortho*-substituted **4** compounds (in **4**: $X = $ H, *o*-CH_3, *o*-CH_2CH_3, *o*-F, *o*-Cl, *o*-Br, *o*-OCH_3). In the considered series the electronic effect of the substituent ranges from the moderately electron-withdrawing halogens to the strongly electron-donating methoxy group. That is, a quite large range of substituent effects has been considered, presumably ensuring confidence in the statistical results of the relevant LFER.

Results and Discussion

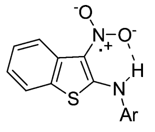
Electrochemical Behavior of 4a−g, 5, and 6. The ease of reduction of a compound is usually determined by the value of $E_{1/2}$, which is an excellent approximation of the standard potential. For the reversible or quasi-reversible electrode processes, this parameter can be estimated as the half-sum of the cathodic and anodic peak potentials involved in the redox reaction as recorded by cyclic voltammetry.[12]

TABLE 1: Values of E_{pc}/V Obtained from the Cyclic Voltammograms Recorded at $\nu = 0.02$ V/s

compound **4**	X	E_{pc}/V	σ[a]
a	H	−1.21	0.00
b	*o*-CH_3	−1.23	−0.14
c	*o*-CH_2CH_3	−1.24	−0.13
d	*o*-F	−1.15	0.06
e	*o*-Cl	−1.13	0.22
f	*o*-Br	−1.12	0.22
g	*o*-OCH_3	−1.29	−0.28

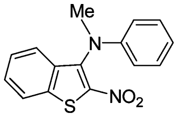
[a] Substituent constants from ref 14.

CHART 1

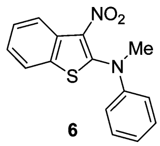


$4^{\bullet-}$

CHART 2



5



6

The redox behavior of (aryl)(3-nitrobenzo[b]thiophen-2-yl)amines **4a−g** was studied by cyclic voltammetry (CV), cycling the potential between 0 and −1.6 V. All the responses were characterized by an irreversible reduction peak; as an example in Figure 1 the voltammogram obtained for compound **4a** at 1.2 V/s is shown. The reaction was irreversible even at very high scan rates. Due to the impossibility to estimate $E_{1/2}$, we decided to investigate the influence of the substituent on the electrochemical behavior, taking into account the value of E_{pc}. The obtained results are collected in Table 1.

The behavior of **4a−g**, i.e., the irreversible reduction, is different from that observed in the instance of the relevant **3**[9b] compounds, and it could be ascribable to the larger stability of compounds **4** (see above). This statement is confirmed by the fact that the E_{pc} values reported in Table 1 are always more cathodic than those for the monoelectronic reduction wave of the series **3**, previously reported.[9b]

The unexpected irreversibility of the reduction observed for these compounds could be due to the fact that the radical anion $4^{\bullet-}$ (Chart 1) which is formed by reduction is even more stabilized by a hydrogen bond than the relevant starting products, thus giving rise to a stable intermediate whose formation then becomes irreversible. Moreover, we cannot exclude that a proton transfer from the $>N-H$ system to the $-NO_2^{-\bullet}$ system could favor the occurrence of an irreversible process, in line with the voltammetric behavior observed.

This kind of electrochemical behavior strictly resembles the general behavior observed in examining the reduction of several nitroaromatic compounds in the presence of water.[13]

To explain this point, we have synthesized *N*-methyl-2-nitro-*N*-phenyl-1-benzothiophen-3-amine (**5**) and *N*-methyl-3-nitro-*N*-phenyl-1-benzothiophen-2-amine (**6**) (Chart 2), that is, the two isomeric amines [in principle deriving by *N*-methylation from (phenyl)(2-nitrobenzo[b]thiophen-3-yl)amine (**3a**) and from (phenyl)(3-nitrobenzo[b]thiophen-2-yl)amine (**4a**), respectively]

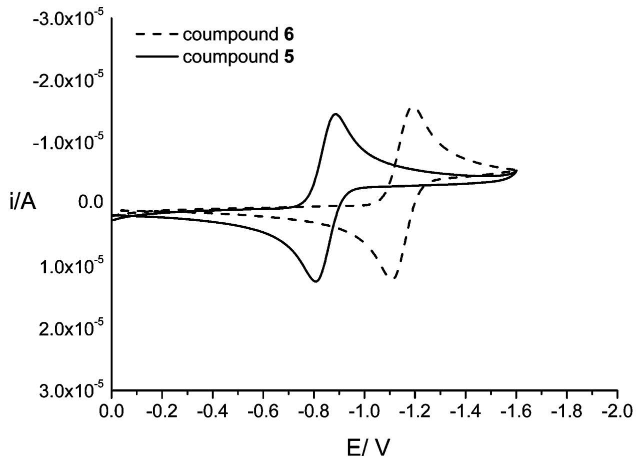


Figure 2. Cyclic voltammograms obtained for **5** and **6** in DMSO solution with 0.1 M $N(Et)_4BF_4$ as the supporting electrolyte ($\nu = 20$ mV/s).

for examining their voltammetric behavior. As a matter of fact, if the different electrochemical behavior (reversibility or irreversibility) were in some way dependent on some stability difference linked to the structure, also in **5** and in **6** the difference could survive. Vice versa, if the different behavior was dependent on the occurrence of a strong stabilizing hydrogen bond in compounds **4**, otherwise absent or much less important in compounds **3**, the difference would disappear because no hydrogen bond can be present.

The interesting result is that both **5** and **6** give a reversible reduction process (see Figure 2), strongly supporting the importance of the formed hydrogen bond in **4a**−**g** and allowing us to discharge the hypothesis of a strong intrinsic difference between compounds of series **3** and **4**, in some way dependent on other structural differences.

The values measured for $E_{1/2}$ concerning **5** and **6**, −0.843 and −1.146 V vs SCE, respectively, are different between themselves and require some comments. The significantly more cathodic value of $E_{1/2}$ measured for **6** indicates that it is less prone to be reduced. This property can be related to the fact that in **6** the nitro group, unlike what happens in the instance of **5**, can enjoy the conjugative interaction of both the nitrogen of the adjacent amino group ($N{-}C{=}C{-}NO_2$ interaction) and the sulfur of the ring ($S{-}C{=}C{-}NO_2$ interaction). This causes not only a higher thermodynamic stability with respect to **5** (see after), but also a lower tendency to be reduced because of the higher negative charge located on the nitro group.

Another interesting observation can be related to the E_{pc} values determined for **5** and **6**, which are −0.89 and −1.20 V, respectively. As a matter of fact, they are practically the same as those recorded for **3a** and **4a** (−0.90 and −1.21 V, respectively). The finding that the partners of the couples **3a** and **5** or **4a** and **6** display almost the same value of the cathodic peak potential further supports the idea that, in the absence of the thermodynamic parameter $E_{1/2}$, the E_{pc} values could be well used for evaluating the substituent effects on the voltammetric behavior.

The performed calculations[11] confirmed the higher stability of **6** with respect to **5** in vacuo ($\Delta E = 0.70$ kcal mol^{-1}) as well as in a solvent (DMSO, dimethyl sulfoxide; $\Delta E = 1.37$ kcal mol^{-1}). The deviation from planarity of the NO_2 group, almost null for **5** (3.2° in vacuo; 3.3° in DMSO), is quite large for **6** (−20.0° in vacuo; −13.0° in DMSO), showing a lesser conjugation between the NO_2 group and the benzothiophene ring. In both **5** and **6** the same benzothiophene ring could conjugate with the phenyl moiety via the nitrogen atom. The extent of this conjugation can be assessed by measuring the deviation from the angle between the planes defined by phenyl and benzothiophene rings: this value is larger for **5** (127.7° in vacuo; 133.4° DMSO) than for **6** (−40.0° in vacuo; −32.1° DMSO); this more extended conjugation in **6** can possibly be the source of its higher stability in comparison with **5**.

Application of LFER to Electrochemical Measurements. The calculated ΔE_{pc} values measured at $\nu = 0.02$ V/s for **4a**−**g** have been tentatively plotted versus σ_p Hammett constants,[14] looking for the occurrence of "only" electronic effects, as already observed for the series of compounds **3** *ortho*-substituted in a similar study of their voltammetric behavior.[8b]

The electrochemical data give a good monoparametric LFER ($\rho_o = 329 \pm 31$, $i = -1.19 \pm 0.01$, $r = 0.978$, $n = 7$) by using the σ_p constants, which range from +0.22 to −0.28 ($\Delta\sigma_p = 0.50$).[14]

Conclusions

On the whole the following observations can be derived from the data collected: (i) Once more,[8b] the simple electronic "classical" effects of the substituents present in conjugated positions and thus quantified by means of σ_p substituent constants[14] are able to well correlate the electrochemical properties for the *ortho*-substituted **4a**−**g**. This result confirms the previous ones obtained by studying the behavior of the relevant **3a**−**g**.[9b] We remark that once again also the effect of the bulky *o*-bromine substituent can be evaluated simply using the σ_p substituent constant (this peculiar behavior could be probably linked to the special nature of the C−NH−Ar system, which seems characterized by very low steric requirements). (ii) A high susceptibility constant has been calculated, significantly higher than those measured for *ortho*-substituted compounds **3a**−**g**. Accordingly, a cross-correlation gave a good result: a plot of data concerning **4a**−**g** (E_{pc}) versus those of **3a**−**g** ($E_{1/2}$) furnished a slope much larger than unity ($s = 1.56 \pm 0.16$, $i = 0.23 \pm 0.14$, $r = 0.976$).

We stress again that the Hammett relationship and the cross-correlations have been performed considering a comparison between a nonthermodynamic parameter (such as E_{pc}) and a thermodynamic parameter (such as $E_{1/2}$). Anyway, also in this comparison the results of the cross-correlation retain a sure physical meaning.

The susceptibility constant calculated for **4a**−**g** appears "in absolute" interestingly high notwithstanding the fact that the present substituents and the nitro group are present on two different aromatic rings bound through an amino moiety. As a matter of fact, the observed susceptibility constant is comparable to that observed for *meta*- and *para*-substituted nitrothiophenes where, in contrast, the substituent and the nitro group are linked to the same ring, that is, the thiophene ring.[15] This result once more confirms the interestingly high ability of the −NH− bridge to transmit the substituent electronic effects, already observed by some of us by examining the NMR behavior of compounds of series **3** or **4**.[2d,10]

Experimental Section

Chemistry. Compounds **4a**−**g**, **5**, and **6** have been synthesized according to procedures recently reported by some of us.[2d]

Electrochemical Characterization. The redox behavior of the compounds was studied by CV; all of the electrochemical measurements were performed under a nitrogen atmosphere, at room temperature, using a single-compartment, three-electrode cell in DMSO solution with 0.1 M $N(Et)_4BF_4$ as the supporting electrolyte containing the compound under investigation at 3 mM concentration.

Electrode potentials were measured with respect to an aqueous saturated calomel electrode (SCE). A Pt wire was used as the counter electrode. The cyclic voltammograms were recorded using a CHInstruments model 660A (Austin, TX) controlled by a personal computer via CHInstruments software; the working electrode was a Pt disk of 0.071 cm^2 geometrical area, sealed inside a Teflon support. The cyclic voltammograms were recorded at different potential scan rates, from 20 to 1200 mV/s. At each scan rate four voltammogramms were sequentially recorded, obtaining superimposable responses.

DFT Calculations. The geometries of both **5** and **6** have been fully optimized to obtain the more stable conformation both in vacuo and in solution. All calculations have been performed with the Gaussian 03 series of programs,[11] employing the density functional theory in conjunction with the B3LYP functional and a double-ζ plus polarization function basis set (6-31G*).[11] The solvent (DMSO) was accounted for implicitly by using the SCRF-CPCM method as implemented in Gaussian 03.[11]

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Supporting Information Available: Geometries of compounds **5** and **6** and the atomic point charges for the in vacuo systems and for the solvated systems (Figures 1−3). This material is available free of charge via the Internet at http://pubs.acs.org.

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