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Regioselective addition of DDQ on a quinoid ring: an entry into chiral zwitterionic bridging ligands

Gabriel Canard,*a Zhongrui Chen,a Apriliyani Suryaningtias,a Marion Jean,b Nicolas Vanthuyne,b Michel Giorgi,c Christian Rousselb and Olivier Siri*a

The regioselective insertion of DDQ into a C-H bond of the 6π + 6π electron zwitterionic benzoquinonemonoimines 4a-c results in the formation of the novel chiral C-substituted quinoid ligands 11a-c. These Michael adducts feature a preserved zwitterionic form and a quaternary stereogenic carbon center as evidenced by the single crystal X-ray structure of the derivative 11a. The ECD spectra, optical rotations and racemization barriers of the two enantiomers of 11a were measured subsequently to their separation by a preparative chiral HPLC. Because the racemization of 11a is stopped in basic media, compounds 11a-c give a new entry in chiral zwitterionic bridging ligands.

Introduction

The 2,5-dihydroxy-1,4-benzoquinone 1 (Figure 1) featuring a [O,O,O,O] donor set has been extensively used as a bridging ligand to build polymetallic complexes where the effective intermetallic communication can lead, for example, to spin-spin couplings or mixed-valence states.1 During the last decades, several new classes of bridging ligands were developed by replacing from one to four of the “O” groups of 1 by isoelectronic “NR” ones producing the “amino/imino” quinoid ligands 2-6 (Figure 1).2 These replacements can tune the physico-chemical properties of the resulting metallic complexes by introducing unsymmetrical donor sets and/or by selecting the steric and electronic characteristics of the R substituents.2 Interestingly, when two amino fragments are introduced on the quinoid skeleton in 3 and 4, two different electronic distributions are obtained. Indeed, if the quinoidal structure is retained in the structure of 3 having a [N,O,N,O] donor set, the [N,N,O,O] coordinating system of 4 induces an intramolecular proton transfer producing a zwitterion being more stable than its corresponding canonical form (Figure 1).3

This zwitterionic form gives rise to specific physico-chemical properties such as a permanent electric dipole that can guide the self-assembly of 4 derivatives on surfaces.4 The zwitterion 4 is also, as the other members of 1-6 series, an efficient coordinating ligand and was incorporated into metallic complexes5 that were applied in catalysis,6 optical recording,7 electrochromism8 or vapochromism.9 On the other hand, this particular electronic distribution of 4 gives rise to two different kinds of reactivity towards organic and electrophilic reagents (Figure 2).

![Figure 1](image1.png)

**Fig 1.** Stepwise replacement of the “O” groups of 1 by isoelectronic “NR” ones in bridging quinoid ligands 2-6.

![Figure 2](image2.png)

**Fig 2.** Previously reported reactions of 4 with electrophilic organic reagents.
The addition of a strong acid (HCl) or of a strong alkylating agent ((R’’O)BF₄) on 4 produces the localization of the upper 6 π electron system through the formation of a single O-R’ bond (R’ = H, Me or Et) in the positively charged derivatives 7 and 8 (Figure 2). On the other hand, the reaction between 4 and the organic electron acceptors tetracyanoethylene (TCNE) or 7,7’,8,8’-tetracyanoquinodimethane (TCNQ) yielded the formation of the unexpected adducts 9 and 10 where a regioselective carbon-carbon bond was formed between the two starting components and was preserving the zwitterionic form thanks to an intramolecular proton transfer (Figure 2). This insertion of TCNE or TCNQ into the central upper C-H bond was shown to bring the slow cooling of a concentrated toluene solution of 4a-c at room temperature in a 1:1 ratio results in the progressive formation of orange-red precipitate of the adducts 11a-c (Figure 3). A first proof of the insertion of DDQ in the C-H bond of 4a-c was given by the corresponding ²H NMR and ¹³C NMR spectra recorded in DMSO-d₆. For example, the two C(sp³)-H signals of 4a located at δ= 4.95 and δ= 5.47 ppm were replaced by a single downfield shifted singlet at δ= 5.59 ppm in the spectrum of 11a (see the supporting information). If the disappearance of the downfield shifted ¹H NMR signal of H₅ could result from the expected C-C oxidative coupling between two molecules of 4a, this hypothesis was excluded by the presence of 16 signals in the ¹⁵C NMR spectrum of 11a whose structure was confirmed by high resolution mass-spectrometry and single crystal X-ray diffraction analyses (see below).

**Results and discussion**

**Organic synthesis.**

The reaction between DDQ and the 6π+6π zwitterions 4a-c at room temperature in a 1:1 ratio results in the progressive formation of orange-red precipitate of the adducts 11a-c (Figure 3). A first proof of the insertion of DDQ in the C-H bond of 4a-c was given by the corresponding ²H NMR and ¹³C NMR spectra recorded in DMSO-d₆. For example, the two C(sp³)-H signals of 4a located at δ= 4.95 and δ= 5.47 ppm were replaced by a single downfield shifted singlet at δ= 5.59 ppm in the spectrum of 11a (see the supporting information). If the disappearance of the downfield shifted ¹H NMR signal of H₅ could result from the expected C-C oxidative coupling between two molecules of 4a, this hypothesis was excluded by the presence of 16 signals in the ¹⁵C NMR spectrum of 11a whose structure was confirmed by high resolution mass-spectrometry and single crystal X-ray diffraction analyses (see below).

**Single crystal X-ray diffraction.**

The slow cooling of a concentrated toluene solution of 11a afforded diffracting single crystals suitable for an X-ray structure analysis (Figure 4). Details of the structure determination are given in the experimental part and in Table S1 (see the supporting information). As observed previously with TCNE and TCNQ, the molecular structure of 11a revealed that a single C-C bond with a length of 1.535(9) Å has been regioselectively formed between DDQ and the zwitterion 4a.
This insertion is occurring in the C-H bond adjacent to the two C=O bonds of 4a which retains its zwitterionic form characterized by an equalization of the C-C and C-O bond lengths of its upper O-C=C-O moiety as well as the equal C-C and C-N bond lengths of its lower N-C=C-N moiety. The newly formed C-C bond involves one of the two DDQ carbon atoms bearing a cyano group as already observed when such addition occurred between DDQ and various nucleophilic carbon atoms of, for example, silyl enol ethers, \textsuperscript{14} enaminones \textsuperscript{15} or indoles. \textsuperscript{16} If the C=O bond of the DDQ moiety adjacent to the quaternary carbon atom remains a double bond with a length of 1.203(8) Å, the formation of the zwitterion 11a is resulting from a proton transfer from the two starting components confirmed by the new C-OH single bond length of 1.334(8) Å. The crystal packing of the racemic 11a revealed that each enantiomer of 11a is interacting with the other one thanks to a π-π interaction producing a “tête-bêche” arrangement (Figure 4b).

Fig 4. ORTEP views of the crystal structure of 11a showing: a) one enantiomer of 11a; b) the π-π stacking interaction occurring between the two enantiomers of 11a.

Table 1: Chiral HPLC data ((S,S)-Whelk-O1) and specific optical rotations of the two enantiomers of 11a.

<table>
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<th>t(-) (min)\textsuperscript{a}</th>
<th>k(-)\textsuperscript{a}</th>
<th>t(+) (min)\textsuperscript{a}</th>
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<th>([\alpha]\textsubscript{25}\textsuperscript{b} \textsubscript{1}\textsubscript{s} \textsubscript{4}} \textsuperscript{c}</th>
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<td>1\textsuperscript{st} eluted enantiomer</td>
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<td>2\textsuperscript{nd} eluted enantiomer</td>
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<td>1.62</td>
<td>1.90</td>
<td>4.02</td>
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<td>Preparative separation</td>
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<tr>
<td>1\textsuperscript{st} collected fractions</td>
<td>5.48</td>
<td>8.10</td>
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<td></td>
<td>650 (± 50)\textsuperscript{c} &gt; 99%</td>
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<tr>
<td>2\textsuperscript{nd} collected fractions</td>
<td>5.65</td>
<td>7.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 650 (± 50)\textsuperscript{d} &gt; 96%</td>
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\textsuperscript{a} Detected CD sign at 254 nm. \textsuperscript{b} Recorded in methanol. \textsuperscript{c} with c = 0.16 mg.cm\textsuperscript{-3}. \textsuperscript{d} with c = 0.15 mg.cm\textsuperscript{-3}.

Chiral HPLC separation and chirality analysis.

The DDQ insertion in the C-H bond of 4a-c results in the formation of a quaternary stereogenic carbon atom in the corresponding adducts 11a-c. Consequently, an analytical chiral HPLC analysis of 11a was conducted in order to see if its two enantiomers could be separated and therefore characterized. After screening different chiral stationary phases and solvents, a so called (S,S)-Whelk-O1 column was chosen with a mobile phase combining n-heptane, dichloromethane and ethanol containing 0.1% of trifluoroacetic acid (TFA) in an overall 10/10/80 ratio. The addition of an organic acid was required to ensure the elution of the highly polar 11a. These experimental conditions afforded a good enantioselectivity factor α (1.90) and a high resolution Rs (4.02) for the enantiomeric separation of 11a (Table 1 and Figure 5). Nevertheless, we observed the enantiomerization of each separated enantiomer in the acidic mobile phase during the storage of their collected fractions. A subsequent analysis in the acidic mobile phase gave a corresponding enantiomerization barrier of 96.2 kJ.mol\textsuperscript{-1} and a half-time value of 65 minutes at 25°C (see the experimental part and the supporting information).

If this racemization process is quite fast in acidic medium, it is completely stopped when a concentrated ethanol solution of sodium carbonate is added during the collection of the separated fractions.
Therefore, using this strategy and the same experimental conditions (stationary and mobile phases), a chiral separation was conducted on a preparative scale giving up to 25 mg of each enantiomer of 11a with an optical purity exceeding 96% (Table 1). The two enantiomers of 11a give an identical UV-visible spectrum (recorded in the neutralized mobile phase) featuring three intense absorption bands located at ca. 220, 340 and 350 nm that were previously attributed to π → π* transitions of the zwitterionic part (Figure 6). On the other hand, the fourth band at ca. 270 nm could be due to the reduced DDQ moiety. The ECD spectrum of the second eluted enantiomer features multiple Cotton effects and is, as expected, the mirror-image of the ECD spectrum recorded for the first eluted one (Figure 6). The same symmetry is observed when measuring the values of the optical rotations in methanol at 546 nm which reaches up to +650° for the first eluted enantiomer (Table 1).

Fig 5. Chromatograms of the chiral HPLC analysis of the racemic 11a: UV and Circular Dichroism detection at 254 nm on (S,S)-Whelk-O1 using heptane / ethanol and tfa / dichloromethane (1/8/1) as a mobile phase and at 1 mL.min⁻¹.

Fig 6. UV-visible (top) and ECD spectra (below) of the first (green solid line) and the second (red dotted line) eluted enantiomers of 11a (recorded in methanol).

**Racemization mechanism**

If the addition of DDQ on 4a-c is extending the number of such zwitterionic C-substituted derivatives, it is particularly appealing for its concomitant and unprecedented introduction of a chiral centre appended on the upper O-C-C-C-O moiety. This functionalization would be complementary to the single previously reported chiral derivatization of 4 that was performed thanks to the introduction of chiral amines on its lower N-C-C-C-N part. Considering that the use of 11a-c as chiral ligands requires experimental conditions that prevent its racemization, two preliminary experiments were conducted to give first insights of the corresponding racemization process.

The first one was the determination of the racemization barrier that showed a first-order kinetic when using an acidic solution (see the supporting information). If the Michael addition is often used to create chiral centres, it can compete with its reversible dissociation in a Michael –retro-Michael tandem process. This process was found to be responsible of the racemization of 11a because the ¹H NMR spectrum of an equimolar mixture of 11a and 4c (in DMSO-d₆) produces in less than 20 minutes the appearance of traces of the cross coupling products 4a and 11c (Figure 7 and Figure S2 in the SI). Within 18 hours,
this exchange produces an almost equimolar mixture of the four components 4a, 4c, 11a and 11c which are distinguished from one to another in the corresponding 1H NMR spectrum by the different chemical shifts of their quinoidal H3 and H4 signals (Figure 7 and Figure S2 in the SI). Because no external acidic source was added during this experiment, the retro-Michael process is probably induced or catalyzed by the partially dissociated phenolic and acidic protons H2 (Figure 7) which are inactive when a base is added. Moreover the absence of any detectable traces of 4a-c in the 1H NMR of 11a-c shows that if the Michael –retro-Michael equilibrium is responsible of the racemization of 11a, it must be largely shifted toward the formation of the 4-DDQ adducts.

**Experimental**

**Materials and methods.**

Compounds 4a-c were prepared according to literature procedure. All the reagents and anhydrous solvents were purchased from Alfa Aesar or Sigma Aldrich and were used without further purification. Column chromatography was performed using silica gel (60-120 mesh). Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F254 (0.5 mm) aluminium plate. Visualization of the spots on TLC plates was achieved by exposure to UV light. 1H and 13C NMR spectra were recorded on a JEOL ECS400 NMR spectrometer. Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm). High-resolution mass spectrometry (HRMS) analysis was performed on a SYNAPT G2 HDMS (Waters). Absorption spectra were recorded using the residual protonated solvent signal as an internal standard (For proton: CDCl3 7.26 ppm; Acetone-d6 2.05 ppm. For 13C: CDCl3 77.0 ppm; Acetone-d6 30.8 ppm. The multiplicity of the signals is designated by the following abbreviations: s, singulet; br, broad singulet; d, doublet; t, triplet; br t, broad triplet; m, multiplet. Coupling constants, J, are reported in Hertz (Hz). High-resolution mass spectrometry (HRMS) analysis was performed on a SYNAPT G2 HDMS (Waters). Absorption spectra were recorded using the residual protonated solvent signal as an internal standard (For proton: CDCl3 7.26 ppm; Acetone-d6 2.05 ppm. For 13C: CDCl3 77.0 ppm; Acetone-d6 30.8 ppm. The multiplicity of the signals is designated by the following abbreviations: s, singulet; br, broad singulet; d, doublet; t, triplet; br t, broad triplet; m, multiplet. Coupling constants, J, are reported in Hertz (Hz).

**Organic Synthesis**

11a: To a solution of 4a (300 mg, 1.21 mmol, 1 equiv.) in CH2Cl2 (40 mL), was added DDQ (300 mg, 1.32 mmol, 1.1 equiv.). The mixture was stirred at room temperature overnight before toluene (20 mL) was added. Most of the CH2Cl2 was evaporated under reduced pressure. The resulting precipitate was collected by filtration and successively washed with toluene and Et2O. A drying under vacuum afforded the desired product 11a as a red powder (536 mg, 1.12 mmol, 93%). 1H NMR (400 MHz, DMSO-d6, 294 K): δ = 9.37 (br t, JHH = 6.3 Hz, 2H), 5.59 (s, 1H), 3.42 (m, 4H), 1.58 (quint, JHH = 7.3 Hz, 4H), 1.31 (sext, JHH = 7.2 Hz, 4H), 0.90 ppm (t, JHH = 7.3 Hz, 6H); 13C NMR (400 MHz, MeOD-d4, 294 K): δ = 180.3, 169.0, 154.4, 154.3, 143.1, 135.0, 115.5, 115.1, 106.3, 87.7, 81.7, 47.0, 42.6, 29.8, 19.5, 13.6 ppm; UV-Vis (DMSO): λmax (ε х 10-3) = 348 (25.1), 359 (25.7), 489 nm (1.6); HRMS (ESI-TOF): calcd for C22H16N2O2Cl2+: [M+H]+ 477.1091, found 477.1090.

11b: To a solution of 4b (100 mg, 0.602 mmol, 1 equiv.) in MeOH (6 mL), was added DDQ (m = 150 mg, 0.661 mmol, 1.1 equiv.). The mixture was stirred at room temperature overnight. The resulting precipitate was filtered off, washed with MeOH and CH2Cl2. A crystallization from hot toluene afforded the desired product 11b as a red powder (177 mg, 0.450 mmol, 75%). 1H NMR (400 MHz, DMSO-d6, 294 K): δ = 9.47 (m, 2H), 5.46 (s, 1H), 3.01 ppm (d, JHH = 5.2 Hz, 6H); 13C NMR (100 MHz, DMSO-d6, 294 K): δ
Acknowledgements

Conclusions

Single crystal X-ray diffraction

Chiral HPLC

7c: To a solution of 4c (40 mg, 0.177 mmol, 1 equiv.) in MeOH (4 mL) was added DDQ (41 mg, 0.181 mmol, 1.02 equiv.). The mixture was stirred at room temperature overnight. The resulting precipitate was filtered off, washed successively with MeOH and CH$_2$Cl$_2$ before it was dried under vacuum affording the desired product 11c as an orange powder (36 mg, 0.079 mmol, 45%);

Conclusions

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Notes and references


18. The origin of this band is beyond the scope of the present study.

