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Intramolecular charge effects in the electrochemical oxidation of aminoxyl radicals†

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The redox potentials of a series of aromatic nitroxides derived from *tert*-butyl phenyl nitroxide are determined by cyclic voltammetry in non-aqueous solution. It is shown that the first oxidation potential as well as the reduction potential strongly depend on the electron donating and withdrawing substituents of the compounds. The first results on the influence of a negative charge in proximity to the aminoxyl group on the redox properties of aromatic nitroxides, are reported. A remarkably strong intramolecular "charge effect" is probably responsible for the observed high potential shift of 560 mV in the case of the carboxylate **4b**.

Introduction

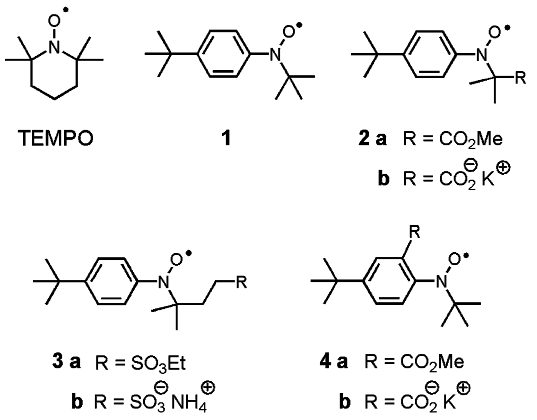
Nitroxides[1] are free organic radicals, which have an unpaired electron resulting in paramagnetic properties. They can be reduced[2] to hydroxylamines or oxidised[3] to *N*-oxo ammonium cations. Aliphatic cyclic nitroxides, such as derivatives of TEMPO are often used in biological ESR studies[4,5] as paramagnetic probes. In this case, their reduction in biological systems is an undesired reaction which leads to diamagnetic species and therefore the loss of the EPR signal.[2] Biologists require nitroxide derivatives that are inert in the presence of biological reductants such as ascorbic acid.[2] Furthermore it has been shown that nitroxide radicals are reversibly oxidised to their corresponding *N*-oxo ammonium cations in a one-electron process, providing electron transfer mediators used in the catalytic oxidation of organic compounds.[3,6–9]

Consequently the structure depending redox properties of nitroxide radicals are to be controlled. Indeed, the influence of different structural parameters such as ring size and substituent independent inductive and electrostatic effects[10] on the thermodynamic redox properties of cyclic aliphatic nitroxides have been demonstrated by electrochemical methods.[6,11,12] The electrochemical properties of the linear aliphatic di-tert-butyl nitroxide (DTBNO) have been studied in detail.[9,13] However, to our knowledge there are only few data reported in literature about the electrochemical behaviour of aromatic nitroxides.[14,15] This lack of information and the enormous potential in the applications mentioned above emphasise the importance of the electrochemical characterisation of aminoxyl radicals in general and aromatic nitroxides in particular. In the present study, we report the very first results of the influence of a negative charge in proximity to the aminoxyl group on the redox properties of *tert*-butyl aryl nitroxide derivatives in electrochemical reactions in non-aqueous solution. The work focuses in particular on the first oxidation process leading to the corresponding *N*-oxo ammonium cations.

Experimental

The studied nitroxide radicals **1**–**4** were synthesised according to literature protocols (Scheme 1).[16–18] The compounds **2a** and **3a** carry a carboxylic ester and sulfonic ester group, respectively on the *tert*-butyl substituent. In compound **4a** an ester group has been attached directly to the aromatic cycle. Hydrolysis of **2a**, **3a** and **4a** afforded the corresponding anions **2b**, **3b** and **4b** bearing the negative charge in the vicinity of the aminoxyl group.

The electrochemical experiments were conducted in an air-tight, three-electrode glass cell, controlled by a commercially available computer-controlled potentiostat (AUTOLAB PGSTAT 30, Eco Chemie, The Netherlands). A platinum wire and a saturated calomel electrode (SCE) were used as a counter and a reference electrode, respectively. Since non-aqueous solvents were used as the electrolyte media, the



Scheme 1 Structures of the studied nitroxides.

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† In memory of the late Professor André Rassat, former Director of the Chemistry Department of Ecole Normale Supérieure Paris.

Table 1 Oxidation potentials (V) of the studied nitroxides[a]

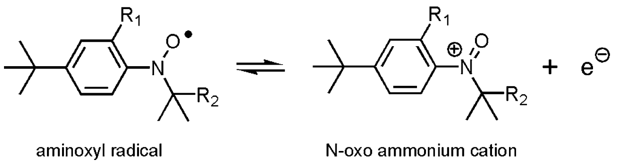
		I (first oxidation wave)				II (higher oxidation waves)	
Compound	E_{pa}	E_{pc}	$E^{\circ\prime b}$	$E_{pa} - E_{pc}$	$I_{pa}/I_{pc}{}^c$	E_{pa}	$I_{pa}(II)/I_{pa}(I)^c$
TEMPO	0.688	0.620	0.65^d	0.068	1.01	^{e}	
1	0.749	0.679	0.71^f	0.070	1.14	$1.766,^g$ 2.31	0.18, 0.27
2a	0.904	0.831, 0.522	0.87	0.073	1.48, 4.43	—	
2b	0.075	—	—			^{h}	
3a	0.842	0.779	0.81	0.063	1.07	—	
3b	0.768	0.707	0.74	0.061	1.64	1.797	0.67
4a	0.918	$0.844,^i$ 0.07	0.90^i	0.074^i	2.8, 16.5	1.475, 1.826	0.12, 1.83
4b	0.358	0.298	0.33	0.060	1.67	1.738	0.37

[a] 0.1 M $TBABF_4$ in acetonitrile, glassy carbon electrode, SCE, sweep rate 0.1 V s^{-1}. [b] $E^{\circ\prime} = (E_{pa} + E_{pc})/2$. [c] The peak currents (I_{pa} and I_{pc})[20a] were measured from the respective baseline currents. [d] Lit.,[14] $E^{\circ\prime} = 0.64$ V calculated from Ag/AgCl ref. electrode. [e] Not explored. [f] Lit.,[14] $E^{\circ\prime} = 0.75$ V calculated from Ag/AgCl ref. electrode. [g] $E_{pc} = 1.692$ V, $E_{pa} - E_{pc} = 0.074$ V. [h] $E_{pa} = 0.31$ V, 0.81 V, 1.39 V, 1.72 V. [i] Determined at higher sweep rate (0.5 V s^{-1}).

reference electrode was kept in a side arm separated from the electrochemical cell *via* a porous frit. The side arm was filled with the solvent–supporting electrolyte solution. A glassy carbon disk electrode, having a disk radius of 0.05 cm, was used as the working electrode. The working electrode was polished prior to each experiment on successively finer grades of carborundum paper (P1200 down to P4000), and then using a 0.3 μm aqueous alumina slurry on a wetted, napped polishing cloth. Acetonitrile was refluxed over barium oxide and distilled under argon prior to use. The supporting electrolyte employed was a 0.1 M solution of tetrabutylammonium tetrafluoroborate ($TBABF_4$) in acetonitrile. $TBABF_4$ had been freshly recrystallised and dried at 70 °C, for at least 24 h before use. Prior to experimentation argon gas was bubbled into the electrolyte solution to remove oxygen, and was flushed over the cell solution during the electrochemical measurements. Cyclic voltammograms (CV) were recorded at room temperature (22 ± 1 °C) and at a potential sweep rate of 0.1 V s^{-1} unless otherwise stated.

Results and discussion

The redox potentials of the described compounds (Scheme 1) were determined by cyclic voltammetry in acetonitrile using a glassy carbon disc electrode (Tables 1 and 2). For all aromatic nitroxides in this study we assigned the first oxidation potential to the formation of the corresponding *N*-oxo ammonium cation (Scheme 2). Like TEMPO, the cyclic voltammograms of the anodic oxidation of compounds **1** and **3a** exhibit signals corresponding to a fully reversible one electron transfer (Fig. 1, 2). The electrochemical oxidation of the compounds **2a**, **3b**, **4a** and **4b** is only "quasi reversible" in the investigated conventional timescale. The small peak separations $E_{pa} - E_{pc}$ vary from 60 to 74 mV, suggesting relatively fast electron transfer kinetics.[19,20] The apparent formal potentials $E^{\circ\prime}$ in Table 1 were estimated as half of the sum of anodic and cathodic peak potentials: $E^{\circ\prime} = (E_{pa} + E_{pc})/2$. In the case of **4a**, $E^{\circ\prime}$ had to be determined at higher sweep rates, due to the shorter life time of its *N*-oxo ammonium cation. A series of CV measurements with varying sweep rate display the tendency of a peak current ratio I_{pa}/I_{pc} approaching almost unity with



Scheme 2 Electrochemical oxidation of the aromatic nitroxides.

Table 2 Reduction potentials (V) of the studied nitroxides[a]

Compound	E_{pc}	E_{pa}	$I_{pc}/I_{pa}{}^b$	$I_{pc}/I_{pa}{}^b$
TEMPO	-1.61^b	—		0.58
1	−1.28	−1.04	1.40	0.78
2a	−1.13	−0.93	1.52	0.69
2b	—	—		
3a	−1.25	—		0.72
3b	−1.40	—		0.37
4a	−1.18	—		0.61
4b	−1.4	—		0.61

[a] 0.1 M $TBABF_4$ in acetonitrile, glassy carbon electrode, SCE, sweep rate 0.1 V s^{-1}. [b] The peak currents (I_{pa} and I_{pc})[20a] were measured from the respective baseline currents. [c] Lit.,[15] $E^{\circ\prime} = 1.74$ V.

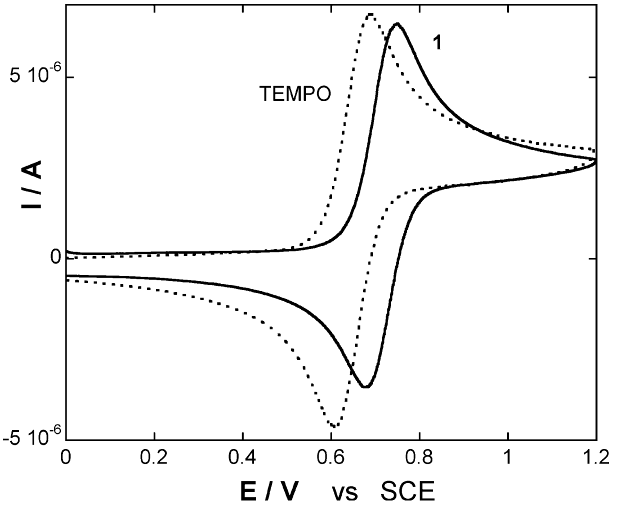


Fig. 1 Cyclic voltammograms of TEMPO (2.5 × 10^{-3} M, broken line) and **1** (2.4 × 10^{-3} M) in acetonitrile containing 0.1 M $TBABF_4$ with a sweep rate of 0.1 V s^{-1}.

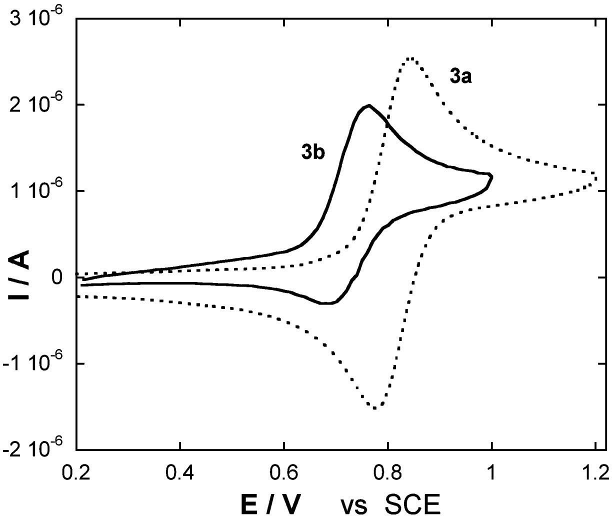


Fig. 2 Cyclic voltammograms of **3a** (1.1×10^{-3} M, broken line) and **3b** (0.9×10^{-3} M) in acetonitrile containing 0.1 M $TBABF_4$ with a sweep rate of 0.1 V s^{-1}.

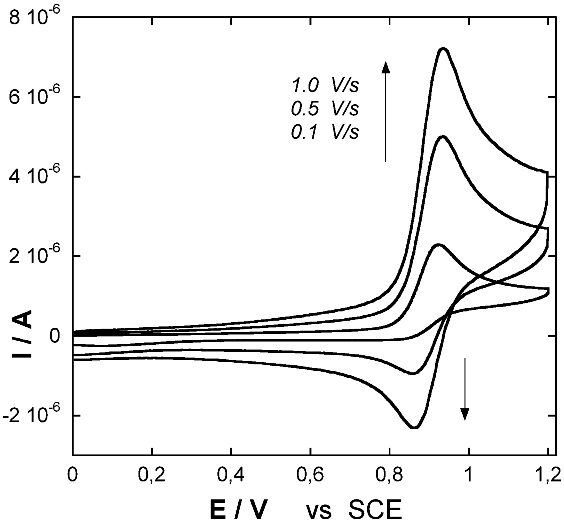


Fig. 3 Cyclic voltammograms of **4a** (1.0×10^{-3} M) at different sweep rates (ν) in acetonitrile containing 0.1 M $TBABF_4$ at 20 °C. ν/V s^{-1}: 0.1, 0.5, 1.0.

increasing sweep rate (Fig. 3), indicating that the effect of the following chemical reaction on the electrode process can be ruled out. The diffusion coefficients D_0 of **2a** (1.4×10^{-5} cm^2 s^{-1}) (Fig. 4) and **4a** (1.1×10^{-5} cm^2 s^{-1}) in acetonitrile were calculated from the slope of the linear region between the anodic peak current (I_{pa}) and the square root of the sweep rate (for values higher than 0.05 V s^{-1}). They are close to the value obtained for compound **1** (1.6×10^{-5} cm^2 s^{-1}).[14]

The electrochemical oxidation of TEMPO ($E^{\circ\prime}$ = 0.64 V) is more favourable than that of the neutral aromatic nitroxides **1**, **2a**, **3a** and **4a** (Table 1). The higher oxidation potentials are probably due to the better delocalisation of the unpaired electron in the aromatic nitroxides and the fact that the localised charge of the TEMPO cation is better solvated in a polar electrolyte. It is likely that the nitroxides **2a**, **3a** and **4a** are less readily oxidised than **1** ($E^{\circ\prime}$ = 0.71 V) because of the inductive effect of their electron-withdrawing substituents. In compound **4a**, the ester group is conjugated to the aminoxyl function giving rise to the highest oxidation potential $E^{\circ\prime}$ (0.90 V) among the studied derivatives.

Both negatively charged nitroxides **3b** and **4b** show lower oxidation potentials than their corresponding neutral derivatives **3a** and **4a** (Fig. 2, 5). We believe an intramolecular electrostatic interaction to be the origin for this so called “charge effect”.[21] Indeed the negative charge of the carboxylate group probably thermodynamically stabilises the positive

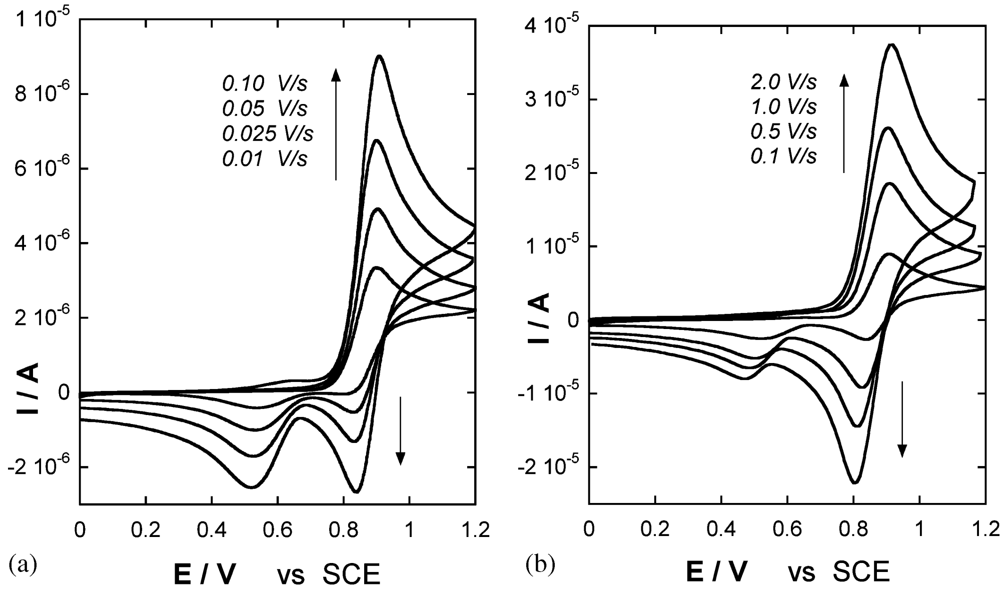


Fig. 4 Cyclic voltammograms of **2a** (3.8×10^{-3} M) at different sweep rates (ν) in acetonitrile containing 0.1 M $TBABF_4$ at 20 °C. ν/V s^{-1}: (a) 0.01, 0.025, 0.050, 0.1; (b) 0.1, 0.5, 1.0, 2.0.

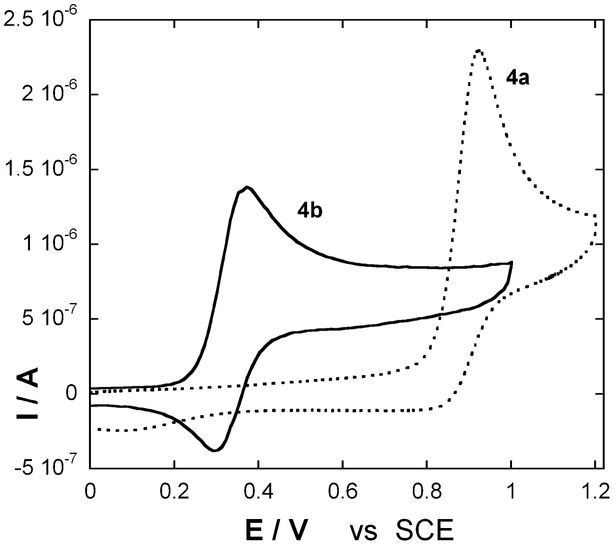


Fig. 5 Voltammetric oxidation of **4a** (1.0×10^{-3} M, broken line) and **4b** (0.7×10^{-3} M) in acetonitrile containing 0.1 M $TBABF_4$ at a sweep rate of 0.1 V s^{-1}.

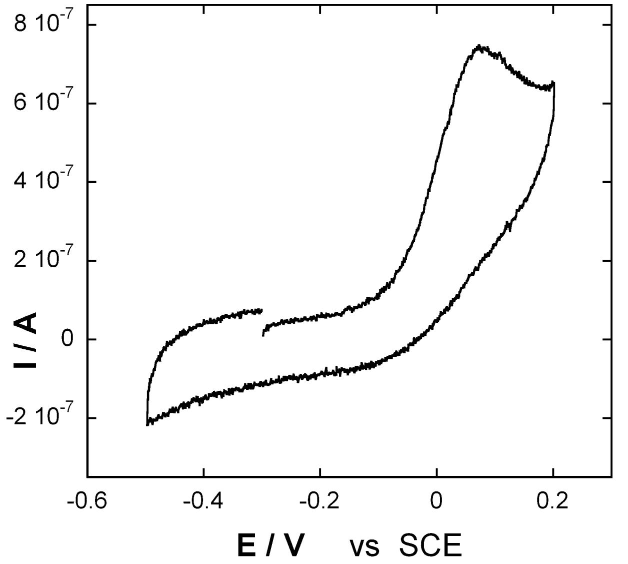


Fig. 7 Voltammetric oxidation of **2b** (0.6×10^{-3} M) in acetonitrile containing 0.1 M $TBABF_4$ at a sweep rate of 0.1 V s^{-1}.

charge appearing in the oxo ammonium after oxidation of **3b** and **4b**, respectively. Compared to **3a**/**3b** (ΔE_{pa} = 74 mV) the shift of the anodic peak potential for the compounds **4a**/**4b** is about 7.6 times higher (ΔE_{pa} = 560 mV). The gain of reversibility for the anodic oxidation of **4b**, compared to **4a**, is a hint for a kinetically more stable *N*-oxo ammonium cation. The proximity of the carboxylate group in the *ortho* position and the rigid structure of compound **4b** probably allow for a cyclic conformation of the corresponding *N*-oxo ammonium *via* an intramolecular electrostatic interaction (Fig. 6). On the contrary, the oxidation product of sulfonate ester **3b** appears to be chemically less stable compared to the corresponding methylester **3a**.

The cyclic voltammogram of **2a** shows an additional wave with E_{pc} = 0.522 V probably resulting from the reduction of the decomposition products of its *N*-oxo ammonium cation. When increasing the reversibility of the electron transfer reaction at higher sweep rates the importance of the chemical side product is decreasing rapidly (Fig. 4). The same effect is observed for compound **4a** (Fig. 3, 5).

The voltammogram of **2b** shows at least 5 not well defined irreversible waves (Table 1). Assuming that the first anodic peak potential of 0.075 V (Fig. 7) corresponds to the formation of the *N*-oxo ammonium cation the shift of the anodic peak potential would be even higher (ΔE_{pa} = 830 mV) than in the case of **4a**/**4b**. The chemical instability of the *N*-oxo ammonium cation under the experimental conditions is probably leading to various electroactive species. One possible reaction could be the irreversible unimolecular decarboxylation of the cation forming an instable nitrone (Scheme 3).[22] At present we are not yet able to conclusively explain these results.

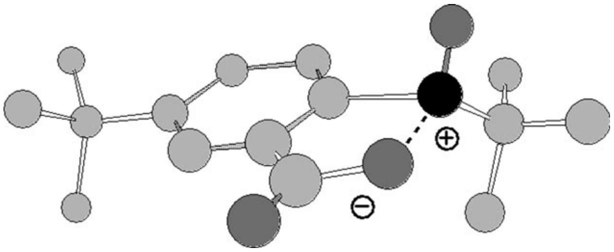
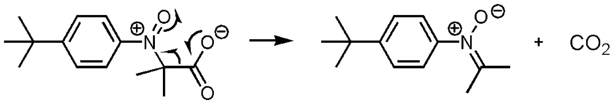
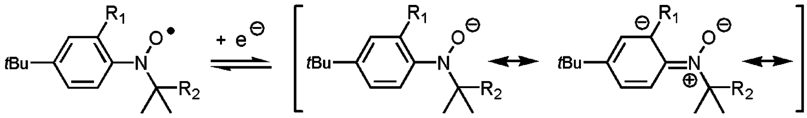


Fig. 6 Postulated conformation of the *N*-oxo ammonium cation of **4b** showing the stabilising electrostatic interaction (broken line). Hydrogen atoms are omitted.

Excepting **2a** and **3a**, all the studied compounds show more than one anodic oxidation wave at higher potentials. **1**, **3b**, **4a** and **4b** display an irreversible oxidation wave with E_{pa} around 1.8 V. In all cases, the relative intensity of the first and the second or third anodic waves is quite different comparing the anodic peak current ratios and depend strongly on the sweep rate. For example, in the case of compound **1** the second wave is relatively decreasing and the third wave increasing with higher sweep rate compared to the first wave and *vice versa*. At present, we cannot determine the origin of the second oxidation wave. It seems impossible to generate a dication from the unstable *N*-oxo ammonium cations. We rather suppose that the generated *N*-oxo ammonium undergoes chemical reactions leading to new electroactive compounds which are subsequently oxidised. According to the literature,[23] nitrosobenzene is oxidised in acetonitrile at 1.83 V and 2,4-dimethyl nitrosobenzene at 1.78 V. It is thus possible that the new electroactive compounds derived from the *N*-oxo ammonium cations of **1**, **3b**, **4a** and **4b** possess a similar structure since their oxidation potential is about 1.8 V. A dipolar electrostatic interaction



Scheme 3 Plausible mechanism for the decomposition of the *N*-oxo ammonium cation of **2b** to the corresponding nitrone.



Scheme 4 Electrochemical reduction of the aromatic nitroxide to the stabilised hydroxylamine anion.

between the nitroxide radical and acetonitrile has been suggested in the literature.[24] The nucleophilic attack of the oxidised nitroxide by acetonitrile affording the nitroso derivative would be a plausible mechanism. For nitroxide **3b**, also the unimolecular decomposition of the *N*-oxo ammonium *via* an intramolecular nucleophilic substitution could be envisaged.

The electrochemical reduction of the aromatic nitroxides reveals an irreversible wave. The reduction potentials are relatively low compared to TEMPO[14,15*a*,25] (Table 2), probably due to the mesomeric effect of the aromatic cycle, stabilising the negative charge on the oxygen (Scheme 4). Moreover, the neutral nitroxides **2a**, **3a** and **4a** are more readily reduced than **1** ($E_{pc} = -1.23$ V). We have measured, respectively a shift of 150, 30 and 100 mV towards less negative potentials again partly owing to inductive effects. Ester and sulfonate ester substituents are electron withdrawing groups explaining the lower reduction potentials of **2a**, **3a** and **4a**. The negatively charged nitroxides **3b** and **4b** are more reluctant to reduction than their corresponding neutral nitroxides with potential shifts of −150 and −220 mV, respectively. In contrast to the *N*-oxo ammonium cation of **4b**, the dianion probably favours a conformation in which the negative charges are distant, minimizing the repulsive electrostatic interaction. A similar trend was observed for analogous aliphatic TEMPO derivatives.[26]

Conclusions

In order to better understand the electrochemical behaviour of a series of aromatic nitroxide derivatives the redox potentials of 7 derivatives were determined exploiting cyclic voltammetric measurements. It is shown that the first oxidation potential as well as the reduction potential strongly depend on the electron donating or withdrawing substituents. There is much evidence for an intramolecular "charge effect" being responsible of the observed remarkably high potential shift in the case of the carboxylates **4b** and **2b**. The modulation of the redox potentials of aromatic nitroxides by molecular engineering could be achieved and thus potential applications of the aminoxyl radicals as electron mediators in electrocatalysis or as probes for pH or metal cation sensing are envisaged. In order to elucidate the mechanisms of the chemical reactions following the first oxidation process, systematic preparative electrolyses are planned.

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