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Reaction of 3,3′-bis(2-phenyl-5,5-dimethyl-4-oxopyrrolinylidene) 1,1′-dioxide with the methoxide anion

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The title reaction in methanol includes the addition of MeO^- to the carbonyl group of a pyrrolinone ring followed by ring opening, and the one-electron oxidation of the formed anion results in the formation of a stable nitroxide, as found by cyclic voltammetry and EPR spectroscopy.

Conjugated dinitrones – 3,3′-bis(2-R-5,5-dimethyl-4-oxopyrrolinylidene) 1,1′-dioxides (DNs) (Figure 1) – are compounds with high electron withdrawing ability formed by the smooth oxidative dimerization of 2-R-5,5-dimethyl-1-oxopyrrolin-4-ones,[1] and they can form long-lived molecular ions in aprotic solvents,[2,3] MeCN–H_2O mixtures and H_2O.[4] The electrochemical reduction of DNs is an EE process in DMF and MeCN, and two well separated one-electron diffusion controlled cathodic peaks are observed in cyclic voltammograms (CVs).[3] The first peak retains its reversibility in MeCN–H_2O mixtures and H_2O;[4] this is a unique phenomenon in the electrochemistry of nitrones, allowing us to consider DNs as potential precursors of redox active labels for biotechnology.[4] For this purpose, it is necessary to understand DNs reactivity toward nucleophiles because solutions used in biotechnologies can contain nucleophilic species. A nucleophile can attach to the C=C bond, nitrone carbon atom or carbonyl groups. We studied the reaction of DN (R = Ph) **1** with the MeO^- anion in MeOH and MeCN–MeOH mixtures by means of cyclic voltammetry and EPR spectroscopy.

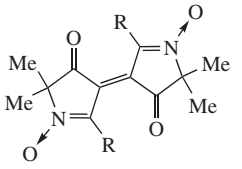


Figure 1 Structure of 3,3′-bis(2-R-5,5-dimethyl-4-oxopyrrolinylidene) 1,1′-dioxides.

The CV† of **1** in MeOH is characterized by two peaks within the potential sweep from 0.4 to –0.8 V. The first peak [1C–1A, Figure 2(*a*)] is one-electron and reversible ($E_p^{1A} - E_p^{1C} = 0.06$ V, Table 1) corresponding to the formation of the radical anion of **1**, whose EPR spectrum was measured under electrochemical

† The CV measurements of **1** were performed at 298 K in an argon atmosphere in MeOH or MeCN with a small admixture of MeOH at a stationary platinum electrode ($S = 0.08$ cm^2) with 0.1 M Et_4NClO_4 as a supporting electrolyte with the sweep rates of $0.1 \leqslant \nu \leqslant 0.7$ V s^{-1}. A PG 310 USB potentiostat (HEKA Elektronik GmbH, Germany) was used for CV measurements. Peak potentials are quoted with reference to a saturated calomel electrode (s.c.e.). Concentration of **1** was 0.0015 M. 1C reduction peak current is diffusion controlled for the electrochemical reduction of **1** in MeOH and MeCN with the small addition of MeOH, *i.e.*, $I_p^{1C}\nu^{-0.5} = \text{const}$, where I_p^{1C} is the peak current, and ν is the potential sweep rate. The peak potential difference is $E_p^{3A} - E_p^{3C} = 0.06$ V (Table 1).

Table 1 Experimental redox potentials[a] of compound **1** and reaction mixtures of **1** with MeONa and K_2CO_3.

Compounds (ratio)	Solvent	E_p^{1C}/V	E_p^{1A}/V	E_p^{2C}/V	E_p^{2A}/V	E_p^{3C}/V	E_p^{3A}/V
1	MeOH	–0.26	–0.20	–0.40	—[b]	0.00	0.06
1	MeCN : MeOH[c]	–0.53	–0.47	–0.91	–0.82	–0.26	–0.20
MeONa : **1** (1:1)	MeOH	—	—	—	—	0.02	0.08
K_2CO_3:**1** (1:1)	MeOH	—	—	—	—	0.04	0.10

[a] Peak potentials are listed as E_p^{iC} and E_p^{iA}, where *i* is the peak number in the CV curve, symbols C or A indicate the cathodic or anodic branch of the CV curve, respectively. Potential sweep rate is 0.1 V s^{-1}. [b] Anodic peak 2A is not observed. [c] See Online Supplementary Materials.

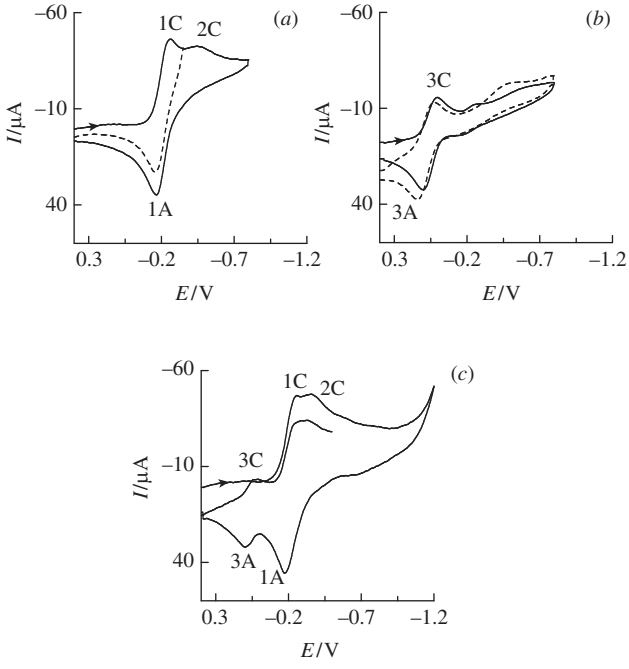
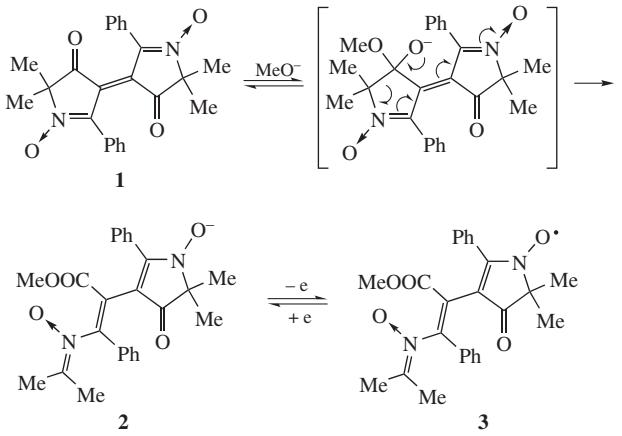


Figure 2 CV of **1** in MeOH within potential sweep regions $-0.8 < E < 0.4$ V (solid line), $-0.35 < E < 0.4$ V (dotted line) (*a*), $-1.2 < E < 0.4$ V (*c*) and CV of the reaction mixtures MeONa : **1** (solid line), K_2CO_3 : **1** (dotted line) in MeOH in 5 min after the onset of reaction (*b*). (Arrows indicate the direction of potential sweep).



Scheme 1

reduction at the potential E_p^{1C} in MeOH [Figure 3(*a*)].‡ In contrast to electrochemical reduction in MeCN,[3] the second peak is essentially irreversible in MeOH [2C, Figure 2(*a*)] and corresponds to the formation of dianion **1**. The latter was proved by electrochemical reduction in MeCN–MeOH mixtures.§

The addition of sodium methoxide (MeONa : **1** = 1:1) to an electrochemical cell led to a CV with a new reversible one-electron redox peak 3A–3C within the same range of potential sweep. This peak can be attributed to the reversible oxidation of anionic product **2** formed as a result of the reaction of **1** with MeO^- (Scheme 1). The use of the MeOH–K_2CO_3 (K_2CO_3 : **1** = 1 : 1) system as a source of MeO^- *in situ* resulted in a similar CV of the reaction mixture [Figure 2(*b*)]. The only peak 3A–3C was observed after the reaction was completed.§

The methoxide anion can be obtained in the electrochemical reduction of MeOH at the potentials exceeding –1.0 V.¶ The extension of the potential sweep up to –1.2 V led to the appearance of one-electron peak 3A at the anodic branch of CV in the first cycle of potential sweep [Figure 2(*c*)] and redox peaks 3A–3C at both anodic and cathodic branches in the second and subsequent cycles. The electrochemical reduction of **1** in MeCN with the addition of MeOH as a source of MeO^- is similar§ except for peak 2C, which is reversible. Table 1 summarizes the peak potentials.

The reversibility of redox peak 3A–3C indicates the stability of radical **3**, which is the product of one-electron oxidation of anion **2**. Indeed, the electrochemical reduction of **1** in MeOH at the potential E_p^{1C} was accompanied by the EPR spectrum‡ of radical anion **1** (a_N = 0.439 mT) [Figure 3(*a*)], whose characteristics are close to those described ealier.[2,3] Electrolysis at –1.2 V¶ for 10 min with the subsequent electrochemical oxidation at potential E_p^{3A} resulted in the superposition of the EPR spectra of radical anion **1** and radical **3** (the intensity of the latter increased in time), and the EPR spectrum of **3** became dominating after 20 min electrolysis [Figure 3(*b*)]. The EPR spectrum of **3**

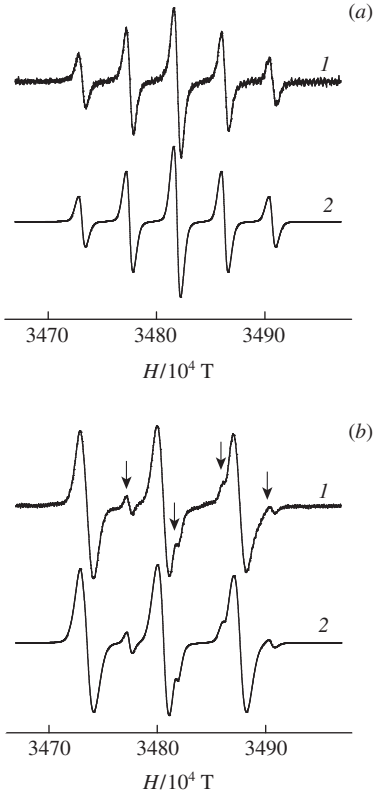


Figure 3 (*a*) EPR spectrum of the radical anion of **1** in MeOH and (*b*) superposition of EPR spectra of the radical anion of **1** and nitroxide **3** under electrochemical oxidation at E_p^{3A} after electrolysis at –1.2 V (*1* – experiment, *2* – simulation, spectral lines of the residual EPR spectrum of the radical anion of **1** are indicated by arrows).

is characterized by hyperfine interaction with one ^{14}N nucleus only. Corresponding hyperfine coupling constant (HFCC) is a_N = = 0.703 mT in MeOH.

To determine the structure of anionic product **2**, the reaction of **1** with MeONa (1:1) in MeOH§ was carried out. The main reaction product was identified as $C_{25}H_{25}N_2O_5Na$ by HPLC-MS analysis.†† The use of the MeOH–K_2CO_3 system allowed us to decrease the concentration of by-products in reaction mixture and to determine the structure of **2**, which was identified as potassium 4-{1-methoxy-3-phenyl-3-[oxido(propan-2-ylidene)-λ^5-azanyl]-1-oxoprop-2-en-2-yl}-2,2-dimethyl-5-phenyl-3-oxo-2,3-dihydro-1*H*-pyrrol-1-olate on the basis of 1D and 2D (HBMC) NMR, IR and UV-VIS spectra.§ Salt **2** can be oxidized by atmospheric oxygen or PbO_2 in MeOH to form stable nitroxide **3** (Scheme 1) with HFCC a_N = 0.703 mT, which is consistent with that obtained under the electrochemical oxidation of **2** in MeOH at the potential E_p^{3A}.

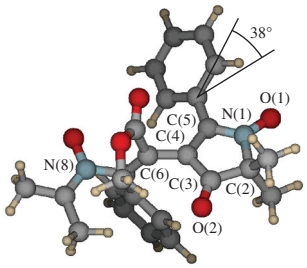


Figure 4 Structure of nitroxide **3** according to (U)B3LYP/6-31+G* calculations.

‡ The EPR spectra were recorded on a Bruker ELEXSYS E540 spectrometer (X-band, MW power of 20 mW, modulation frequency of 100 kHz and modulation amplitude of 0.005 mT). A standard electrochemical cell for EPR measurements equipped with a Pt cathode was used for the electrochemical generation of paramagnetic species. Simulations of the experimental EPR spectra were performed with the Winsim 2002 program[6] (the accuracy in calculating *a* is ±0.0001 mT).

§ For experimental details of reaction depicted in Scheme 1, characteristics of compound **2**, studies of electrochemical reduction of **1** in MeCN–MeOH mixtures by cyclic voltammetry, see Online Supplementary Materials.

¶ The electrochemical generation of MeO^- begins at a cathode double layer at more negative potentials than –1.0 V in MeOH and –1.5 V (*vs.* s.c.e.) in MeCN with the addition of MeOH due to the reduction of H^+ from MeOH.

†† A MicrOTOF-Q hybrid quadrupole time-of-flight mass spectrometer (Bruker Daltonics, Germany) was used for HPLC-MS analysis.

Nitroxide **3** has a typical value of ^{14}N HFCC for vinylnitroxides, which is approximately twice lower than corresponding values for non-conjugated nitroxides. (U)B3LYP/6-31+G* calculations‡‡ of the optimized geometry of radical **3** (Figure 4) showed that the phenyl fragment at the 5-position and the *N*-oxylpyrrolinone ring are non-planar, the side chain at the 4-position is turned relative to the plane of the *N*-oxylpyrrolinone ring, and the conjugation of double bonds is disturbed. Therefore, no hyperfine interaction is observed with the ^{14}N nucleus of the nitrone group at the 8-position. Calculated HFCC with the ^{14}N nucleus (0.621 mT) is comparable with the experimental value.

Thus, the reaction of 3,3′-bis(2-phenyl-5,5-dimethyl-4-oxopyrrolinylidene) 1,1′-dioxide with MeO^- in MeOH leads to the addition of MeO^- to the carbonyl group of a pyrrolinone ring followed by ring opening (Scheme 1). The one-electron oxidation of the formed anion results in the formation of corresponding nitroxide.

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‡‡ The quantum-chemical calculations were performed using the GAMESS suite of programs.[5] The geometries of radical **3** were fully optimized at the (U)B3LYP/6-31+G* level of theory. The PCM model was used to describe the solvent.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.11.017.

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