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Reactivity of substituted 4–oxothiazolidine derivatives in electron transfer reactions: A spectroelectrochemical study and mechanistic aspects

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ABSTRACT

The electrochemical reduction of (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)-N-phenylethanamide (designated as compound**2**) as a mixture of the (2E,5Z) and (2Z,5Z) isomers in DMSO to (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-N-phenylethanamide (compound**1**) was investigated by electrochemical (cyclic voltammetry with a stationary and rotating disc electrode) and spectroelectrochemical (electron paramagnetic resonance and UV-vis absorption)*in situ*techniques. A reduction mechanism, which consisted of an ECE-Disp sequence and was followed by the protonation of the strong electrogenerated base dianion, was proposed. The results indicate the presence of the same intermediate species, the dianion, when starting from either compound**2**by electrochemical reduction, or from compound**1**in presence of TBOH in DMSO. The suggested mechanism, which is based on the experimental results, corroborated with the gas phase and the solvent-dependent semiempirical PM3-MO calculations, was rationalized in terms of the electronic structure and the reactivity of the intermediate species involved.

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1. Introduction

Push-pull alkenes are substituted olefins that contain one or two electron-donating groups (D) on one end of a C=C bond and one or two electron-accepting groups (A) on the other end. The electronic D-A interactions *via* the C=C bond result in a polarization of the "push-pull" system (Scheme 1) [1].

Consequently, an increase of the push-pull character is associated with a decrease of the π -bond character of the polarized C=C bond. Therefore, the corresponding π -bond order of the C-D and C-A bonds is increased. The push-pull effect has a decisive influence on both the dynamic behavior and the chemical reactivity of these compounds. The 5-substituted 4-oxothiazolidines (compounds 1 and 2) with one or two exocyclic double bonds attached to the thiazolidinone ring (Fig. 1) are typical examples of push-pull compounds that can exist in different configurational and conformational forms.

One of the characteristic processes of push-pull alkenes, which is based on a lowering of the rotational barrier of the C=C bond

at the C(2) position, is the Z/E isomerization that may occur under controlled conditions [2,3]. The equilibrated mixtures of the structurally related 4–oxothiazolidines consist of the intramolecular H–bonded (2E,5Z)–isomer and the intermolecular H–bonded (2Z,5Z)–isomer in varying proportions depending on polarity of the solvent [4,5].

There is considerable interest in oxothiazolidine derivatives, such as compounds **1** and **2** (Fig. 1), due to their broad range of biological activity [6] and diverse physicochemical properties, which include increasing the enaminic reactivity towards electrophiles and which can be exploited in the preparation of the precursors that lead to push-pull polyenes [7,8].

The redox properties of the heterocyclic compounds that contain structural fragments with different donor–acceptor properties are determined by the character of the constituting moieties and the interactions between them. Therefore, a better knowledge of the redox behavior of these compounds, as well as of the identification and reactivity of the intermediate species involved, is of major importance.

Previous studies on the redox processes of these compounds have detailed the oxidative bromine-mediated rearrangement of **1** that leads to **2**. In addition, the regioselective reduction of **1** in strong alkaline media (using a tenfold excess of NaBH₄ in EtOH) was investigated [9].

Heterogeneous electron transfer (HET) reactions that involve an organic species in solution usually generate a radical ion, which

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Fig. 1. Structures of the selected 5-substituted 4-oxothiazolidines 1 and 2.



Scheme 1. Polarization of the push-pull system.

may react in subsequent reactions with the various components of the solution (solvent, electrophiles, nucleophiles, or non–electro active species). Electrochemical methods accompanied by digital simulations can provide the thermodynamic and kinetic characterization of the electron transfer (ET) step. However, to understand the complex reaction mechanisms that were determined by the HET step at a molecular level and the reactivity of the intermediate species involved, the use of electrochemical and spectral in situ techniques, in conjunction with theoretical modeling based on quantum mechanical calculations, is required [11–15].

The aim of the present paper is to investigate behavior the electrochemical reduction the of of two typical push-pull compounds the series in (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)

-N-phenylethanamide, which is termed compound **2** in this paper, and (*Z*) – (5–ethoxycarbonylmethyl–4–oxothiazolidin–2–ylidene) -N-phenylethanamide, which is termed compound **1**, as well as the reaction sequence that is responsible for the electrochemical reduction of **2** in the aprotic solvent, dimethyl sulfoxide (DMSO), while in the presence of protic impurities (impurities that are always present in commercially available solvents that are used without further purification) and which is reflected by the overall reaction: **2**+2e⁻+2H⁺=**1**.

Compound **2** (Fig. 2) was synthesized as a mixture of the (2*E*,5Z)–**2a** and (2*Z*,5Z)–**2b** isomers at a 63:37 ratio according to previously published methods [7,15].

Cyclic and linear voltammetry with stationary and rotating disc electrode (RDE) in DMSO were coupled with *in situ* UV-vis absorption and electron paramagnetic resonance (EPR) spectral techniques. To outline the influence of the electrogenerated bases (EGB) on the reduction mechanism, the experiments were per-



Fig. 2. Configurational isomers of (5–ethoxycarbonylmethylidene–4–oxothiazolidin –2–ylidene)–*N*–phenylethanamide: a) (2*E*,5Z)–**2a** and b) (2*Z*,5Z)–**2b**.

formed in the presence of the added base, tetrabutyl ammonium hydroxide (TBOH).

Taking into account the previously reported regioselective reduction of **1** to (Z)–(5–(2–hydroxyethyl)–4–oxothiazolidin–2–ylidene)–N–(2–phenylethylethanamide) [9] in strong alkaline media, we investigated the electrochemical behavior of this compound in DMSO in the absence and presence of TBOH. Furthermore, the possibility of the reverse pathway that leads from **1** to **2** was also considered.

The identification and the investigation of the reactivity of the intermediate species were performed, and a reduction mechanism of **2** to **1** in polar aprotic solvents (DMSO) is proposed. Semiempirical gas phase and solvent dependent PM3–MO calculations reasonably account for the proposed reaction mechanism.

2. Experimental

Cyclic voltammetry (CV) experiments were performed using a VOLTALAB-40 electrochemical device with a thermostated one-compartment electrolytic cell that included a stationary and rotating Pt-EDI 101 disc working electrode with a diameter of 2 mm, a Pt counter electrode and a Ag/Ag⁺ guasi reference electrode, calibrated in respect with the ferrocene/ferrocenium couple $(E^{\circ'}_{Fc/Fct} = 0.460 \text{ V vs. SCE})$. All measurements were performed at room temperature in DMSO with 0.1 M tetra-*n*-butyl ammonium hexafluorophosphate (TBAHFP) as the supporting electrolyte. Prior to each experiment, the solutions in the electrochemical cell were degassed with high purity Ar. The Ar atmosphere was maintained over the solution in the cell during the measurements. Experimental results correlated with the results that were obtained by numerical simulations, which were accomplished by the software DigiSim 3.03 Bioanalytical Systems Inc. using the default settings with the assumption of planar diffusion and the Butler-Volmer law for electron transfer. Optical spectra were recorded during the chemical and electrochemical reduction on a Unicam Helios- α UV-vis spectrophotometer and a Radelkis potentiostat. The cell was equipped with an optically transparent electrode (OTE), Pt counter electrode and Ag/Ag⁺ reference electrode. The radical species for the EPR studies were generated in situ by the electrochemical reduction at the potential of the redox couple on the cyclovoltammogram [16,17], using the same solvent and supporting electrolyte as in the electrochemical experiments. The spectra were recorded on a JEOL FA 100 spectrometer in the X-band frequency using peroxylamine disulfonate ($a_N = 1.3 \text{ mT}, g = 2.0055$) as an internal standard. The simulation of the EPR spectra was performed using the computer software, WinSim [18]. Solvent-dependent semiempirical MO calculations were determined using the PM3 hamiltonian AMPAC program package and the HyperChem release 7 software (Hypercube Inc., Gainesville, Florida), RHF was used for the closed shell structures and both ROHF and UHF were used for the open shell structures. The solvent effect was considered under the framework of the COSMO solvation model [19], implemented into AMPAC, based on the dielectric continuum model, with the parameters and settings for DMSO; a dielectric constant of 48.9, a refractive index of 1.48 and a sphere of solvation radius of 0.3 nm.

3. Results and discussions

Preliminary studies on the electrochemical reduction of **2** have pointed to the ECECE reaction sequence and were verified by the DigiSim simulations [20]. The previously proposed mechanism, which consisted mainly of an ECE–Disp sequence in which the chemical step between the first and the second ET was assigned to the possible 2*E*,5*Z*/2*Z*,5*Z* configurational isomerization. It may be summarized as follows:

 $2\mathbf{a} + e^- = 2\mathbf{a}^- \quad E_1^\circ = -0.8 \, \text{V}$

 $2a^{-\bullet} \leftrightarrow 2b^{-\bullet}$

 $2\mathbf{b} + e^- = 2\mathbf{b}^ E_2^\circ = -0.6 V$

 $2a^{-\bullet} + 2b^{-\bullet} = 2a + 2b^{2-}$ or $2b + 2a^{2-}$

Dianions are strong electrogenerated bases and can undergo protonation by protic impurities in the solution and they can evolve to the final reduction product, compound 1 according to the overall reaction: $2 + 2e^{-} + 2H^{+} = 1$. A detailed mechanistic scheme in which the intermediate species that are involved in the overall reaction sequence are identified as chemically defined species is presented in Scheme 2. The proposed mechanism is based on our previous IR and NMR spectral studies on related compounds in which both of the configurational isomers of 2 were characterized by IR and NMR spectra [7]. It was determined that the (2E,5Z)-isomer, which was characterized by an intramolecular hydrogen bond [IR/KBr spectra, v_{max}: 3462 (N–H), 1653 (C=O) exo, 1599 (C2=C2')], is dominant in nonpolar solvents such as CHCl₃. However, in polar solvents (DMSO), the predominant (2Z,5Z)-form $[IR/KBr spectra, v_{max}: 3323 (N-H), 1674 (C=O) exo, 1600 (C2=C2')]$ is stabilized by intermolecular resonance-assisted hydrogen bonding and strong 1,5-type S-O interactions within the S-C=C-C=O moiety. Thermal *E*/*Z* isomerization was studied in the solid state by temperature-dependent IR spectra [21] and in solvents of different polarity (CDCl₃ and DMSO) by dynamic NMR spectroscopy [2–4]. The analysis of the IR spectra recorded in solid state revealed the temperature-dependent equilibrated mixtures of both isomers in varying proportions and stability.

The present study brings new experimental evidence for the characterization of the different intermediates and reaction sequences, which are presented in Scheme 2, by using cyclic and linear voltammetry with stationary and rotating disc electrode, as well as *in situ* EPR and UV-vis spectroelectrochemistry. In this Scheme, starting compound **2** indicates a mixture of the (2*E*,5*Z*)–**2a** and (2*Z*,5*Z*)–**2b** configurational isomers.

The first step in Scheme 2 corresponds to the monoelectronic reduction of the starting compound (consisting of both configurational isomers) to the corresponding anion radicals, $2b^{-}$ at the potential of -0.6 V and $2a^{-}$ at the potential of -0.8 V, according to the simulated DigiSim mechanism. Isomer 2a is reduced at a more negative potential than 2b due to intramolecular H-bond stabilization, as previously reported. This observation is based on solvent and temperature-dependent IR spectra [21]. As reduction is accompanied by a reduced double bond character of the C(2)=C(2') bond, E/Z isomerization is thermodynamically favored and is supported by solvent and temperature-dependent CV [20], as well as by the RDE results shown below. The anion radicals are sufficiently stable and can be characterized by the EPR spectra.



Fig. 3. a) CV of freshly dissolved compound **2** ($c=4 \times 10^{-3} \text{ mol dm}^{-3}$) in 0.1 M TBAHFP/DMSO, $v=0.1 \text{ Vs}^{-1}$ –curve 1, curve 2 – after about 45 min, and curve 3 – CV recorded at 40 °C, b) RDE curves of the cathodic waves of **2** at rotating rates 100–4000 rpm, *insert*: plot of the limit current density ratio $j_{l,lc}/j_{l,llc}$ in function of the square root of the rotation rate at E=-0.75 V, i.e. potential in between E_{lc} ° and E_{llc} °.

-0,8

E vs (Ag/Ag⁺) / V

-0,4

0.0

0.4

The second step in Scheme 2 involves the homogeneous disproportionation between the anion radicals of both isomers, which leads to the starting compound (dominant isomer **2a**) and the $2b^{2-}$ dianions (or $2b + 2a^{2-}$). The dianions, $2a^{2-}$ and $2b^{2-}$, are strong EGB and they can abstract protons either from the protic impurities present in the solvent or from the substrate itself (self–protonation). Protonation of the dianion (step 3) leads to the final reduction product of **1b** *via* the typical keto–enol equilibrium (step 4).

This reaction sequence and all intermediate species involved are characterized and supported by experimental and theoretical results.

3.1. Electrochemical results

-1,6

-1,2

Cyclic voltammetry of compound 2 dissolved in a solution of 0.1 M TBAHFP/DMSO, presented in the potential range of -1.5 to 0.1 V (Fig. 3a), two irreversible waves that were characterized by $E^{\circ'} = -0.6$ V (Ic) and $E^{\circ'} = -0.8$ V (IIc). The current density ratio $j_{\rm Ic}/j_{\rm IIc}$ is about 0.2 at small scan rates (up to 0.1 V s⁻¹) (Fig. 3a, curve 1). After several polarization cycles, or by increasing the temperature, the current ratio increases and the peak Ic becomes dominant at 40 °C [20]. Taking into account that in non–polar solvents, such as CDCl₃, isomer **2a** is the highly dominant isomer [7], peaks Ic and IIc were assigned to the monoelectronic reduction of isomers **2b** and **2a**, respectively. The CV results, which were supported by the DigiSim simulations, point to an ECE–Disp mechanism.

I Overall reaction:



II Reduction mechanism:







Starting compound obtained by synthesis as isomer mixture (2E,5Z)/(2Z,5Z) = 63/37 % [8, 22]
** And other resonance forms with negligible contribution of structure 1 due to the unfavorable charge distribution

Scheme 2. Overall reaction (I) and proposed mechanism (II) for the electrochemical reduction of compound 2 to compound 1 in DMSO, in presence of protic impurities.

The ECE-Disp sequence that is proposed is further supported by the RDE curves recorded at rotating rates in the range of 100-4000 rpm (Fig. 3b). At low rotating rates, up to 500 rpm, only the second reduction wave is observed. However, increasing of the rotating rate favors the appearance and the increase of the first reduction wave, and at a rotating rate of 4000 rpm, only the Ic wave assigned to the 2b isomer is observed. The plot of the limiting current density ratio, $j_{\rm LIC}/j_{\rm LIC}$ as function of the rotating rate (Fig. 3b insert) supports this evolution.

The value of the slope $dE_{1/2}/d(\log \omega) = 23 \text{ mV}$, along with the prior analysis of the CV data in Fig. 3a, confirmed the hypothesis of an ECE-Disp 2 mechanism with the kinetic control by the homogeneous ET reaction [22] and a significant effect of disproportionation for the potential values between Ic and IIc [23].



Fig. 4. EPR spectra obtained by in situ electrochemical reduction of compound **2** in DMSO, at a potential between the lc and llc waves: a) experimental and b) simulated.

These results are consistent with an E/Z isomerization that occurs in polar solvents [10,20] during electrochemical reduction and are in agreement with the previous dynamic ¹H NMR studies, which have outlined this type of isomerization as one of the characteristic processes of the push–pull alkenes [3,24].

3.2. EPR results

To identify the paramagnetic species in the reduction process of **2**, EPR spectra were obtained during the in situ electrochemical reduction at a potential between the Ic and IIc waves.

The experimental EPR spectrum is well resolved (Fig. 4a) and confirmed the presence of a relatively stable paramagnetic species. The paramagnetic species was assigned to the electrogenerated anion radical of the dominant 2a isomer from the starting compound. The EPR spectrum becomes asymmetric over time and is likely due to a mixture with the anion radical of the isomer **2b**, which has a similar g-value, but slightly different hyperfine splitting (hfs). The larger value of the g-factor (2.0062) is in the range of the reported values for other sulfur containing anion radicals, and this points to a radical center that is close to the sulfur atom, as opposed to a carbonyl centered species [25]. A significant spin density on the sulfur atom, which is ascribed to the higher spin-orbit coupling constant of sulfur ($\lambda = -382 \text{ cm}^{-1}$, compared to that of oxygen, $\lambda = -152 \text{ cm}^{-1}$), is indicated by the g-value shift against the value of the free electron (2.0023) [26]. The spectrum was simulated (Fig. 4b) with the EPR parameters presented in Table 1.

The hfs pattern attests for a π -type radical and is due to the interaction of the unpaired electron with three protons and one nitrogen atom. The assignment of the hfs constants due to the different positions within the molecule was performed by comparing the anion radicals of the related 5-substituted



Fig. 5. Absorption spectra recorded on electrolysis of compound **2** ($c=4 \times 10^{-5} \text{ mol dm}^{-3}$) in DMSO a) at a potential between the Ic and IIc waves, after 0, 5, 10, 15 min; b) absorption spectra of compound **2** ($c=5 \times 10^{-5} \text{ mol dm}^{-3}$) in DMSO at high c_{TBOH}/c_2 molar ratios (from 16 to 48).

2–alkylidene–4–oxothiazolidines [10] with the calculated MO spin distributions, as discussed below.

The highest hfs was assigned to the vinyl proton of the double bond at the C(5) position, and is in agreement with the structure of both radical species that are presented in Scheme 2. Next splittings are due to the double bond vinyl proton at the C(2) position and the NH proton of the heterocyclic ring. The distribution of the hfs constants attests for the delocalization of the unpaired electron within the planar moiety of the molecule that comprises the conjugated thiazolidinone ring with the double bonds at the C(2) and C(5) positions.

3.3. UV-vis spectroelectrochemistry

Aside from the primary anion radicals generated by HET, to detect the diamagnetic transient species, such as the anions and dianions, UV–vis spectra were recorded during the *in situ* electrochemical reduction of **2**. The curves obtained during the electrochemical reduction at a potential in between waves Ic and IIc, as well as with the gradual addition of TBOH in DMSO, are presented in Fig. 5.

The starting compound, a mixture of the configurational isomers **2a** and **2b** in a 63:37 ratio [27], presents a band at 372 nm (Fig. 5a). This band decreases in time and a new broad absorption band centered at 400 nm is formed, which indicates the presence of new species. In time, this band becomes asymmetric towards 440 nm and decreases. The absorption band at 440 nm was assigned to the

Radical species	Hyperfine splitting constants (mT)				Line width (mT)	
	<i>a</i> _N (3) ^a	<i>a</i> _H (8)	<i>a</i> _H (10)	<i>a</i> _H (6)		
Anion radical 2a -•	0.070	0.425	0.253	0.080	0.028	

^a Numbers correspond to atom numbering presented in Fig. 2.

anion radical that was identified and characterized under similar conditions by EPR spectroscopy.

Based on the similarity with the spectra that were recorded in the presence of TBOH added in DMSO (data not presented), the band at 400 nm was assigned to the anion that was formed by the ionization of the NH–lactam group due to the action of the electrogenerated base anion radical on the substrate. Up to a $c_{\text{TBOH}}:c_2 = 1:1$ molar ratio, this process is reversible and the addition of water recovers the starting compound. The acid character of the thiazolidinone ring is reflected by the reported pK_a value (18.5) for 4–oxothiazolidine in DMSO [28] and is ascribed to the sulfur substitution in the 5–membered ring. A similar behavior was noted for the electrochemical reduction of the related 5–substituted–*N*–phenylethanone derivative in DMSO [10]. A highly stabilized anion has been postulated as an intermediate in the reduction process of **2** with NaBH₄ [9].

The spectra were recorded by in situ spectroelectrochemistry after prolonged electrolysis or at high TBOH/substrate molar ratios, as shown in Fig. 5b; this figure also shows the decrease of the absorption band at 400–440 nm, along with the progressive increase of the absorption bands at 350–370 nm and 316 nm. This behavior is consistent with the disproportionation reaction of the anion radical, resulting in the partial recovery of the starting compound (372 nm) and the **2b**^{2–} dianion (350 nm), which was further protonated to the final reduction product, compound **1b** (316 nm), *via* the typical keto–enol equilibrium (Scheme 2, steps 2–4). Further support for this assignment is substantiated by the time evolution of the absorbance at these wavelengths, $A = f(\log t)$, where A was recorded at a potential value between waves Ic and IIc, (Fig. 6).

A convenient method to present data in a transmission chronoabsorptometry experiment is to plot the normalized absorbance (ratio of the absorbance at time t to the absorbance in the absence of the chemical reaction) as a function of time (log t). Comparison of these plots with the theoretically calculated curves for different mechanisms offers further diagnostic criteria for a complex reaction mechanisms that involve coupled chemical reactions to electron transfer steps [29].



Fig. 6. Normalized absorbance $A = f(\log t)$ for the bands at 372 (starting compound), 350 (dianion), 316 (reaction product) and 440 nm (anion radical).

The normalized absorbance at 372 nm decreases to a minimum, whereas the band at 440 nm initially increases due to the accumulation of the anion radical, and the minimum on the 372 nm curve corresponds to the maximum on the curve at 440 nm. The further decrease of the absorbance at 440 nm, parallel to the increase in absorbances at 350 nm, (dianion), and at 372 nm (starting compound **2**) may be considered as support for the subsequent homogeneous disproportionation reaction (Scheme 2, step 2). The time evolution of the absorbance at 316 nm, which increases simultaneously with the absorbance at 350 nm, that is after the appearance of the dianion in the system, gives further evidence for its assignment to the reaction product of the dianion protonation, **1b**, presumably in the enolic form (Scheme 2, step 3).

The evolution of the bands, presented in Fig. 6, is consistent with a reaction sequence [29]:

$$A + e \rightarrow B$$

$$2B \rightarrow A + C$$

 $C\,\rightarrow\,D$

where A stands for starting compound **2**, B for the anion radical, C for the dianion and D for reaction product **1b**. This is supported by the spectral behavior of compound **1** that was obtained as a pure (Z)–isomer by synthesis [8,24] and was recorded on the gradual addition of TBOH in DMSO.

The family of spectra in Fig. 7 shows a typical keto–enol tautomeric equilibrium, (step 4 in Scheme 2) which is highlighted by a decrease of the absorption band at 307 nm that corresponds to the keto form of **1b** [9], along with the increase of the bands at 322 and 340 nm and an isobestic point at 316 nm. In basic media, the tautomeric equilibrium of compound **1b** is shifted towards the less stable enolic form and these bands were assigned to the enolate anion **1b**⁻ (322 nm) and the dianion **1b**^{2–} (340 nm), respectively. For $c_{\text{TBOH}}/c_{\text{1b}}$ molar ratios of up to 6.4:1, a reversible behavior is observed, and the substrate 1b can be entirely recovered by acidifying the solution with 7.01 mM trichloroacetic acid.



Fig. 7. Keto–enol equilibrium of compound **1**: absorption spectra of **1** ($c=4 \times 10^{-5} \text{ mol dm}^{-3}$) in DMSO, at different c_{TBOH}/c_2 molar ratios (from 0 to 10).



Fig. 8. Shape of the PM3 calculated single occupied molecular orbital (SOMO) of anion radical **2a^{-•}** in DMSO.

By comparing the spectra that were recorded after the prolonged electrolysis of compound **2** and/or at high c_{TBOH}/c_2 molar ratios (Fig. 5b) with those of **1** in presence of TBOH (Fig. 7), it was inferred that the same intermediate species was identified, which was characterized by the absorption band at 340–350 nm. This species, the dianion $2b^{2-}$ or $1b^{2-}$ (resonance formulae A and B of the same species, Scheme 2, step 3), may be obtained either by starting from compound **2** by electrochemical reduction at potentials higher than wave IIc and/or disproportionation of the anion radicals (step 2, Scheme 2), or from **1** in the presence of TBOH in DMSO and it represents experimental evidence for the proposed reaction mechanism. These results were validated by the semiempirical MO calculations that are discussed below.

3.4. MO calculations

The aim of the MO calculations was to provide theoretical support to the proposed electrochemical reduction mechanism in DMSO in the presence of protic impurities ($2a,b+2e^-+2H^+ \rightarrow 1b$, Scheme 2) and to obtain insight into the electronic structure and reactivity of the different intermediates that were observed by the experimental results. Therefore, all steps in Scheme 2 were analyzed and all of the intermediate species, such as the anion radicals, dianions, and enolate anions, were calculated. The reverse sequence of $1 \rightarrow 2$ was also examined and the possibility of the 2E,5Z/2Z,5Z isomerization of the intermediate reduction species was considered.

3.4.1. Radical anions

The anion radicals obtained from the 2a and 2b isomers, as depicted in Scheme 2, were optimized in the gas phase and in DMSO. The geometry of the anion radicals was similar to the corresponding neutral molecules, and the increased stability of the anion radical (2E,5Z)- $2a^{-\bullet}(\Delta H = -828.93 \text{ kJ mol}^{-1})$ when compared to (2Z,5Z)–**2b**^{-•} (ΔH = –811.86 kJ mol⁻¹) was due to intramolecular H-bonding and was experimentally supported by solvent and temperature IR spectra [20]. However, the calculated -N-H-O=Cdistance of the anion radical was 0.232 nm, which is higher than that in the neutral molecule (0.187 nm) and denotes a weaker interaction compared to the neutral molecule. Therefore this molecule presents a tendency for E/Z isomerization. The calculated charge distribution of the anion radicals 2a-• and 2b-• attests for the resonance formulae of both isomers that were assigned in Scheme 2. First, the reduction of the exocyclic C(5)=C(5') bond is reflected by an increased repulsion due to high negative net charges on both C atoms (-0.324 and -0.279 for (2Z,5Z)-2b-• and -0.308 and -0.276



Fig. 9. a) Potential energy surface calculated in DMSO for the 2*E*,5*Z*/2*Z*,5*Z* isomerization of the anion radical **2a**^{-•} (open circles) and dianion **2a**^{2–} (full symbols), with respect to the rotation around C(2)=C(2') bond, dihedral angle (-S-C=C-C-). ΔH_{rel} represents the formation enthalpy including solvation with respect to the minimum of the (2*E*,5*Z*)–**2a** isomer (left) of the anion radical and dianion, respectively; b) Evolution of the bond orders *P*(2–2') (open triangles) and *P*(5–5') (full symbols) during the 2*E*,5*Z*/2*Z*,5*Z* isomerization of the anion radical **2a**^{-•}.

for $(2E,5Z)-2a^{-\bullet}$ and a lower bond order (1.341-1.351 vs. 1.837) in the corresponding neutral molecules. Second, the lower bond order for the exocyclic C(2)=C(2') bond compared to the neutral molecule attests for a possible isomerization during the reduction process.

The electronic structure of the anion radicals accounted for the experimental EPR spectra (Fig. 4a), with the highest splitting (0.425 mT) (highest calculated spin density) assigned to the exocyclic C(5)=C(5') bond proton, which is in agreement with the structure of the anion radicals that were presented in Scheme 2. The next greatest hfs (0.253 mT) was assigned to the proton on the exocyclic C(2)=C(2') bond, whereas the smallest splittings were assigned to the lactam nitrogen and proton. The assignment of the EPR spectra was performed by comparison with the semiempirical MO calculations and assumed a π -type radical and a McConnell-type formula:

$$a_K = Q_{CH}^H \rho_K$$

where *Q* is the spin polarization parameter (a proportionality constant that is expressed in magnetic field units) and ρ is the spin density in the p_z MO occupied by the unpaired electron (unpaired



Scheme 3. Tautomeric keto-enol equilibrium of compound 1b, with the numbering used in the calculations (Table 3).

Table 2

PM3-calculated electronic parameters for the dianions $2b^{2-}$ and $1b^{2-}$ in DMSO (formation enthalpy including solvation, ΔH , and energies of the frontier orbitals, $\varepsilon_{\text{HOMO}}$, $\varepsilon_{\text{LUMO}}$).

Radical species	ΔH (kJ mol ⁻¹)	$\varepsilon_{\rm HOMO}~({\rm eV})$	$\varepsilon_{\rm LUMO}~({\rm eV})$
2b ²⁻ , 1b ²⁻	-1127.93	-5.97	-0.031

 π -electron population at the adjacent carbon atom k). Even if the semiempirical PM3 calculations are not the appropriate methods for the spin density calculations, the spin density in the p_z orbital and the shape of the molecular orbital occupied by the single electron (SOMO) in the anion radical (Fig. 8) attests for the delocalization of the unpaired electron onto the thiazolidinone ring, the exocyclic double bonds and the carbonyl groups, and supports the assignment of the splitting constants that are presented in Table 1, as well as the higher g-factor values that were experimentally observed.

3.4.2. Dianions

The dianions were calculated starting from either the optimized geometries of neutral compound **2**, $[2a,b+2e^-]$ or from **1** $[1b-2H^+]$. When starting from **2**, the dianions were generated either by HET at the electrode at potential values that were greater than wave IIc, or by homogeneous ET and disproportionation of the anion radicals (Scheme 2, step 2). The results indicated that the same structure is obtained by either the two-electron reduction of **2**, $(2b^{2-})$ or by deprotonation of **1b**, $(1b^{2-})$, which corresponds to resonance formulae A and B in Scheme 2 and is characterized by the electronic parameters in Table 2.

The charge distribution is consistent with equal contributions from structures A and B in Scheme 2 with the high negative charges (-0.798 and -0.767) representing the oxygen atoms of the lactam and carbonyl groups (form B) and (-0.369 and -0.514) the exocyclic double bond carbon atoms at the C(5) position (form A), respectively.

3.4.3. Reactivity of the intermediate species

2E,5Z/2Z,5Z isomerization is one of the characteristic reactions of the investigated push-pull oxothiazolidines and was observed by experimental data during the electrochemical reduction of **2a,b** to **1b**. The isomerization was analyzed in terms of the solvent–dependent PM3–MO calculations, which began with the anion radical $2a^{-\bullet}$, or the dianion $2a^{2-}$.

The reaction paths for the possible 2E,5Z/2Z,5Z isomerization of the anion radical $2a^{-\bullet}$ and the dianion $2a^{2-}$, with respect to the dihedral angle–S–C=C–C–, as well as the evolution of the bond order of the exocyclic C(2)–C(2'), P(2–2') and the C(5)–C(5'), P(5–5') double bonds are presented in Fig. 9.

The highest energy point in Fig. 9a corresponds to a dihedral angle of 83–86 deg and energy barriers of 96 and 63 kJ mol⁻¹ for the anion radical $2a^{-}$ and the dianion $2a^{2-}$, respectively. These data indicate a possible, but slow, isomerization process during electrochemical reduction. This result is within the range of the values reported for related compounds from dynamic ¹H NMR studies of thermal E/Z isomerization in DMSO [3], and it is in agreement with the temperature dependence of the cyclic voltammetry curves, which showed that isomer **2b** is favored at higher temperatures [20]. Analysis of the calculated bond orders in Fig. 9b indicates a lower C(2)=C(2') bond order in the (2E,5Z)- $2a^{-\bullet}$ (1.585) when compared to (2Z,5Z)–**2b**^{-•} (1.732), which points to an enhanced conjugation due to the intramolecular H-bond in 2a^{-•} equal values (\sim 1.35) for the C(5)=C(5') in both isomers are consistent with the electrochemical reduction that occurrs at this bond and attests for the structures assigned to the anion radicals in Scheme 2 (step 1). The evolution of the bond orders during the isomerization of the anion radicals $2a^{-}/2b^{-}$ in Fig. 9b shows a reverse variation, where the minimum of the C(2)=C(2') bond order corresponds to the highest energy point and coincides with a maximum value of the C(5)=C(5') bond order. In other words, the weakening of the C(2)=C(2') bond is accompanied by a reinforcement of the C(5)=C(5') bond, which indicates the transition state of the structure in Fig. 9b.

3.4.4. Tautomerization of 1b:

The tautomeric equilibrium (Scheme 3, or step 4 in Scheme 2) was analyzed, and the relevant results are presented in Table 3.

The keto form is more stable by -141.4 kJ mol⁻¹ and the lower energy values of the HOMO and the LUMO attest for the increased e⁻-acceptor (and poorer e⁻ -donor) properties of the keto form when compared to the enol form of **1b**. The charge distribution, shown in Table 3, is in agreement with the structure for both the keto (high bond order for both carbonyl groups and the intermediate between the single and double bond order for the ring 12–13

Table 3

PM3-calculated Δ H (formation enthalpy including solvation), energies of the frontier orbitals, ε_{HOMO} , ε_{LUMO} and selected bond orders for the **1b** tautomers.

Tautomer	ΔH (kJ mol ⁻¹)	$\varepsilon_{\rm HOMO}~({\rm eV})$	$\varepsilon_{\text{LUMO}}$ (eV)	$p_{9-10}{}^{a}$	<i>p</i> ₁₂₋₁₃	p_{13-17}	<i>p</i> ₁₅₋₁₈
1b keto form	-514.59	-9.035	-0.969	1.786	1.525	1.721	1.721
1b enol form	-373.21	-8.038	-0.629	1.716	1.531	1.067	1.039

^a Numbers correspond to atom numbering presented in Scheme 3.

bond) and the enol (low bond orders for the C–O bonds and the intermediate (\sim 1.5) bond order for the ring 12–13 bond) forms. The keto form is present mostly in acidic and neutral conditions, whereas the enol form is favored under basic conditions.

In our experimental conditions, in DMSO, in the presence of TBOH or electrochemically generated negative species, like anion radicals or dianions (such as electrogenerated bases), the enolate anions and the dianions are favored. The similarity of the absorption spectra recorded in the electrochemical reduction to those in the presence of TBOH is experimental evidence in this respect. Consequently, all of these intermediates were calculated, and the energetics of the global reaction, $2a,b+2e^-+2H^+=1b$, was evaluated for both the enol and the keto forms of 1b. The results indicate that the global reduction of **2a,b** to the **1b**-enol is slightly endothermic (52.72 and 33.14 kJ mol⁻¹ for **2a** and **2b**, respectively), whereas the **1b**-keto form is largely exothermic (-88.58 and $-108.28 \text{ kJ} \text{ mol}^{-1}$ for **2a** and **2b**, respectively). Therefore, the acid-base properties of these species play an important role in the overall electrochemical reduction of 2 to 1 and must be considered for the complete understanding of the reaction mechanism.

4. CONCLUSIONS

The electrochemical reduction of (5–ethoxycarbonylethylidene–4–oxothiazolidin–2–ylidene)–*N*–phenylethanamide (**2**) to (*Z*)–(5–ethoxycarbonylmethyl–4–oxothiazolidin–2–ylidene)– *N*–phenylethanamide (**1**) in DMSO in the presence of protic impurities was investigated by coupled in situ electrochemical (CV with stationary and RDE) and spectral (EPR, UV–vis absorption) techniques. A reduction mechanism, which consisted of an ECE–Disp sequence that was followed by the protonation of the strong EGB, was proposed. The same intermediate species, the dianion $2b^{2-}$ or $1b^{2-}$ (different resonance formulae of the same species, shown in Scheme 2, step 3), was identified either starting from compound **2** by electrochemical reduction or from compound **1** in the presence of TBOH in DMSO. The proposed reaction mechanism is supported by the experimental results and by the semiempirical solvent–dependent PM3–MO calculations that were performed.

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