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Electrochemical behavior of *N*-oxyphthalimides: Cascades initiating self-sustaining catalytic reductive *N*—*O* bond cleavage

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Abstract

N-oxyphthalimides are stable and easily accessible compounds that can produce oxygen radicals upon 1-electron reduction. We present a systematic study of electrochemical properties of N-oxyphthalimide derivatives (PI-ORs) in DMF by cyclic voltammetry. In all cases, electron transfer to the substrate leads to decomposition of the intermediate radical anion via the N—O bond cleavage. In the case of benzyloxyphthalimide or its derivatives containing electron-donating substituents, reductive electron transfer induces the chain decomposition of the substrate to phthalimide (PI) radical-anion and the corresponding carbonyl compound. The PI radical-anion product is a powerful reductant that can transfer an electron to the reactant PI-OR, thus establishing a catalytic cycle for reductive N—O scission. This self-catalytic process is reflected in a considerable decrease in the reduction current for the substrate (<1e$^-$/molecule). By contrast, reductive fragmentations of benzyl derivatives containing electron-withdrawing substituents in the aromatic ring or at the benzylic position, as well as tosyl and alkyl derivatives, occur *via* a 1-electron mechanism. A sequence of N—O and C—C scissions was engineered to support the intermediacy of O-centered radicals in these processes.

KEYWORDS

cyclic voltammetry, dissociative electron transfer, electrochemically induced cyclic reactions, *N*-hydroxyphthalimide derivatives, radical anions

1 | INTRODUCTION

N-Hydroxyphthalimide (NHPI) and its *O*-substituted derivatives (PI-ORs, Figure 1) play an increasingly important role in organic synthesis and medicinal chemistry.[1–16] In particular, the highly reactive *N*-oxyl radicals generated from NHPI and its analogues are widely used in the selective liquid-phase oxidation of organic substrates,[1–3] such as alkanes, alkylarenes, alkenes, alkynes, alcohols, and ethers, as well as in oxidative cross-coupling reactions.[4–7]

Because the phthalic protecting group can easily be removed, PI-ORs are the main precursors of organic *O*-substituted hydroxylamines (Scheme 1, direction **A**), valuable intermediates in the synthesis of biologically active compounds.[8–12] In reactions with various reducing agents, PI-ORs can undergo a wide spectrum of

This paper is dedicated to Professor Waldemar Adam on the occasion of his 80th birthday

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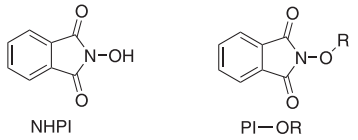


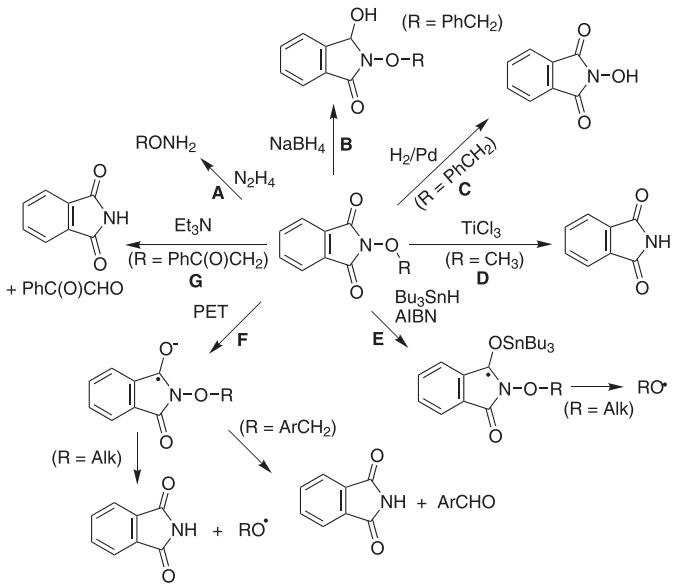
FIGURE 1 The structures of *N*-hydroxyphthalimide (NHPI) and its *O*-substituted derivatives (PI-OR)

transformations and participate in processes that lead to the selective cleavage of either the CO pi-bond ($NaBH_4$ as the reducing agent, direction **B**),[17] the C—O bond (H_2/Pd as the reducing agent, direction **C**),[18] or the N—O bond ($TiCl_3$,[19] Bu_3SnH, or Ph_3SnH as the reducing agent, directions **D-E**[13–16]). The reactions with R_3SnH in the presence of the radical initiator AIBN are believed to proceed via attack of R_3Sn• radical at the carbonyl oxygen followed by a β-scission to form an oxygen-centered free radical. The N—O bond cleavage can occur in radical anions (RAs) of PI-ORs that are generated *via* 1-electron reduction (direction **F**) under irradiation in the presence of a photosensitizer.[20–25] Recently, the photochemical versions of these reductive fragmentations started to find an increasing number of new applications.[26–30]

Despite a large number of studies on the reductive fragmentation of PI-ORs accompanied by the N—O bond cleavage, most of them include formation of PI-OR RAs as transient components of complex catalytic cycles. Direct detection of these species and possible intermediates of their further transformations remains elusive. Because a variety of different PI-ORs and reducing agents were used in the literature, the results of the published studies are often difficult to analyze and to compare systematically. For example, reduction of a number of O-alkyl derivatives of NHPI with Bu_3SnH affords oxygen-centered free radicals.[14] These findings can be attributed to the specific coordination of the Sn-radicals with the substrate.[31–33] On the other hand, photochemical reductive fragmentation of NHPI derivatives did not reveal reactivity consistent with the formation of free radicals.[25] Furthermore, yet another mechanism is possible if the α-C—H bond of the N—O—CHR_2 moiety is acidic (eg, in β-keto derivatives[34]). In the latter case, the reaction can be induced by bases (Scheme 1, direction **G**) produced in the primary reactions of organic RAs. This mechanistic diversity renders reductive fragmentation of NHPI derivatives an interesting and challenging topic.

In addition to organic synthesis, understanding the processes of the formation and decomposition of PI-OR RAs gains increasing importance for medicinal chemistry. In this field, there is a need for new structural units capable of releasing active functional groups or generating reactive free radicals directly in living tissues, eg, *via* photoinduced electron transfer.[35–37] Compounds having such properties can be particularly useful for the development of approaches to the therapy of hypoxic tumors, which are difficult to treat with cytotoxic drugs with other mechanisms of action.[38–40] The key feature of PI-ORs examined in the present work is the presence of the relatively weak N—O bond, which is susceptible to cleavage *via* reductive 1-electron transfer.[41–43] These compounds provide an interesting counterpart to organic peroxides,[44–51] a related class of biologically active antiparasitic and antitumor compounds containing a weak O—O bond.

In order to obtain data on the mechanism of reductive reactions of PI-ORs, the present work applied



SCHEME 1 Transformations of *N*-hydroxyphthalimide derivatives (PI-ORs) in the presence of reducing agents and bases

electroanalytical methods to investigate electrochemical properties of these compounds. The electrochemical behavior of NHPI derivatives has been scarcely studied. Only a few of cyclic voltammetric peak potentials for the electroreduction (ER) of selected *O*-acyl derivatives of NHPI in acetonitrile[20,21] and the polarographic half-wave potentials in methanol[52] are known. One can also mention ER of benzyloxyphthalimide in aprotic medium in the presence of chlorotrimethylsilane that led to silylation of the substrate.[53]

In this work, we studied electrochemical behavior of 15 PI-ORs by cyclic voltammetry (CV) on a glassy carbon working electrode in DMF in the presence of tetrabutylammonium perchlorate as a supporting electrolyte. The electrochemically induced N—O bond cleavage in PI-ORs was general, but the substrate structure had effect on the reduction potentials and subsequent transformations. These results provide insights into the thermodynamics of electron transfer reactions, stability of the corresponding RAs, and the reductive cascades that follow the N—O fragmentation.

2 | EXPERIMENTAL

Cyclic voltammograms were recorded, and controlled potential electrolysis were implemented with an IPC-Pro potentiostat (Econix) (the accuracy of the scan rate is 1.0%; the accuracy of the potential setting is 0.25 mV). Experiments were performed in a 10-mL 5-neck glass conical-shaped electrochemical cell with a water jacket for thermal control. The glassy carbon disk electrode ($d = 1.7$ mm) served as the working electrode; a platinum wire (insulated by a ceramic membrane in electrolysis), as the auxiliary electrode. A graphite rod was utilized as a cathode for the electrolysis. A saturated calomel electrode (SCE) served as the reference electrode, which was linked to the solution under study by a bridge with a porous ceramic diaphragm filled with the supporting electrolyte. The potentials were corrected for the ferrocene oxidation potentials under the same conditions (0.47 V vs SCE). The solutions were kept under thermally controlled conditions at 25 ± 0.5°C and then deaerated by bubbling argon. Electrochemical experiments were performed under an argon atmosphere. A typical experiment was carried out using 5 mL of a substrate solution at a concentration of 5 mmol/L. Listed peak potentials correspond to the points of the maximum current on cyclic voltammograms (Table 1).

Electrolysis of **1** was carried out at the potential of the first step of the ER (−1.75 V). The solution was sampled for GC after passing 0.20, 0.30 and 0.40 F of electricity. Gas chromatography was performed on Chromatec-Crystal 5000 instrument with flame ionization detector; injector temperature was 250°C, column temperature was raised from 70°C to 250°C at rate of 15°C/min, helium was used as the carrier gas, flow rate was 2.19 mL/min; GC column phase: dimethylsiloxane; phase thickness: 1.0 μm; column inner diameter: 0.32 mm;

TABLE 1 Voltammetric peak potentials (V) of the compounds at a glassy carbon electrode in a 0.1 M Bu_4NClO_4 solution in DMF relative to Fc/Fc^+. The value of n is the number of electrons per molecule; it was estimated with respect to the ferrocene oxidation peak current ($v = 0.05$ V s^{-1}).

Compound	$-E^p_1$	$-E^p_2$	$-E^p_3$	$-E^p_4$	n
PI	-	1.941	-	2.694	0.67
PI + AcOH	-	1.926	-	-	2
PI + Bu_4NOH	-	-	-	2.649	
1	1.765	1.940	2.288	2.701	< 0.4
1a	-	-	2.290	-	
2	1.768	1.945	2.464	2.693	< 0.4
2a	-	-	2.457	-	
3	1.764	1.947	2.448	2.692	< 0.4
3a	-	-	2.431	-	
4	1.749	1.920	2.272	2.656	< 0.4
4a	-	-	2.097[a] 2.321[a]	-	
PI +**4a**	-	1.913[a]	2.283[a]	2.742[a]	
5	1.765	1.935	2.280	2.650	< 0.4
6	1.764	1.944	2.348	2.645	< 0.4
7	1.757	1.943	2.350	2.670	< 0.4
8	1.788	-	-	2.652	~1
8 + AcOH	1.757	1.952	-	-	
9	1.857	-	-	2.679	~1
9 + AcOH	1.770	1.967	-	-	
10	1.688	-	2.276	2.635	~1
10 + AcOH	1.694	1.943	-	-	
11	1.746	-	-	2.633	~1
11 + AcOH	1.727	1.966	-	-	
12	1.618	1.963	-	2.724	~1
13	1.640	-	-	2.715	~1
13 + AcOH	1.620	1.940	-	-	
14	1.799	-	-	2.714	~1
14 + AcOH	1.787	1.937	-	-	
15	1.592	1.952	-	2.744	~2/3
16	1.656	-	-	2.775	~1

[a]The voltammetric peak potentials for PI and **4a** when they are simultaneously present in the solution are not equal to those for separately prepared solutions of these compounds (see Figure 6).

column length: 30 m. In the course of electrolysis, a gradual decrease of intensity of N-(benzyloxy)phthalimide **1** GC peak and simultaneous increase of GC peaks of benzaldehyde **1a** and phthalimide **PI** were observed. Components of the mixture were identified by the retention times which were determined for individual compounds **1**, **1a**, and **PI**.

Compounds **1a-4a**, phthalimide (PI), DMF ("extra dry"), Bu_4NClO_4, and 1.5 M Bu_4NOH aqueous solution were purchased from Acros Organics. Procedures for the synthesis and purification and the establishment of the structures of compounds **1-11** were reported earlier.[4] Compounds **12**, **13**, and **15** were synthesized by the reaction of NHPI with benzoyl chloride,[54] acetyl chloride,[55] and tosyl chloride,[54] respectively. N-Ethoxyphthalimide **14** was prepared by the reaction of NHPI with ethyl bromide and sodium acetate[56] (Figure 2, Table 1).

1,3-dioxoisoindolin-2-yl 2-(naphthalen-1-yl)acetate 16. EtOAc (5 mL) was added to a mixture of 2-(naphthalen-1-yl)acetic acid (372 mg, 2 mmol), N-hydroxyphthalimide (326 mg, 2 mmol), and N,N′-dicyclohexylcarbodiimide (454 mg, 2.2 mmol). Resultant suspension was stirred for 72 hours at room temperature, then rotary-evaporated to dryness, suspended in CH_2Cl_2 (5 mL), transferred to a silica gel column (wet packed using CH_2Cl_2) and eluted with CH_2Cl_2. The first fraction was rotary-evaporated to give 1,3-dioxoisoindolin-2-yl 2-(naphthalen-1-yl)acetate **16** (588 mg, 1.77 mmol, 89%) as a slightly yellow powder. M. p. = 138-139°C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1H, ArH), 7.93-7.80 (m, 4H, ArH), 7.80-7.70 (m, 2H, ArH), 7.68-7.58 (m, 1H, ArH), 7.58-7.42 (m, 3H, ArH), 4.44 (s, 2H, CH_2); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 167.9 (COO), 162.0 (CON), 134.9, 134.0, 131.9, 129.03, 129.00, 128.96, 128.3, 128.1, 127.0, 126.2, 125.6, 124.1, 123.6, 35.7 (CH_2); IR (KBr): ν_{max} = 1816, 1785, 1737, 1373, 1355, 1189, 1137, 1067, 1043, 970, 877, 779, 694, 519 cm^{-1}; elemental analysis calcd. for $C_{20}H_{13}NO_4$: C 72.50, H 3.96, N 4.23; found: C 72.51, H 3.95, N 4.21.

2.1 | Electrolysis of 1,3-dioxoisoindolin-2-yl 2-(naphthalen-1-yl)acetate 16

At the potential −1800 mV, 48.8 mg (0.147 mmol) of **16** was electrolyzed. After consumption of 1.00 F, the electrolysis was stopped, and the obtained dark-orange solution was diluted with H_2O (10 mL) and extracted by petroleum ether (3 × 7 mL). The organic extracts were combined and washed with H_2O (3 × 10 mL), concentrated in vacuum of the water aspirator. 1-Methylnaphthalene **17** (7.0 mg, 0.049 mmol, 33%) was isolated by TLC (20 × 15 cm plate, layer thickness 0.2 mm; silica gel 60 Å, specific surface [BET] ~ 500 m^2/g, particle size 5–17 μm, with UV_{254} fluorescent indicator) using petroleum ether as eluent. The purity and identity of 1-methylnaphthalene[57] were confirmed by ^{1}H and ^{13}C NMR. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.03-7.97 (m, H), 7.88-7.81 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.56-7.44 (m, 2H), 7.42-7.29 (m, 2H), 2.70 (s, 3H) ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 134.4, 133.7, 132.8, 128.7,

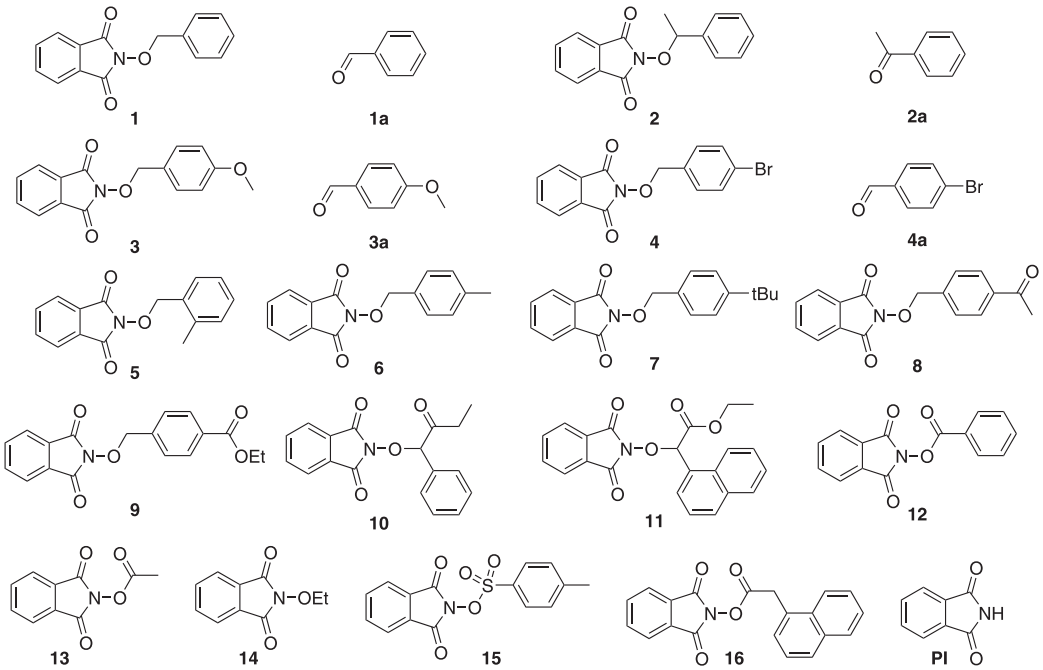


FIGURE 2 Structures of the compounds discussed in this study

126.7, 126.5, 125.8, 125.70, 125.66, 124.2, 19.5. It should be noted that the yield of 1-methylnaphthalene was probably underestimated due to its volatility at reduced pressure that was used for rotary evaporation of the solvent before and after TLC.

3 | RESULTS AND DISCUSSION

3.1 | Electrochemical behavior of 1, 1a, and PI

The cyclic voltammograms of benzyloxyphthalimide **1** in DMF (Figure 3) show a reduction peak at −1.765 V. The peak is chemically irreversible at the scan rates of 0.025-0.100 V s^{-1} but becomes partially reversible at the higher scan rates. Therefore, RA is a short-lived intermediate, and the electron transfer to the substrate **1** is followed by a fast chemical reaction.

Yet another distinguishing feature of the electrochemical behavior of compound **1** under these conditions is a substantial decrease in the cathodic peak current with respect to the 1-electron level. At the minimum potential scan rate (v), a 3-fold decrease with respect to the ferrocene oxidation current at the same value of v was observed. This decrease becomes smaller with increasing scan rate, and a simultaneous increase in the chemical reversibility of the peak is observed. Therefore, the formation of RA of **1** causes the progression of the subsequent chemical chain reactions where the starting compound **1** is consumed in the near-electrode region.

At the expanded cathodic potential scan range, the cyclic voltammogram of **1** (Figure 3, on the right) shows the peaks corresponding to ER of phthalimide PI (−1.940 and −2.701 V) and benzaldehyde **1a** (−2.288 V) after the first reduction stage. Presence of these products is evident from a comparison of the cyclic voltammograms of these compounds measured under the same conditions. Furthermore, the addition of phthalimide PI and benzaldehyde **1a** to a solution of **1** leads to an increase in the corresponding peaks. The formation of phthalimide and benzaldehyde **1a** in the ER of compound **1** was additionally confirmed by GC analysis of the electrolysis solution (see the experimental part).

It should be noted that the presence of both PI and benzaldehyde **1a** in the solution has virtually no effect on both the reduction peak current for **1** and the peak current on the reverse scan after the first reduction stage and, consequently, has no effect on the decomposition rate. This is evidence that the stages giving PI and **1a** are apparently not rate determining in the overall mechanism of ER of **1**.

The mechanism for ER of benzaldehyde **1a** under aprotic conditions involves dimerization of the benzaldehyde RA.[58] Due to the self-protonation of PI RA, its peak current (−1.940 V) corresponds to two-third electrons, the reduction peak of its anion being observed at more cathodic potentials (−2.701 V).[59,60]

Many electrochemically initiated reactions are base-catalyzed processes, in which electric current serves to generate a base at the cathode.[61] Such reactions can also be initiated by addition of an external base and be suppressed by addition of acids (for example, see[62]). We found that addition of acetic acid to a solution of **1** did not decrease the reduction peak currents for the decomposition products PI and benzaldehyde.

Because the decomposition of **1** in the presence of acetic acid is not suppressed, the decomposition of **1** does not involve base catalysis. Instead, it should be associated with the formation of RA that triggers the chain reaction (Scheme 2). It is most likely that the RA of PI rather than RA of benzaldehyde serves as an electron carrier because PI is reduced much earlier than benzaldehyde and,

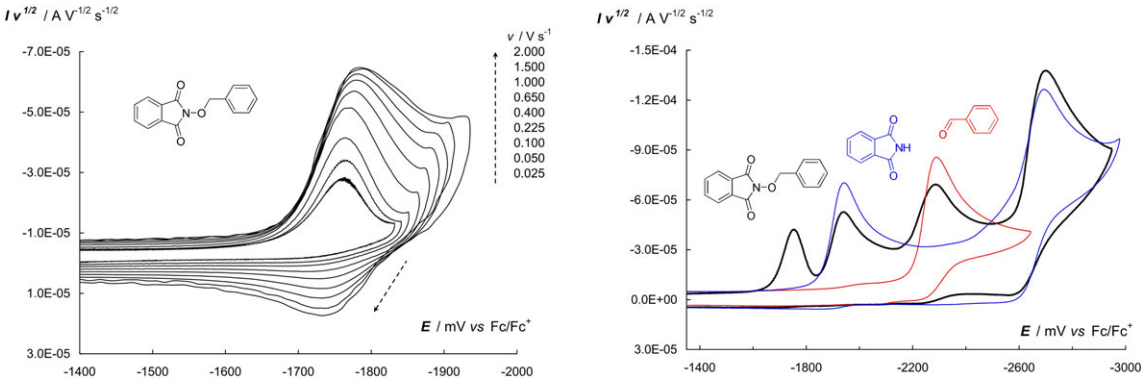
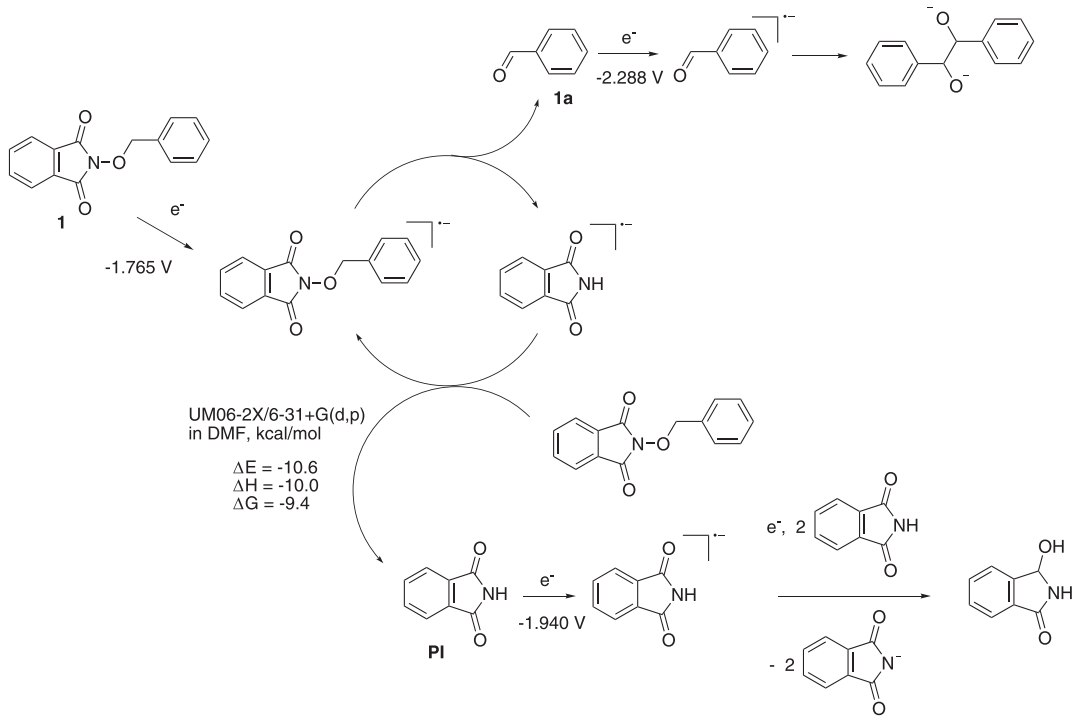


FIGURE 3 Cyclic voltammograms of solutions of compound **1** (5 mmol L^{-1}) obtained at different potential scan rates and normalized to the square root of the scan rate (*left*) and at a scan rate of 0.100 V s^{-1} compared with the voltammograms for PI and **1a** (*right*) in DMF containing 0.1 M Bu_4NClO_4

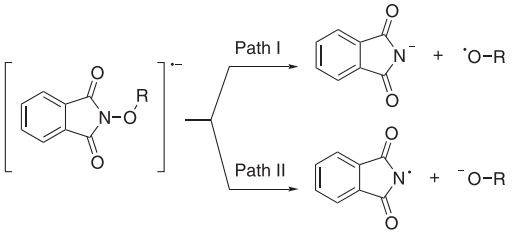


SCHEME 2 Mechanism of the electroreduction of **1** in a 0.1 M Bu_4NClO_4 solution in DMF (the peak potentials in the cyclic voltammograms are given relative to Fc/Fc^+)

consequently, has a higher electron affinity. This conclusion is consistent with the proposed mechanism of photodegradation of **1**[25] and with the −9 kcal/mol free energy for the latter step according to DFT calculations (Scheme 2).

A priori, the N—O bond cleavage in the RAs can proceed via 2 alternative pathways: Path I where the extra electron stays at the nitrogen or Path II where the negative charge goes to the oxygen (Scheme 3).

In the number of papers, the reductive decomposition of alkoxyphthalimides[13–16] and acyloxyphthalimides[20–24] is assumed to involve the formation of O-centered radicals. However, reductive N—O scission benzyloxyphthalimide and its analogues under similar conditions[25] did not provide alkoxy radicals trappable by a fast intramolecular reaction (cyclization). In order to differentiate between the 2 mechanisms, we used result from DFT computations summarized in Table 2.



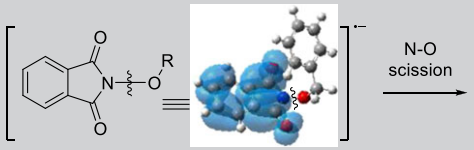
SCHEME 3 Alternative pathways of N—O bond scission in the PI-OR radical anion

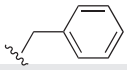
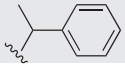
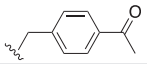
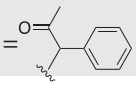
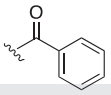
According to the computational results, PI-OR RAs adopt perpendicular geometry around the N—O bond where the non-bonding orbitals at the 2 heteroatoms avoid interaction with each other and instead overlap with the vicinal acceptor σ*-orbitals (lone pair of N with the σ*O—C bond, the p-type lone pair of O with the σ*N—C bonds). This perfect matching of the donor and acceptor properties of the 2 "chameleonic" functional groups[63] assures that the breaking N—O bond is constrained to orthogonality with the π-system of the PI moiety. As the result, electron reduction does not lead to a significant N—O bond length increase whereas the elongation of each of C=O bonds is quite significant (Figure 4, Table 3).

Interestingly, the driving force for the 2 fragmentation paths strongly depends on substituent at oxygen. For R = alkyl, the Path II fragmentation with the formation of an alkoxy anion is so strongly disfavored (ΔG ~ +20-30 kcal/mol), that the only viable fragmentation mode is the Path I that produces the phthalimide anion and an alkoxy radical (ΔG ~ −20 kcal/mol). When R has a carbonyl group directly attached to the oxygen, the balance between the 2 pathways is much more delicately poised. Both processes are exergonic, but the formation of alkoxy radical (Path I in Scheme 3) is still slightly more favorable.

In our opinion, the difficulties in the detection of O-centered radicals do not necessarily indicate their

TABLE 2 DFT calculations of thermochemistry for the 2 possible paths of N—O bond cleavage in radical anions of PI-ORs



Compound	Scission result[b]	E[a]	H[a]	G[a]
1 R = 	PI^- + $RO^{\cdot}$	−4.2	−7.4	−21.5
	$PI^{\cdot}$ + RO^-	39.2	35.5	21.1
2 R = 	PI^- + $RO^{\cdot}$	−2.1	−4.5	−17.7
	$PI^{\cdot}$ + RO^-	41.2	37.6	24.1
8 R = 	PI^- + $RO^{\cdot}$	−2.3	−5.2	−19.8
	$PI^{\cdot}$ + RO^-	39.7	36.2	22.1
10′[c] R = 	PI^- + $RO^{\cdot}$	−4.1	−6.9	−20.4
	$PI^{\cdot}$ + RO^-	32.8	29.7	15.0
12 R = 	PI^- + $RO^{\cdot}$	1.7	−0.9	−13.5
	$PI^{\cdot}$ + RO^-	6.7	4.4	−9.0
13 R = 	PI^- + $RO^{\cdot}$	1.5	−0.8	−13.7
	$PI^{\cdot}$ + RO^-	11.3	9.0	−5.0
14 R = 	PI^- + $RO^{\cdot}$	−2.5	−5.7	−17.9
	$PI^{\cdot}$ + RO^-	45.4	41.9	29.0

[a]UM06-2X/6-31 + G(d,p) in DMF, kcal/mol.

[b]PI = phthalimide.

[c]Compound **10′** has a shortened alkyl chain compared with the experimentally studied compound **10**.

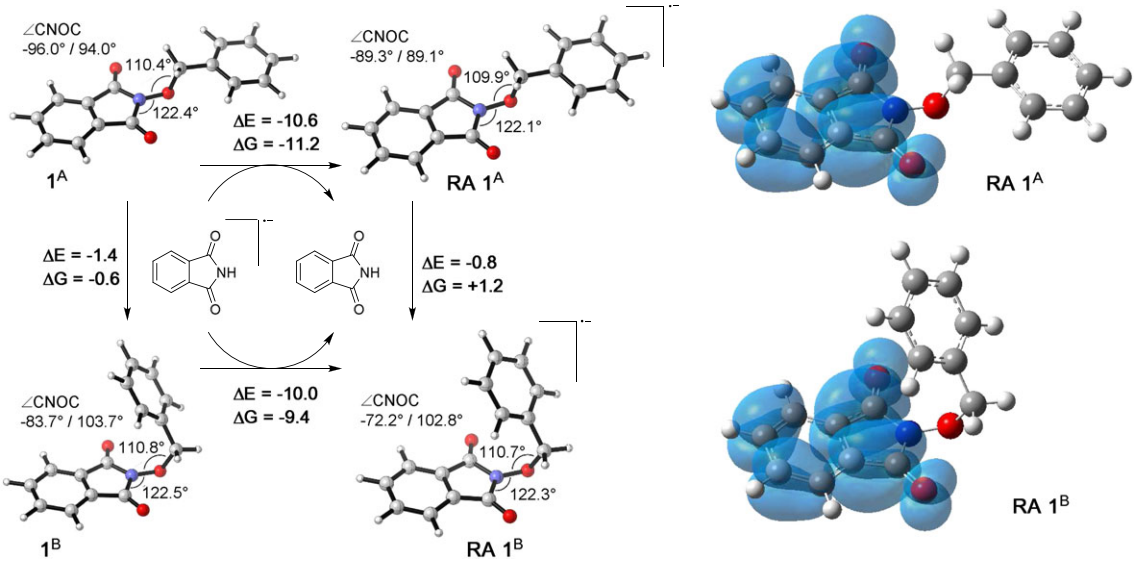


FIGURE 4 Calculated geometries (*left*) and distribution of spin density (*right*) in radical anion (RA) of PI-OR **1**

absence. It is known that the decomposition of organic RAs often gives rise to radical ion pairs (ie, cage clusters in the "sticky" dissociative electron transfer mechanism)[64] and the chemical properties of these ion pairs can differ from those of the isolated particles (see, for example,[65]). The PI anion in the cage cluster can be protonated by benzyloxy radical to form PI and RA of benzaldehyde **1a** (Scheme 4).

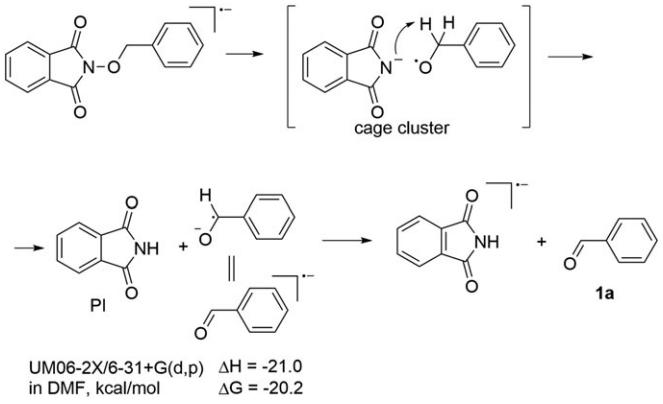
In order to provide in independent evaluation of the above processes, we used DFT calculations with solvent (DMF) corrections (see the SI part for computational details). The calculated thermodynamics of proton

TABLE 3 Calculated geometry parameters of radical anion of PI-OR **1**

	(1^A)	(Ra 1^A)	(1^B)	(Ra 1^B)
C=O bond[a,b]	1.208 / 1.208	1.249 / 1.249	1.209 / 1.207	1.250 / 1.246
N—O bond[b]	1.358	1.363	1.358	1.365
∠CNOC[a]	−96.0° / 94.0°	−89.3° / 89.1°	−83.7° / 103.7°	−72.2° / 102.8°

[a]Formatted as proximal/distal as seen in Figure 4.

[b]Reported in Å.



SCHEME 4 Possible mechanism of benzyloxyphthalimide RA decomposition

transfer from the $PhCH_2O$ radical to phthalimide anion suggests that this process is highly favorable ($\Delta G \sim -20$ kcal/mol). The high acidity of C—H bond adjacent to the radical center originates from the increased stability provided to the product (radical-anion of benzaldehyde) by a 2-center/3-electron bond between the radical and the anionic center.

Similar mechanism has been recently suggested for the decomposition of 2-nitro-1-phenylethanol RA, where the nitromethane anion was protonated by α-hydroxybenzyl radical.[65] The location of the excess electron on the nitrogen atom, which is less electronegative than oxygen, can be explained in terms of the general principle, according to which the formation of a more-difficult-to-oxidize anion is thermodynamically more favorable.[66] PI anion in aprotic medium is oxidized in the far region (>2 V relative to SCE in acetonitrile with Bu_4NPF_6),[66] whereas the benzyl alcohol anion is oxidized much more easily (at −0.567 V relative to Fc/Fc^+[67]; the oxidation potential of ferrocene in acetonitrile with 0.1 M Bu_4NPF_6 relative to SCE is 0.40 V[68]).

The difference between the reduction potentials of PI and benzaldehyde **1a** (>300 mV) indicates that benzaldehyde RA reduces PI with an equilibrium constant of an order of 10^6 according to the equation:

$$\lg K = -\frac{nF\Delta E}{2.303RT}$$

The self-protonation of PI RA (protonation of PI RA by PI) is a side process, which can terminate chain reaction. The effect of the self-protonation is even stronger under electrolysis conditions, during which PI is accumulated in the bulk of the solution. According to the results of coulometry for **1**, it is necessary to pass the current of 0.4 F through the solution for the complete consumption of the substrate, whereas the reduction peak current for **1** with respect to the 1-electron level at the minimum scan rate in CV is 0.3 (see above).

3.2 | Electrochemical behavior of 2-2a, 3-3a, 4-4a, and 4-7

The electrochemical behavior of analogs of **1** containing various substituents both at the benzylic position and in the aromatic ring (Table 1) was studied under analogous conditions.

The presence of a methyl group at the benzylic position of substrate **2** slightly increases the life-time of RA, as evidenced by the partial chemical reversibility of the first stage of ER at lower scan rates in comparison to compound **1** (Figure 5).

At more cathodic potentials, the cyclic voltammogram shows peaks (Figure 5) at potentials corresponding to those of PI and acetophenone **2a** (-2.464 V). These peaks grow after the addition of these compounds to the solution. As in the case with compound **1**, the reaction is not initiated by the addition of Bu_4NOH to the solution and not suppressed by acetic acid.

We obtained similar results in the study of the electrochemical behavior of compound **3** containing a *p*-

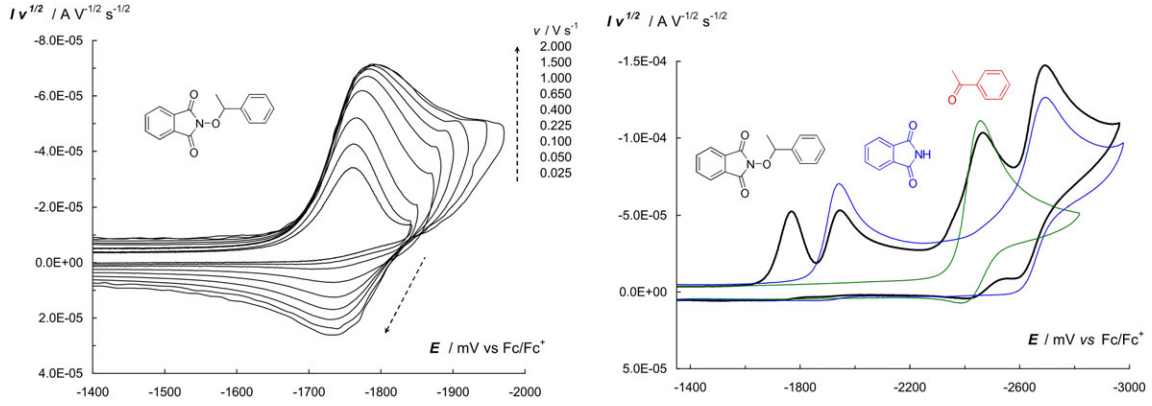


FIGURE 5 Cyclic voltammograms of solutions of compound **2** (5 mmol L^{-1}) measured at different scan rates and normalized to the square root of the scan rate (*left*) and at a scan rate of 0.100 V s^{-1} compared with the voltammograms for PI and **2a** (*right*) in DMF containing 0.1 M Bu_4NClO_4

methoxy group in the aromatic ring. Figure 6 (*left*) illustrates the decomposition of **3** to PI and 4-methoxybenzaldehyde **3a**. The cyclic voltammogram of N-(4-bromobenzyloxy)phthalimide **4** (Figure 6, *right*) is somewhat different from the voltammograms of the compounds considered above. Thus, the peak current for ER of PI is larger, and the peak current for its anion is small. In addition, the peak potential for the decomposition product is not consistent with that for a solution of 4-bromobenzaldehyde **4a**. However, the peaks in the voltammogram for mixture of PI and **4a** are in agreement with the peaks for the products observed in the voltammogram of **4**. Therefore, the observed profile of the voltammogram of **4** can be attributed to the specific electrochemical behavior of PI and 4-bromobenzaldehyde **4a** in mixture.

The formation of PI and related aldehydes was observed also in ER of 2-methyl, 4-methyl, and 4-*tert*-butyl derivatives (structures **5**-**7**, Table 1). Therefore, in aprotic medium, the electrochemical reduction of the benzyloxyphthalimide derivatives containing electron-donating (compounds **1**-**3**, **5**-**7**) or weakly electron-withdrawing (compound **4**) substituents leads to chain decomposition with the formation of PI and the corresponding carbonyl compounds **1a**-**4a**. All of the compounds are reduced at rather similar potentials, and a 2.5-3-fold decrease in the peak current for ER with respect to the 1-electron level under the same conditions is observed. These data are indicative of similar rates of the rate-limiting step in the decomposition of different compounds. The constants for these reactions vary within 10^0-10^1 s^{-1}.

3.3 | Electrochemical behavior of 8-11

The electrochemical behavior of derivatives **8**-**11** containing π-electron-withdrawing substituents in the aromatic ring or at the benzylic position substantially differs from the behavior of the above-considered compounds (Figure 7). Thus, features indicative of the chain reaction following the electron transfer, such as a substantial decrease in the peak current for ER of the substrate with respect to the 1-electron level and the presence of the reduction peak for PI at more cathodic potentials of cyclic voltammograms, are lacking. All the above-considered

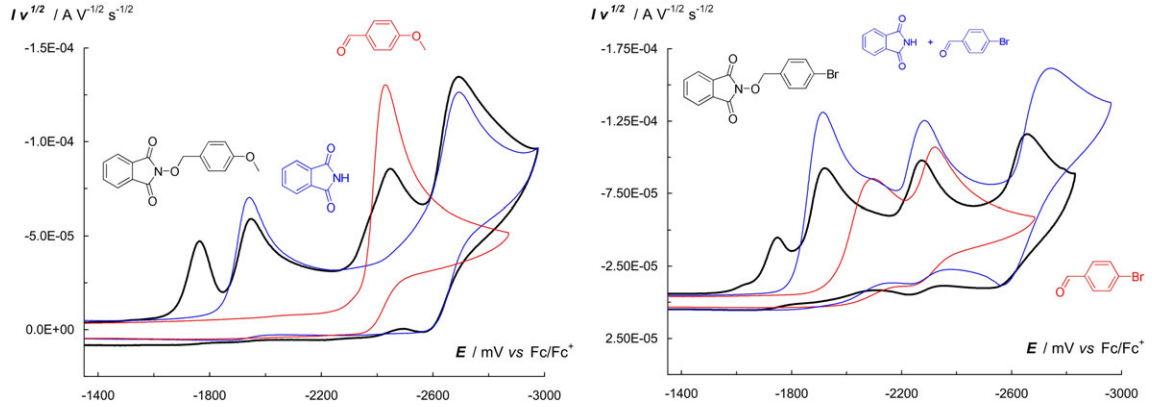


FIGURE 6 Cyclic voltammograms of solutions (5 mmol L^{-1}) of compounds **3** (*left*) and **4** (*right*) compared with the voltammograms of PI and **3a** (**4a**) at a potential scan rate of 0.100 V s^{-1} in DMF containing 0.1 M Bu_4NClO_4

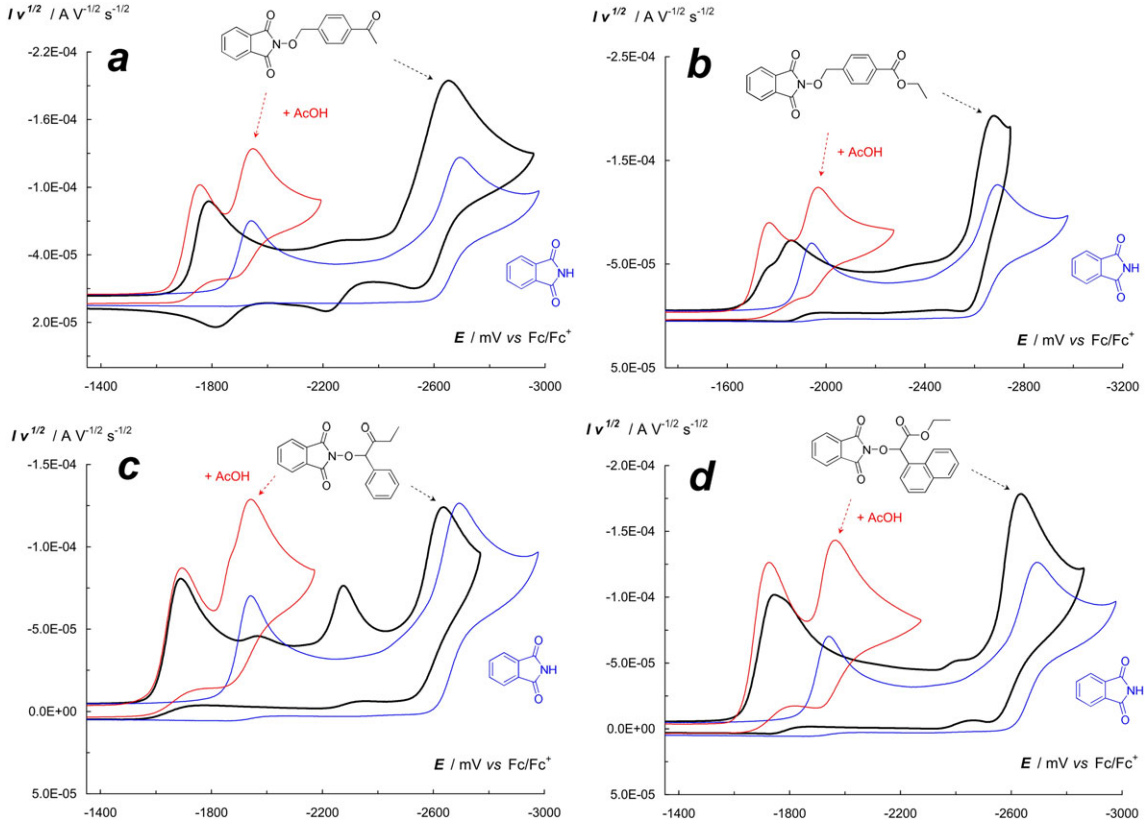


FIGURE 7 Cyclic voltammograms of solutions (5 mmol L^{-1}) of compounds **8** (*A*), **9** (*B*), **10** (*C*), and **11** (*D*) in the absence and in the presence of a molar equivalent of acetic acid compared with the voltammograms of PI at a potential scan rate of 0.100 V s^{-1} in DMF containing 0.1 M Bu_4NClO_4

(Figure 7) cyclic voltammograms show reduction peaks at potentials similar to the reduction potentials for the PI anion (Table 1). The addition of acetic acid to the solution causes the appearance of the reduction peak of PI (p*K* of acetic acid in DMSO, the properties of which are similar to those of DMF, is 12.05,[69] whereas p*K* of PI under the same conditions is 13.4[70,71]; consequently, the equilibrium favors the protonation of the PI anion).

It should be noted that the reductive fragmentation cascade products, ie, the carbonyl compounds containing strong electron-withdrawing substituents, can undergo ER at earlier potentials compared with PI or the substrate. In this case, one would expect an increase in the current peak for ER of the substrate and the disappearance of the peaks for ER of PI, which is consumed in the protonation of the reduction products of carbonyl compounds, such as dianions formed by the dimerization of the corresponding RAs.

3.4 | Electrochemical behavior of compounds 12-15

In order to examine the question raised in the introduction about the difference in the reactions of RAs of benzyl-, alkyl-, and acyl-substituted NHPI, we studied the electrochemical behavior of compounds **12**-**14**. The corresponding cyclic voltammograms are shown in Figure 8 along with the voltammograms of tosyl derivative **15**. Based on these results, the following conclusions can be drawn.

The reduction of derivatives **12**-**14** occurs *via* a 1-electron mechanism, whereas the reduction peak for **15** is somewhat lower—~2/3 e^-. The process is chemically irreversible at the applied scan rate range. The only exception is the case of alkyl derivative **14**, where reduction becomes partially reversible with an increase in the scan rate. As in all the cases considered previously, the cyclic voltammograms of these compounds show reduction peaks at potentials similar to the reduction peak potentials for the PI anion. In addition, the voltammograms of the benzoyl (**12**) and tosyl (**15**) derivatives show strong peaks at potentials similar to the reduction peak potentials for PI. On the other hand, the corresponding peaks in the voltammograms of the acetyl (**13**) and ethyl (**14**) derivatives are weak, but they sharply increase after the addition of acetic acid.

It can be concluded that the possible primary decomposition products in the case with ethyl derivative **14**, like

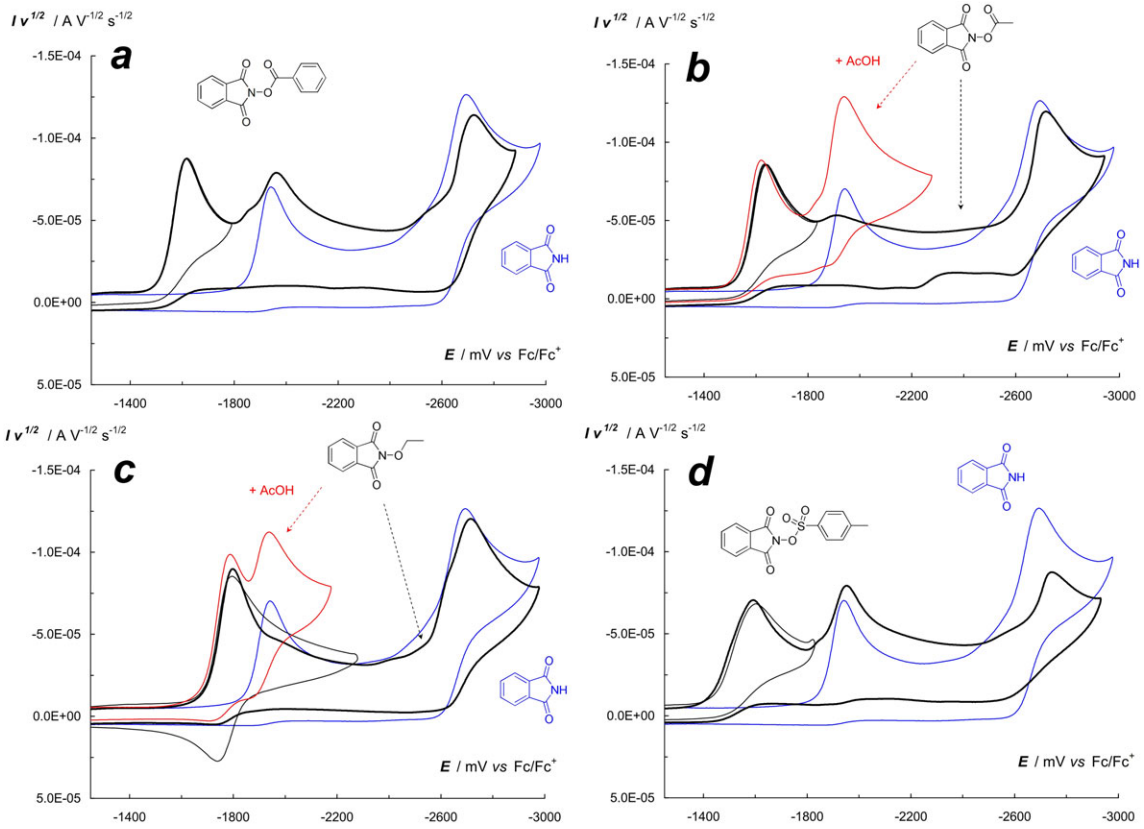


FIGURE 8 Cyclic voltammograms of a solution of compound **12** (*A*), **13** (*B*), **14** (*C*), and **15** (*D*) (5 mmol L^{-1}, black and gray lines) compared with the voltammogram of PI (blue line) at a potential scan rate of 0.100 V s^{-1} in DMF containing 0.1 M Bu_4NClO_4. Cyclic voltammograms of **13** (*B*) and **14** (*C*) in the presence of 1 molar equivalent of acetic acid (red line)

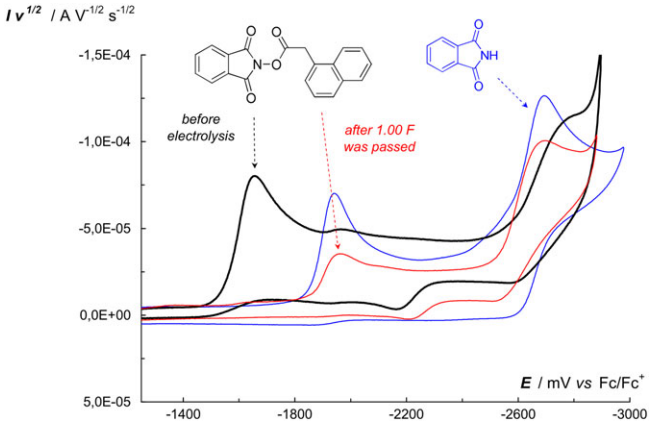
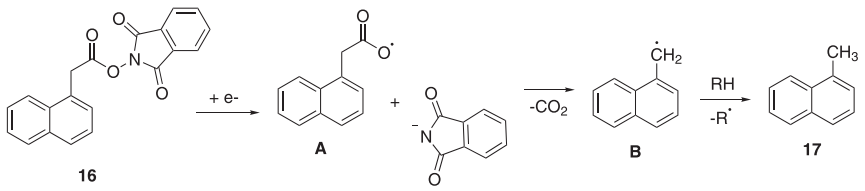


FIGURE 9 Cyclic voltammograms of solution of compound **16** (5 mmol L^{-1}) before and after 1.00 F at the potential −1800 mV was passed through the solution at a potential scan rate of 0.100 V s^{-1} in DMF containing 0.1 M Bu_4NClO_4

in the mechanism shown in Scheme 4, are the PI anion that is detected in the cyclic voltammogram and the ethoxy radical. The location of the excess electron on the nitrogen atom of the phthalimide moiety after the dissociation of RA of **14** should be facilitated by the fact that, compared with the benzyl alcohol anion, the ethoxy anion is oxidized at even earlier potentials (at −0.703 V relative to Fc/Fc^+[67]). The 1-electron reduction of the substrate indicates that ethoxy radical is not reduced and not involved in a chain process (Schemes 3, 4, 4) under the experimental conditions. Hydrogen abstraction from the components of the medium is one of the possible alternative reactions for the ethoxy radical. The hydrogen abstraction from the medium by a free radical that is formed through dissociative electron transfer is described in the literature.[72]

Due to the presence of more electron-deficient substituents, N-acyloxy and N-tosyloxy derivatives of PI (**12**, **13** and **15**, respectively) are reduced at slightly less negative potentials (from −1.64 to −1.59 V relative to Fc/Fc^+). Cyclic voltammograms of **12** and **15** contain the reduction peaks corresponding to both PI and PI anion, whereas cyclic voltammogram of acetyloxy derivative **13** contains strong PI anion peak and almost no PI peak. PI formation can be explained if one proposes that reductive ET gives PI anion and O-centered radical (PhCOO• or Me-*p*-C_6H_4-SO_3•). The latter can abstract hydrogen from the medium and form an acid (PhCOOH or Me-*p*-C_6H_4-SO_3H) that protonates PI anion. An alternative



SCHEME 5 Plausible pathway of electrochemical reduction of N-((1-naphthyl)acetoxy)phthalimide **16** confirmed by isolation of the final product, 1-methylnaphthalene **17**

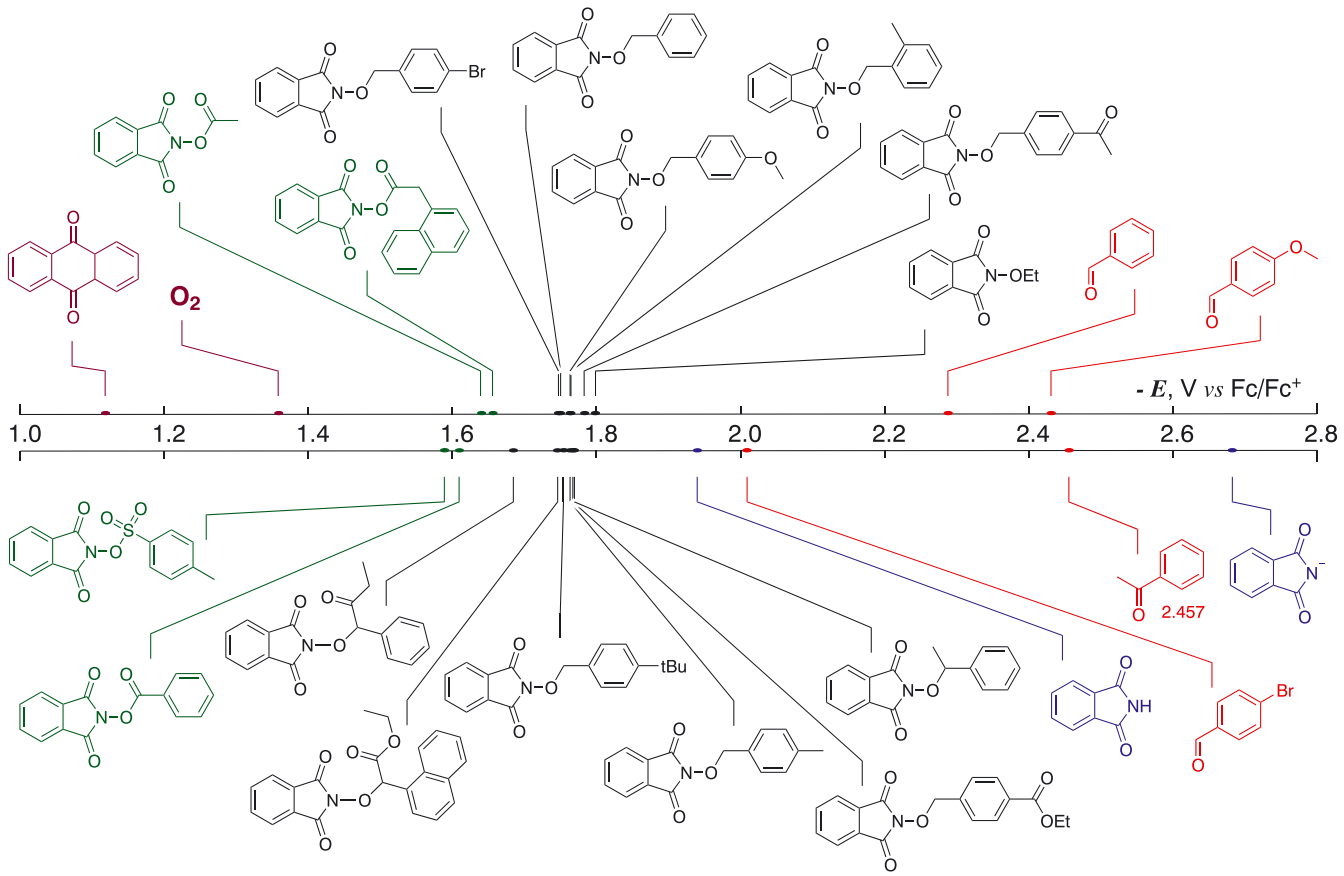


FIGURE 10 The reduction potentials of PI-ORs in comparison to carbonyl compounds, anthraquinone, and oxygen

process where the O-centered radical undergoes decarboxylation does not produce acid. If the latter scenario dominates, no PI would be observed as we see in case of compound **13**. The experimental differences discussed earlier may reflect the fact that rates of decarboxylation in AlkCOO and $ArCH_2COO$ radicals are faster than in ArCOO radicals.[73]

3.5 | Electrochemical behavior of compound 16—direct evidence for the formation of O-centered radicals in the reductive fragmentations of PI-ORs

Electrochemical behavior of N-((1-naphthyl)acetoxy) phthalimide **16** (Figure 9) is similar to that of N-acetoxyphthalimide **13**. No starting compound was detected electroanalytically after passage of 1 F of electricity at potential of reduction of **16** (−1800 mV). Peaks of phthalimide anion and small amounts of phthalimide were observed on cyclic voltammogram.

To confirm the reaction pathway (Scheme 5), preparative electrochemical reduction of **16** was conducted. 1-Methylnaphthalene, the product of double covalent bond scission (N—O/C—C), was isolated instead of naphthyl acetic acid (see the Experimental part for additional details).

This result confirms that ET to the N-((1-naphthyl) acetoxy)phthalimide **16** gives PI anion and acyloxy radical **A** that undergoes decarboxylation giving the naphthylmethyl radical **B**. The latter species abstracts hydrogen

atom from the medium to form 1-methylnaphthalene **17**. The isolation of C—C scission products such as **17** is a characteristic sign of O-centered radical formation in the reaction. This additional fragmentation would be impossible if the primary N—O fragmentation would give an O-centered anion.[32]

4 | CONCLUSION

In summary, the N—O bond cleavage is a general process in a variety of radical-anions of *N*-hydroxyphthalimide derivatives. According to DFT computations, all of these RAs have negative N—O bond dissociation enthalpies towards the formation of N-centered anions and O-centered radicals. The free energies of dissociation are even more negative due to the favorable entropic contribution. In the case of benzyloxyphthalimide or its derivatives containing electron-donating substituents at the benzylic position or in the aromatic ring, the electron transfer induces the cyclic chain decomposition of the substrate to phthalimide and the corresponding carbonyl compound (the peaks for these compounds are detected in the cyclic voltammograms). The key feature of this cascade that it produces new radical-anions (aldehyde and PI), both of which are stronger reductants than the initially formed PI-OR radical-anion. As the result, electron transfer from the product RAs to the reactant PI-OR is exergonic and a catalytic cycle where electron serves as a catalyst[74] can be established.

Presence of this self-sustaining catalytic electron transfer process is reflected in a considerable decrease in the reduction current for the substrate in aprotic medium with respect to $1e^-$/molecule. The reduction of benzyl derivatives containing electron-withdrawing substituents in the aromatic ring or at the benzylic position, as well as of tosyl and alkyl derivatives, occurs *via* a 1-electron mechanism.

Due to the electron-deficient properties of the phthalimide moiety, the decomposition of RAs of *N*-hydroxyphthalimide derivatives can result in the location of the negative charge on the nitrogen atom accompanied by the elimination of the oxygen-centered free radical. This property is of fundamental importance in the application of *N*-hydroxyphthalimide derivatives in pharmaceutics. PI-ORs studied in this work are reduced at relatively early potentials (alkyl derivatives, at −1.80 V relative to Fc/Fc^+; benzyl derivatives, at −1.75/−1.77 V; carboxyl and tosyl derivatives, at −1.60/−1.64 V). The evaluated potentials are only slightly more negative than the reduction potentials for oxygen (−1.37 V[75]) and anthraquinone (−1.16 V) (Figure 10).

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