

Change of Selectivity in C–H Functionalization Promoted by Nonheme Iron(IV)-oxo Complexes by the Effect of the *N*-hydroxyphthalimide HAT Mediator

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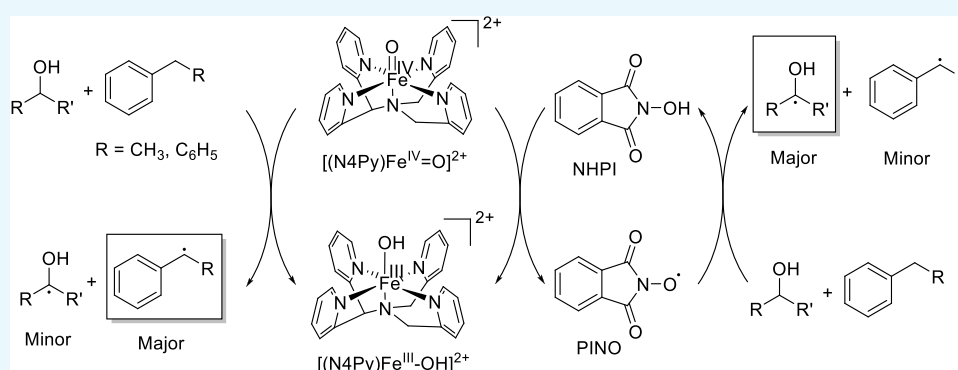
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ABSTRACT: A kinetic analysis of the hydrogen atom transfer (HAT) reactions from a series of organic compounds to the iron(IV)-oxo complex $[(N4Py)Fe^{IV}(O)]^{2+}$ and to the phthalimide *N*-oxyl radical (PINO) has been carried out. The results indicate that a higher activating effect of α -heteroatoms toward the HAT from C–H bonds is observed with the more electrophilic PINO radical. When the *N*-hydroxy precursor of PINO, *N*-hydroxyphthalimide (NHPI), is used as a HAT mediator in the oxidation promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$, significant differences in terms of selectivity have been found. Product studies of the competitive oxidations of primary and secondary aliphatic alcohols (1-decanol, cyclopentanol, and cyclohexanol) with alkylaromatics (ethylbenzene and diphenylmethane) demonstrated that it is possible to modify the selectivity of the oxidations promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$ in the presence of NHPI. In fact, alkylaromatic substrates are more reactive in the absence of the mediator while alcohols are preferably oxidized in the presence of NHPI.

INTRODUCTION

Selective functionalization of C–H bonds has been the subject of intense investigation in recent years, offering a useful strategy for the synthesis and late stage derivatization of complex organic molecules.¹ Among the most promising systems for the selective oxidation of C–H bonds, nonheme iron complexes, biomimetic complexes of natural oxygenases, have attracted special attention due to the high efficiency generally observed under mild reaction conditions, employing sustainable oxidants like H_2O_2 .^{2,3} Many of them proved to be particularly versatile and efficient catalysts in a number of oxidation reactions of synthetic interest. In the presence of oxidants, such as H_2O_2 , peroxyacids, $KHSO_5$, and iodosobenzene, the active species, iron(IV) or iron(V)-oxo complexes, are formed, which are capable of promoting a wide variety of oxidative processes such as those involving the transfer of a hydrogen atom (HAT) from C–H bonds of hydrocarbons and alcohols.^{3,4}

Aminoxyl radicals such as the phthalimide *N*-oxyl radical (PINO) represent another important class of reagents able to promote C–H functionalization involving HAT reactions. Good results in terms of selectivity and catalytic efficiency have been obtained in the aerobic oxidation, under mild conditions, of several classes of organic compounds catalyzed by *N*-hydroxyphthalimide (NHPI), where the HAT from the organic substrate to PINO represents the key step of the catalytic cycle.^{5–14}

In a recent study, we have shown that a nonheme-iron complex and NHPI can be used in combination with the activation of organic substrates involving two consecutive HAT

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reactions. In particular, we found that the room-temperature stable iron(IV)-oxo complex $[(N4Py)Fe^{IV}(O)]^{2+}$ formed by oxidation of the nonheme-Fe complex $[(N4Py)Fe^{II}]^{2+}$ ($N4Py$: N,N -bis(2-pyridylmethyl)- N -bis(2-pyridyl)-methylamine)^{15–22} is able to promote the oxidation of NHPI to PINO, which acts as a HAT mediator (Figure 1).²³ Kinetic studies have shown

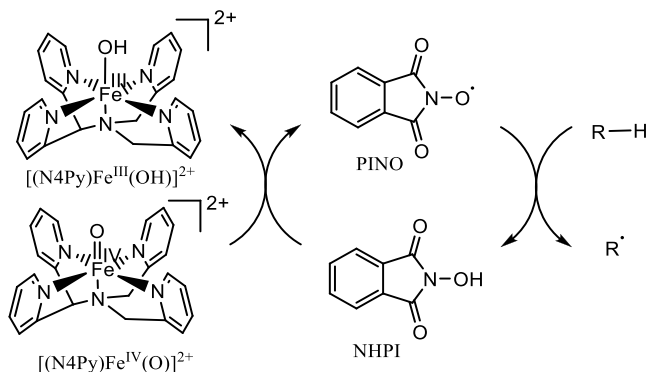


Figure 1. Oxidation of hydrocarbons with $[(N4Py)Fe^{IV}(O)]^{2+}$ mediated by NHPI.

that the presence of the mediator significantly increases the oxidation rate of hydrocarbons such as triphenylmethane, toluene, ethylbenzene, and cyclohexane. In accordance with the kinetic data, product analysis studies confirmed an increase in the reactivity in the presence of the mediator system, leading to higher yields of hydrocarbon oxidation products in shorter times.

In reactions involving a HAT process like those promoted by PINO and other aminoxyl radicals or iron-oxo complexes, reactivity and selectivity depend on electronic, steric, and stereoelectronic effects.²⁴ In previous studies, we have focused our attention to enthalpic and polar effects.^{25–27} The former are related to the differences in dissociation energies (BDE) between the O–H bond of the N–OH derivative or the

Fe(III)–OH complex and the C–H bond of the substrate (Figure 2a).

The higher reactivity of PINO as compared to $[(N4Py)Fe^{IV}(O)]^{2+}$ is related to the difference of about 10 kcal/mol in the dissociation energies (BDE) of the O–H bond in the corresponding hydroxy derivatives NHPI and $[(N4Py)Fe^{III}-OH]^{2+}$ (87 kcal/mol and 78 kcal/mol, respectively).^{28–30}

In HAT processes, in addition to enthalpic effects, polar effects also play a fundamental role. Several experiments indicated the involvement of a polar transition state whose kinetic barrier is highly dependent on the polarity match between the electronic features of the substrate and the oxidizing species (Figure 2b).^{25–27,31–37}

Since the weight of the polar effects in HAT reactions may be different in iron(IV)-oxo complexes and N -oxyl radicals, a change in the actual oxidizing species can affect the overall selectivity. On this basis, in the present study, we have focused our attention on the possibility of modifying the selectivity in the C–H functionalization promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$ in the presence of the NHPI mediator.

For this purpose, we have investigated, via kinetic and product studies, the oxidation of an extended series of organic substrates, i.e., hydrocarbons (1–6), alcohols (7–12), ethers (13–15), benzaldehyde (16), and amides (17–20) (Figure 3) containing C–H bonds activated by the presence of aryl substituents or heteroatoms in the α -position. Product analyses of competitive oxidation reactions have been carried out with mixtures of substrates. The results obtained in terms of selectivity with the iron(IV)-oxo complex/ N -hydroxy mediator system have been compared with those obtained in competitive oxidations with the iron(IV)-oxo complex in the absence of the mediator.

RESULTS AND DISCUSSION

Kinetic studies were performed by spectrophotometric analysis. For the reaction promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$, the iron-oxo complex (1.5 mM in CH_3CN) was prepared by

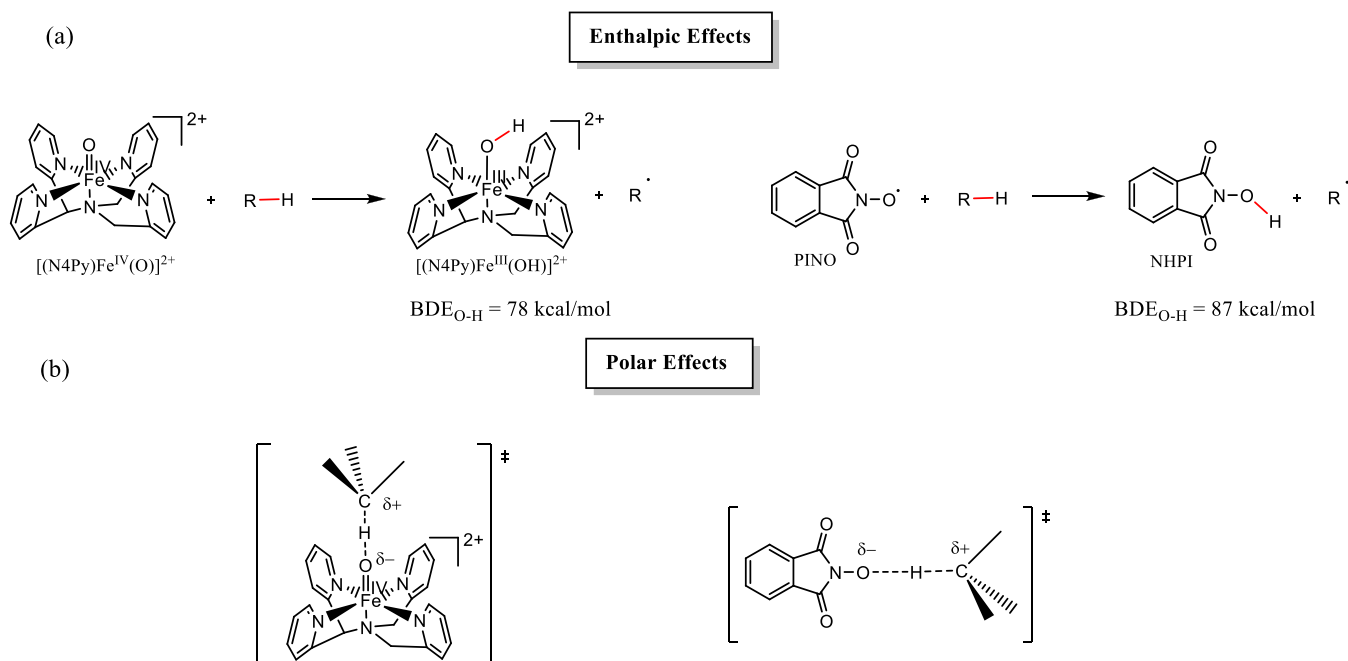


Figure 2. Enthalpic and polar effects in the HAT from hydrocarbons promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$ and PINO.

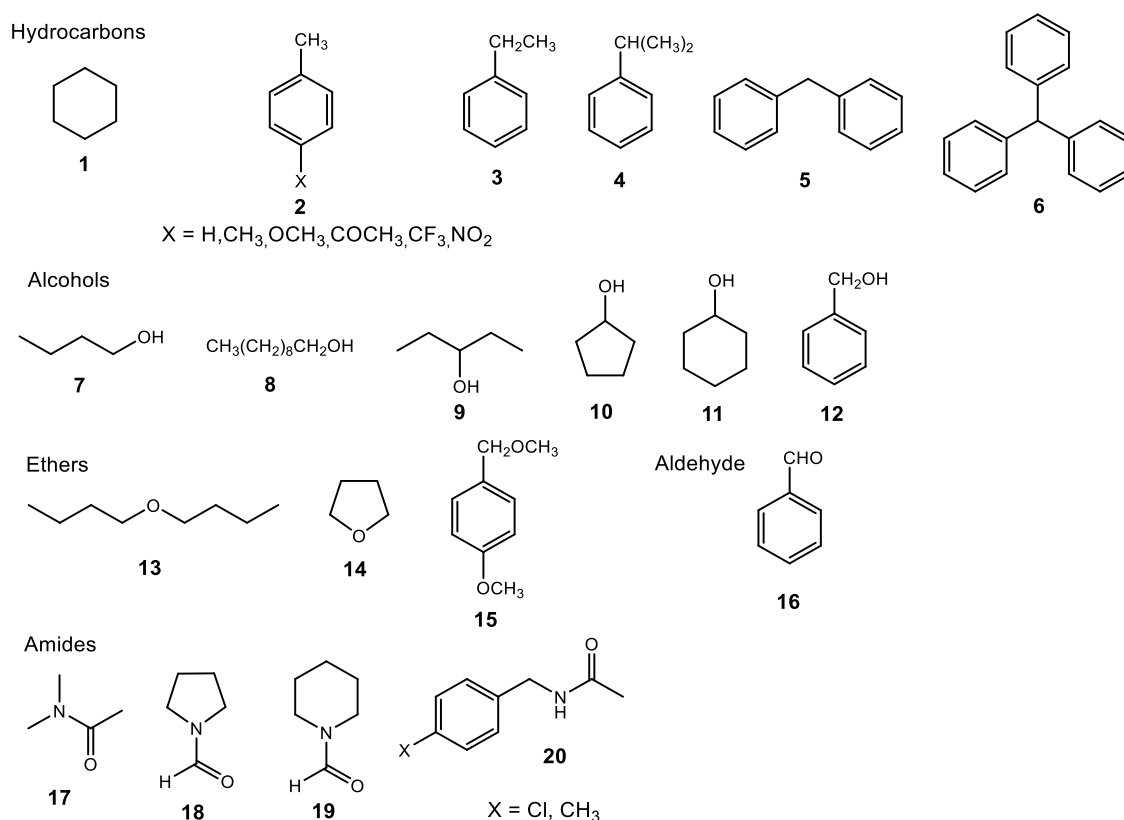


Figure 3. List of H donors investigated.

oxidation of the corresponding iron(II) complex $[(N4Py)Fe^{II}(OTf)_2]$ with PhIO (1.2 mol equiv).^{15–22} Substrate oxidation was monitored by following the decay of the $[(N4Py)Fe^{IV}(O)]^{2+}$ band centered at 695 nm ($\epsilon = 400 \text{ M}^{-1} \text{ cm}^{-1}$).¹⁶ Substrates were added in large excess (at least 10-fold) to attain pseudo-first-order conditions. In all cases, clean first-order decays were observed and linear fits were obtained by plotting the pseudo-first-order rate constants (k_{obs}) as a function of the concentration of hydrogen donors. From the slope of these plots, the second-order rate constants ($k_{2, \text{Fe}=\text{O}}$) were determined (see Figures S1–S22 in the Supporting Information). The $k_{2, \text{Fe}=\text{O}}$ values are displayed in the third column of Table 1 together with those previously reported in the literature.^{15,38–40}

For PINO-promoted HAT reactions, kinetic studies were carried out generating PINO via oxidation of NHPI with cerium(IV) ammonium nitrate in CH_3CN at $T = 25 \text{ }^\circ\text{C}$.⁶ The decay of the *N*-oxyl radical was recorded at the λ_{max} of PINO (380 nm).^{5–13} Second-order rate constants ($k_{2, \text{PINO}}$) were determined using an excess of the substrate as described above for the reactions with $[(N4Py)Fe^{IV}(O)]^{2+}$ (see Figures S23–S33 in the SI). The $k_{2, \text{PINO}}$ values are displayed together with literature values²⁸ in the fourth column of Table 1.

Kinetic studies were also performed for the oxidation of all substrates with $[(N4Py)Fe^{IV}(O)]^{2+}$ in the presence of NHPI (20 mol % with respect to $[(N4Py)Fe^{IV}(O)]^{2+}$) under the same conditions of the experiments carried out in the absence of a mediator. The decay of $[(N4Py)Fe^{IV}(O)]^{2+}$, in this case, does not follow a clean first-order process. As a complex kinetic treatment is associated with the decay of the iron(IV)-oxo complex in the presence of the NHPI mediator,²³ the decay half-life of $[(N4Py)Fe^{IV}(O)]^{2+}$ ($t_{1/2}^{\text{med}}$) has been

reported for the mediated HAT processes (for the decay traces see Figures S34–S56 in the SI). $t_{1/2}^{\text{med}}$ values and substrate concentrations used for the decay half-life determination are reported in Table 2. In the same table, the decay half-life of the iron(IV)-oxo complex $[(N4Py)Fe^{IV}(O)]^{2+}$ in the oxidation of organic compounds 1–20 in the absence of NHPI ($t_{1/2}^{\circ}$) and the mediation efficiency ($t_{1/2}^{\circ}/t_{1/2}^{\text{med}}$) values are also reported.

As an example, time-resolved absorption spectra recorded in the reaction of cyclohexanol with $[(N4Py)Fe^{IV}(O)]^{2+}$ (a), with PINO (b), and with $[(N4Py)Fe^{IV}(O)]^{2+}$ in the presence of NHPI (20 mol %) (c) in CH_3CN at $25 \text{ }^\circ\text{C}$ are shown in Figure 4.

From the data reported in Table 1, it is apparent that the rate constants for the reactions with PINO are 2–3 orders of magnitude higher than those observed in the oxidations promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$ as expected on the basis of the previously mentioned 10 kcal/mol higher BDE of the O–H bond in NHPI with respect to $[(N4Py)Fe^{III}-OH]^{2+}$.^{28–30} In the HAT process involving hydrocarbons 1–6, for both systems, the k_2 values decrease upon increasing the C–H BDE and a linear correlation is observed between $\log k_2$ values and C–H BDEs (see Figures S57 and S58 in the SI).

For the series of 4-substituted toluenes 2 ($X = \text{H}, \text{CH}_3, \text{OCH}_3, \text{COCH}_3, \text{CF}_3, \text{NO}_2$), the k_2 values increase with the electron-donating strength of the aryl substituent as expected for a HAT process promoted by electrophilic radicals and in accordance with the enthalpic and polar effects discussed above. When the $\log(k_2^X/k_2^{\text{H}})$ values for the reactions with $[(N4Py)Fe^{IV}(O)]^{2+}$ and PINO were plotted against the Okamoto–Brown substituent constants σ^+ ,⁴² good Hammett-type correlations were obtained (Figures S59 and S60). The

Table 1. C–H bond Dissociation Energies (C–H BDEs) and Second-Order Rate Constants (k_2) for Hydrogen Atom Transfer (HAT) from Hydrocarbons, Alcohols, Benzaldehyde, Ethers, and Amides (1–20) to $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and PINO Measured in CH_3CN at $T = 25\text{ }^\circ\text{C}$

substrate	C–H BDE (kcal mol ⁻¹) ^a	$k_{2, \text{Fe}=\text{O}}$ (M ⁻¹ s ⁻¹) ^b	$k_{2, \text{PINO}}$ (M ⁻¹ s ⁻¹) ^b
Hydrocarbons			
cyclohexane (1)	99.5	4.6×10^{-6c}	0.014 ^g
4-X-C ₆ H ₄ CH ₃ (2)			
X=H	88.1	2.1×10^{-4c}	0.11 ^g
X=CH ₃	87.8	3.3×10^{-4}	0.57
X=OCH ₃	86.6	9.9×10^{-4}	0.93
X=COCH ₃		1.6×10^{-4}	0.07
X=CF ₃		1.6×10^{-4}	n.d.
X=CN		n.d.	0.022 ^g
X=NO ₂	88.8	9.3×10^{-5}	4.9×10^{-3}
C ₆ H ₅ CH ₂ CH ₃ (3)	85.4	5.0×10^{-3d}	0.95 ^g
C ₆ H ₅ CH(CH ₃) ₂ (4)	84.5	3×10^{-3d}	1.3 ^g
(C ₆ H ₅) ₂ CH ₂ (5)	84.5	0.01	2.9
(C ₆ H ₅) ₃ CH (6)	81	0.043 ^d	27
Alcohols			
CH ₃ CH ₂ CH ₂ CH ₂ OH (7)	94.9	2.6×10^{-4}	0.35
CH ₃ (CH ₂) ₈ CH ₂ OH (8)	94.5	2.1×10^{-4}	0.47
CH ₃ CH ₂ CH(OH)CH ₂ CH ₃ (9)	93.1	8.0×10^{-4}	1.7
cyclopentanol (10)		1.0×10^{-3}	1.8
cyclohexanol (11)	92.8	1.3×10^{-3}	3.4
C ₆ H ₅ CH ₂ OH (12)	79	4.95×10^{-2e}	14
Ethers			
(CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂) ₂ O (13)	93.7	3.5×10^{-4}	0.57
tetrahydrofuran (14)	92.1	4.6×10^{-4}	1.0
4-CH ₃ OC ₆ H ₄ CH ₂ OCH ₃ (15)	84.7	0.039	11.3
Aldehyde			
C ₆ H ₅ CHO (16)	83.1 ^f	8.2×10^{-2f}	0.31
Amides			
N,N-dimethylacetamide (17)		6.6×10^{-5}	0.51
N-formylpyrrolidine (18)		2.5×10^{-3}	1.9
N-formylpiperidine (19)		4.0×10^{-4}	0.44
4-X-C ₆ H ₄ CH ₂ NHCOCH ₃ (20)			
X=Cl		0.013	2.4
X=CH ₃		0.021	11

^aRef 41. ^bAverage of at least three independent determinations. Error \pm 5%. Correlation coefficients $0.972 < r^2 < 0.999$. k_2 values are obtained by dividing the kinetic constants by the number of equivalent hydrogen atoms in the substrate that would react with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ or PINO. ^cRef 15. ^dRef 38. ^eRef 39. ^fRef 40. ^gRef 28.

negative ρ values as well as the good linearity obtained with the σ^+ constants are in accordance with the stabilizing effect of electron-donating substituents on the partial positive charge, which develops on the benzylic position in the transition states (TS) (polar effects). Interestingly, the two systems show a different selectivity: PINO-promoted HAT is more sensitive to the electronic effects of the aryl substituents with a ρ value (-1.3)⁴³ far more negative than that of $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ (-0.56). The difference can be likely ascribed to the higher charge separation in the TS of the reaction with PINO, which has a more pronounced electrophilic character compared to the iron(IV)-oxo complex (see Figure 2b).

The different polar effects operating in the HAT processes promoted by $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and PINO are also evident in the reactions with aliphatic alcohols 7–11. From the kinetic data reported in Table 1, it can be noted that rate constants for the reactions with PINO are always more than 3 orders of magnitude higher than those found in the reactions with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ ($k_{2, \text{PINO}}/k_{2, \text{Fe}=\text{O}} > 10^3$). This large difference in reactivity can be ascribed to the higher

stabilization, exerted by the α -hydroxy group, of the partial positive charge that develops in the HAT TS for the reaction with PINO.³⁴ The relative reactivity PINO/ $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ observed in the HAT from aliphatic alcohols is significantly higher than that from hydrocarbons ($k_{2, \text{PINO}}/k_{2, \text{Fe}=\text{O}} < 10^3$) leading to interesting outcomes in terms of HAT selectivity with the two classes of substrates. Comparison of k_2 values for HAT from cyclohexanol and ethylbenzene or diphenylmethane indicates an inversion of selectivity, with the former substrate more reactive than hydrocarbons with PINO, and an opposite relative reactivity observed with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$.

With benzyl alcohol 12, the $k_{2, \text{PINO}}/k_{2, \text{Fe}=\text{O}}$ ratio is lower than those found with aliphatic alcohols, as expected on the basis of its higher reactivity. Interestingly, HAT from benzaldehyde 16 is characterized by the smallest difference in the $k_{2, \text{PINO}}$ and $k_{2, \text{Fe}=\text{O}}$ values. This result can be explained by the almost complete lack of polar effects in the formation of the benzoyl radical.³⁶

Table 2. Decay Half-Life of the Iron(IV)-oxo Complex [(N4Py)Fe^{IV}=O]²⁺ (1.5 mM) in the Oxidation of Organic Compounds 1–20 Promoted by [(N4Py)Fe^{IV}=O]²⁺ in the Absence ($t_{1/2}^0$) or in the Presence of NHPI (20 mol %) ($t_{1/2}^{\text{med}}$) in CH₃CN at T = 25 °C and Mediation Efficiency ($t_{1/2}^0/t_{1/2}^{\text{med}}$)

substrate	[substrate] (M)	$t_{1/2}^0$ (s) ^a	$t_{1/2}^{\text{med}}$ (s) ^b	mediation efficiency ($t_{1/2}^0/t_{1/2}^{\text{med}}$)
cyclohexane (1) ^c	0.8	3.2×10^4	9.9×10^2	32
4-X-C ₆ H ₄ CH ₃ (2)				
X=H ^c	1.0	1.7×10^3	52	32
X=CH ₃	0.2	2.7×10^3	33	83
X=OCH ₃	0.15	2.4×10^3	18	1.3×10^2
X=COCH ₃	0.4	4.2×10^3	1.3×10^2	32
X=CF ₃	0.6	5.7×10^3	1.0×10^2	57
X=NO ₂	1	3.6×10^3	1.5×10^2	25
C ₆ H ₅ CH ₂ CH ₃ (3) ^c	0.3	1.1×10^3	40	27
(C ₆ H ₅) ₂ CH ₂ (5)	0.03	1.2×10^3	62	19
(C ₆ H ₅) ₃ CH (6) ^c	0.03	4.5×10^2	33	14
CH ₃ CH ₂ CH ₂ CH ₂ OH (7)	0.25	5.4×10^3	13	4.2×10^2
CH ₃ (CH ₂) ₈ CH ₂ OH (8)	0.2	1.3×10^4	17	7.6×10^2
CH ₃ CH ₂ CH(OH)CH ₂ CH ₃ (9)	0.25	4.9×10^3	15	3.3×10^2
cyclopentanol (10)	0.2	6.3×10^3	24	2.6×10^2
cyclohexanol (11)	0.2	3.4×10^3	11	3.1×10^2
cyclohexanol- <i>d</i>	0.2	2.3×10^4	42	4.0×10^2
C ₆ H ₅ CH ₂ OH (12)	0.03	2.3×10^2	17	14
(CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂) ₂ O ^c (13)	0.25	1.9×10^3	1.0×10^2	19
tetrahydrofuran (14)	0.2	2.1×10^3	18	1.1×10^2
4-CH ₃ OC ₆ H ₄ CH ₂ OCH ₃ (15)	0.03	3.5×10^2	11	31
C ₆ H ₅ CHO (16)	0.03	6.0×10^2	2.0×10^2	3
<i>N,N</i> -dimethylacetamide (17)	0.4	6.0×10^3	2.4×10^2	25
<i>N</i> -formylpyrrolidine (18)	0.2	5.2×10^2	29	18
<i>N</i> -formylpiperidine (19)	0.25	1.7×10^3	1.1×10^2	16
4-X-C ₆ H ₄ CH ₂ NHCOCH ₃ (20)				
X=Cl	0.03	1.0×10^3	53	19
X=CH ₃	0.03	5.8×10^2	27	21

^aDecay half-life in the absence of NHPI. ^bDecay half-life in the presence of NHPI (0.3 mM). ^cRef 23.

With ethers 13–15 and amides 17–20, the C–H activating effect of the oxygen and nitrogen atoms in the α position, mainly due to polar effects, is again responsible for the higher HAT reactivity of PINO with respect to [(N4Py)Fe^{IV}(O)]²⁺. The presence of the activating benzyl group in 4-methoxybenzyl methyl ether 15 and 4-*X-N*-benzylacetamides 20 (X = CH₃, Cl) causes a lower $k_{2 \text{ PINO}}/k_{2 \text{ Fe=O}}$ ratio, as observed with benzyl alcohol.

The results of the mediation efficiency, evaluated as the ratio of the decay half-life of the iron(IV)-oxo complex [(N4Py)-Fe^{IV}=O]²⁺ in the absence and in the presence of the NHPI mediator ($t_{1/2}^0/t_{1/2}^{\text{med}}$) are reported in Table 2 for all substrates. No significant variation of the $t_{1/2}^0/t_{1/2}^{\text{med}}$ values was observed by changing the substrate concentration. The values reported in Table 2 show a significant dependence of mediation efficiency on the substrate structure. The lowest efficiency is observed with benzaldehyde ($t_{1/2}^0/t_{1/2}^{\text{med}} = 3$), in line with the smallest difference of the k_2 values in the reaction with PINO and [(N4Py)Fe^{IV}(O)]²⁺. On the contrary, mediation efficiencies of $t_{1/2}^0/t_{1/2}^{\text{med}} > 260$ were determined in the oxidation of aliphatic alcohols, where $k_{2 \text{ PINO}}/k_{2 \text{ Fe=O}}$ differences are large due to polar effects (see above). On the same line, it is interesting to note that in the oxidation of *para*-substituted toluenes, the electron-donating power of the *para*-substituent has a positive effect on the mediation efficiency with the $t_{1/2}^0/t_{1/2}^{\text{med}}$ values that regularly decrease from 135 for OCH₃ to 25 for NO₂. Interestingly, comparison of the reaction of cyclohexanol with cyclohexanol-*d*, deuterated α to the

hydroxyl group, showed an increase in the decay half-life of the iron(IV)-oxo complex [(N4Py)Fe^{IV}=O]²⁺ both in the absence of NHPI (from $t_{1/2}^0 = 6.3 \times 10^3$ to $t_{1/2}^0 = 2.3 \times 10^4$ s) and in the presence of NHPI (from $t_{1/2}^{\text{med}} = 24$ to $t_{1/2}^{\text{med}} = 42$ s). The kinetic isotope effect observed when the α -C–H bond is replaced by an α -C–D bond is confirmed by the results of competitive experiments (vide infra).

To test if the variation of relative reactivity between aliphatic alcohols and alkylaromatic compounds in the presence of the NHPI mediator, inferred by the kinetic data, might be applied to alter the HAT selectivity in preparative oxidation reactions, we carried out competitive oxidation starting with mixtures of cyclohexanol and a series of alkylaromatic hydrocarbons (toluene, ethylbenzene, cumene, diphenylmethane, and triphenylmethane) with [(N4Py)Fe^{IV}=O]²⁺ either in the presence or in the absence of NHPI (20 mol %) in CH₃CN (see details in the Experimental Section). The related results are reported in Table 3 with products and yields referring to the amount of the oxidant.

For all couples of substrates tested, addition of the NHPI mediator resulted in significantly higher product yields, thus confirming the results of the previous kinetic analysis. Interestingly, in all experiments, cyclohexanone yields are increased by a larger amount than alkylaromatics in the presence of the NHPI mediator, in accordance with the higher mediation efficiency for alcohol oxidation.

In the oxidations of cyclohexanol/toluene and cyclohexanol/cumene mixtures, either in the absence or in the presence of

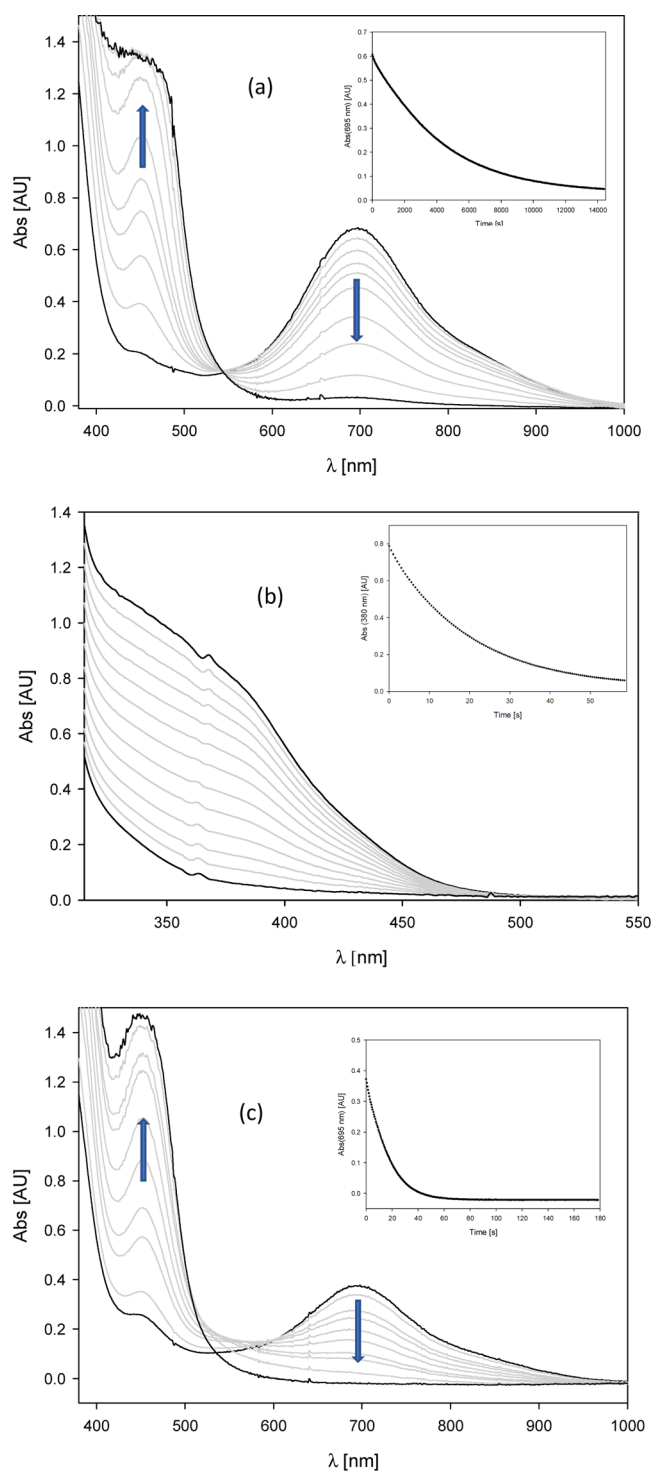


Figure 4. Time-resolved absorption spectra recorded in the reaction of: (a) cyclohexanol (200 mM) with $[(N4Py)Fe^{IV}=O]^{2+}$ (1.5 mM) (inset, decay of absorbance recorded at 695 nm), (b) cyclohexanol (15 mM) with PINO (1 mM) (inset: decay of absorbance recorded at 380 nm), and (c) cyclohexanol (200 mM) with $[(N4Py)Fe^{IV}=O]^{2+}$ (1.5 mM) in the presence of 20 mol % NHPI (inset: decay of absorbance recorded at 695 nm) in CH_3CN at 25 °C.

the mediator, the yield of cyclohexanone was always higher than those of products derived from alkylaromatic substrates. On the same line with the cyclohexanol/triphenylmethane mixture, no inversion of selectivity can be observed in the presence of NHPI with triphenylmethanol always being more

abundant than cyclohexanone, in accordance with the results of kinetic studies (triphenylmethane has much higher reactivity than cyclohexanol).

Interesting results are obtained in the competitive oxidations of cyclohexanol/ethylbenzene and cyclohexanol/diphenylmethane mixtures. An inversion of selectivity was observed with the alkylaromatic substrates, which are more reactive in the absence of the mediator (65 and 78% total yields of benzylic oxidation products for the cyclohexanol/ethylbenzene and cyclohexanol/diphenylmethane mixtures, respectively), and cyclohexanol, which is instead more reactive in the presence of NHPI (70 and 63% of cyclohexanone for the cyclohexanol/ethylbenzene and cyclohexanol/diphenylmethane mixtures, respectively).

Competitive oxidations have been also carried out with the cyclohexanol-*d*/ethylbenzene mixture. In this case, no inversion of selectivity was observed with the alkylaromatic substrate, which is more reactive than the deuterated alcohol either in the absence and in the presence of NHPI. This result is in accordance with the significant lower reactivity of the α -C–D bond in cyclohexanol-*d* with respect to the α -C–H bond in cyclohexanol, in line with a rate-determining HAT process promoted by PINO.⁴⁴

Additional competitive experiments have been carried out using mixtures of ethylbenzene and other aliphatic primary (1-decanol, **9**) and secondary (cyclopentanol, **11**) alcohols. The results reported in Table 2 indicate that the oxidation of the aliphatic alcohols promoted by $[(N4Py)Fe^{IV}=O]^{2+}$ in the presence of NHPI are characterized by a decay half-life ($t_{1/2}^{med}$) lower than that found with ethylbenzene, thus an inversion of selectivity induced by the NHPI mediator might be expected also in these competitive oxidations.

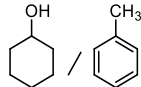


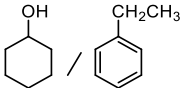



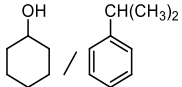



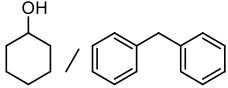

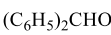
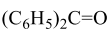
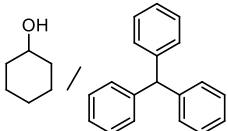

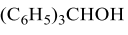
The results of the oxidations with $[(N4Py)Fe^{IV}=O]^{2+}$ either in the presence or in the absence of NHPI (20 mol %) in CH_3CN are reported in Table 4. It can be readily noted that in both cases, an inversion of selectivity was again observed, with ethylbenzene, which is more reactive with $[(N4Py)Fe^{IV}=O]^{2+}$ in the absence of the HAT mediator, and the alcohols, which are instead more reactive with the $[(N4Py)Fe^{IV}=O]/NHPI$ system.

Finally, we have also carried out a preliminary study of the effect of the iron(IV)-oxo complex structure on the reaction selectivity using $[(Bn-TPEN)Fe^{IV}(O)]^{2+}$ as an oxidant in the competitive oxidation of the cyclohexanol/ethylbenzene and cyclohexanol/diphenylmethane mixtures. The results reported in Table 3 clearly show an increase in selectivity for the oxidation of alcohol in the presence of NHPI; however, no inversion of selectivity is observed with cyclohexanol that is more reactive than ethylbenzene both in the absence and in the presence of NHPI. Diphenylmethane is instead more reactive than cyclohexanol both in the reaction with $[(Bn-TPEN)Fe^{IV}(O)]^{2+}$ and with the $[(Bn-TPEN)Fe^{IV}(O)]^{2+}/NHPI$ system. The difference can be likely attributed to the higher reactivity of $[(Bn-TPEN)Fe^{IV}(O)]^{2+}$ with respect to $[(N4Py)Fe^{IV}(O)]^{2+}$, as reported in previous studies of HAT reactions promoted by the two iron(IV)-oxo complexes.¹⁵

CONCLUSIONS

The results of kinetic analysis of the HAT reactions promoted by the iron(IV)-oxo complex $[(N4Py)Fe^{IV}(O)]^{2+}$ and the phthalimide *N*-oxyl radical PINO clearly indicate that polar effects are more important with the latter more electrophilic HAT reagent. The higher activating effect of α -heteroatoms

Table 3. Product Analysis in the Competitive Oxidation of Cyclohexanol and Alkylaromatics Promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$ in the Presence or the Absence of 20 mol % NHPI as the Mediator in CH_3CN^a

Substrates	Reaction time	Products (Yields %) ^b	Selectivity (% Cyclohexanone)			
	1 h					
		No mediator	21	3.0	87	
		+ NHPI	66	2.6	96	
	5 min					
		No mediator	7	< 0.5	12	36
		+ NHPI	43	3	15	70
		No mediator ^c	< 0.5	< 0.5	16	< 2
		+ NHPI ^c	19	3.7	37	32
		No mediator ^d	7	< 0.5	4.6	60
		+ NHPI ^d	20	< 0.5	8.0	71
	5 min					
		No mediator	8	4	2	57
		+ NHPI	48	7	5	80
	5 min					
		No mediator	10	17	19	22
		+ NHPI	37	2	20	63
		No mediator ^d	1.0	24	39	1.5
		+ NHPI ^d	12	10	40	19
	5 min					
		No mediator	< 1	60	< 2	
		+ NHPI	17	55	24	

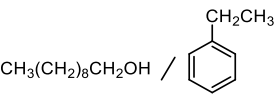

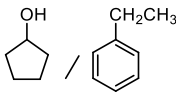
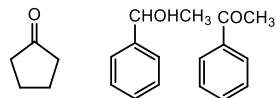

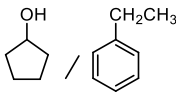


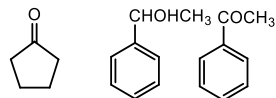



^a $[(N4Py)Fe^{IV}(O)]^{2+}$ (19 mM), NHPI (3.8 mM), and substrates (190 mM) in CH_3CN (1.5 mL). ^bYields (mol %) refer to the amount of oxidant and have been determined by GC. The same products and relative yields are observed under argon. ^cCyclohexanol-*d* as the substrate. ^dReaction with $[(Bn-TPEN)Fe^{IV}(O)]^{2+}$ as the oxidant.

toward the HAT from C–H bonds to the aminoxyl radical thus causes significant differences in terms of selectivity when the *N*-hydroxy precursor of PINO (NHPI) is used as a HAT mediator in the oxidation promoted by $[(N4Py)Fe^{IV}(O)]^{2+}$. Accordingly, product studies in the competitive oxidations of aliphatic alcohols (1-decanol, cyclopentanol, and cyclohexanol) with alkylaromatics (ethylbenzene and diphenylmethane) showed that higher yields of products from alkylaromatic substrates are observed in the oxidations with $[(N4Py)Fe^{IV}(O)]^{2+}$, while the opposite is observed in the

presence of the NHPI mediator with a higher yield of the alcohol oxidation products.

Further studies on the $[(N4Py)Fe^{IV}(O)]^{2+}$ /NHPI system, including its application to selective C–H oxidation of functionality-rich molecules and modification of reaction selectivity by changing the structures of the metal-oxo complexes and the *N*-hydroxy mediator, are currently under investigation in our laboratories. These studies will hopefully allow the identification of the most efficient and selective combination of the oxidant/mediator systems.

Table 4. Product Analysis in the Competitive Oxidation of Primary (1-Decanol 9) and Secondary (Cyclopentanol 11) Alcohols with Ethylbenzene Promoted by $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ in the Presence or the Absence of 20 mol % NHPI as the Mediator in CH_3CN ^a

Substrates	Reaction time	Products (Yields %) ^b	Selectivity (% alcohol oxidation)			
 $\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OH}$ / 	5 min	 $\text{CH}_3(\text{CH}_2)_8\text{CHO}$  				
			No mediator	4.5	< 0.5	15
		+ NHPI	30	2.2	20	57
  / 	5 min	   				
			No mediator	2.4	< 0.5	18
		+ NHPI	70	< 0.5	25	74

^a $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ (19 mM), NHPI (3.8 mM), and substrates (190 mM) in CH_3CN (1.5 mL). ^bYields (mol %) refer to the amount of the oxidant and have been determined by GC.

EXPERIMENTAL SECTION

Materials. All reagents and solvents were purchased at the highest commercial quality and were used without further purification unless otherwise stated. Iodosylbenzene was prepared by a literature method⁴⁵ and stored at $-20\text{ }^\circ\text{C}$ under an inert atmosphere. $\text{Fe}(\text{CH}_3\text{CN})_2(\text{OTf})_2$ ($\text{OTf} = \text{CF}_3\text{SO}_3$) was prepared according to a literature procedure from Fe(II) chloride.⁴⁶ $[(\text{N4Py})\text{Fe}(\text{OTf})_2]$ and $[(\text{Bn-TPEN})\text{Fe}(\text{OTf})_2]$ were obtained by metalation of the ligands N4Py and Bn-TPEN with $\text{Fe}(\text{OTf})_2$, as reported in the literature.⁴⁷ $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]$ and $[(\text{Bn-TPEN})\text{Fe}^{\text{IV}}=\text{O}]$ were prepared by reacting $\text{Fe}(\text{N4Py})(\text{OTf})_2$ and $\text{Fe}(\text{Bn-TPEN})(\text{OTf})_2$ with excess solid PhIO.¹⁵

Kinetic Studies of the Reaction of Hydrocarbons, Amides, and Ethers by PINO. Spectrophotometric measurements were performed on a single-beam ultraviolet–visible (UV–Vis) spectrophotometer using a quartz cuvette (10 mm path length) at $25\text{ }^\circ\text{C}$. To a solution of cerium (IV) ammonium nitrate (0.5 mM in CH_3CN), a solution of NHPI (1 mM in CH_3CN) was added, followed by the solution of the substrate (10–25 mM in CH_3CN).

Kinetic Studies of the Oxidation of Hydrocarbons, Alcohols, Aldehydes, Ethers, and Amides by $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ in the Absence or in the Presence of NHPI Mediators. Spectrophotometric measurements were performed on a single-beam UV–Vis spectrophotometer using a quartz cuvette (10 mm path length) at $25\text{ }^\circ\text{C}$. A solution of $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ (1.5 mM in CH_3CN) was prepared by oxidation of the corresponding iron(II) complex $[(\text{N4Py})\text{Fe}(\text{OTf})_2]$ with a slight excess of solid PhIO (1.2 equiv). After 30 min, the solution was filtered. For the experiments in the presence of the mediator, NHPI (20 mol % with respect to $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$) was added. Finally, the solution of the substrate (0.03–1 M) was added. Time-resolved spectra were recorded in a 380–1000 nm range.

Product Analysis of the Intermolecular Oxidation of Organic Compounds with $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ or $[(\text{Bn-TPEN})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ in the Absence and in the Presence of

NHPI. A solution of $[(\text{N4Py})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ or $[(\text{Bn-TPEN})\text{Fe}^{\text{IV}}=\text{O}]^{2+}$ (19 mM in CH_3CN) was prepared by oxidation of the corresponding iron(II) complexes with a slight excess of solid PhIO (1.2 equiv). After 30 min, the solution was filtered. For the experiments in the presence of the mediator, NHPI (20 mol % with respect to the iron(IV)-oxo complexes) was added. Finally, the solutions of substrates (190 mM) were added. The mixture was vigorously stirred at $25\text{ }^\circ\text{C}$ for 5 min under air. Then, a solution of sodium metabisulfite was added to quench the reaction, followed by an internal standard (nitrobenzene or bibenzyl). The reaction mixture was filtered over a short pad of SiO_2 with AcOEt and analyzed by GC and ^1H NMR. Quantitative analysis were performed by GC (see Figures S61–S80 in the SI).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c03679>.

Instruments and general methods; dependence of k_{obs} for the decay of $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and PINO on the concentration of hydrocarbons, alcohols, benzaldehyde, ethers, and amides; decay of absorbance at 695 nm in the oxidation with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ in the absence and in the presence of NHPI; correlations between $\log k_2$ for the reaction of hydrocarbons with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and with PINO with C–H bond dissociation energies ($\text{BDE}_{\text{C-H}}$); Hammett plots for the reaction of *para*-substituted toluenes with $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and with PINO; and GC analysis of the competitive oxidation of aliphatic alcohols/alkylaromatics mixtures promoted by $[(\text{N4Py})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ and $[(\text{Bn-TPEN})\text{Fe}^{\text{IV}}(\text{O})]^{2+}$ in the absence or the presence of the NHPI mediator (PDF)

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Notes

The authors declare no competing financial interest.

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