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Reactivity of Phthalimide *N*-Oxyl Radical (PINO) toward the Phenolic O−H Bond. A Kinetic Study

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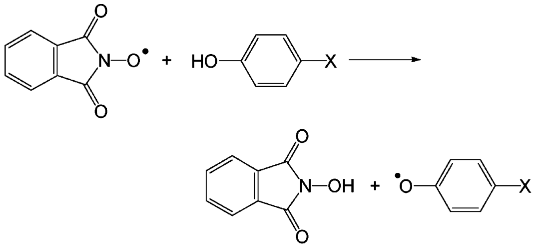
Abstract: The reactivity of the phthalimide *N*-oxyl radical (PINO) toward the OH bond of a series of substituted phenols was kinetically investigated in CH_3CN. The reaction selectivity and the deuterium kinetic isotope effect were determined. Information on the kinetic solvent effect was also obtained with phenol as the substrate.

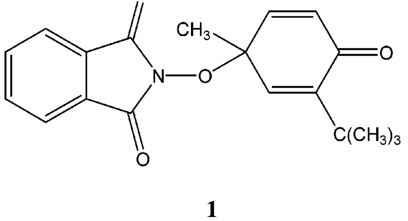
The phthalimide-*N*-oxyl radical (PINO) is attracting continuous attention due to its role in the aerobic oxidation of the C−H bond in a wide variety of organic substrates[1] (aliphatic hydrocarbons,[2] alkylbenzenes,[3] alcohols,[4] benzylamines,[5] and *N*-alkylamides[6]) induced by *N*-hydroxyphthalimide (NHPI) and O_2 in the presence of a metal salt cocatalyst (Ishii reaction). Thus, a relevant number of studies aimed at assessing the reactivity of PINO toward the C−H bond are presently available.[7−13] In contrast, there is very little quantitative information with respect to the reaction of PINO with phenolic OH bonds, which leads to the formation of phenoxyl radicals (reaction 1), as recently shown by the ESR study of Pedulli and his associates.[11] This information would instead be of great interest not only to extend our knowledge on the reactivity of the important class of the *N*-oxyl radicals but also considering the fact that reaction 1 can play an important role in the NHPI-mediated oxidative degradation of lignin promoted by the laccase/O_2 system,[14] a process that has a potential application in the pulp and paper industry.[15] Thus, we have considered it of interest to carry out a kinetic investigation of the reaction of PINO with a number of substituted phenols. Most of the reactions were studied in CH_3CN, but some information on the solvent effect was also obtained. The results of this study are presented herewith.



(1)

PINO has been generated by reaction of NHPI with $Pb(OAc)_4$ in CH_3CN containing 1% AcOH as reported in the literature.[10,16] In this solvent, the spectrum of PINO was the same as that found by Masui ($\lambda_{max} = 380$ nm[8]). As in AcOH, the spontaneous decay of PINO in CH_3CN followed second-order kinetics in line with a dimerization process. The rate constant was 0.4 $M^{-1}\ s^{-1}$, very close to that observed in AcOH.[10] The slow decay of PINO, followed spectrophotometrically at its λ_{max}, was strongly accelerated in the presence of phenol, in line with the occurrence of reaction 1. This is also clearly shown by the fact that the decay is extremely slower when the phenol is replaced by anisole. Furthermore a decrease (more than 3 times) of the decay rate of PINO was found when AcOH was replaced by CD_3COOD, to convert C_6H_5-OH in C_6H_5OD, indicating a substantial kinetic isotope effect.

We also made an attempt to obtain some information on the products of reaction 1 using a substituted phenol (2-*tert*-butyl-4-methylphenol) as substrate in order to simplify the analysis of the reaction mixture. It was found that the major product (**1**) was that coming from the cross-coupling of PINO and the phenoxyl radical (see Supporting Information).



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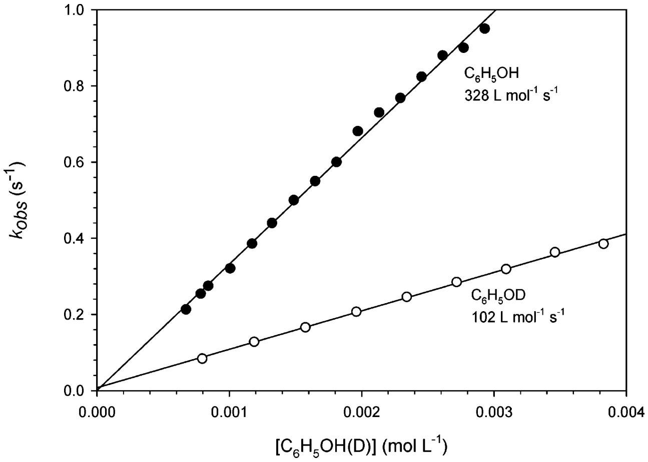

FIGURE 1. Dependence of k_{obs} on the concentrations of C_6H_5OH or C_6H_5OD in CH_3CN at 25 °C.

TABLE 1. Second-Order Rate Constants (M^{-1} s^{-1}) for the Reaction of the PINO Radical with 4-X-Substituted Phenols in CH_3CN at 25 °C

X	k_H[a]	k_D[b]	k_H/k_D
CN	6.0	1.6	3.7
CF_3	6.4		
$COOCH_2CH_3$	23.0		
Br	248		
Cl	298		
H	328	102	3.2
C_6H_5	2680		
CH_3	2850	910	3.1

[a] Reactions run in CH_3CN containing 1% CH_3COOH. [b] Reactions run in CH_3CN containing 1% CD_3COOD.

Using an excess of phenol, the decay of PINO was found to follow clean first-order kinetics. From the observed first-order rate constants (k_{obs}) plotted against the phenol concentration (see Figure 1 for the reaction of C_6H_5OH and C_6H_5OD), the second-order rate constants for the reaction of 4-X-C_6H_4OH or 4-X-C_6H_4OD with PINO have been determined. The values are listed in Table 1.[17]

From the data reported in Table 1, it can be noted that the kinetic deuterium isotope effects (KDIEs), determined for phenol, 4-cyanophenol, and 4-methylphenol, are not very high and are in the range 3.1−3.7. These values are much lower than the theoretical maximum of $k_H/k_D \cong 10$, which can be calculated for a thermoneutral hydrogen atom transfer between two oxygen-centered radicals in a linear and symmetrical transition state.[18] Thus, our results indicate a nonsymmetrical transition state for the reaction of PINO with phenols even though the process is almost thermoneutral.[19]

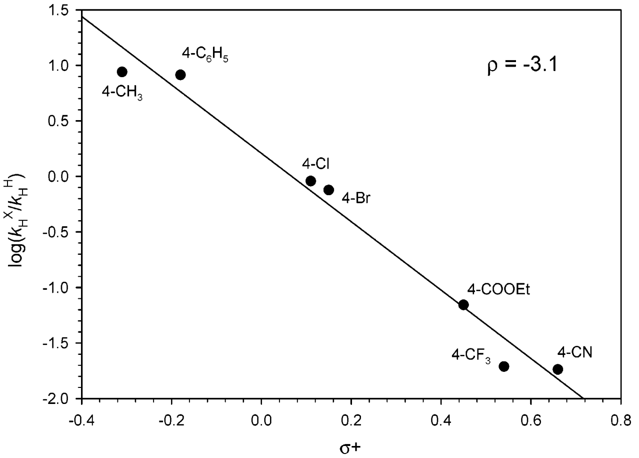

FIGURE 2. Hammett plot for the reaction of substituted phenols with PINO in CH_3CN at 25 °C.

The data reported in Table 1 also show that the rate constants regularly increase by increasing the electron-donating properties of the substituent. When the log($k_H{}^X/k_H{}^H$) values were plotted against the substituent constants σ^+, a good Hammett correlation was obtained ($r^2 = 0.978$) (Figure 2) with a ρ value of −3.1.

This relatively high and negative ρ value and the fact that the kinetic data correlate much better with σ^+ than with σ values ($r^2 = 0.957$) suggest a transition state (TS) where a partial electron transfer (ET) from the phenolic ring to the PINO has occurred.[21]

It can be of interest to attempt a more detailed mechanistic discussion by following the recent suggestion by Mayer and his associates that a reaction between an oxyl radical and phenol can be better seen as proton coupled electron transfer (PCET) rather than as classical hydrogen atom transfer (HAT).[24] In a PCET reaction a hydrogen-bonded complex is first formed between the reactants, and the electron and the proton are transferred through different orbitals. Thus, for reaction 1, the O−H hydrogen should be transferred (as a proton) to a σ-lone pair on the PINO oxygen, whereas the electron is transferred from a 2p-π orbital on the phenol to the 2p singly occupied orbital on the PINO oxygen. However, very likely, at the transition state the electron jump takes place when the proton transfer is not yet complete, leading to a charge unbalance whereby a partial positive charge resides in the phenol moiety and a partial negative charge on the PINO oxygen, thus nicely accounting

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(15) Argyropoulos, D. S.; Menachem, S. B. *Biotechnology in the Pulp and Paper Industry*; Eriksson, K. E. L., Ed., Springer-Verlag: Berlin, Heidelberg, 1997; pp 127−158.

(16) 1% AcOH was added to increase the solubility of $Pb(OAc)_4$.

(17) Second-order kinetics are observed since the rate of the initial hydrogen atom transfer from the phenol to the PINO is much slower than the rate of recombination of the phenoxyl radical with the PINO.[10] The second-order rate constants reported in Table 1 are those experimentally determined and were not divided by 2.

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(19) O−H bond dissociation energy (BDE) of NHPI is 88.1 kcal mol^{-1},[11] only 0.5 kcal mol^{-1} higher than that of phenol (87.6 kcal mol^{-1}).[20] HAT from 4-methylphenol to PINO is exothermic for ca. 2.2 kcal mol^{-1},[20] whereas HAT from 4-cyanophenol to PINO is slightly endothermic for ca. 0.9 kcal mol^{-1}.[20]

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(21) A full-fledged electron transfer is unlikely being strongly endergonic; the reduction potential of PINO in CH_3CN is 1.07 V vs NHE,[22] whereas the oxidation potential of the phenols investigated are in the range 1.7−2.4 V vs NHE in CH_3CN.[23]

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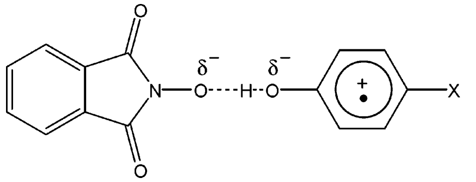


FIGURE 3. Limit transition state structure for the reaction of PINO with phenols.

TABLE 2. Rate Constants (M^{-1} s^{-1}) for the Self-Decomposition of PINO (k_d) and for Reaction of PINO with Phenol in Various Solvents at 25 °C

solvent ($\beta_2{}^H$)	k_d	k (PhOH)
HFP[a] (0.03)	0.9	$>3 \times 10^3$
CCl_4[a] (0.05)	4.0	$>3 \times 10^3$
CH_3COOH (0.42)	0.6[b]	550
CH_3CN[a] (0.44)	0.4	328

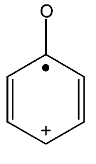
[a] In the presence of 1% CH_3COOH. [b] Reference 10.

for the high and negative ρ value observed.[25] This situation is depicted in Figure 3, where a limit structure of the transition state is reported.[26] Plausibly, the entity of this charge balance should depend on the electrophilic character of the oxyl radical, increasing as the radical becomes more electrophilic. Thus, it is reasonable that a significantly lower negative ρ value (−1.02) was determined in the HAT from substituted phenols to the *tert*-butoxy radical (a much less electrophilic radical than PINO[12]) in CH_3CN.[27]

A charge unbalanced TS with a limited transfer of the proton from the phenol to PINO can also explain the relatively small KDIE values that have been observed, as well as the decrease in k_H/k_D values when we move from 4-cyanophenol ($k_H/k_D = 3.7$) to 4-methylphenol ($k_H/k_D = 3.1$). Accordingly, on going from electron-withdrawing (CN) to electron-donating (Me) substituents, the charge unbalance at the transition state should increase (the electron jump becomes easier), and this should imply a less extent of proton transfer at the transition state with consequent lowering of the KDIE.

To investigate the solvent effect upon the reaction of PINO with phenol, kinetics were also carried out in AcOH, 1,1,1,3,3,3-hexafluoro-2-propanol (HFP), and CCl_4.[28] First of all, it was observed that in HFP and CCl_4 the decay of PINO is a second-order reaction, as already found in AcOH[10] and CH_3CN. The decay rate constants are reported in Table 2, and it is interesting to note that the PINO decay occurs at a similar rate in solvents that strongly differ in their ability as hydrogen bond donors, as measured by Abraham's $\alpha_2{}^H$ values.[29] In particular, decay rates are very close in HFP ($\alpha_2{}^H = 0.77$) and in CH_3CN ($\alpha_2{}^H = 0.09$).

Thus, the reactivity of PINO seems little influenced by hydrogen bond formation at the radical center. This behavior contrasts with the observation by Lucarini et al. that the lifetime of phenoxyl radicals is significantly increased in the presence of HFP as a consequence of hydrogen bonding.[30] A tentative explanation is that in phenoxyl radicals the resonance structure involving charge separation (like structure A) plays a significant role, which can be further increased by hydrogen bonding. This possibility is probably lacking for PINO as the resonance structure B with charge separation should be of little importance because of the strong electron-withdrawing effect of the carbonyl groups.



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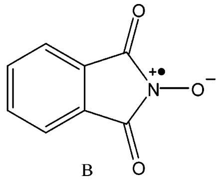

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The rate constants for the reaction of PINO with phenol in the various solvents, also displayed in Table 2, show that PINO reacts at a very similar rate in CH_3CN and AcOH, whereas the reactivity in CCl_4 and HFP is much higher (only a lower limit value of ~3×10^3 M^{-1} s^{-1} can be given). These findings are in agreement with the hypothesis by Ingold and his associates that for a reaction of the type XH + $Y^{\bullet}$ (XH = phenols, hydroperoxides, and anilines)[31,32] the reactivity should almost exclusively depend on the hydrogen-accepting ability of the solvent, as measured by the Abraham $\beta_2{}^H$ values.[33] The lower is the $\beta_2{}^H$ value, the higher is the reactivity. Accordingly, the results reported in Table 2 can be perfectly rationalized on this basis as CH_3CN and AcOH have similar $\beta_2{}^H$ values (0.44 and 0.42, respectively), whereas $\beta_2{}^H$ is much lower for CCl_4 (0.05) and HFP (0.03).

As mentioned before, PINO is the reacting intermediate in the degradation of lignin induced by the laccase/NHPI/O_2 system. Since in lignin the most probable reaction centers are phenolic O−H and α-hydroxy-substituted C−H bonds,[34] we felt it of interest to acquire information on the relative reactivity of PINO toward these two types of bonds.[36] To this purpose we have compared the reactivity of PINO with 4-hydroxybenzyl alcohol and 4-methoxybenzyl alcohol. The measured rate

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[25] Calculations by Mayer and co-workers[24] have shown that in the transition state of the phenoxyl/phenol exchange more positive charge is present in the phenol moiety with respect to the starting phenol.

[26] Figure 3 represents a limit structure of the transition state that serves only to visualize the consequence of the electron shift occurring when the proton is only partially transferred (PCET). Of course, it must be considered that the positive charge in the ring is partially neutralized by the negative charge developing on oxygen, and thus in the transition state there actually is only a partial positive charge in the phenyl ring, in line with calculations.[25]

[27] Determined at 130 °C: Kim, S. S.; Lim, S. Y.; Ryou, S. S.; Lee, C. S.; Yoo, K. H. *J. Org. Chem.* **1993**, *58*, 192−196.

[28] It was possible to examine only a few solvents, since in many cases there were problems related to the solubility of the PINO generating system or to a fast reaction of PINO with the solvent.

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[33] Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521−529.

[34] Lignin is a tridimensional polymer built from phenolic and nonphenolic phenylpropane units linked together by different bonds.[35] A large number of phenolic ArOH groups and benzylic ArCH(OH)R groups are present.

[35] Sarkanen, K. V. *Lignins: Occurrence, Formation, Structure and Reactions*; Sarkanen, K. V., Ludwig, C. H., Eds., Wiley-Interscience: New York, 1971; pp 95−195.

constants were 936 M^{-1} s^{-1} for 4-hydroxybenzyl alcohol and 100 M^{-1} s^{-1} for 4-methoxybenzyl alcohol. Thus, with PINO, the phenolic O−H bond is more reactive (about 10 times) than the C−H bond of the benzylic CH_2OH, which suggests that initial hydrogen transfer from the phenolic OH might be the key process in the degradation of lignin by laccase/NHPI/O_2. In this respect, further work is planned to study the reactivity of PINO toward phenolic lignin model compounds.

Finally, it can also be remarked that the above result contrasts with the fact that the BDE of the phenolic O−H bond is significantly higher (as much as 5.3 kcal mol^{-1} according to theoretical calculations)[37] than that of the α-hydroxy-substituted benzylic C−H bond.[38] Thus, PINO, an *N*-oxyl radical, conforms to the general behavior that the reactions of $RO^{\bullet}$ with the phenolic O−H are intrinsically favored from the kinetic point of view with respect to the corresponding reactions with the benzylic C−H. Zavitsas and Chatgillialoglu have attributed this behavior to the fact that in the transition state the antibonding interactions are smaller for O···H···O than for O···H···C systems.[40] However, it should also be considered that hydrogen atom abstraction from a phenolic O−H and a benzylic C−H might take place by different mechanisms: PCET in the former case, classical HAT in the second.

In conclusion, the results reported in this work provide significant information with respect to the reaction of phthalimide-*N*-oxyl radical with phenolic OH bonds. The high selectivity and the relatively low deuterium kinetic isotope effects suggest a nonsymmetrical transition state, and it seems possible to describe the process as proton-coupled electron transfer (PCET) rather than as a classical hydrogen atom transfer (HAT). The rate constant for the reaction of PINO with phenol increases as the solvent becomes a weaker hydrogen bond acceptor, in accordance with the predictions by Ingold and his associates concerning the kinetic solvent effects for reactions of phenols with hydrogen atom abstracting species. Finally, the reactivity of PINO is about 10 times higher toward phenolic O−H bonds than toward α-hydroxy-substituted benzylic C−H bonds. This result may have a bearing with respect to the mechanism of the NHPI-mediated oxidative degradation of lignin promoted by the laccase/O_2 system.

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Supporting Information Available: Instrumentation, materials, kinetic measurements, reaction of PINO with 2-*tert*-butyl-4-methylphenol, and ^1H NMR and ^{13}C NMR spectra of the cross-coupling product **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Hydrogen atom transfer from benzylic C−H bonds to PINO, in the oxidation of nonphenolic lignin model compounds by the laccase/NHPI/O_2 system, has been reported in the literature; see: D'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P. *New J. Chem.* **2002**, *26*, 1791−1794. Baiocco, P.; Barreca, A. M.; Fabbrini, M.; Galli, C.; Gentili, P. *Org. Biomol. Chem.* **2003**, *1*, 191−197.

(37) Reynisson, J.; Steenken, S. *Org. Biomol. Chem.* **2004**, *2*, 578−584.

(38) It should also be considered that the reactivity of the C−H bond is enhanced by the presence of the *para* O−H group ($\sigma^+ = -0.92$) more than the reactivity of the O−H group is enhanced by the presence of the *para* CH_2OH group ($\sigma^+ = -0.04$),[39] even though the ρ value for the reaction of PINO with benzyl alcohols in CH_3CN (−0.68)[12,13] is less negative than the ρ of the reaction with phenols.

(39) Girault, J. P.; Dana, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 993−994.

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