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Hydroxylamines as Oxidation Catalysts: Thermochemical and Kinetic Studies

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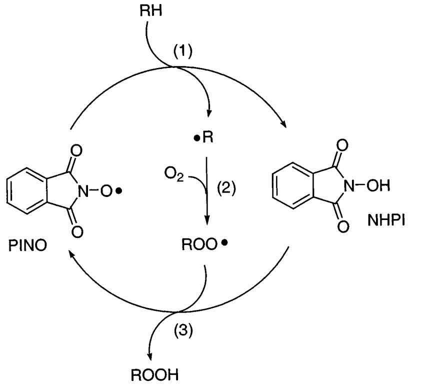
Bond dissociation enthalpies (BDE) of hydroxylamines containing alkyl, aryl, vinyl, and carbonyl substituents at the nitrogen atom have been determined by using the EPR radical equilibration technique in order to study the effect of the substituents on the O−H bond strength of these compounds. It has been found that substitution of an alkyl group directly bonded to the nitrogen atom with vinyl or aryl groups has a small effect, while substitution with acyl groups induces a large increase of the O−H BDE value. Thus, dialkyl hydroxylamines have O−H bond strengths of only ca. 70 kcal/mol, while acylhydroxylamines and *N*-hydroxyphthalimide (NHPI), containing two acyl substituents at nitrogen, are characterized by BDE values of ca. 80 and 88 kcal/mol, respectively. Since the phthalimide *N*-oxyl radical (PINO) has been recently proposed as an efficient oxidation catalyst of hydrocarbons or other substrates, the large BDE value found for the parent hydroxylamine (NHPI) justifies this proposal. Kinetic studies, carried out in order to better understand the mechanism of the NHPI-catalyzed aerobic oxidation of cumene, are consistent with a simple kinetic model where the rate-determining step is the hydrogen atom abstraction from the hydroxylamine by cumylperoxyl radicals.

Introduction

The oxidation and, in general, the functionalization of organic substrates, such as aliphatic hydrocarbons, is a primary essential tool in organic synthesis and in industrial chemistry. Recently, it has been shown that *N*-hydroxyphthalimide (NHPI) is an effective catalyst for the oxidation of organic compounds by molecular oxygen under mild conditions.[1,2] This reaction is believed to occur (see Scheme 1) via the intermediation of carbon-centered radicals from the substrate produced by the phthalimide *N*-oxyl radical (PINO), generated in situ. Under aerobic conditions, the resulting alkyl radicals are readily trapped by molecular oxygen to give peroxyl radicals that in turn abstract the hydrogen atom from NHPI regenerating PINO and giving rise to a hydroperoxide.

SCHEME 1



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[1] Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 810. Iwahama, T.; Yoshima, Y.; Keitoku, T.; Sagakuchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502. Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 222. Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.

[2] Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651. Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671. Cecchetto, A.; Minisci, F.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Tetrahedron Lett.* **2002**, *43*, 3605. Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, *7*, 688−689.

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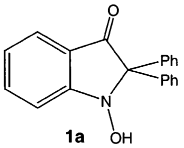
TABLE 1. EPR Spectral Parameters of Nitroxides 1b−8b and PINO and BDE Values of the O−H Bond in the Parent Hydroxylamines 1a−7a and NHPI

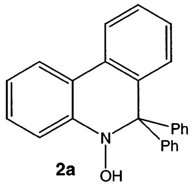
radical	solvent[a]	a_N/gauss	other/gauss	g factor	BDE/kcal mol^{-1}
1b	B	9.28	3.09 (1H), 2.89 (1H) 1.03 (2H)	2.0058	70.6 ± 0.3
2b	B	10.80	2.71 (2H), 1.03 (2H)	2.0058	71.4 ± 0.3
3b	B	10.88	1.03 (2H)	2.0056	69.7 ± 0.4
4b	B	5.72	1.57 (2H)	2.0055	72.8 ± 0.4
5b	B	5.82	0.79 (1H), 0.67 (1H)	2.0062	78.5 ± 0.5
6b	B/BuOH (10:1)	7.20	8.05 (3H)	2.0065	79.2 ± 0.5
7b	B/BuOH (10:1.5)	7.25		2.0068	80.2 ± 0.5
8b	B	7.43	1.53 (3H), 0.64 (2H)	2.0065	-
PINO	BuOH	4.36	0.45 (2H)	2.0073	88.1 ± 0.6

[a] B = benzene.

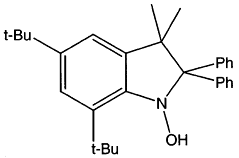
According to this mechanism, the key step of the overall reaction is the abstraction by PINO of a hydrogen atom from RH (Scheme 1, eq 1) that will proceed at an acceptable rate only if the value of the bond dissociation enthalpy (BDE) of the O−H bond formed is higher or similar to the strength of the C−H bond cleaved, thus making the knowledge of the BDE of NHPI of great importance. Since the C−H BDE values in the great majority of organic compounds are in the range 85−100 kcal/mol[3] while the only experimentally determined O−H BDE values measured of hydroxylamines are close to 70 kcal/mol,[4] reaction 1 seems strongly endothermic and thus hardly feasible on thermodynamic grounds. It should be pointed out, however, that BDE measurements have only been reported for dialkylhydroxylamines while NHPI contains two carbonyl substituents adjacent to the NOH group. Since these might induce a strengthening of the O−H bond with respect to alkyl substituents, we have undertaken a thermochemical study on NHPI and other hydroxylamines in order to investigate the effect of alkyl, aryl, vinyl, and carbonyl substituents on the O−H bond strength. The investigated hydroxylamines, beside NHPI, are those shown below.



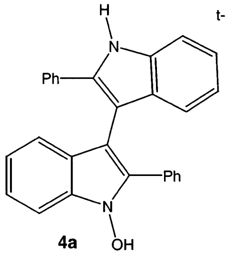
1a



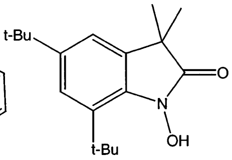
2a



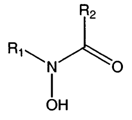
3a



4a



5a



6a; R_1=Me, R_2=Ph

7a; R_1=CMe$_3$, R_2=3,5-(NO$_2$)$_2$C$_6$H$_3$

8a; R_1=Ph, R_2=Ph

Kinetic studies have also been carried out in order to measure the absolute rate constants for reactions 1 and 3 and to better clarify the mechanism of the PINO-catalyzed oxidations. Kinetic EPR was used in the former case while, to obtain the value of the rate constant for hydrogen atom abstraction from NHPI by peroxyl radicals, the effect of the addition of the hydroxylamine on the rate of the thermally initiated autoxidation of cumene was investigated.

Results and Discussion

Thermochemistry. The determinations of the bond dissociation enthalpies of hydroxylamines were done by using the EPR radical equilibration technique that has been largely used in our laboratory in order to measure BDE values of the O−H bond in phenols[5,6] and of the N−H bond in aromatic amine antioxidants.[7] This technique consists of measuring the equilibrium constant for the hydrogen atom transfer reaction between a hydroxylamine, an appropriate reference compound, AH (eq 4), whose BDE value is already known, and the corresponding radicals.

$$R_2NO{-}H + A^\bullet \overset{K_e}{\rightleftharpoons} R_2NO^\bullet + A{-}H \qquad (4)$$

In the present cases, 2,2,6,6-tetramethylpiperidine-1-hydroxyl and several phenols were used as reference derivatives. The persistent nitroxide radicals were generated, at room temperature in degassed solutions of an appropriate solvent, from the corresponding hydroxylamines by hydrogen exchange with the commercial nitroxide TEMPO and the less persistent ones by photolysis with UV light in the presence of about 10% of di-*tert*-butylperoxide. Benzene was used as solvent when possible, while mixtures of benzene and *tert*-butyl alcohol or *tert*-butyl alcohol alone were used with some derivatives sparingly soluble in apolar solvents.

An examination of the measured hyperfine splitting constants and g-factors, reported in Table 1, shows that the spectroscopic parameters are strongly dependent on the nature of the substituent linked to the nitroxide function. In fact, a_N decreases and the g-factor increases by substituting alkyl groups, linked to the nitrogen atom, with vinyl or acyl groups. In nitroxides with conjugated C=X groups, the decrease of the hyperfine splitting constant at nitrogen is a well-known effect, easily un-

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[3] McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

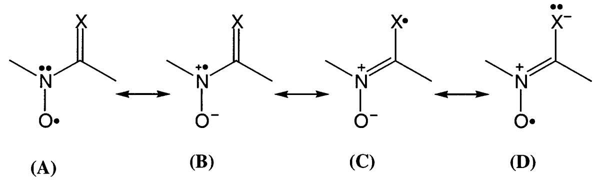
[4] Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 8610−8614.

[5] Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063. Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259. Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Amorati, R.; Minisci F. *J. Org. Chem.* **2001**, *66*, 5456−5462.

[6] Brigati, G.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 4828−4832.

[7] Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Valgimigli, L.; Gigmes, D.; Tordo, P. *J. Am. Chem. Soc.* **1999**, *121*, 11546−11553.

derstandable on the basis of the resonance structures **A**−**D**, due to the delocalization of spin density on X when this is a carbon atom and due to a redistribution of spin density within the NO group from nitrogen to oxygen when X is the strongly electronegative oxygen atom.[8] Thus, while substitution of an alkyl with an aryl group induces a decrease of spin density on both nitrogen and oxygen atoms, substitution with an acyl group produces a strong decrease of spin density on nitrogen and a small increase on oxygen, the latter effect being consistent with the larger *g*-value measured in acyl nitroxides.[8]



To measure the BDE values of the O−H bond different methods of generation were used due to the different persistence of the nitroxides from **1a**−**8a** and NHPI. In the case of **1a**, **2a**, **3a**, and **4a**, which gave rise to very persistent radicals, diluted benzene solutions of hydroxylamine ((2−8) × 10^{-4} M) and of TEMPO (5 × 10^{-5} M) were mixed, degassed, and introduced in the EPR cavity so that the equilibrium constant for the hydrogen atom exchange (eq 5) could be studied.

$$\mathrm{TEMPO}^{\bullet} + \mathrm{R_2NO{-}H} \rightleftharpoons \mathrm{TEMPO{-}H} + \mathrm{R_2NO}^{\bullet} \qquad (5)$$

The concentration ratio of the two species was adapted so that EPR spectra resulting from the superimposition of lines from both TEMPO and one of the nitroxides **1b**−**4b** could be simultaneously detected. The relative amounts of the two radicals were obtained either by numerical integration of the spectra or by computer simulation, while the concentrations of the corresponding hydroxylamines were calculated by difference as shown in eq 6, where $[\mathrm{TEMPO}]_0$ and $[\mathrm{R_2NOH}]_0$ are the initial concentrations of the two species.

$$K_e = \frac{[\mathrm{R_2NO}^{\bullet}]([\mathrm{TEMPO}]_o - [\mathrm{TEMPO}])}{[\mathrm{TEMPO}]([\mathrm{R_2NOH}]_o - [\mathrm{R_2NO}^{\bullet}])} \qquad (6)$$

The equilibrium constant K_e was used to calculate the free energy of the hydrogen atom transfer reaction from the hydroxylamine to TEMPO, which was put equal to the enthalpy of reaction, by assuming that the entropic contribution is negligible.[5] The BDE value of **1a**−**4a** was then calculated by means of eq 7 by using the known[4] BDE value (69.6 kcal/mol) of TEMPOH (i.e., the hydroxylamine precursor of TEMPO).

$$\mathrm{BDE(R_2NO{-}H)} = \mathrm{BDE(TEMPO{-}H)} - RT \ln K_e \quad (7)$$

The values obtained for **1a**, **2a**, **3a**, and **4a**, i.e., 70.6, 71.4, 69.7, and 72.8 kcal/mol, respectively, are close to those of TEMPOH and of other alkylhydroxylamines[4] despite the presence of an aryl group directly bonded to the nitrogen atom in **1a**, **2a**, and **3a** and of both an aryl and a vinyl group in **4a**.

FIGURE 1. Experimental EPR spectrum of nitroxide **6b** in benzene at room temperature (above). Below it is shown a portion of the experimental EPR spectrum obtained by partial oxidation of a mixture of **6a** and BHT and its computer simulation.

The three acyl hydroxylamines **5a**−**7a**, instead, behaved differently. Actually, when mixing solutions of these hydroxylamines with TEMPO in a wide range of concentrations, the three-line spectrum of TEMPO remained unchanged and no signals due to the nitroxides **5b**, **6b**, or **7b** were detected. This was a clear indication that the O−H bond in these acyl hydroxylamines is much stronger than in TEMPOH or in **1a**−**4a**. Thus, to measure the BDE values of **5a**−**7a**, reference compounds having stronger O−H bonds had to be used. By testing different phenols, 2,6-di-*tert*-butyl-4-methylphenol (BHT), characterized by an O−H BDE of 81.0 kcal/mol,[5] was found to be the most suitable one.

The equilibration experiments were done by preparing solutions of BHT (ca. 0.3 M) and of each hydroxylamine (ca. 0.03 M) in benzene containing some *tert*-butyl alcohol (see Table 1) and di-*tert*-butyl peroxide as photoinitiator. The radicals were generated photolytically by a short flash of filtered UV light. Figure 1 shows, as an example, the EPR spectra of nitroxide **6b** (above) and of its mixture with the phenoxyl radical from BHT (below). Since these experiments were performed on concentrated solutions of the radical precursors, the initial concentration of BHT and $\mathrm{R_2NOH}$ could be used in the calculation of K_e (eq 6) while the relative concentrations of the equilibrating radical species were determined by both simulation and numerical integration of the EPR spectra. As expected, the BDE values for the three acyl nitroxides were found to be much larger than those of **1a**−**4a**, i.e., 78.5, 79.2, and 80.2 kcal/mol for **5a**, **6a**, and **7a**, respectively.

When trying to measure the equilibration constant between **8a**, BHT, and the corresponding radicals, complex EPR spectra were obtained that could not be interpreted due to the formation of unidentified secondary radical species. Attempts made by substituting BHT with **6a** were again unsuccessful because, also in this case, spectra of secondary species were detected.

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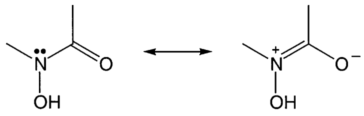
(8) Aurich, H. G. In *The Chemistry of Amino, Nitroso, Nitro Compounds and of their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1982; Chapter 14.

Finally, the same equilibration procedure was carried out with mixtures of NHPI and a number of ring-substituted phenols characterized by O−H bond strengths larger than 80 kcal/mol. Since NHPI is sparingly soluble in benzene, *tert*-butyl alcohol was used as solvent for the EPR radical equilibration experiments in order to satisfy one of the conditions requested, i.e., large concentrations of the two radical precursors.[5] When studying mixtures of NHPI and BHT, only the EPR spectrum of the phenoxyl radical was observed even by using trace amounts of the phenol. Since this indicates that the BDE value of the hydroxylamine is much larger than that of BHT, other phenols characterized by larger O−H bond strengths were used. The most suitable one was 3,5-di-*tert*-butylphenol, whose BDE value in benzene is 86.6 kcal/mol.[5] When photolyzing approximately equimolar mixtures of this phenol (0.056 M) and of NHPI (0.051 M) containing some di-*tert*-butyl peroxide, the resulting phenoxyl and nitroxide radicals were observed in a 1:1 ratio. This means that the BDE value of NHPI is 0.05 kcal/mol lower than that of the reference compound if entropic contributions are neglected.[5] Another phenol that, when mixed with NHPI (0.012 M), shows the presence of both radicals is 4-cyanophenol[9] (0.94 M). In this case, the determination of the equilibrium constant gives a difference between the BDEs of the phenol and the hydroxylamine of 3.7 kcal/mol. Although the experimental determination of the BDE of 4-cyanophenol has never been reported, this can be straightforwardly estimated in benzene solution by the substituent additivity rule[10] as 89.0 kcal/mol.[6]

It is important to emphasize the fact that these measurements have been carried out in *tert*-butyl alcohol where, as in other hydrogen bond acceptor (HBA) solvents, the BDE value of substituted phenols may be considerably different from that one measured in benzene due to the solvation of the OH group.[11,12] Actually, in the case of phenols, the BDEs have been found to increase by ca. 2.2 kcal/mol on passing from benzene to *tert*-butyl alcohol when no substituents are present in the ortho positions, by ca. 1.0 kcal/mol for 2,6-dimethyl substituted phenols, while in 2,6-di-*tert*-butylphenols they seem to be substantially unaffected.[11] Thus, we can estimate the BDE values of the two reference compounds in the solvent used for the present determinations, as 88.8 and 91.2 kcal/mol for 3,5-di-*tert*-butylphenol and for 4-cyanophenol, respectively, and thus the O−H bond strength of NHPI in *tert*-butyl alcohol as 88.1 ± 0.6 kcal/mol.

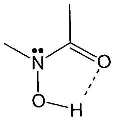
To estimate the bond dissociation enthalpy in non-HBA solvents such as benzene, the following considerations can be made. If NHPI behaves as a phenol without *ortho* substituents, the BDE value should be lower than in Me_3COH by 2.2 kcal/mol (i.e., 85.9 kcal/mol). Since, however, NHPI contains carbonyl groups at the right distance from the hydroxyl proton to give an intramolecular hydrogen bond, it seems more likely that the solvent effect is lower and similar to that observed in 2-methoxyphenol where the OH group is intramolecularly hydrogen bonded to the *ortho* substituent. A reasonable estimate is that in non-HBA solvents the BDE value of NHPI should be ca. 1 kcal/mol lower, that is about 87 kcal/mol.

In conclusion, it is clear on the basis of the experimental results collected that the strength of the O−H bond in hydroxylamines is strongly dependent on the nature of the substituents linked to the nitrogen atom. Actually, while in dialkyl hydroxylamines the O−H BDE value is ca. 70 kcal/mol, in alkyl acyl hydroxylamines is about 10 kcal/mol larger and in diacyl hydroxylamines is even larger. To understand the reasons for this behavior, it should be pointed out that the BDE value is a measure of the energy difference between the nitroxide radical and the parent hydroxylamine; thus, any factor inducing a stabilization of the hydroxylamine or a destabilization of the nitroxide increases the strength of the O−H bond. The higher BDE values observed in acyl hydroxylamines are likely due to the larger resonance stabilization arising from structures with charge separation that instead do not contribute to the mesomeric system in dialkyl hydroxylamines.



(E) **(F)**

Moreover, as discussed above on the basis of the computational results reported by Aurich,[8] the presence of the C═O group in acyl nitroxides reduces the importance of the mesomeric structure (**B**) due to its electron-acceptor character, this implying a destabilization of these species with respect to alkyl nitroxides. Another reason for the larger BDEs of acyl hydroxylamines is the likely formation of an intramolecular hydrogen bond that may stabilize the starting compound, while obviously, it is absent in the corresponding nitroxide.



It seems of some interest, for prediction purposes, that the BDE values of the hydroxylamines roughly correlate with the *g*-values of the corresponding nitroxide radicals as shown in Figure 2. An explanation of this behavior can be found in the fact that the larger values of BDE in the hydroxylamines and of the *g*-factors in the corresponding radicals are both the result of the presence of the electronegative carbonyl substituent which increases the importance of polar mesomeric structures, as discussed previously. This correlation may be very useful for roughly estimating BDE values of hydroxylamines simply from the measure of the *g*-factor of the corresponding nitroxides.

Kinetic Experiments. To measure the rates by which PINO radicals can abstract a hydrogen atom from a given substrate (RH, eq 1), and thus the rates of the catalyzed oxidation by molecular oxygen, we have carried out kinetic studies by using both EPR spectroscopy to monitor the decay of radical species and a differential pressure transducer to measure the oxygen consumption in a closed system. The reactivity of PINO with several

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(9) The measured spectroscopic parameters of 4-cyanophenoxyl radical are: a_H(ortho) = 6.86 G, a_H(meta) = 2.31 G, a_N = 1.38 G, g = 2.0054.

(10) Borges dos Santos, R. M.; Martinho Simões, J. A. *J. Phys. Chem. Ref. Data* **1998**, *27*, 707−739.

(11) Pedrielli, P.; Pedulli, G. F. *Gazzetta* **1997**, *127*, 509.

(12) De Heer, M. I.; Korth, H. G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969.

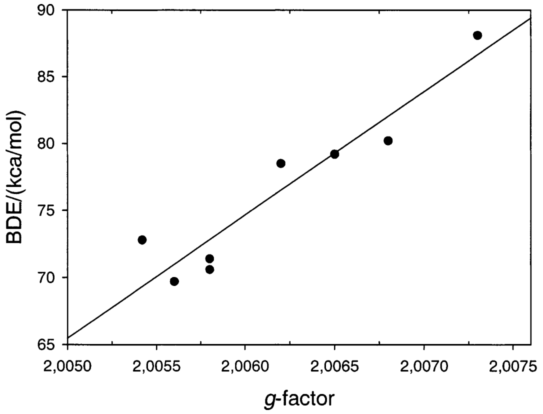

FIGURE 2. Correlation among the O−H bond dissociation enthalpy values of hydroxylamines and the *g*-factors of the corresponding nitroxide radicals.

substrates containing an easily abstractable hydrogen atom has been previously studied in ACN containing pyridine by Masui and co-workers[13] by using UV spectroscopy. EPR was used to determine the rate constant of hydrogen abstraction from RH by PINO, following the decay of the EPR signals of these radicals in the presence of increasing amounts of the substrate. PINO was produced photochemically from NHPI and dicumyl peroxide (20% by weigth) in benzene solutions containing 10% acetonitrile, and the investigated compounds RH were toluene, ethylbenzene, isopropylbenzene (cumene), benzyl alcohol, cyclohexane, and adamantane. The decay of PINO followed good first-order kinetics both in the absence and in the presence of the oxidizable substrate. In the former case, this is likely due to a fragmentation at one of the carbonyl carbon−nitrogen bonds, similarly to what previously reported by Perkins and co-workers for an other acylnitroxide.[14] This behavior differs from that one described by Masui and co-workers who observed second-order decay when PINO was produced electrochemically in ACN pyridine mixtures.[13] Actually, we have found that the kinetics of decay of this nitroxide strongly depends on the time of irradiation and on the solvent composition. Therefore, all kinetic measurements were carried out by using freshly prepared samples shortly irradiated with a flash of light. Under these conditions, the decay traces were nicely described by eq 7, where k_d is the first-order rate constant for self-decay and k_H is the second-order rate constant for hydrogen abstraction by RH. The factor 2 before k_H is required since the alkyl radical formed by hydrogen abstraction from RH is expected to subtract a second molecule of the nitroxide from the solution by a fast combination reaction to give the adduct PINO−R.

$$\ln\frac{[\mathrm{PINO}]_t}{[\mathrm{PINO}]_0} = -(k_d + 2k_H[\mathrm{RH}])t \qquad (7)$$

Measurements were carried out by using different substrate concentrations compatible with a decay lasting at least 20 s. The experimentally determined values of the pseudo-first-order rate constant $k_{EPR} = k_d + 2k_H[\mathrm{RH}]$ are plotted in Figure 3 as function of the substrate concentration and the resulting k_H obtained from the slopes of these plots are shown in Table 2. It should be pointed out that the presently determined values for ethylbenzene and benzyl alcohol are similar to those measured by Masui, i.e., 1.85 and 15.6 M^{-1} s^{-1}, respectively, in a different solvent and by a different experimental technique.[13] In the case of ethylbenzene, measurements were also done by using the perdeuterated derivative $C_6D_5CD_2CD_3$; the corresponding room-temperature rate constant was 0.22 M^{-1} s^{-1}, this implying a kinetic isotope effect of 8.7. Table 2 also reports the rate constants given in the literature[15] for the related hydrogen abstraction reaction from RH by *tert*-butylperoxyl radicals, k_p. It is seen that the reactivity of PINO with the various substrates is larger than that of *tert*-butylperoxyl radicals, although the observed difference depends on the nature of the oxidizable substrate being larger with benzyl alcohol than with the aromatic hydrocarbons presumably because of polar effects.[2]

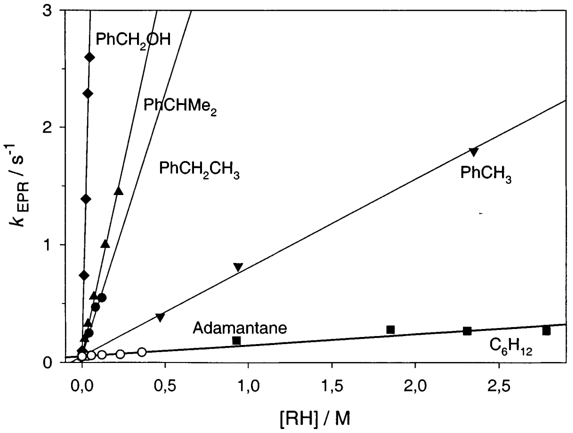

FIGURE 3. Pseudo-first-order rate constants for the decay of PINO radicals in the presence of different amounts of hydrogen atom donors in benzene + 10% ACN.

TABLE 2. Absolute Rate Constants, k_H, for the Hydrogen Abstraction Reaction from RH by PINO in Benzene + 10% ACN at 25 °C (Eq 1) and by the *tert*-Butylperoxyl Radical, k_p,[15] at 30 °C[a]

RH	$k_{H\ (PINO)}$/M^{-1} s^{-1}	k_p[b]/M^{-1} s^{-1}	$k_{H\ (PINO)}/k_p$
PhC*H*$_3$	0.38	0.036	10.5
PhC*H*$_2$CH$_3$	2.24	0.20	11.2
PhC*H*Me$_2$	3.25	0.22	14.8
PhC*H*$_2$OH	28.3	0.13	218
cyclohexane	0.047	0.0034	13.8
adamantane	0.047		

[a] The k_d value for the first-order self-decay of PINO in the absence of hydrocarbons was 0.1 s^{-1}. [b] These are the overall rate constants independent of the number of labile hydrogens.

To better understand the factors determining the rate of NHPI-catalyzed oxidation of hydrocarbons, we have also investigated the thermally initiated autoxidation of cumene, chosen as a model system, by measuring the rate of oxygen uptake in the presence and in the absence of NHPI. The autoxidation was followed by monitoring the oxygen consumption in a closed system with an automatic

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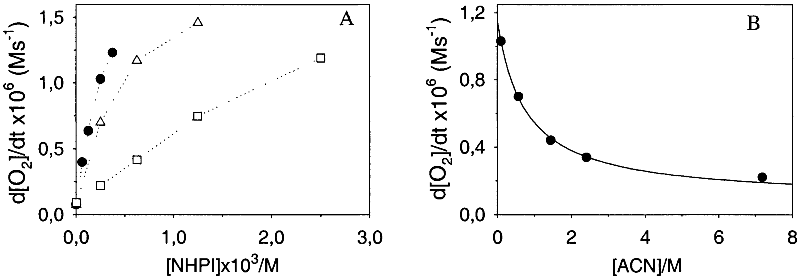

FIGURE 4. Dependence of the oxygen consumption rate, observed during the AMVN (5.0×10^{-3} M) initiated autoxidation of cumene (0.89 M) at 30 °C in chlorobenzene, on the NHPI concentration (A) and on the content of the ACN in solution (B). The three plots of part A were obtained at different ACN concentrations (●, 0.5%; Δ, 3%; □ 37.5%), while the data reported in part B were obtained at an NHPI concentration of 2.5×10^{-4} M.

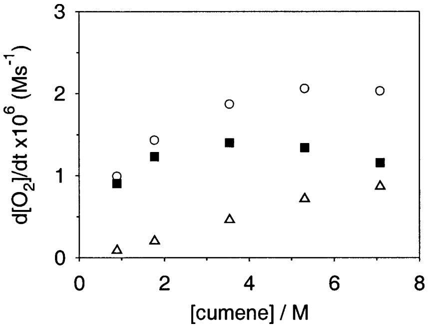

FIGURE 5. Oxygen consumption rates at 30 °C observed during the autoxidation of cumene, at increasing concentration, in chlorobenzene and ACN 0.5% in the presence of AMVN 5.0×10^{-3} M: Δ, without NHPI; ○, in the presence of NHPI 2.5×10^{-4} M; ■, difference between the catalyzed and the noncatalyzed oxygen consumption rates.

recording gas absorption apparatus, built in our laboratory, that uses as detector a commercial differential pressure transducer.[16]

The autoxidations were carried out at 30 °C in chlorobenzene solutions containing cumene (0.89 M), 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN) as initiator (0.005 M), and variable amounts of NHPI ($0-2.5 \times 10^{-3}$ M). The oxygen uptake traces showed an initial induction period of several minutes where the rate of oxidation was low, then $d[O_2]/dt$ increased becoming linear with time. When plotting this rate of oxygen consumption as function of the hydroxylamine in solution (see Figure 4), good linearity was observed for low NHPI concentrations, while at a higher content of hydroxylamine the rate of oxidation was lower than expected. To study the effect of solvent on the rate of reaction, these experiments were carried out in the presence of increasing amounts of acetonitrile (ACN), a solvent having good hydrogen bond accepting properties. It is seen that by increasing the ACN concentration a large reduction of the rate of reaction as well as a decrease of the nonlinearity of the plots are observed. Experiments have also been performed by changing the rate of initiation R_i, i.e., the AMVN concentration, and the cumene concentration. The rate of oxidation was found to increase linearly with the square root of R_i, while the dependence on the oxidizable substrate concentration is shown in Figure 5.

All these observations can be rationalized on the basis of the reaction mechanism reported in eqs 8−13, where the first four reactions describe the hydrocarbon oxidation in the absence of catalyst and the last two represent the catalytic cycle in the presence of a hydroxylamine.

$$\mathrm{In} \xrightarrow{R_i} \mathrm{R}^\bullet \tag{8}$$

$$\mathrm{R}^\bullet + \mathrm{O_2} \rightarrow \mathrm{ROO}^\bullet \tag{9}$$

$$\mathrm{ROO}^\bullet + \mathrm{RH} \xrightarrow{k_p} \mathrm{R}^\bullet + \mathrm{ROOH} \tag{10}$$

$$2\ \mathrm{ROO}^\bullet \xrightarrow{2k_t} \text{products} \tag{11}$$

$$\mathrm{R_2NO{-}H} + \mathrm{ROO}^\bullet \xrightarrow{k_f} \mathrm{R_2NO}^\bullet + \mathrm{ROOH} \tag{12}$$

$$\mathrm{R_2NO}^\bullet + \mathrm{RH} \xrightarrow{k_H} \mathrm{R}^\bullet + \mathrm{R_2NO{-}H} \tag{13}$$

By solving the simultaneous differential equations describing the time evolution of the various species, under the assumption that the steady-state approximation holds for all free radical species, eq 14 can be obtained for the rate of oxygen consumption; the first term to the right describes the noncatalyzed and the second one the catalyzed oxidation.

$$-\frac{d[O_2]}{dt} = k_p[\mathrm{RH}]\left(\frac{R_i}{2k_t}\right)^{1/2} + k_f[\mathrm{R_2NO{-}H}]\left(\frac{R_i}{2k_t}\right)^{1/2} \tag{14}$$

When using low concentrations of the oxidizable substrate, the only important term is the last one, and therefore, the rate of oxidation is expected to depend on (i) the hydroxylamine concentration, (ii) the square root of the rate of initiation, and (iii) the inverse of the square root of the rate of termination of the peroxyl radicals from the substrate. Experimentally, it was found that the first two predictions are actually verified since $-d[O_2]/dt$ changes linearly with the NHPI concentration, at least for low contents of the hydroxylamine (see Figure 4), and with the square root of the initiator concentration. According to the proposed kinetic model the rate of oxidation should be independent of the substrate concentration. From Figure 5, showing the results of a series

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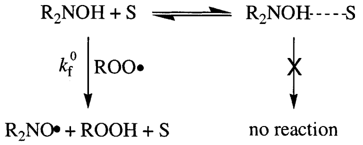
of measurements carried out at different cumene concentrations, both in the absence and in the presence of NHPI, it appears that the plot obtained by subtracting the rate of noncatalyzed to the rate of catalyzed oxidation does not significantly depend on the cumene concentration.

On the basis of eq 14, the slope of the plot reporting $-d[O_2]/dt$ against [NHPI] will provide $k_f(R_i/2k_t)^{1/2}$. Since both R_i and $2k_t$ can be measured independently, the rate constant k_f for the hydrogen atom abstraction from NHPI by the peroxyl radical representing the rate-determining step of the overall reaction can be obtained. However, due to the low solubility of NHPI in PhCl, all experiments were performed in the presence of some ACN that, as shown in Figure 4, reduces the rate of oxidation with respect to PhCl. The results of a more complete series of data obtained at different solvent compositions are reported in Figure 4B. The reduced rate of oxidation observed at high ACN concentrations is due to the formation of hydrogen bonding between ACN and the hydroxyl proton of NHPI and can be analyzed in terms of a simple model, proposed by Ingold and co-workers,[17] based on the assumptions that the HBA solvent, S, and substrate, R_2NO-H, give rise to 1:1 hydrogen-bonded complex, $R_2NO-H\cdots S$, in equilibrium with the hydroxylamine, which is much less reactive toward peroxyl radicals.



On the basis of this model, the measured rate constant for a given solvent composition, k_f^S will be given by eq 15, where [S] is the concentration of the ACN, k_f^0 is the rate constant of the free hydroxylamine, and K^S is the equilibrium constant for the complexation of NHPI by ACN.

$$k_f^S = \frac{k_f^0}{1 + K^S[S]} \qquad (15)$$

Analysis of the data of Figure 4B provides the $k_f^0 = 7.2 \times 10^3$ M^{-1} s^{-1} and $K^S = 1.3$ M^{-1} by using the measured values of $R_i = 5.5 \times 10^{-9}$ M s^{-1} and $2k_t = 1.6 \times 10^4$ M^{-1} s^{-1} in chlorobenzene at 30 °C.[18]

Conclusions

The present study provides a rationalization of the catalytic effect of the phthalimide-*N*-oxyl radical (PINO) in the aerobic oxidation of several organic substrates. The unusually high hydrogen abstracting activity of this nitroxide radical is justified by the large bond dissociation enthalpy (BDE) of the O−H bond in the corresponding hydroxylamine (NHPI), which is ca. 18 kcal/mol larger than that of dialkyl hydroxylamines. The BDE value of acyl hydroxylamines, approximately 10 kcal/mol larger than that of dialkyl hydroxylamines, conclusively demonstrates that acyl substituents at the nitrogen atom are capable of increasing the strength of the hydroxylamine O−H bond. This is attributed to resonance effects both in the acyl substituted and in the corresponding nitroxide radicals as well as to intramolecular hydrogen bonding in the acyl hydroxylamine.

Kinetic studies carried out in order to investigate the catalytic behavior of NHPI on the oxidation of cumene are consistent with a simple kinetic model where the rate determining step is the hydrogen atom abstraction from the hydroxylamine by the cumylperoxyl radicals (eq 12). It should, however, be emphasized that this model relies on the assumption that the rate of hydrogen abstraction from cumene by the nitroxide radical (PINO) is significantly large to allow the steady-state concentration of the various radical species to be reached within reasonably short times. With other substrates less reactive than cumene, the kinetics of the aerobic oxidation might be more complicated.

Due to the low solubility of NHPI in apolar solvents, the effect of adding to the reaction medium increasing concentrations of a hydrogen-bond acceptor solvent, such as ACN, that can complexate the hydroxylic group of NHPI, was also investigated. The considerable reduction of the rate of oxidation, observed in the presence of ACN, provided additional evidence that the slower step of the cumene oxidation is the reaction of NHPI with peroxyl radicals. It seems possible that, with a more lipophilic diacyl hydroxylamine catalyst, the efficiency of the oxidation could substantially improve.

Experimental Section

Materials. Solvents were of the highest grade commercially available and were used as received. The hydroxylamines **1a**,[19] **5a**,[20] **6a**,[21] and **7a**[22] and the stable nitroxides **2b**,[23] **3b**,[24] and **4b**[25] were prepared according to literature procedures, while **8a** and NHPI were commercial products. The hydroxylamines **2a** (mp = 159−161 °C from benzene/petroleum ether; IR ν = 3475 and 1600 cm^{-1}), **3a** (mp = 176−177 °C from ligroin; IR ν = 3400 and 1600 cm^{-1}), and **4a** (mp = 184−185 °C from benzene/petroleum ether; IR ν = 3415 a 3300 cm^{-1}), were obtained from **2b**, **3b**, and **4b**, respectively, by reduction with phenylhydrazine according to the method described in ref 19.

EPR Spectra. The EPR spectra were recorded on a Bruker ESP 300 spectrometer equipped with a Hewlett-Packard 5350B microwave frequency counter for the determination of the *g*-factors, which were corrected with respect to that of perylene radical cation in concentrated H_2SO_4 ($g = 2.00258$). The nitroxide radicals were generated photochemically in deoxygenated benzene or *tert*-butyl alcohol solutions of the hydroxylamine under study and di-*tert*-butyl peroxide (10% v/v) contained in Suprasil quartz EPR tubes sealed under nitrogen. The sample was inserted in the cavity of an EPR spectrometer and photolyzed with the unfiltered light from a

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500 W high-pressure mercury lamp. The temperature was controlled with a standard variable-temperature accessory and was monitored before and after each run with a copper–constantan thermocouple.

Determination of the O–H BDE Values. The bond dissociation enthalpies of the O–H bond were obtained from the equilibrium constants K_e (eq 6) in the case of the reactions between TEMPO and one of the hydroxylamines **1a**–**4a**, since all the nitroxide radicals derived from these hydroxylamines are very long-lived, and thus, the total radical concentration remains constant during the course of the experiment. These measurements were carried out by introducing in the EPR cavity degassed benzene solutions of mixtures of a hydroxylamine ($(2-8) \times 10^{-4}$ M) and TEMPO ($(1-5) \times 10^{-5}$ M) and by determining the relative concentrations of the two nitroxides either by integration of the EPR signals or by computer simulation of the spectrum.

In the case of the hydroxylamines **5a**–**7a** and of NHPI, the reference compound was a phenol whose O–H BDE value was known. The equilibrating radicals were produced by photolyzing deoxygenated benzene or *tert*-butyl alcohol solutions containing the hydroxylamine under investigation (0.1–0.5 M), an appropriate reference compound (0.1–0.5 M), and di-*tert*-butyl peroxide. The molar ratio of the two radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_e (eq 4). The equilibrium constants were found to be independent of the initial product concentrations and on the rate of initiation. The initial concentrations of the two reactants were used for this purpose since these were high enough to avoid significative consumption during the course of the experiment. Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer simulated ones. In these cases, an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the two species including their relative intensities.[5]

Kinetic Measurements by EPR. The rate of hydrogen abstraction from the investigated hydrocarbons and benzyl alcohol by the PINO radical was measured at 298 K by kinetic-EPR. An EPR quartz tube containing a nitrogen-saturated benzene solution containing 10% acetonitrile, dicumyl peroxide (20% by weight), and NHPI (10^{-3} M), and increasing amounts of the investigated compound, i.e., toluene, ethylbenzene, isopropylbenzene, benzyl alcohol, and cyclohexane, was placed in the thermostated cavity of a Bruker ESP 300 spectrometer equipped with a Bruker ER033M field-frequency lock.

PINO was produced photochemically by a short pulse of UV light from an unfiltered 500 W high-pressure Hg-lamp and the decay of its ESR spectrum monitored as function of time. For each experiment, a single time-sweep EPR scan was recorded with the following settings: microwave power 5 mW, time constant 4 ms, conversion time 20–164 ms.

Autoxidation Experiments. Autoxidation experiments were performed in a two-channel oxygen uptake apparatus, based on a Validyne DP 15 differential pressure transducer, that has already been described elsewhere.[16] The entire apparatus was immersed in a thermostated bath that ensured a constant temperature within ±0.1 °C.

In a typical experiment, an air-saturated chlorobenzene solution containing cumene (0.89 M), and variable amounts of NHPI ($0-2.5 \times 10^{-3}$ M) were equilibrated at 30 °C with a reference solution containing the same reaction mixture and a large amount of α-tocopherol (ca. 10^{-4} M) instead of NHPI. After equilibration, a concentrated chlorobenzene solution of the radical initiator 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN) (0.005 M) was injected in both the reference and sample flasks and the oxygen consumption in the sample was measured, after calibration of the apparatus, from the differential pressure recorded with time between the two channels. This instrumental setting allowed us to have the N_2 production and the oxygen consumption derived from the azo-initiator decomposition already corrected from the measured reaction rates. Initiation rates, R_i, were determined for each conditions in preliminary experiments by the inhibitor method using α-tocopherol as reference antioxidant: $R_i = 2[\alpha\text{-tocopherol}]/\tau$. Experiments were also performed by changing the rate of initiation R_i, i.e., the AMVN concentration, the cumene concentration, and in the presence of different amounts of acetonitrile (ACN).

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