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New free-radical halogenations of alkanes, catalysed by *N*-hydroxyphthalimide. Polar and enthalpic effects on the chemo- and regioselectivity

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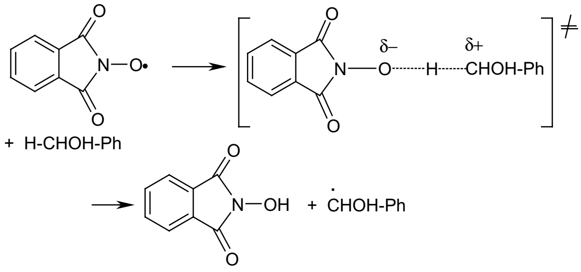
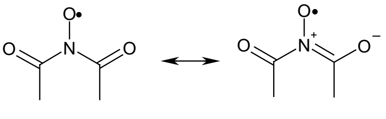
Abstract—Reactions of alkanes with different halogenating systems are compared in order to explore the reactivity of phthalimido-*N*-oxyl radical in hydrogen abstraction; the importance of polar effects is emphasised.

Recently we have evaluated[1] the bond dissociation enthalpies (BDE) of the O–H bonds of a variety of hydroxylamine derivatives, showing how the BDE values strongly increase from alkyl- or arylhydroxylamine ($\approx$70 kcal mol^{-1}) to mono- and di-acylhydroxylamines (88.1 kcal mol^{-1} for *N*-hydroxyphthalimide, NHPI). Moreover, we have determined[1] the absolute rate constant for hydrogen abstraction from a series of C–H bonds by phthalimido-*N*-oxyl (PINO) radical, generated in situ from NHPI (0.38, 2.4, 3.3, 28.3 and 0.047 M^{-1} s^{-1} at 25 °C, respectively, for Ph–CH$_3$, Ph–CH$_2$–Me, Ph–CHMe$_2$, Ph–CH$_2$OH and cyclohexane) giving for the first time a quantitative basis for the catalytic activity of NHPI in aerobic oxidations.[2,3] The hydrogen abstractions by *t*-BuOO· radical are considerably slower[3] (0.036, 0.20, 0.22, 0.13, 0.0034 M^{-1} s^{-1} at 25 °C, respectively, for Ph–CH$_3$, Ph–CH$_2$–Me, Ph–CHMe$_2$, Ph–CH$_2$OH and cyclohexane) in spite of the fact that, BDE values for O–H bonds in NHPI and ROO–H being identical (88 kcal mol^{-1}), the enthalpic effect in hydrogen abstraction by PINO and *t*-BuOO· radicals should be quite similar. The rate difference is particularly marked with Ph–CH$_2$OH, where hydrogen abstraction is 218 times faster by PINO than by *t*-BuOO· radical, and we[3,4] have suggested that this different behaviour could be due to a more pronounced electrophilic character of the PINO radical (Eq. 1) compared to the peroxyl radical.



(1)

Nitroxyl radicals are generally electrophilic, but the polar character should be considerably enhanced by the presence of two carbonyl groups in PINO (Eq. 2)



(2)

The effect should be similar to the one observed[5] with acylperoxyl, RC(=O)–OO·, compared to alkylperoxyl, R–OO·, radicals: the former are more electrophilic than the latter. This phenomenon could be more marked with PINO than with acylperoxyl radicals, because nitrogen can settle a positive charge, as in Eq. 2, better than carbon or oxygen.

The absolute rate constants in hydrogen abstraction from substituted benzyl alcohols would support the

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Keywords: *N*-Hydroxyphthalimide; Alkane halogenation; Free-radicals.

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importance of the electrophilic character of PINO radical, since a good Hammett correlation was found.[6] Exceptions are observed in the cases of *p*-nitro- and *p*-cyanobenzyl alcohols, which have the same rate constants as unsubstituted benzyl alcohol. A possible explanation of what appears to be a contradictory behaviour could be related to a capto-dative effect, which exceeds the sum of the individual substituent (–OH and –NO_2 or –CN) effects by a synergetic stabilisation. In this letter we report new free-radical halogenations of alkanes and substituted alkanes, catalysed by NHPI, which further confirm the marked polar effect in hydrogen abstraction from C–H bonds by PINO radical.

When cyclohexane was oxidised by HNO_3 under nitrogen or oxygen atmosphere in the presence of NHPI and $CuCl_2$, chlorocyclohexane was obtained without traces of dichlorocyclohexanes at 35% conversion, based on HNO_3, indicating that the introduction of a Cl atom deactivates the alkyl group towards further chlorination. On the opposite, polychlorination easily occurs by Cl_2 chlorination, even at lower conversions. No chlorination by $CuCl_2$ occurs under the same conditions in the absence of NHPI, suggesting that hydrogen abstraction from C–H bonds by PINO radical (Eq. 3), generated from NHPI and HNO_3 or NO_2 (Eqs. 4 and 5) is a key step of the process.

$$\succ\mathrm{N{-}O^{\bullet}} + \mathrm{R{-}H} \rightarrow \succ\mathrm{N{-}OH} + \mathrm{R^{\bullet}} \tag{3}$$

$$\succ\mathrm{N{-}OH} + \mathrm{HNO_3} \rightarrow \succ\mathrm{N{-}O^{\bullet}} + \mathrm{NO_2} + \mathrm{H_2O} \tag{4}$$

$$\succ\mathrm{N{-}OH} + \mathrm{NO_2} \rightarrow \succ\mathrm{N{-}O^{\bullet}} + \mathrm{HNO_2} \rightarrow \mathrm{NO} + \mathrm{NO_2} \tag{5}$$

The resulting cyclohexyl radical reacts very rapidly[7] with $CuCl_2$, leading to chlorocyclohexane (Eq. 6).

$$\mathrm{R^{\bullet}} + \mathrm{CuCl_2} \xrightarrow{k_6} \mathrm{R{-}Cl} + \mathrm{CuCl} \quad k_6 > 10^9\,\mathrm{M^{-1}\,s^{-1}} \tag{6}$$

Cu(II) is continuously regenerated from CuCl by oxidation with HNO_3, NO_2 or O_2. With stoichiometric amount of HNO_3 under N_2 atmosphere the overall stoichiometry is expressed by Eq. 7.

$$3\mathrm{RH} + 2\mathrm{HNO_3} + 3\mathrm{HCl} \rightarrow 3\mathrm{RCl} + 2\mathrm{NO} + 4\mathrm{H_2O} \tag{7}$$

In the presence of O_2 with catalytic HNO_3, NO is continuously oxidised to NO_2 and the stoichiometry is given by Eq. 8. Also in this case, chlorination is inhibited in the absence of NHPI.

$$\mathrm{RH} + \tfrac{1}{2}\mathrm{O_2} + \mathrm{HCl} \rightarrow \mathrm{RCl} + \mathrm{H_2O} \tag{8}$$

In principle, the alkyl radical $R^{\bullet}$ can also rapidly react with O_2, NO_2 or NO (the rates of all these reactions are often diffusion controlled), but the much higher concentration of $CuCl_2$ in the reaction medium makes the chlorination quite selective.

In order to evaluate the extent of polar and enthalpic effects for hydrogen abstraction a series of substituted alkanes has been investigated. Only monosubstitution occurs and the results are reported in Table 1. The use of Cl_2 instead of $CuCl_2$ leads to a complex mixture of polysubstituted derivatives, due to the high reactivity and low selectivity of the chlorine atom. By using Br_2 instead of $CuCl_2$ under the same conditions, bromination of the alkane takes place; in this case the alkyl bromides are formed through the fast reaction of alkyl radical with Br_2 (Eq. 9)

$$\mathrm{R^{\bullet}} + \mathrm{Br_2} \rightarrow \mathrm{RBr} + \mathrm{Br^{\bullet}} \tag{9}$$

The bromine atom abstracts a hydrogen atom from NHPI regenerating the PINO radical (Eq. 10); HBr is oxidised to Br_2 by HNO_3 or NO_2.

$$\succ\mathrm{N{-}OH} + \mathrm{Br^{\bullet}} \rightarrow \succ\mathrm{N{-}O^{\bullet}} + \mathrm{HBr} \tag{10}$$

We expect Eq. 10 to be much faster than hydrogen abstraction from C–H bonds of alkanes by $Br^{\bullet}$ for enthalpic reasons (BDE values of the O–H bond in ROO–H and of the H–Br bond are identical, 88 kcal mol^{-1}, and we have evaluated[1] that hydrogen abstraction from NHPI by R–OO$^{\bullet}$ radical is about seven orders of magnitude faster, that is, $7.2\times10^3\,\mathrm{M^{-1}\,s^{-1}}$ at 30 °C, than hydrogen abstraction from the C–H bonds of alkanes, which is about $10^{-4}\,\mathrm{M^{-1}\,s^{-1}}$). This is clearly

Table 1. Isomer distribution in chlorination, bromination and acetoxylation of substituted alkanes, catalysed by NHPI[a]

Method	Substrate (isomer distribution)						
	Cl—CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$	
A	4.9	4.7	13.6	34.0	42.8	traces	
B	3.8	5.1	15.3	32.2	43.6	traces	
C	6.1	5.5	13.6	30.9	43.9	---	
D	---	traces	7.1	35.4	57.5	---	
Cl_2[12]	1.8	9.4	21.3	23.9	26.5	17.2	
Me_2NCl[12]	---	---	6.8	19.4	71.6	2.2	
	MeOCO—CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$		
A	6.1	12.1	28.3	53.5	---		
C	6.3	16.0	27.0	50.7	---		
Me_2NCl[12,13]	---	0.7	6.3	87.3	6.7		
Me_2NBr[14]	---	0.4	5.9	87.0	6.8		
	MeOCO—CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$			
Cl_2[15]	5.4	30.1	44.5	18.7			
B	8.2	27.1	64.7	traces			
C	9.4	26.6	64.0	traces			
Br_2[15]	35.0	19.6	45.4	---			
Me_2NCl[13]	---	13.3	79.9	6.7			
	O$_2$N—CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$	
A	---	---	9.2	32.2	58.6	---	
	AcO—CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$
D	---	3.5	5.4	20.5	28.3	42.3	---
	CH$_3$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_2$—	CH$_3$
D	---	45.9	36.9	17.2			
Me_2 NCl[16]	1.1	55.6	29.0	14.3			

[a] Typical procedures of halogenation and acetoxylation are: (A) a solution of 2 mmol of substrate, 0.4 mmol of HNO_3, 2 mmol of $CuCl_2$ and 0.4 mmol of NHPI in 10 mL of AcOH were stirred at 100 °C for 5 h under N_2, the solution was diluted by water, extracted by CH_2Cl_2 and analysed by GLC, as previously[9] reported: a 31% conversion based on HNO_3 was obtained; (B) as in (A) under O_2, 47% conversion; (C) as in (A) with 2 mmol of Br_2 instead of $CuCl_2$ and 0.02 mmol of $Cu(OAc)_2$ at 80 °C, 35% conversion; (D) as in (A) with 2 mmol of I_2 instead of $CuCl_2$, 37% conversion.

supported by the observed selectivities, quite different from those found in free-radical bromination by Br_2 in the absence of NHPI (Table 1).

In the presence of I_2 the alkyl iodides, initially formed from alkyl radicals, undergo solvolysis (the solvent is acetic acid) under the reaction conditions, leading to acetoxy derivatives. The reaction is catalytic in I_2, since it is regenerated from HI, formed during the solvolysis, by oxidation with HNO_3 or O_2; the concentration of I_2 in the solution, however, must be kept relatively high in order to overcome the competition of the alkyl radical reactions with NO_2 or O_2. No hydrogen abstraction can take place by iodine atom from either NHPI or C–H bonds, due to the low BDE value for H–I, but PINO radical is generated according to Eqs. 4 and 5.

In Table 1 some results obtained with a series of substituted alkanes by NHPI catalysis are compared with the analogous results obtained both in halogenations with Cl_2 and Br_2, where $Cl^\cdot$ and $Br^\cdot$ are the hydrogen abstracting species, and in what Deno[8] has called the 'Minisci halogenation', where amino radical cations, $R_2NH^{+\cdot}$, from protonated haloamines are the hydrogen abstracting species.[9] All these results suggest that:

(i) In the reactions catalysed by NHPI, chemoselectivity is much higher than in free-radical halogenations by Cl_2 or Br_2: the introduction of a halogen atom or an acetoxy group determines a significant deactivation of the substrate, allowing selective monosubstitution even at considerable conversions. This behaviour is more similar to halogenation by *N*-haloamines, which is particularly sensitive to polar effects, than to halogenation by Cl_2 or Br_2.

(ii) The regioselectivity for chlorination and bromination in the presence of NHPI is quite similar, strongly suggesting the involvement of the same hydrogen abstracting species (PINO radical, Eq. 3); this regioselectivity is quite different from the one observed with Cl_2 or Br_2 in the absence of NHPI, which suggests a large polar effect in hydrogen abstraction by PINO radical, even though this effect is lower compared to $R_2NH^{+\cdot}$ radicals. Differences in acetoxylation selectivity are likely related to the solvolysis of the initially formed alkyl iodides.[10]

(iii) The enthalpic effects also considerably affect selectivity: the methyl group, even if it is the least deactivated by the polar substituents, reacts only in traces, due to the higher BDE values of the C–H bonds compared to those in the $-CH_2-$ group. Also the similar selectivity in positions 1 and 2 of 1-chlorohexane can be explained in terms of higher polar deactivation of position 1, balanced by the more favourable enthalpic effect.

(iv) In the acetoxylation of *n*-heptane position 2 is somewhat more reactive than positions 3 and 4, which show the same reactivity, as already[9] observed with *N*-chloroamines. All these results strongly support the hypothesis that the higher reactivity of PINO radical, compared to peroxyl ($ROO^\cdot$), in the hydrogen abstraction from C–H bonds must be related to a more pronounced electrophilic character, as shown by Eqs. 1 and 2. Unfortunately, a direct comparison between PINO and peroxyl radicals in hydrogen abstraction from substituted alkanes is prevented by the difficulty of having clean reactions with peroxyl radicals.

The effectiveness of the catalytic activity is not high with alkanes, as we have evaluated[1] the first order rate constant for self-decay of PINO radical to be $0.1\,s^{-1}$ at 25 °C, whereas the rate of hydrogen abstraction from cyclohexane by PINO is rather low ($0.047\,M^{-1}\,s^{-1}$ at 25 °C); thus a considerable amount of NHPI is consumed during the catalytic process. A higher effectiveness has been observed with more reactive substrates: benzyl alcohol[4,6] is 600 times more reactive than cyclohexane in hydrogen abstraction by PINO, while cumene[11] is 70 times more reactive than cyclohexane. This gives particular interest to the functionalisation of these substrates.[4,6,11]

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