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Kinetic Study of the Phthalimide *N*-Oxyl (PINO) Radical in Acetic Acid. Hydrogen Abstraction from C−H Bonds and Evaluation of O−H Bond Dissociation Energy of *N*-Hydroxyphthalimide

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The reactions of the phthalimide *N*-oxyl (PINO) radical with several hydrocarbons having different C−H bond dissociation energies (BDEs) were investigated in HOAc at 25 °C. The slope of the Evans−Polanyi plot is 0.38, which indicates that the reactions are mildly exothermic or almost thermoneutral. This finding is supported by the O−H BDE of *N*-hydroxyphthalimide (NHPI), 375 ± 10 kJ mol^{-1}, obtained by means of a thermodynamic cycle. The observed kinetic isotope effects (KIEs) are related to the reaction free-energy changes, which can be explained by a Marcus-type equation. The comparison of the PINO radical reactions with analogous hydrogen atom abstraction reactions of the dibromide radical implies that HBr$_2$• reactions are more exothermic than the PINO radical reactions. This factor is put forth to explain the different KIEs.

Introduction

Nitroxyl radicals are intriguing species that are used as electron paramagnetic resonance (EPR) spin traps, antioxidants, and catalysts for organic reactions.[1−3] In the past decade, nitroxyl-radical-catalyzed oxidation of alcohols has been popular;[4] however, most nitroxyl radicals are mild (selective) oxidants and do not oxidize organic compounds completely. These R$_2$NO• radicals are characterized by weak R$_2$NO−H bonds, and they do not undergo the reactions that are being studied here.

A remarkable catalytic reactivity of *N*-hydroxyphthalimide (NHPI) for the autoxidation of methyl arenes was discovered by Ishii, and a number of related NHPI-catalyzed reactions have since been reported.[5] In the catalytic systems, the phthalimide *N*-oxyl (PINO) radical, which is the one-electron oxidized form of NHPI, abstracts a hydrogen atom from hydrocarbons. These hydrogen abstraction processes are supported by the kinetic isotope effect (KIE).[6−8] Surprisingly, even cyclohexane, whose C−H bond dissociation energy (BDE) is 400 kJ mol^{-1}, can be oxidized to cyclohexanone and adipic acid by an NHPI/Co/Mn catalyst.[9] To understand the catalytic system, it is necessary to know the precise O−H BDE of NHPI. Minisci et al. reported a lower limit of the O−H BDE in NHPI (360 kJ mol^{-1}) and proposed detailed mechanisms for the oxidations of benzyl alcohols and *N*-alkylamides.[10,11]

Previously, we studied the reactions of the PINO radical with substituted toluenes, benzaldehydes, and benzyl alcohols.[6] In those reactions, the PINO radical abstracts a hydrogen atom from a C−H bond of hydrocarbon (RH). This step is followed by a radical recombination reaction of a carbon-centered radical (R•) with another PINO radical to form a radical adduct PINO−R, as shown in Scheme 1.

$$k_{\mathrm{obs}} = 2k_{\mathrm{PR}}[\mathrm{RH}] \tag{1}$$

SCHEME 1. Reaction Scheme for PINO• with Hydrocarbon

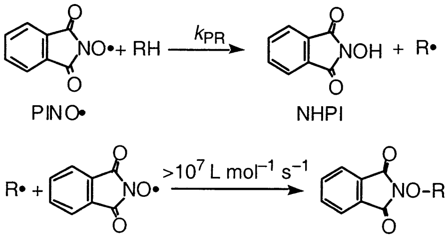
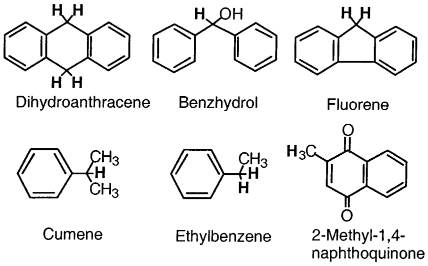


CHART 1. Substrates for Hydrogen Atom Abstraction Reactions



We confirmed, by ^{1}H NMR, that the particular adduct was formed in the reaction of PINO• with *p*-xylene.[6] We found remarkably large KIEs (k_H/k_D = 17−28), which implies that quantum mechanical tunneling operates in the PINO radical reactions. Here, we expand our studies into the reactions of PINO• with several hydrocarbons shown in Chart 1, which have a range of C−H BDEs.

We have estimated the O−H BDE of NHPI by a semiempirical equation, using a thermodynamic cycle.[12] Moreover, by measuring the KIEs for several hydrocarbons, it was revealed that the KIE values are related to the reaction free-energy changes. We shall also compare the reactivities of the PINO and HBr$_2$ radicals.

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TABLE 1: Rate Constants, k_{PR} per Active Hydrogen Atom, for the Reaction of the PINO Radical with Hydrocarbons in HOAc at 25 °C, and Their C−H Bond Dissociation Energies (BDEs)

entry	substrate	number of H atoms	BDE (kJ mol^{-1})	k_{PR} (per H) (L mol^{-1} s^{-1})
1	9,10-dihydroanthracene	4	315[a]	2510
2	benzhydrol	1	326[b]	57.5
3	Ph_3CH	1	339[c]	58.5
4	fluorene	2	339[d]	20.3
5	benzyl alcohol	2	340[e]	5.65[g]
6	Ph_2CH_2	2	351[c]	6.63
7	cumene	1	353[a]	26.6
8	1-methylnaphthalene	3	356[a]	1.43
9	ethylbenzene	2	357[a]	2.68
10	benzaldehyde	1	364[a]	10.6[g]
11	toluene	3	376[a]	0.207[g]
12	2-methyl-1,4-naphthoquinone	3	376[f]	0.0133
13	cyclohexane	12	400[a]	0.00193

[a] From ref 14. [b] From ref 15. [c] From ref 16. [d] From ref 17. [e] From ref 18. [f] From ref 19. [g] From ref 6.

Experimental Section

The general experimental procedure was described previously.[6] All the chemicals were commercially obtained and used without further purification. To study the KIEs, cyclohexane-d_{12} (99.6% D), ethylbenzene-d_{10} (99+% D), and fluorene-d_{10} (98% D) were purchased from Aldrich and used as received. Benzhydrol-*d* was synthesized by following a literature method,[13] and ^{1}H NMR spectroscopy was used to confirm that 99.8% of benzhydrol was Ph_2CDOH. The rate constants were measured in HOAc at 25.0 ± 0.1 °C under an argon atmosphere by UV−Vis spectrophotometers (models UV-3101 and 2501, Shimadzu) and a stopped-flow spectrophotometer (model RMS 1000, OLIS).

To measure the oxidation potential of NHPI, dimethyl sulfoxide (DMSO, 99.9%, Aldrich) and tetrabutylammonium hexafluorophosphate (electrochemical grade, Fluka) were used as received. For cyclic voltammetry, a computer-controlled potentiostat/galvanostat (model 263A, EG&G Princeton Applied Research) was used with a platinum working electrode, a platinum wire counter electrode, and a $Ag/AgNO_3$ reference electrode (0.01 mol L^{-1} of $Ag/AgNO_3$ and 0.1 mol L^{-1} of Bu_4NPF_6 in acetonitrile). The cyclic voltammograms were recorded at room temperature.

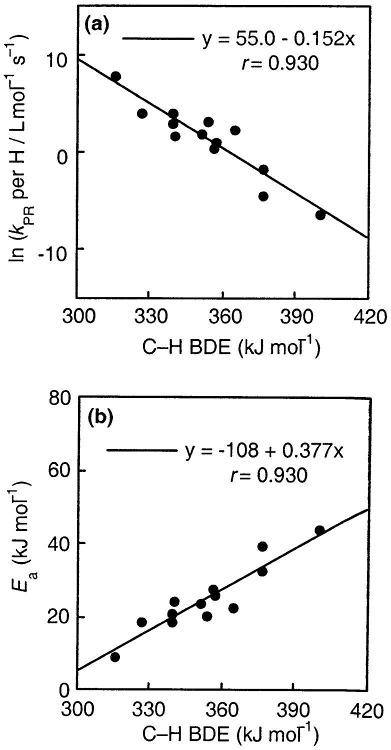


Figure 1. (a) Plot of ln(k_{PR} per hydrogen atom) against the C−H bold dissociation energies (BDEs) for the reaction of the PINO radical with hydrocarbons in HOAc at 25 °C. (b) Evans−Polanyi plot (see text for details).

Results and Discussion

Rate Constants versus C−H Bond Dissociation Energies. To investigate the reactivity of PINO• more in detail, the rate constants for its reactions with various hydrocarbons that have different C−H BDEs were measured. Table 1 lists the obtained rate constants per reactive hydrogen atom. One can see that the k_{PR} values (per H) decrease as the C−H BDEs increase.

Figure 1a presents a plot of ln(k_{PR} per H) against the C−H BDE, and there is a good correlation between the rate constants and the BDEs, which indicates that the activation energies for the reaction are related to the C−H BDEs of hydrocarbons. Evans and Polanyi proposed a linear correlation of reaction activation energies with reaction enthalpy changes in hydrogen abstraction reactions.[20−23]

$$E_a = \alpha \Delta H^\circ + \text{constant} \qquad (2)$$

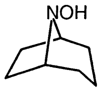
According to Evans and Polanyi, the magnitude of the slope decreases as the reaction exothermicity increases. Therefore, when the reaction is exothermic, the slope, α, approaches zero. In contrast, when the reaction is endothermic, α approaches a value of 1; when the reaction is thermoneutral, the value of α is close to 0.5. A plot of E_a against BDE is shown in Figure 1b by assuming that the pre-exponential factors of these reactions are constant. Because k_{PR} (per hydrogen atom) = $A \exp[-E_a/(RT)]$, if we assume that A is constant ($A = 1 \times 10^5$ L mol^{-1} s^{-1}),[24] eq 2 can be rewritten as eq 3:

$$\ln(k_{PR} \text{ per H}) = \frac{-1000\alpha\Delta H^\circ(\text{kJ mol}^{-1})}{RT} + \text{constant} \qquad (3)$$

From either Figure 1a or b, α is 0.38 ± 0.05, inferring that the reactions of PINO• with the hydrocarbons listed in Table 1 are mildly exothermic or almost thermoneutral.

The O−H BDE of NHPI. To establish whether the reactions of PINO• with the previously described hydrocarbons are exothermic or not, we must know the O−H BDE of NHPI. Unfortunately, the precise BDE of NHPI has not been reported;[25]

TABLE 2: Bond Dissociation Energies (BDEs) of O−H Bonds in Hydroxylamines and Oximes in Dimethyl Sulfoxide (DMSO)[a]

	pK_{HA}	$E_{ox}(A^-)$ (V vs Fc^+/Fc)	BDE ($kJ\ mol^{-1}$)
NHPI	12.9[b]	−0.079[c]	373[c]
		−0.047[d]	376[d]
t-Bu(*i*-Pr)C═NOH	25.5	−0.965	360
t-Bu_2C═NOH	24.4	−1.035	347
(PhCO)(*i*-Pr)NOH	18.7	−0.769	340
(PhCO)(*t*-Bu)NOH	19.6	−0.879	334
	32.4	−1.764	322
Et_2NOH	29.6	−1.645	318
TEMPOH	31.0	−1.997	292
t-Bu_2NOH	31.1	−2.070	285

[a] From ref 12. [b] From ref 26. [c] From this work (1 mmol L^{-1} NHPI). [d] From this work (2 mmol L^{-1} NHPI).

however, it is suggested that the BDE would be larger than 360 kJ mol^{-1}.[10] Furthermore, we estimated the BDE using eq 4.[12]

$$\text{Bond dissociation energy (kJ mol}^{-1}) = 5.73pK_{HA} + 96.5E_{ox}(A^-) + 307 \quad (4)$$

Here, pK_{HA} are the acid dissociation constants of the acids in DMSO, and $E_{ox}(A^-)$ are the oxidation potentials (in volts, versus ferrocenium/ferrocene) of their conjugate bases in DMSO. Fortunately, the pK_{HA} value of NHPI in DMSO is reported as 12.9;[26] however, the oxidation potential of NHPI in DMSO was not reported. Therefore, we measured the oxidation potential in DMSO by cyclic voltammetry (see Figure S1 in the Supplemental Information). Although reversible oxidation−reduction waves are reported in acetonitrile with bases such as pyridine,[8,27] the cyclic voltammogram in DMSO was not reversible, probably because of the lessened stability of the PINO radical in DMSO. One can see clear oxidation waves in Figure S1; however, the oxidation waves were sensitive to the experimental condition. The peak potentials of oxidation were different from each other: −0.079 V (1 mmol L^{-1}) and −0.047 V (2 mmol L^{-1}). We attempted to measure the oxidation potential with 3 mmol L^{-1} of NHPI; however, the cyclic voltammogram broadened and the oxidation peak became unclear. Table 2 shows the obtained oxidation potentials and calculated BDEs from eq 4. The oxidation potential of 1 mmol L^{-1} NHPI gave a BDE value of 373 kJ mol^{-1}, and that of 2 mmol L^{-1} NHPI gave a BDE value of 376 kJ mol^{-1}. We propose the O−H BDE of NHPI to be 375 ± 10 kJ mol^{-1}, considering experimental error. This value is the highest value for any of the hydroxylamines listed in Table 2. Such a high BDE of NHPI is adequate to explain the Evans−Polanyi plot's result: the reactions of the PINO radical with the hydrocarbons in Table 1 are, indeed, mildly exothermic or thermoneutral.

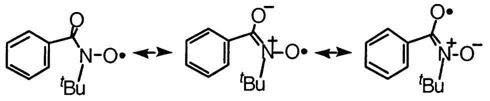
Very recently, Pedulli et al. reported the O−H BDE of NHPI to be 369 kJ mol^{-1}, which was measured in *t*-BuOH.[28] Their value is slightly smaller than our value (375 ± 10 kJ mol^{-1}). Generally speaking, hydroxyl groups tend to form hydrogen bonds with polar solvents. Such hydrogen bonds could lead to a higher O−H BDE than that in a nonpolar solvent.[12] Although two values for the BDE of NHPI were obtained by different methods in different solvents, the difference between our value (375 kJ mol^{-1}) and Pedulli's value (369 kJ mol^{-1}) is only 6 kJ mol^{-1}, which is quite good agreement.[29]

One can notice that a hyperfine coupling constant, a_N, of the PINO radical (4.23 G) is quite small, in comparison with that of other nitroxyl radicals.[30−32] The π-spin density, ρ_N, at nitrogen can be calculated by eq 5:[33]

$$\rho_N = \frac{a_N\ (G)}{33.1\ G} \quad (5)$$

Table 3 shows the reported hyperfine coupling constants and calculated spin density of selected nitroxyl radicals, rate constants of hydrogen abstraction reactions, and BDEs of the corresponding hydroxylamines.

In Table 3, the ρ_N value of the PINO radical is 0.13, which is fairly small, compared to that of other nitroxyl radicals. Jenkins et al. proposed that *lone-pair delocalization from nitroxide nitrogen would tend to fix the unpaired electron on oxygen.*[38] Therefore, if the two acyl groups of NHPI withdraw electron density from the nitrogen atom and fix the unpaired electron on an oxygen atom (N−O•), this would strengthen the O−H bond of NHPI. However, if the unpaired electron exists principally on the carbonyl oxygen (structure III), we also must consider the π-spin density on the oxygen. As we can see in Table 3, the estimated ρ_N value of (PhCO)(*t*-Bu)NO• is 0.24, which is smaller than that of $(CF_3)_2NO$• ($\rho_N = 0.28$). Although one might expect the BDE of (PhCO)(*t*-Bu)NOH to be larger than that of $(CF_3)_2NOH$, the actual BDE of PhCON(*t*-Bu)OH (323 kJ mol^{-1}) is smaller than that of $(CF_3)_2NOH$ (346 kJ mol^{-1}), which is reflected in the difference of the rate constants for hydrogen abstraction reactions from toluene. Jenkins et al. measured the π-spin density on oxygen in ^{17}O-labeled (PhCO)-(*t*-Bu)NO• and found that 12% of the π-spin exists on the carbonyl oxygen.[38,40] We are not sure how much π-spin exits on the carbonyl oxygen of the PINO radical. However, the two acyl groups of PINO• would delocalize the nitrogen lone pair to a greater extent than on the (PhCO)(*t*-Bu)NO•. Such delocalization might fix the unpaired electron on oxygen in N−O, making the O−H bond of NHPI stronger. Indeed, the rate constant for the reaction of the PINO radical with toluene is faster than that of (PhCO)(*t*-Bu)NO•, by a factor of 10^6.



I II III

Kinetic Isotope Effect versus Reaction Free-Energy Change. The reactions of the PINO radical with toluene, benzaldehyde, and benzyl alcohol show KIEs of 27.1, 27.5, and 16.9, respectively, in HOAc at 25 °C.[6] We proposed that quantum mechanical tunneling takes part in the PINO radical reactions. However, these KIEs are substantially larger than Masui's value for benzhydrol ($k_H/k_D = 10.6$ at 25 °C in acetonitrile). We measured the KIE for benzhydrol in HOAc and obtained $k_H/k_D = 11.8$, as listed in Table 4. This value is smaller than the KIE values for toluene, benzaldehyde, and benzyl alcohol but still lies outside the maximum for normal hydrogen abstraction reactions. Therefore, we explored the KIEs for several hydrocarbons that have different C−H BDEs. As shown in Table 4, the KIE values obtained for fluorene and ethylbenzene were 13.3 and 21.6, respectively. It seems that the value of KIE increases as the C−H BDE increases. However, the KIE value of cyclohexane was 24.0, which is clearly smaller than those of toluene and benzaldehyde. Figure 2 shows a plot of $\ln(k_H/k_D)$ against C−H BDE.

In hydrogen abstraction reactions, the KIE value passes through a maximum when the transition state is symmetric: the

TABLE 3: Hyperfine Coupling Constants and Spin Densities of Nitroxyl Radicals, Rate Constants of Hydrogen Abstraction Reactions, and O−H Bond Dissociation Energies (BDEs) of the Corresponding Hydroxylamines

nitroxyl radical	a_N (G)	ρ_N	$2k_{PR}$ (L mol^{-1} s^{-1})	O−H BDE (kJ mol^{-1})
PINO•	4.23[a]	0.13	1.2 (toluene at 25 °C)[e]	375[h]
$(CF_3)_2NO$•	9.4[b]	0.28	1.8×10^{-2} (toluene at 25 °C)[b]	346[b]
(PhCO)(*t*-Bu)NO•	7.95[c]	0.24	2.9×10^{-7} (toluene at 75 °C)[f]	323[i]
TEMPO•	15.4[d]	0.47	9.4×10^{-5} (*p*-xylene at 135 °C)[g]	291[j]

[a] From ref 30. [b] From ref 34. [c] From ref 32. [d] From ref 35. [e] From ref 6. [f] From ref 36. [g] From ref 37. [h] From this work. [i] From ref 38. [j] From ref 39.

TABLE 4: Kinetic Isotope Effect for the Reaction of the PINO Radical with Hydrocarbons in HOAc at 25 °C

	BDE[a] (kJ mol^{-1})	k_H[b] (L mol^{-1} s^{-1})	k_D[b] (L mol^{-1} s^{-1})	k_H/k_D
benzhydrol	326	57.5	4.87	11.8
fluorene	330	20.3	1.53	13.3
benzyl alcohol[c]	340	5.65	0.335	16.9
ethylbenzene	357	2.68	0.124	21.6
benzaldehyde[c]	364	10.6	0.386	27.5
toluene[c]	376	0.207	7.63×10^{-3}	27.1
cyclohexane	400	1.93×10^{-3}	8.04×10^{-5}	24.0

[a] See Table 1. [b] k_H and k_D = k_{PR} per hydrogen atom in Scheme 1. [c] From ref 6.

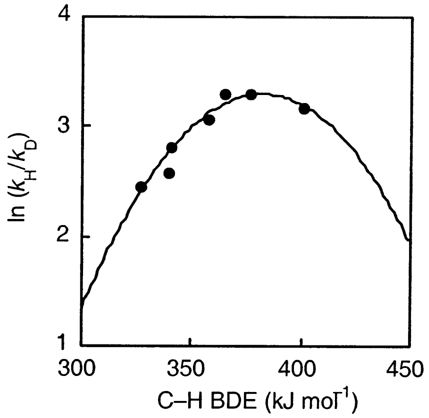


Figure 2. Plot of ln(k_H/k_D) against C−H BDE for the reactions of the PINO radical with hydrocarbons in HOAc at 25 °C.

reaction is thermoneutral. A quantitative relationship between the isotope effect and the reaction free-energy change can be expressed by a Marcus-type equation:[41]

$$\ln\left(\frac{k_H}{k_D}\right)_{obs} = \ln\left(\frac{k_H}{k_D}\right)_{max}\left[1 - \left(\frac{\Delta G_R{}^\circ}{4\Delta G_0{}^\ddagger}\right)^2\right] \qquad (6)$$

Here, $\Delta G_R{}^\circ$ is the reaction free-energy change and $\Delta G_0{}^\ddagger$ is the intrinsic energy barrier of the reaction. Therefore, an observed KIE has a maximum when $\Delta G_R{}^\circ = 0$. In Figure 2, it seems that ln(k_H/k_D) reaches a maximum around at ~360−390 kJ mol^{-1}, considering the experimental error. The obtained O−H BDE of NHPI is 375 ± 10 kJ mol^{-1}, and it is quite reasonable that the reaction of the PINO radical with toluene or benzaldehyde has the maximum KIE.

Reactivity of the PINO Radical, Versus That of HBr$_2$ Radical. We have previously studied the reaction of HBr$_2$• with various methyl arenes in HOAc.[42]

$$\text{HBr}_2\bullet + \text{RH} \xrightarrow[+\text{H}^+]{k_{\text{dibromide}}} 2\text{HBr}_2\bullet + \text{R}\bullet$$

$$\text{PINO}\bullet + \text{RH} \xrightarrow{k_{\text{PR}}} \text{NHPI} + \text{R}\bullet$$

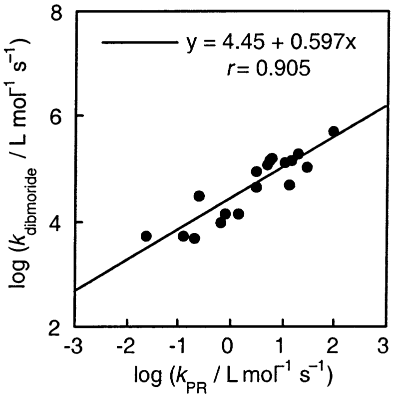
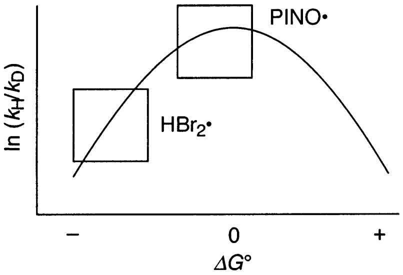


Figure 3. Comparison of the PINO radical reaction with HBr$_2$ radical reaction in HOAc.

CHART 2. Dependence of KIE on ΔG°



To compare the reactivity of PINO• with that of HBr$_2$•, we plotted the rate constants of HBr$_2$• reactions with several methyl arenes against those of the PINO• reactions, as shown in Figure 3. (The rate constants themselves are listed in Table S1 in the Supplemental Information.)

Even though the HBr$_2$• reactions are much faster than the PINO• reactions, a good correlation was obtained between the two. The slope of the line in Figure 3 is 0.60 ± 0.07, which is consistent with the reactivity of HBr$_2$• being higher than that of PINO•: the more reactive species is the less selective (the reactivity−selectivity principle).[43] Moreover, this finding indicates that the reactions of HBr$_2$• are more exothermic than the PINO• reactions. If we take the pre-exponential factors of HBr$_2$• reactions as being constant, the α value in eq 2 for HBr$_2$• reactions can be obtained as 0.23 ± 0.04 (0.38 × 0.60 = 0.23), which indicates that the reactions of HBr$_2$• are quite exothermic. This is to be expected, given the oxidizing strength of the HBr$_2$ radical. Considering the difference of redox potentials between PINO•/NHPI and $Br_2{}^{\bullet-}/2Br^-$,[27,44] the reaction free-energy changes of the HBr$_2$• reactions must be more negative than those of the PINO• reactions. Such high exothermicities of the HBr$_2$• reactions might explain why the KIE values for HBr$_2$• reaction fall in the normal range, k_H/k_D = 5.3−8.5.[42] Large negative values of $\Delta G_R{}^\circ$ make ln(k_H/k_D)$_{obs}$ smaller than ln(k_H/k_D)$_{max}$ in eq 6. This phenomenon is illustrated in Chart 2. Moreover, larger reaction free-energy changes are unfavorable for the hydrogen tunneling, because the transition state is not symmetric.

Conclusions

Hydrogen abstraction by the phthalimide *N*-oxyl (PINO) radical from various hydrocarbons was investigated kinetically in HOAc. The slope of the Evans−Polanyi plot was 0.38, which implies that the reactions of the PINO radical with hydrocarbons (C−H bond dissociation energies of 315−400 kJ mol^{-1}) are mildly exothermic to thermoneutral. By applying an equation based on a thermodynamic cycle that uses a newly measured oxidation potential, the O−H BDE of NHPI was determined to be 375 ± 10 kJ mol^{-1}, which is the highest value known for a hydroxylamine. Moreover, the dependence of the KIEs on the C−H BDEs reaches its maximum at ∼360−390 kJ mol^{-1}. Considering the magnitude of the KIEs, it is reasonable that the maximum effect was obtained when the reaction free-energy change was close to zero. The value obtained for the O−H BDE of NHPI aids in understanding the catalytic system. Further kinetic studies in the presence of air or an O_2 atmosphere, combined with kinetic simulation studies, will provide a greater understanding of the NHPI catalytic system.

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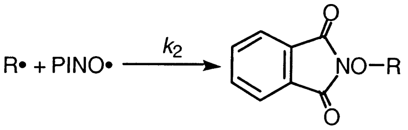
Supporting Information Available: The second-order rate constants for reactions of PINO• or HBr_2• with selected methyl aromatic compounds, the cyclic voltammograms of NHPI in DMSO, and an additional plot of kinetic data for the reaction of PINO• with cyclohexane (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Appendix

In this paper, we estimated the O−H BDE of NHPI to be 375 ± 10 kJ mol^{-1}. The BDE is smaller than C−H BDE of cyclohexane (400 kJ mol^{-1}). Therefore, reaction A1 is slightly endothermic, which means the equilibrium constant of reaction A1 must be <1. In that case, the carbon-centered radical (R•) might react with NHPI instead of another PINO•, and the kinetic trace would then not follow the pseudo-first-order kinetics.

$$\mathrm{PINO\bullet} + \mathrm{RH} \underset{k_{-1}}{\overset{k_1 = k_{\mathrm{PR}}}{\rightleftharpoons}} \mathrm{NHPI} + \mathrm{R\bullet} \qquad \text{(A1)}$$



(A2)

Generally, the rate equation of reactions A1 and A2 can be expressed by eq A3, using the steady-state approximation.

$$\mathrm{rate} = \frac{k_1[\mathrm{PINO\bullet}][\mathrm{RH}]}{1 + \left(\dfrac{k_{-1}[\mathrm{NHPI}]}{k_2[\mathrm{PINO\bullet}]}\right)} \qquad \text{(A3)}$$

We investigated the reaction of the PINO radical with cyclohexane in the presence of excess NHPI (up to 20 mmol L^{-1}), as shown in Figure S2 of the Supplemental Information. Each kinetic trace still followed an excellent first-order fitting, and the obtained pseudo-first-order rate constants were not affected by the concentration of NHPI. Therefore, the second term of the denominator in eq A3 must be smaller than 1 (for example, <0.1).

$$\frac{k_{-1}[\mathrm{NHPI}]}{k_2[\mathrm{PINO\bullet}]} < 0.1 \qquad \text{(A4)}$$

This inequality must hold even under extreme conditions, such as [NHPI] = 20 mmol L^{-1}. The lower limit of k_{-1} can be estimated using [PINO•] = 0.2 mmol L^{-1} and $k_2 = 1 \times 10^7$ L mol^{-1} s^{-1}.[6]

$$k_{-1} < 1 \times 10^4\ \mathrm{L\ mol^{-1}\ s^{-1}} \qquad \text{(A5)}$$

From the data in Figure S2, $k_1 = 0.023$ L mol^{-1} s^{-1} (= k_{obs}/2[cyclohexane]). Therefore, the equilibrium constant of reaction 1 must be larger than 2.3 × 10^{-6}.

$$K_1 > 2.3 \times 10^{-6} \qquad \text{(A6)}$$

This value leads to an upper limit of the reaction free-energy change for the reaction of the PINO radical with cyclohexane.

$$\Delta G^\circ < 32\ \mathrm{kJ\ mol^{-1}} \qquad \text{(at 25 °C)} \qquad \text{(A7)}$$

This is the upper limit for the reaction of the PINO radical with cyclohexane to correspond with the kinetic data. As we saw, the BDEs of NHPI and cyclohexane are 375 and 400 kJ mol^{-1}, respectively. Therefore, the reaction enthalpy change is 25 kJ mol^{-1}.

$$\Delta H^\circ\ (\approx \Delta G^\circ) = 25\ \mathrm{kJ\ mol^{-1}} \qquad \text{(A8)}$$

If the reaction entropy change can be ignored because so little structural change occurs, the reaction free-energy change for the reaction of PINO• with cyclohexane is 25 kJ mol^{-1}, which is smaller than the requirement (32 kJ mol^{-1}) in eq A7.

References and Notes

(1) Denisov, E. T.; Denisova, T. G. *Handbook of Antioxidants*, 2nd ed.; CRC Press: Boca Raton, FL, 2000.

(2) Volodarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic Chemistry of Stable Nitoxides*; CRC Press: Boca Raton, FL, 1994.

(3) Rozantsev, E. G. *Free Nitroxyl Radicals*; Plenum Press: New York, 1970.

(4) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174 and references therein.

(5) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393−427.

(6) Koshino, N.; Saha, B.; Espenson, J. H. Submitted.

(7) Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520−4526.

(8) Ueda, C.; Noyama, M.; Ohmori, H.; Masui, M. *Chem. Pharm. Bull.* **1987**, *35*, 1372−1377.

(9) Iwahama, T.; Syojyo, K.; Sakaguchi, S.; Ishii, Y. *Org. Process Res. Dev.* **1998**, *2*, 255−260.

(10) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 688−689.

(11) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671−2676.

(12) Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 10819−10823.

(13) Jones, G. I.; Mouli, N.; Haney, W. A.; Bergmark, W. R. *J. Am. Chem. Soc.* **1997**, *119*, 8788−8794.

(14) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 81st ed.; CRC Press: Boca Raton, FL, 2000.

(15) Rothberg, L. J.; Simon, J. D.; Bernstein, M.; Peters, K. S. *J. Am. Chem. Soc.* **1983**, *105*, 3464−3468.

(16) Parker, V. D. *J. Am. Chem. Soc.* **1992**, *114*, 7458−7462.

(17) Arends, L. W. C. E.; Mulder, P.; Clark, K. B.; Wayner, D. D. M. *J. Phys. Chem.* **1995**, *99*, 8182−8189.

(18) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

(19) Finkelshtein, E. I. *J. Phys. Org. Chem.* **2001**, *14*, 543−550.

(20) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11−29.

(21) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973.

(22) Gardner, K. A.; Kuehnert, L. L.; Mayer, J. M. *Inorg. Chem.* **1997**, *36*, 2069−2078.

(23) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190−5196.

(24) The Arrhenius plot (ln k_{PR} per hydrogen atom) for the PINO• reactions gives the following pre-exponential factors: 8.9×10^4 L mol^{-1} s^{-1} (*p*-xylene) and 2.9×10^5 L mol^{-1} s^{-1} (toluene). Data in ref 6 were used for the calculation.

(25) After this manuscript was submitted, Pedulli et al. reported their work in ref 28.

(26) Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L.; Ragnarsson, U. *J. Chem. Res., Synop.* **1993**, 446−447.

(27) Gorgy, K.; Lepretre, J.-C.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.-L. *Electrochim. Acta* **1998**, *44*, 385−393.

(28) Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747−1754.

(29) Pedulli et al. estimated the BDE as 364 kJ mol^{-1} in non-hydrogen bond acceptor solvents in ref 28.

(30) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810−6813.

(31) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 3094−3098.

(32) Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc., Chem. Commun.* **1975**, 880−881.

(33) Chatgilialogu, C.; Malatesta, V.; Ingold, K. U. *J. Phys. Chem.* **1980**, *84*, 3597−3599.

(34) Doba, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 3958−3963.

(35) Kreilick, R. W. *J. Phys. Chem.* **1967**, *46*, 4260−4264.

(36) Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2803−2808.

(37) Opeida, I. A.; Matvienko, A. G.; Ostrovskaya, O. Z. *Kinet. Catal.* **1995**, *36*, 480.

(38) Jenkins, T. C.; Perkins, M. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 717−720.

(39) Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 8610−8614.

(40) Jenkins, T. C.; Perkins, M. J.; Terem, B. *Tetrahedron Lett.* **1978**, 2925−2926.

(41) Cleland, W. W.; O'Leary, M. H.; Northrop, D. B. *Isotope Effects on Enzyme-Catalyzed Reactions*; University Park Press: Baltimore, MD, 1977.

(42) Metelski, P. D.; Espenson, J. H. *J. Phys. Chem. A* **2001**, *105*, 5881−5884.

(43) Pross, A. *Theoretical and Physical Principles of Organic Reactivity*; Wiley: New York, 1995.

(44) Stanbury, D. M. *Adv. Inorg. Chem.* **1989**, *33*, 69−137.