Alkane Oxidation with Molecular Oxygen Using a New Efficient Catalytic System: *N*-Hydroxyphthalimide (NHPI) Combined with Co(acac)$_n$ (*n* = 2 or 3)[†]

Yasutaka Ishii,* Takahiro Iwahama, Satoshi Sakaguchi, Kouichi Nakayama, and Yutaka Nishiyama

Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564, Japan

A novel class of catalysts for alkane oxidation with molecular oxygen was examined. *N*-Hydroxyphthalimide (NHPI) combined with Co(acac)$_n$ (*n* = 2 or 3) was found to be an efficient catalytic system for the aerobic oxidation of cycloalkanes and alkylbenzenes under mild conditions. Cycloalkanes were successfully oxidized with molecular oxygen in the presence of a catalytic amount of NHPI and Co(acac)$_2$ in acetic acid at 100 °C to give the corresponding cycloalkanones and dicarboxylic acids. Alkylbenzenes were also oxidized with dioxygen using this catalytic system. For example, toluene was converted into benzoic acid in excellent yield under these conditions. Ethyl- and butylbenzenes were selectively oxidized at their α-positions to form the corresponding ketones, acetophenone, and 1-phenyl-1-butanone, respectively, in good yields. A key intermediate in this oxidation is believed to be the phthalimide *N*-oxyl radical generated from NHPI and molecular oxygen using a Co(II) species. The isotope effect (k_H/k_D) in the oxidation of ethylbenzene and ethylbenzene-d_{10} with dioxygen using NHPI/Co(acac)$_2$ was 3.8.

Introduction

Oxidative catalytic transformations of organic compounds with molecular oxygen (dioxygen) play a very important role in organic synthesis.[1] In particular, selective catalytic oxidation using dioxygen as the primary oxidant represents a critical technology and is an area of continued research and development. Several transition metal-catalyzed selective oxidations of alkanes involving the combined use of dioxygen and reducing agents such as H$_2$,[2] NaBH$_4$,[3] RCHO,[4] etc., have been reported. Recently, halogenated metalloporphyrins have been shown to be efficient catalysts for the direct reaction of alkanes with dioxygen without coreductants or stoichiometric oxidants to give alcohols and/or carbonyl compounds.[5] However, the development of an aerobic oxidation system in the absence of a reducing agent remains a very important and challenging subject in oxidation chemistry.

N-Hydroxyphthalimide (NHPI) was first used by Masui *et al.* as an efficient electron carrier in the electrochemical oxidation of secondary alcohols to ketones.[6] In the course of our study on the aerobic oxidation of benzylic compounds catalyzed by vanadomolybdophosphates,[7] we found that NHPI is a unique catalyst for the activation of molecular oxygen, as well as for the oxygenation of benzylic compounds such as fluorene[8] and the dehydrogenation of alcohols[9] with dioxygen under mild conditions. However, it is difficult to oxidize alkanes such as cyclohexane and toluene using NHPI alone.

We recently found that the catalytic activity of NHPI is markedly enhanced by the presence of a very small amount of Co(acac)$_n$ (*n* = 2 or 3) (0.05 equiv with respect to NHPI) as a cocatalyst. Thus, cycloalkanes and alkylbenzenes can be efficiently oxidized to the corresponding carbonyl compounds in an oxygen atmosphere under moderate conditions. This report presents our findings on the catalysis of alkane oxidations with atmospheric oxygen using NHPI combined with Co(acac)$_n$ (*n* = 2 or 3).

Results

1. Oxidation of Cycloalkanes with Dioxygen Using NHPI Combined with Transition Metals. The oxidation of cyclohexane (**1**) to a cyclohexanone (**2**)/

[†] Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (b) Hill, C. L. *Activation and Functionalization of Alkanes*; Academic Press: New York, 1989. (c) Simandi, L. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer Academic Publisher: Boston, 1992. (d) *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*; Barton, D. H. R., Martell, A. E., Sawyer, D. T., Eds.; Plenum Press: New York, 1993. (e) Mennier, B. *Chem. Rev.* **1992,** *92,* 1411. (f) Busch, D. H.; Alcock, N. W. *Ibid.* **1994,** *94,* 585.

(2) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1981,** *103,* 7371.

(3) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1979,** *101,* 6456.

(4) (a) Kaneda, K.; Haruna, S.; Imanaka, T.; Kawamoto, K. *J. Chem. Soc., Chem. Commun.* **1990,** 1467. (b) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991,** 1. (c) Murahashi, S.-I.; Oda, Y.; Naota, T. *J. Am. Chem. Soc.* **1992,** *114,* 7913. (d) Mukaiyama, T. Yamada, T. *Bull. Chem. Soc. Jpn.* **1995,** *68,* 17. (e) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1993,** *58,* 6421.

(5) (a) Lyons, J. E.; Ellis, P. E., Jr. *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Dekker: New York, 1994; p 291, and references cited therein. (b) Ellis, P. E., Jr.; Lyons, J. E. *J. Chem. Soc., Chem. Commun.* **1989,** 1188. (c) Ellis, P. E., Jr.; Lyons, J. E. *J. Chem. Soc., Chem. Commun.* **1989,** 1190. (d) Ellis, P. E., Jr.; Lyons, J. E. *J. Chem. Soc., Chem. Commun.* **1989,** 1316. (e) Ellis, P. E., Jr.; Lyons, J. E. *Catal. Lett.* **1989,** *3,* 389. (f) Lyons, J. E.; Ellis, P. E., Jr. *Catal. Lett.* **1991,** *8,* 45. (g) Ellis, P. E., Jr.; Lyons, J. E. *Coord. Chem. Rev.* **1990,** *105,* 181. (h) Lyons, J. E.; Ellis, P. E., Jr.; Durante, V. A. *Studies in Surface Science and Catalysis*; Grasselli, R. Ed.; Elsevier: New York, 1991; Vol. 67, p 99. (i) Ellis, P. E., Jr.; Lyons, J. E. *Prepr. Am. Chem. Soc., Div. Pet. Chem.* **1990,** *35,* 174. (j) Lyons, J. E.; Ellis, P. E., Jr.; Wagner, R. W.; Thompson, P. B.; Gray, H. B.; Hughes, M. E.; Hodge, J. A. *Prepr. Am. Chem. Soc., Div. Pet. Chem.* **1992,** *37,* 307.

(6) (a) Masui, M.; Ueshima, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1983,** 479. (b) Masui, M.; Hara, S.;Ueshima, T.; Ozaki, S. *Chem. Pharm. Bull.* **1987,** *31,* 4209.

(7) (a) Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1993,** *58,* 6421. (b) Nakayama, K.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Chem. Lett.* **1993,** 1699. (c) Fujibayashi, S.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. *Chem. Lett.* **1994,** 1345.

(8) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahama, T.; Nishiyama, Y. *J. Org. Chem.* **1995,** *60,* 3934.

(9) Iwahama, T.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1995,** in press.
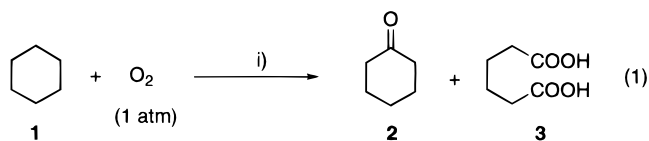
i) NHPI (10 mol%), Co(acac)$_2$ (0.5 mol%), CH$_3$COOH, 100 °C, 6 h

cyclohexanol (**4**) mixture (ketone/alcohol (K/A) oil) is the first step in the two-step process for the production of adipic acid (**3**). Although there are several variants of this oxidation, the principal method is the autoxidation of cyclohexane in the presence of a metal catalyst such as Co or Mn salt.[10,11] An alternative cyclohexane oxidation uses a higher concentration of Co(III) acetate under oxygen pressure (20−30 atm).[12] However, the homogeneous catalytic oxidations of **1** using these methods have several problems, e.g., oxidative attack on the C−H bonds is slow and requires vigorous reaction conditions. To overcome these limitations, a new catalyst for selective oxidation with dioxygen must be identified. Hence, the catalytic oxidation of **1** with atmospheric oxygen under mild conditions is a challenge in industrial catalysis.

The oxidation of **1** with dioxygen (1 atm) using a new catalyst, NHPI, under selected conditions is shown in Table 1. Although a benzylic compound such as fluorene was efficiently oxidized to fluorenone in high yield (80%) with molecular oxygen (1 atm) in the presence of NHPI (10 mol %) in benzonitrile at 100 °C,[8] **1** was not oxidized by NHPI alone under these conditions. Thus, the effects of several transition metal salts on the NHPI-catalyzed oxidation of **1** in a dioxygen atmosphere were examined. An initial survey of representative transition metals demonstrated that a very small amounts of cobalt salts such as Co(acac)$_n$ (n = 2 or 3) significantly facilitated the NHPI-catalyzed aerobic oxidation of **1** under moderate conditions. For example, the oxidation of **1** in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in acetic acid at 100 °C for 6 h (standard conditions) gave cyclohexanone **2** (32%) and adipic acid **3** (38%) as the main products in the 45% conversion of **1** (run 3).[13] Oxidation did not take place in the absence of NHPI under these conditions (run 2). When Co(acac)$_3$ was used in place of Co(acac)$_2$ in this oxidation, **1** was converted to **2** and **3** at a slightly lower conversion (42%) (run 4). Similar effects of Co(acac)$_2$ and Co(acac)$_3$ on the oxidation of **1** were also observed at 75 °C (runs 6 and 7). Oxidation was considerably retarded by the use of acetonitrile as a solvent, while the selectivity of **1** to **2** at 75 °C was improved from 52% to 78% (run 8). Oxidation using Co(OAc)$_2$·4H$_2$O as a cocatalyst was similar to that with Co(acac)$_2$ (run 11). Mn(acac)$_3$, which is often used as a catalyst for autoxidation, was also effective in this oxidation. It is interesting to note that the addition of Mn(acac)$_3$ led to **3** rather than **2** in high selectivity (77%). This oxidation was slightly enhanced by adding Cu-(OAc)$_2$·H$_2$O. In contrast to the effect of Co and Mn salts

(10) Parshall, G, W.; Ittel. S, D. *Homogeous Catalysis*; 2nd ed.; John Wiley and Sons: New York, 1992; p 246, and reference cited therein.

(11) Simandi, L. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer Academic Publisher: Boston, 1992; p 84, and reference cited therein.

(12) (a) Steeman, J. W. M.; Kaarsemaker, S.; Hoftyzer, P. *J. Chem. Eng. Sci.* **1961**, *14*, 139. (b) Miller, S. A. *Chem. Process Eng. (London)* **1969**, *50*, 63. (c) Tanaka, K. *Chem. Tech.* **1974**, 555, and references cited therein.

(13) By the GC-MS measurement of the reaction product of **1**, the formation of glutaric acid (up to 5%) and cyclohexyl acetate (up to 2%) other than **2** and **3** was confirmed.

Table 1. Oxidation of Cyclohexane (1) with Dioxygen Catalyzed by NHPI in the Presence of Metal Salts under Various Reaction Conditions^a

run	NHPI (mol %)	transition metal	temp (°C)	conv (%)	yield, %^{b} 2	3^c
1	10	−	100	1	trace	0
2	−	Co(acac)$_2$	100	trace	trace	0
3	10	Co(acac)$_2$	100	45	32	38
4	10	Co(acac)$_3$	100	42	35	40
5	5	Co(acac)$_2$	100	28	41	37
6	10	Co(acac)$_2$	75	30	48	30
7	10	Co(acac)$_3$	75	22	52	37
8^d	10	Co(acac)$_3$	75	13	78	13
9^e	10	Co(acac)$_2$	100	48	37	39
10^f	10	Co(acac)$_2$	100	38	38	48
11	10	Co(OAc)$_2$·4H$_2$O	100	43	31	44
12	10	Mn(acac)$_3$	100	44	3	77
13	10	Cu(OAc)$_2$·H$_2$O	100	21	43	29
14	10	Fe(acac)$_3$	100	5	90	trace
15	10	Ni(acac)$_2$	100	0	−	−

^{a} **1** (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI and transition metal (0.5 mol%) in acetic acid (12.5 mL) for 6 h. ^{b} Based on **1** reacted. ^{c} Yield of dimethyl adipate after esterification with excess methanol. ^{d} Acetonitrile was used as solvent. ^{e} Co(acac)$_2$ (1 mol%) was used. ^{f} Co(acac)$_2$ (0.25 mol%) was used.

in the NHPI-catalyzed oxidation of **1**, Fe(acac)$_3$ had only a slight effect on the oxidation, and Ni(acac)$_2$ had no effect.

When the quantity of NHPI was halved (5 mol %), **1** was oxidized at a slightly lower conversion (28%) to form **2** and **3** in 41% and 37% selectivities, respectively. However, the effect of the concentration of Co(acac)$_2$ as the cocatalyst was clearly much less than that of NHPI. For the oxidation of **1** by NHPI (10 mol %) in the presence of Co(acac)$_2$ (1 mol %) (run 9), the results were almost the same as those with 0.5 mol % of Co(acac)$_2$ (run 3). It is noteworthy that the present aerobic oxidation of **1** resulted in **3** in higher selectivity, since the autoxidation of **1** in the presence of Co and Mn salts is known to lead to K/A oil (**2** and **4**) rather than **3** as the main product.[12] In particular, it is interesting that **1** was converted into **3** in one step in 77% selectivity by the NHPI/Mn(acac)$_3$ system under atmospheric oxygen at 100 °C.

On the basis of these results, several cycloalkanes were oxidized under standard conditions, i.e., in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in an oxygen atmosphere (1 atm) using acetic acid at 100 °C for 6 h (Table 2).

For the oxidation of cyclopentane (**5**) under these conditions, the results were similar to those of **1** (run 1). However, cyclooctane (**8**) gave 1,4-cyclooctanedione (**10**) (16%) in addition to cyclooctanone (**9**) (50%) and suberic acid (**11**) (16%) in 93% conversion (run 2). Even when the amount of NHPI was reduced to 5 mol %, **8** was oxidized with a higher conversion (86%) (run 3). In contrast to **1**, which was slightly oxidized by NHPI alone, **8** could be oxidized to **9** (63%), **10** (8%), and **11** (17%) in a 37% conversion by NHPI in the absence of any metals (run 4). The 1,4-diketone **10** is believed to be formed *via* intramolecular hydrogen abstraction by a transient peroxy radical generated from **8**, as will be discussed later (Scheme 1). Indeed, the successive oxidation of **9** under these conditions led to dicarboxylic acid **11**, while diketone **10** was not formed at all. Cyclododecane (**12**) was also converted into the corresponding ketone **13** and dicarboxylic acid **14** at a satisfactory conversion (66%) (run 5). During the oxidation of these cycloalkanes, alcohols such as cyclohexanol and cyclooctanol are be-

Table 2. Oxidation of Cycloalkanes with Dioxygen Catalyzed by NHPI in the Presence of Co(acac)2[a]

run	substrate	conv. (%)	products (%) [b, c]		
1	**5**	46	**6** (27)	**7** (32)	
2 [d]	**8**	93	**9** (50)	**10** (16)	**11** (16)
3 [e]	**8**	86	**9** (53)	**10** (17)	**11** (16)
4 [f]	**8**	37	**9** (63)	**10** (8)	**11** (17)
5	**12**	66	**13** (34)	**14** (30)	
6	**15**	77	**16** (15)	**17** (23)	**18** (34)
7 [g]	**19**	65	**20** (71)	**21** (9)	**22** (17)
8	**23**	30	Octanols **24** (57)	Octanones **25** (14)	

[a] Substrate (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol%) and Co(acac)3 (0.5 mol%) in acetic acid (12.5 mL) at 100 °C for 6 h. [b] Based on substrate reacted. [c] Yield of dicarboxylic acid was estimated as dimethyl ester after esterfication with excess methanol. [d] Reaction time was 3 h. [e] NHPI (5 mol%) was used. [f] In the absence of Co(acac)2. [g] Reaction was carried out at 75 °C for 3 h.

lieved to be formed, but very small amounts of the corresponding acetates were detected using GC-MS. It is believed that these alcohols are easily oxidized to ketones and/or dicarboxylic acids since they are more reactive than the starting cycloalkanes. In fact, cyclohexanol **4** was oxidized to **2** in 92% yield in acetonitrile at 75 °C.[9]

Methylcyclohexane (**15**) gave keto carboxylic acid **18** as a major product along with 2-methylcyclohexanone (**16**) and 1-methylcyclohexanol (**17**) (run 6). The independent oxidations of **16** and **17** under these reaction conditions were carried out to reveal the reaction path to **18**. The oxidation of **16** gave **18**, while **17** was a less reactive substrate. Thus, **18** was a further oxidation product of **16**, but not of **17**. The oxidation of adamantane (**19**) at 75 °C for 3 h gave 1-adamantanol (**20**) (71%), in which the tertiary C–H bond was selectively oxygenated, together with small amounts of 2-adamantanone (**21**) (9%) and 1,3-adamantanediol (**22**) (17%) in 65% conversion (run 7). The product ratio of the tertiary C–H bond to the secondary one was approximately 7.8. The aerobic oxidation of **19** using the PW9Fe2Ni heteropolyanion reportedly gives **20** (76%), **21** (12%), and 2-adamantanol (12%) in 29% conversion.[14] On the other hand, the oxidation of *n*-alkane such as *n*-octane (**23**) by this system gave a mixture of 2-, 3-, and 4-octanols **24** and the corresponding octanones **25** (run 8).

2. Oxidation of Alkylbenzenes Using NHPI Combined with Co(acac)2. Various alkylbenzenes are known

(14) Mizuno, N.; Tateishi, M.; Hirose, T.; Iwamoto, M. *Chem. Lett.* **1993**, 2137.

Scheme 1. A Possible Reaction Path for the Oxidation of Cyclooctane (8) by the NHPI–O2 System

i) H-donor : Substrate, NHPI etc.
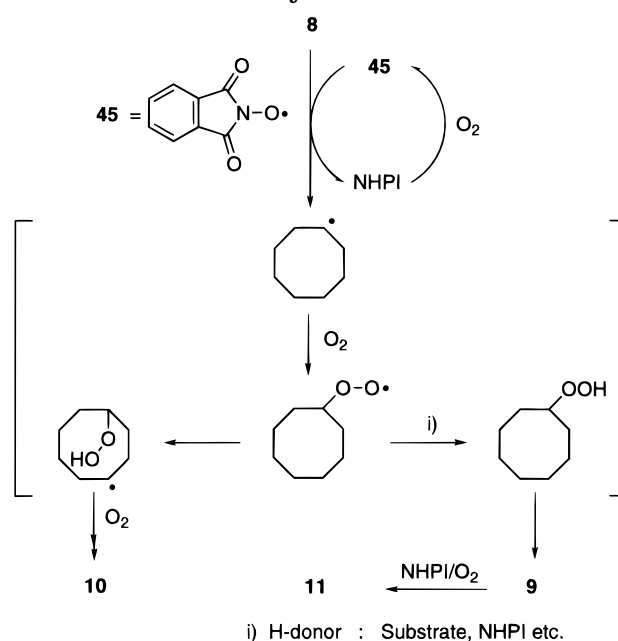
to be oxidized with dioxygen in the presence or absence of transition metals.[15]

The oxidation of several alkylbenzenes with dioxygen was attempted using the NHPI/Co(acac)2 system (Table 3, runs 1–11). The oxidation of toluene (**26**) with NHPI

Table 3. Oxidation of Alkylbenzenes with Dioxygen Catalyzed by NHPI in the Presence of Co(acac)$_2$[a]

run	substrate	conv (%)	products (%)[b]
1	toluene (**26**)	92	benzoic acid (**27**) (99)
2[c]	**26**	9	**27** (trace)
3	*p-tert*-butyltoluene (**28**)	97	*p-tert*-butylbenzoic acid (**29**) (95)
4	*p*-methoxytoluene (**30**)	98	*p*-methoxybenzoic acid (**31**) (85)
5	ethylbenzene (**32**)	91	acetophenone (**33**) (93)
6	*n*-butylbenzene (**34**)	90	1-phenyl-1-butanone (**35**) (67)
7	*p*-xylene (**36**)	94	*p*-toluic acid (**37**) (78), terephthalic acid (**38**) (15)
8[d,e]	**36**	99	**37** (23), **38** (68)
9	*o*-xylene (**39**)	92	*o*-toluic acid (**40**) (80), phthalic acid (**41**) (14)[f]
10[d,e]	**39**	99	**40** (71), **41** (23)
11	cumene (**42**)	31	**33** (54), 2-phenyl-2-propanol (**43**) (10), phenol (**44**) (17)

[a] Substrate (5 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in acetic acid (12.5 mL) at 100 °C for 6 h. [b] Based on substrate reacted. [c] In the absence of Co(acac)$_2$. [d] NHPI (20 mol %) was used. [e] Reaction was carried out at 100 °C for 12 h. [f] Yield of dicarboxylic acid was estimated as dimethyl ester after esterification with excess methanol.

(10 mol %) in the presence of Co(acac)$_2$ (0.5 mol %) in acetic acid in an oxygen atmosphere at 100 °C for 6 h exclusively gave benzoic acid (**27**) (>99%) at 92% conversion (run 1). The same oxidation with **26** by NHPI alone produced only a trace amount of **27** (run 2). Toluene (**26**) has been reported to be oxidized with air in the presence of cobalt(II) 2-ethylhexanoate at 140−190 °C and up to 10 atm of pressure to give **27** in about a 80% yield at 40−65% conversion.[15a] Consequently, the NHPI/Co-(acac)$_2$ system is thought to be a useful catalytic system for the aerobic oxidation of **26**. Similarly, *p-tert*-butyl-toluene (**28**) and *p*-methoxytoluene (**30**) were oxidized to *p-tert*-butylbenzoic acid (**29**) and *p*-methoxybenzoic acid (**31**), respectively, in good yields (runs 3 and 4). In the oxidation of ethylbenzene (**32**), acetophenone (**33**) was obtained in good yield (run 5). *n*-Butylbenzene (**34**) was likewise oxidized to give 1-phenyl-1-butanone (**35**) in slightly lower selectivity (67%). To evaluate the potential for the oxidation of the disubstituted alkylbenzenes, the oxidation of xylene was examined. *p*-Xylene (**36**) was converted into the corresponding mono- and dicarboxylic acids **37** and **38**, the ratio of which depended on the reaction time. The oxidation of **36** under the standard conditions gave *p*-toluic acid (**37**) in a 78% selectivity with a 94% conversion. When the reaction time was prolonged to 12 h, terephthalic acid (**38**) was obtained in 68% yield. However, it was difficult to convert *o*-xylene (**39**) to phthalic acid (**41**) in high selectivity (runs 9 and 10). Cumene (**42**) is known to be oxidized by dioxygen to give cumene hydroperoxide, which is converted to phenol and acetone.[16] However, **42** was oxidized with difficulty by the NHPI/Co(acac)$_2$ system to form acetophenone (**33**) (54%), 2-phenyl-2-propanol (**43**) (10%), and phenol (**44**) (17%) in 31% conversion. The low conversion of **42** was due to the formation of phenol **44**. The oxidation of **42** by this system in the presence of **44** (10 mol %) was markedly inhibited, and only trace amounts of **33** and **43** were formed.

To gain additional insight into NHPI/Co(acac)$_2$-catalyzed aerobic oxidation, the absorption rate of dioxygen during the oxidation of **32** with several catalytic systems was measured using a constant-pressure absorption apparatus. Figure 1 shows the time-dependence curves of the O$_2$ uptake of **32** under atmospheric pressure (1 atm) at 80 °C. It is interesting to compare the rate of O$_2$ uptake by **32** in the NHPI/Co(acac)$_2$ and NHPI/Co(acac)$_3$

(15) (a) Pershall, G. W.; Ittel, S, D. *Homogeous Catalysis*, 2nd ed.; John Wiley and Sons: New York, 1992; p 256. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; p 315.

(16) Reichle, W. T.; Konrad, F. M.; Brooks, J. R. *Benzene and its Industrial Derivatives*; Hancock, E. G., Ed.; Benn: London, 1975.
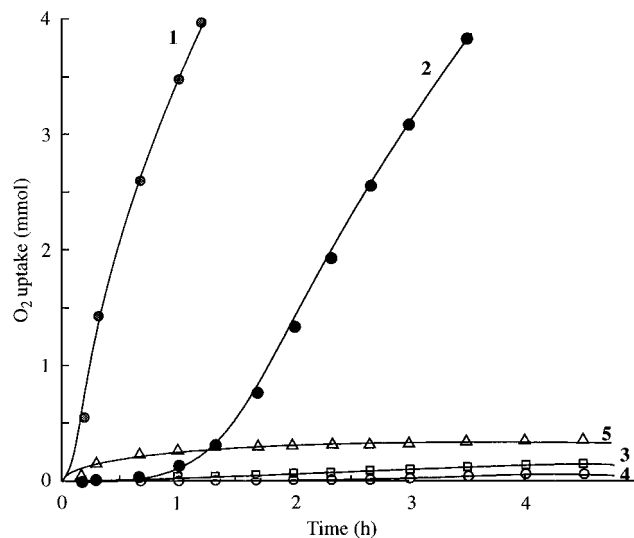

Figure 1. Time dependence curves of O$_2$ uptakes for the oxidation of ethylbenzene (**32**) under atmospheric pressure of dioxygen by various catalysts. Conditions: Ethylbenzene (**32**) (10 mmol) was allowed to react with dioxygen (1 atm) in acetic acid (25 mL) at 80 °C. (**1**) NHPI (10 mol %), Co(acac)$_2$ (0.5 mol %); (**2**) NHPI (10 mol %), Co(acac)$_3$ (0.5 mol %); (**3**) NHPI (10 mol %); (**4**) Co(acac)$_2$ (0.5 mol %); (**5**) AIBN (5 mol %), Co(acac)$_2$ (0.5 mol %).

systems. No induction period was observed in O$_2$ uptake by **32** with NHPI/Co(acac)$_2$, while that with the NHPI/Co(acac)$_3$ system did not occur until after about 1.5 h. Almost no O$_2$ uptake was observed in the oxidation of **32** by NHPI, Co(acac)$_2$, or Co(acac)$_3$ alone. In the same oxidation using the AIBN/Co(acac)$_2$ system, the results were almost the same except for O$_2$ uptake in the early stage of the reaction by radicals generated from AIBN. The isotope effect during the present oxidation was estimated by measuring the oxygen uptake by ethylbenzene (**32**) and ethylbenzene-d_{10} (**32**-d_{10}) (Figure 2). The observed isotope effect, k_H/k_D, was approximately 3.74. In addition, the oxidation of **32** in the presence of hydroquinone (1 mol %) under the standard conditions did not occur at all. These results strongly suggest that the present aerobic oxidation proceeds *via* a reaction pathway similar to that in free radical autooxidation.

Discussion

Masui *et al.* suggested that phthalimide *N*-oxyl (**45**) is a key species in the electrochemical oxidation of alcohols
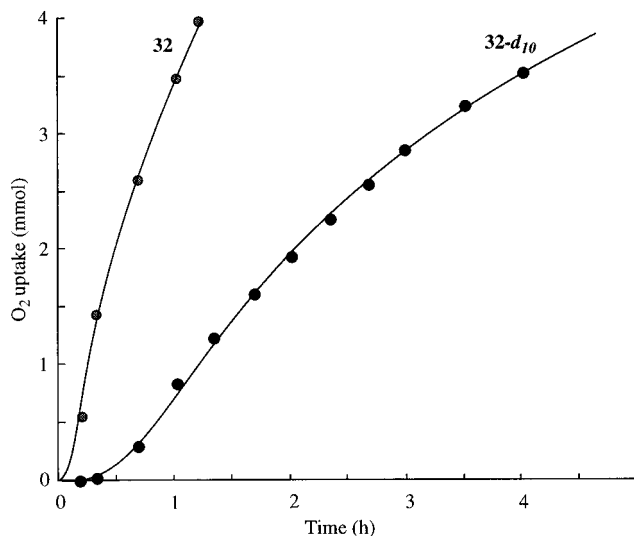
Figure 2. Time dependence curves of O_2 uptakes for the oxidation of ethylbenzene (**32**) and ethylbenzene-d_{10} (**32**-d_{10}) by NHPI/Co(acac)$_2$–O_2 system. Conditions: Ethylbenzene (**32**) (10 mmol) was allowed to react with dioxygen (1 atm) in the presence of NHPI (10 mol %) and Co(acac)$_2$ (0.5 mol %) in acetic acid (25 mL) at 80 °C.
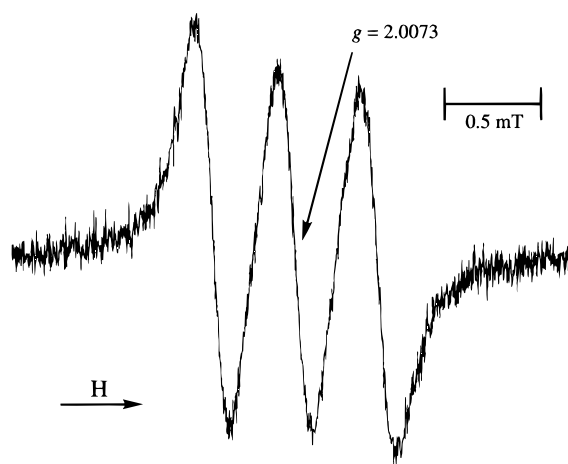

Figure 3. ESR spectrum of *N*-oxyl radical **45** under dioxygen in benzonitrile at 80 °C.

to ketones using NHPI as an electron carrier.[17] To confirm the formation of phthalimide *N*-oxyl (**45**) in the present NHPI-catalyzed aerobic oxidation, electron spin resonance (ESR) measurements were carried out under selected conditions. When a benzonitrile solution of NHPI was exposed to dioxygen at 80 °C for 1 h,[18] the ESR spectrum attributed to **45** was clearly observed as a triplet signal based on hyperfine splitting (hfs) by the nitrogen atom ($g = 2.0074$, $a_N = 0.43$ mT) (Figure 3). The *g*-value and hfs constant observed for **45** were consistent with those ($g = 2.0073$, $a_N = 0.423$ mT) reported by Mackor *et al.*[19] No ESR signal was observed under argon. It is noteworthy that **45** is easily formed by exposing NHPI to molecular oxygen under moderate conditions.

(17) (a) Masui, M.; Hosomi, K.; Tsuchida, K.; Ozaki, S. *Chem. Pharm. Bull.* **1985**, *33*, 4798. (b) Ueda, C.; Nayama, M.; Ohmori, H.; Masui, M. *Chem. Pharm. Bull.* **1987**, *35*, 1372.
(18) ESR spectra were obtained under the following conditions: sweep width 327 ± 2.5 mT; modulation 0.1 mT; and microwave power 1 mW. Benzonitrile containing 10^{-2} mmol of NHPI was exposed under oxygen atmosphere at 80 °C for 1 h. The air in the ESR tube was replaced by dioxygen gas by means of the freeze-pump-thaw method. The ESR parameter was determined by using solid Mn^{2+} ($g = 2.034$) as a standard.

Furthermore, 2-norbornene (**46**) was allowed to react with NHPI under an oxygen atmosphere in acetonitrile at 60 °C. The reaction gave *N*-(2-hydroperoxybicyclo-[2.2.1]heptan-2-yloxy)phthalimide (**47**) in 52% yield (eq 2). Treatment of triphenylphosphine with **47** produced triphenylphosphine oxide (94%) and *N*-(hydroxybicyclo-[2,2,1]heptan-2-yloxy)phthalimide (**48**) (83%) (eq 3). This
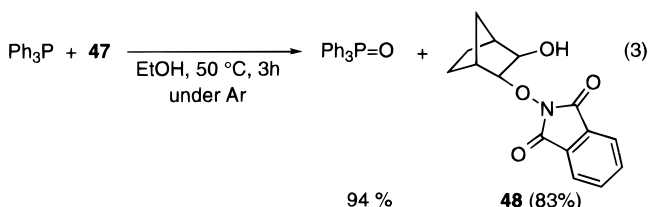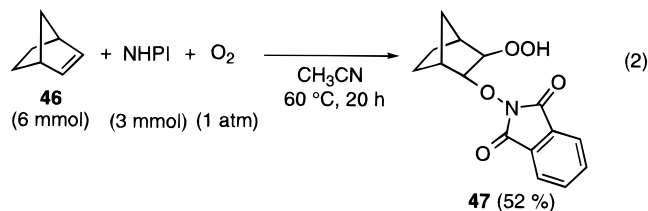
result definitely shows that the radical species **45** is smoothly generated from NHPI and molecular oxygen in the absence of transition metals under mild conditions. Hence, the oxidation process of alkanes such as cyclooctane **8**, which is oxidized by dioxygen using NHPI alone, can be outlined as in Scheme 1. The first step of the reaction is thought to involve the generation of the phthalimide *N*-oxyl radical **45** from NHPI and dioxygen. The resulting **45** abstracts a hydrogen atom from the substrates to form alkyl radicals, subsequent oxygenation of which by dioxygen produces peroxy radicals, which are converted to ketones and/or dicarboxylic acids. In some cases, intramolecular hydrogen abstraction by the resulting alkyl peroxy radical occurs, and leads to the formation of the diketone **10**.

Unfortunately, we are currently unable to clearly explain the role of Co(acac)$_n$ as a cocatalyst in NHPI-catalyzed aerobic oxidation. However, we can make several proposals which seem to agree with the experimental results.

As mentioned earlier, no induction period was observed in the oxidation of ethylbenzene **32** with the NHPI/Co-(acac)$_2$ system. However, oxygen uptake by **32** did not occur until after about 1.5 h with the NHPI/Co(acac)$_3$ system. This finding is in accord with the results of adding NHPI alone to Co(acac)$_2$ or Co(acac)$_3$. When NHPI was added to an acetic acid solution of Co(acac)$_2$, the color of the solution immediately changed from pink to violet, and a mixture of several complexes **49** was obtained. On the other hand, the same procedure with Co(acac)$_3$ led to no color change of the solution, and most of the starting materials were recovered unchanged. However, when ethylbenzene **32** was added to this solution, the color of the solution gradually changed to violet and finally became the same as that in the NHPI/Co(acac)$_2$ system to form complexes similar to those derived from NHPI and Co(acac)$_2$. This result indicates that Co(acac)$_3$ is gradually reduced to Co(II) with **32** *via*

(19) Mackor, A.; Wajer, Th. A. J. W.; de Boer, Th. J. *Tetrahedron* **1968**, *24*, 1623.

a well-known one-electron transfer process,[20] and the resulting Co(II) species readily reacts with NHPI to produce complexes similar to those derived from the NHPI/Co(acac)$_2$ system. These results well reflect the differences in the induction period between the NHPI/Co(acac)$_2$ and NHPI/Co(acac)$_3$ systems during O$_2$ uptake by **32**. The induction period of 1.5 h observed with the NHPI/Co(acac)$_3$ system may represent the time required to reach a threshold concentration of Co(II) by one-electron transfer from **32** to Co(III).

On the other hand, **32** and **1** were oxidized using the complexes **49** obtained from NHPI and Co(acac)$_2$ (eq 4). **32** was oxidized to acetophenone **33** in 69% yield, while **1** failed to be oxidized by these complexes.
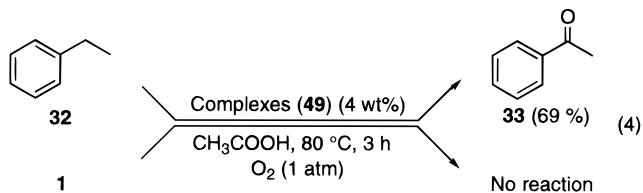
Although the role of the Co(II) species in the NHPI-catalyzed aerobic oxidation is not fully understood, the Co(II) species may be related to the generation of the phthalimide *N*-oxyl radical **45** from NHPI. However, it appears that the present results do not detract from the importance of the discovery of a new mode of dioxygen activation by the NHPI/Co(acac)$_n$ (*n* = 2 or 3) system.

Experimental Section

^{1}H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, with tetramethylsilane as an internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. A GC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). Oxygen-absorption rates were measured with an isobaric gas-absorption apparatus under a closed-flow system (2 ± 0.1 L oxygen/h) equipped with an electrolyzer. ESR measurements were performed on a JEOL-FE-1X (X-band) with 100-kHz field modulation.

All starting materials and catalysts were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

General Procedure for Oxidation of Cycloalkanes. An acetic acid (12.5 mL) solution of cycloalkane (5 mmol), NHPI (82 mg, 10 mol %), and Co(acac)$_2$ (7.5 mg, 0.5 mol %) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 100 °C for 6 h. After removing the solvent under reduced pressure, methanol (25 mL) and a catalytic amount of concd H$_2$SO$_4$ were added to the resulting mixture and stirred at 65 °C for 15 h. The resulting solution was extracted with diethyl ether (20 mL × 3). The combined extracts were dried over anhydrous MgSO$_4$. Removal of solvent under reduced pressure gave a clean liquid, which was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 5/1) to give the corresponding oxygenated products.

Ketones **2**, **6**, **9**, **13**, **16**, **21**, and **24**, alcohols **20** and **25**, and dicarboxylic acids **3**, **7**, **11**, and **14** were identified by comparing the isolated products with authentic samples.

1,4-Cyclooctanedione (10): ^{1}H NMR (CDCl$_3$) δ 1.83−1.87 (m, 4H), 2.40−2.44 (m, 4H), 2.71 (s, 4H); ^{13}C NMR (CDCl$_3$) δ

(20) The oxidation of alkylbenzenes[21] and cyclohexane[22] by Co(III) ion is known to involve one-electron transfer from substrates to Co-(III), yielding Co(II) ion and radical cations.

(21) Heiba, E. I.; Dessau, R. M.; Koehl, W. J. Jr. *J. Am. Chem. Soc.* **1969**, *91*, 6830.

(22) Onopchenko, A.; Schulz, J. G. D. *J. Org. Chem.* **1973**, *38*, 3729.

24.4, 40.6, 41.3, 213.7; IR (NaCl) 2941, 2865, 1697, 1445, 1334, 1108, 1091, 946, 822 cm^{-1}.

1-Methylcyclohexanol (17): ^{1}H NMR (CDCl$_3$) δ 1.21 (s, 3H), 1.36 (s, 1H), 1.44−1.63 (m, 10H); ^{13}C NMR (CDCl$_3$) δ 22.6, 25.6, 29.5, 39.4, 69.9; IR (NaCl) 3352, 2930, 2859, 1170, 1120, 967, 911 cm^{-1}.

6-Oxoheptanoic acid (18): ^{1}H NMR (CDCl$_3$) δ 1.62−1.65 (m, 4H), 2.16 (s, 3H), 2.36−2.40 (m, 2H), 2.45−2.48 (m, 2H), 11.02 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 23.0, 24.0, 29.9, 33.8, 43.2, 179.8, 209.0; IR (NaCl) 3046, 2945, 1712, 1414, 1369, 1235, 1176 cm^{-1}.

1,3-Adamantandiol (22): ^{1}H NMR (CDCl$_3$) δ 1.61−1.77 (m, 14H), 2.34 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 31.1, 34.5, 43.7, 52.5, 70.3; IR (KBr) 3349, 2931, 1333, 1030 cm^{-1}.

General Procedure for Oxidation of Alkylbenzenes. An acetic acid (12.5 mL) solution of alkylbenzenes (5 mmol), NHPI (82 mg, 10 mol %), and Co(acac)$_2$ (7.5 mg, 0.5 mol %) was placed in a three-necked flask equipped with a ballon filled with O$_2$. The mixture was stirred at 100 °C for 6 h. After removal of the solvent under reduced pressure, the products were purified by column chromatography on silica gel to give the corresponding oxygenated products.

Products **27**, **29**, **31**, **33**, **37**, **38**, **40**, **41**, and **44** were identified by comparing of the isolated products with authentic samples.

1-Phenyl-1-butanone (35): ^{1}H NMR (CDCl$_3$) δ 0.98−1.04 (t, *J* = 7.3 Hz, 3H), 1.71−1.85 (m, 2H), 2.92−2.98 (t, *J* = 7.6 Hz, 2H), 7.43−7.58 (m, 3H), 7.95−7.98 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 200.4, 137.1, 132.8, 128.5, 128.0, 40.5, 17.7, 13.9; IR (NaCl) 2963, 1688, 1449, 1214, 692 cm^{-1}.

2-Phenyl-2-propanol (43): ^{1}H NMR (CDCl$_3$) δ 1.55 (s, 6H), 2.40 (s, 1H), 7.19−7.50 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 31.6, 72.4, 124.4, 126.5, 128.1, 149.1; IR (NaCl) 3374, 2976, 2359, 1446, 1363, 764, 699, 544 cm^{-1}.

General Procedure for Measuring Oxygen-Absorption Rates. Oxygen-absorption rates were measured with an isobaric gas-absorption apparatus in a closed-flow system (2 ± 0.1 L oxygen/h) equipped with an electrolyzer using 25 mL of acetic acid containing ethylbenzene (1.06 g, 10 mmol), NHPI (163 mg, 10 mol %) and Co(acac)$_2$ (14.7 mg, 0.5 mol %) at 80 °C. Oxygen absorption was periodically measured in the constant-pressure closed system.

Reaction of 46 with NHPI. An acetonitrile (5 mL) solution of 2-norbornene (564 mg, 6 mmol) and NHPI (489 mg, 3 mmol) was placed in a three-necked flask equipped with a balloon filled with O$_2$. The mixture was stirred at 60 °C for 20 h. After the reaction, acetonitrile was removed under reduced pressure to give a white crystal, which was purified by diethyl ether (30 mL) to give the hydroperoxide **47** in 52% yield.

N-(2-Hydroperoxybicyclo[2.2.2]heptan-2-yloxy)phthalimide (47): ^{1}H NMR (CDCl$_3$) δ 1.16−1.41 (m, 2H), 1.48−1.65 (m, 2H), 2.04 (d, *J* = 10.0 Hz, 1H), 2.31 (s, 1H), 2.94 (s, 1H), 4.14 (d, *J* = 5.3 Hz, 1H), 4.36 (d, *J* = 5.3 Hz, 1H), 7.79−8.55 (m, 4H), 10.65 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 22.9, 25.9, 33.6, 39.8, 41.7, 89.0, 93.6, 123.9, 128.6, 134.9, 164.3; IR (KBr) 3381, 2950, 1789, 1732, 1379, 1188, 993, 878, 699, 520 cm^{-1}. Anal. Calcd for C$_{15}$H$_{15}$NO$_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.17; H, 5.18; N, 4.82.

Reaction of 47 with Triphenylphosphine. An ethanol (30 mL) solution of **47** (289 mg, 1 mmol) and Ph$_3$P (262 mg, 1 mmol) was placed in a three-necked flask, and the mixture was stirred at 50 °C for 3 h under an Ar atmosphere. After the reaction, ethanol was removed under reduced pressure to give a white crystal, which was purified by diethyl ether (30 mL) to give triphenylphosphine oxide in 94% yield along with alcohol **48** (83%).

N-(2-Hydroxybicyclo[2.2.2]heptan-2-yloxy)phthalimide (48): ^{1}H NMR (CDCl$_3$) δ 1.05−1.12 (m, 3H), 1.21 (d, *J* = 10.5 Hz, 1H), 1.46−1.63 (m, 4H), 2.05 (d, *J* = 10.5 Hz, 1H), 2.29 (s, 1H), 2.66 (s, 1H), 3.91 (s, 1H), 4.00 (s, 1H), 7.75−7.87 (m, 4H), 10.65 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 24.0, 24.9, 32.7, 41.3, 43.2, 75.8, 93.2, 123.7, 128.6, 134.7, 164.0; IR (KBr) 3451, 2964, 1783, 1730, 1379, 1186, 999, 878, 782, 703, 518 cm^{-1}.

These values were consistent with those reported in the literature.[23]

Preparation of Complexes 49. A mixture of NHPI (294 mg, 2 mmol) and Co(acac)$_2$ (235 mg, 0.8 mmol) in acetic acid (15 mL) was stirred at 80 °C under an oxygen atmosphere. After 0.5 h, the reaction mixture was evaporated, and an orange solid was obtained. The resulting solid was washed using acetonitrile, and then the complexes **49** were obtained (271 mg).

Oxidation of 1 and 32 Catalyzed by Complexes 49. To a stirred solution of complex (**49**) (21 mg, 4 wt %) in acetic acid (10 mL) was added **1** or **32** (5 mmol), and the reaction mixture was fitted with a balloon filled with oxygen. The

mixture was stirred at 80 °C for 3 h. The workup was performed using the same method as previously described.

Supporting Information Available: Copies of spectra of compounds **10**, **17**, **18**, **22**, **35**, **43**, **47**, and **48** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(23) Ozaki, S.; Hamaguchi, T.; Tsuchida, K.; Kimata, Y. *J. Chem. Soc., Perkin Trans 2* **1989**, 951.