Aerobic Oxidation of Cycloalkanes, Alcohols and Ethylbenzene Catalyzed by the Novel Carbon Radical Chain Promoter NHS (*N*-Hydroxysaccharin)

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Abstract: Replacement of Ishii's *N*-hydroxyphthalimide (NHPI) with the novel carbon radical chain promoter *N*-hydroxysaccharin (NHS) affords, in combination with metal salts, notably Co, or other additives, selective catalytic autoxidation of hydrocarbons, alcohols and alkylbenzenes under mild conditions (25–100 °C, O_2 1 atm). The effects of solvent, temperature and the nature of the additives were investigated to give an optimised oxidation protocol for the various systems. The NHS/Co combination was more reactive than NHPI/Co in the autoxidation of cycloalkanes. In contrast, the opposite order of reactivity was observed in the autoxidation of ethylbenzene and alcohols. It is suggested, on the basis of bond dissociation energy (BDE) considerations, that this is a result of a change in the rate-limiting step with the more reactive ethylbenzene and alcohol substrates. In the autoxidation of the model cycloalkane, cyclododecane, the best results (90% selectivity to a 4:1 mixture of alcohol and ketone at 24% conversion) were obtained with NHS/Co(acac)$_3$ in $PhCF_3$ at 80 °C. Competition experiments revealed that, in contrast to what is commonly believed, formation of the dicarboxylic acid by ring opening is not a result of further oxidation of the ketone product. It is suggested that ring opened products are a result of ß-scission of the cycloalkoxy radical formed *via* (metal-catalysed) decomposition of the hydroperoxide. This is suppressed in the presence of NHS (or NHPI) which efficiently scavenge the alkoxy radicals.

Keywords: alcohols; C–H activation; cycloalkanes; molecular oxygen; oxidation

Introduction

The selective oxidation of saturated hydrocarbons is one of the most challenging subjects in oxidation chemistry. In particular, homogeneous catalytic oxidation of hydrocarbons with molecular oxygen is very important in the chemical industry.[1] Recently Ishii and co-workers discovered that *N*-hydroxyphthalimide (NHPI; **1a**) in combination with cobalt catalyses the autoxidation of hydrocarbons under mild conditions (25–100 °C, O_2 1 atm).[2] The promoting effect of NHPI was explained on the basis of the mechanism shown in Scheme 1. NHPI is converted into its corresponding phthalimide *N*-oxyl (PINO) radical (**2a**) which is able to abstract a hydrogen atom from the organic substrate leading to longer propagation chains and, hence, higher rates and selectivities compared to conventional autoxidation protocols.

The introduction of electron-withdrawing groups in the benzene ring of NHPI was shown to have a beneficial effect on the catalyst performance in the aerobic oxidation of alkylbenzenes[3] and the electrocatalytic oxidation of alcohols.[4] We reasoned that the use of *N*-hydroxysaccharin (NHS; **1b**),[5] in which one carbonyl group (CO) is replaced by the more electron-withdrawing sulphonyl (SO_2) group, could provide an even more effective carbon radical chain promoter (CRCP).[6] In the course of our study on the oxidation of large ring cycloalkanes with molecular oxygen we found that NHS was an efficient catalyst in combination with cobalt salts.[7] In this paper we report details of the NHS-catalysed oxidation of large ring cycloalkanes, ethylbenzene and a wide range of alcohols. Mechanistic considerations based on bond dissociation energies (BDE) provide a plausible rationale for the different activities of NHS and NHPI.

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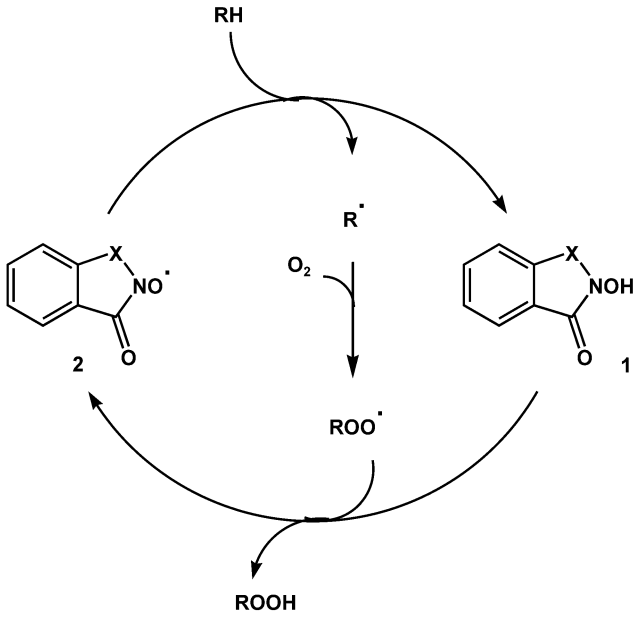


X = CO: NHPI (**1a**), PINO (**2a**); X = SO_2: NHS (**1b**), SINO (**2b**)

Scheme 1.

Results and Discussion

Cycloalkane Oxidation

Under the standard conditions described by Ishii et al. [O_2 1 atm, T = 100 °C in acetic acid, NHPI 10 mol % and $Co(acac)_2$ 0.5 mol %],[2] cyclododecane **3** was oxidised to cyclododecanone **4**, cyclododecanol **5** and 1,12-dodecanedioic acid **6** in 29%, 5% and 30% selectivity, respectively, at 58% conversion (Table 1, run 3). Substitution of NHPI by NHS led to a slightly higher conversion (64%) with comparable selectivity toward the formation of the ketone and alcohol (31% and 8% respectively) (run 2). GC-MS analysis of the crude reaction mixture showed the presence of two different cyclododecadiones and two hydroxycyclododecanones as the main by-products. The formation of these by-products is attributed to competing transannular hydrogen abstraction by an intermediate cyclododecylperoxy radical, analogous to that observed in the autoxidation of cyclohexylbenzene.[8] Decreasing the reaction temperature either with NHS or NHPI, led, as expected, to a decrease of conversion together with an increase in selectivity toward ketone and alcohol (runs 4–7). The slightly higher activity already observed with the NHS system at 100 °C, became more pronounced at 75 °C (47% and 36% conversion with NHS and NHPI respectively). At 50 °C NHPI completely failed to promote substrate oxidation whilst NHS gave 42% conversion, in 24 h, with an increase in overall selectivity (ketone + alcohol) to 61%.

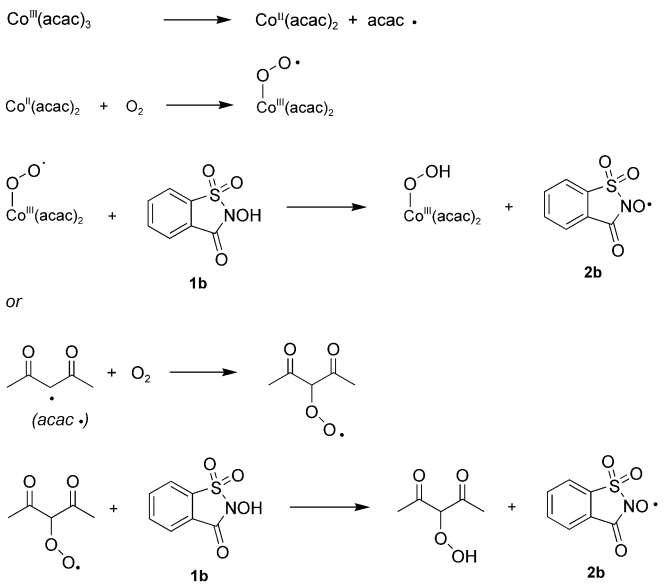
Having shown that NHS is, in combination with $Co(acac)_2$, an effective catalyst for the oxidation of cyclododecane into cyclododecanone under mild conditions, we undertook a comprehensive study of reaction parameters in order to optimize the yield of ketone. Several metal co-catalysts were first screened, in combination with NHS at different temperatures, using acetic acid as solvent (Table 2). $Co(OAc)_2$ and $Co(acac)_2$ gave similar results. At 100 °C $Co(acac)_3$ gave similar results to those obtained with $Co(acac)_2$ but the activity of the former was much more temperature-dependent as shown in Figure 1. At 50 °C a much longer initiation period was observed with $Co(acac)_3$. This result can be explained by the need for a one-electron reduction of $Co(acac)_3$ into $Co(acac)_2$, which is the actual co-catalyst (Scheme 2). This presumably involves one-electron oxidation of the acac ligand which is expected to be much faster at 100 °C than at 50 °C.[9]

The $Co(acac)_2$ could subsequently react with dioxygen to form a superoxocobalt(III) species which abstracts a hydrogen from NHS (Scheme 2), as proposed by Ishii for the Co/NHPI system.[2e] It is worth noting, however, that the oxidation of cobalt(II) by dioxygen is thermo-

Table 1. Oxidation of cyclododecane **3** in AcOH in the presence of $Co(acac)_2$.[a]

Run	Co-catalyst	T [°C]	Time [h]	Conv.[b] [%]	Ketone[b, c] **4** [%]	Alcohol[b, c,d] **5** [%]	Diacid[c, e] **6** [%]
1	none	100	24	<4	0	0	0
2	NHS	100	6	64	31	8	16
3	NHPI	100	6	58	29	5	30
4	NHS	75	8	47	41	10	12
5	NHPI	75	8	36	42	8	23
6	NHS	50	24	42	47	14	20
7	NHPI	50	24	0	0	0	0

[a] Experimental conditions: 0.5 mol % $Co(acac)_2$, 10 mol % co-catalyst (0.3 mmol), 3 mmol **3**, 1 atm O_2, 7.5 mL acetic acid.
[b] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Based on cyclododecane **3** reacted.
[d] Alcohol **5** + ester **7**.
[e] Determined by HPLC using octanoic acid as internal standard.



Scheme 2.

dynamically very unfavourable [redox potential Co(II)/Co(III) around 1.8 V, for O_2/O_2^- $E_0 = -0.3$ V]. For example, Partenheimer[10] reported that the formation of cobalt(III) from cobalt(II) acetate in a refluxing oxygenated solution in acetic acid was initiated by trace amounts of adventitious peroxides. We suggest that a more likely mechanism for initiation by $Co(acac)_3$ involves reaction of the initially formed acac · radical with oxygen, affording the corresponding $acacO_2 \cdot$ species which is scavenged by the NHS to afford the corresponding radical (SINO) which enters the catalytic cycle of Scheme 1 (see Scheme 2). In acetic acid as reaction medium the cobalt(II) is very likely present as $Co^{II}(acac)_2(HOAc)_2$. The HOAc ligand therein will probably be very similar to that in the $Co(OAc)_2$ system, where it has been demonstrated that peroxy radicals, peroxide, peracids etc. can easily enter the Co(II) coordination sphere *via* the highly labile and very weakly bonded HOAc ligand.[10,11] The replacement of Co^{II} by either Cu^{II} (runs 13–15) or Fe^{III} (runs 16 and 17) led to a lower activity without any significant increase in selectivity to ketone.

The autoxidation of cycloalkanes involves the formation of the corresponding cycloalkyl hydroperoxide as the primary oxidation product.[1] Its selective decomposition is the key to a high selectivity toward ketone. Chromium(VI) complexes are known to be efficient radical initiators for hydrocarbon autoxidation and effective catalysts for the decomposition of secondary alkyl hydroperoxides to ketones.[12] The reaction was therefore performed in the presence of 0.5 mol % pyridinium dichromate (runs 18 and 19). The conversion and overall selectivity (ketone + alcohol) were similar to those observed with $Co(acac)_2$ but the ratio of ketone to alcohol was greatly improved and reached 16.8 and 28.5 at 100 °C and 50 °C, respectively. Ruthenium complexes are also well known catalysts for the decomposition of alkyl hydroperoxides. However, when $Ru(CH_3CN)_4Cl_2$ was used as the co-catalyst the oxidation of cyclododecane stopped after 2 hours at about 20–25% conversion at all temperatures, albeit with similar selectivity (57–59%) toward the formation of ketone and alcohol. The formation of a black precipitate indicated that the ruthenium catalyst had decomposed.

From the results summarised in Table 2, Co^{II} salts appeared to be the best co-catalysts in acetic acid. Hence, we subsequently used the combination Co^{II}/NHS to study the aerobic oxidation of cyclododecane in

Table 2. Oxidation of cyclododecane **3** in AcOH in the presence of NHS.[a]

Run	Metal complex	T [°C]	Time [h]	Conv.[b] [%]	Ketone[b, c] **4** [%]	Alcohol[b, c,d] **5** [%]
8	$Co(OAc)_2 \cdot 4\,H_2O$	100	6	64	33	8
9		75	8	50	43	11
10		50	24	45	52	13
11	$Co(acac)_3$	100	5	64	30	9
12		50	24	22	48	29
13	$Cu(OAc)_2 \cdot 4H_2O$	100	8	55	32	9
14		75	10	28	34	25
15	$Cu(acac)_2$	100	6	45	31	14
16	$Fe(acac)_3$	100	6	31	33	26
17		75	24	24	38	35
18	$(py)_2Cr_2O_7$	100	6	58	42	3
19		50	24	45	57	2
20	$Ru(CH_3CN)_4Cl_2$	100	2	21	32	25
21		75	2	24	36	23

[a] Experimental conditions, 0.5 mol % metal complex, 10 mol % NHS (0.3 mmol), 3 mmol **3**, 1 atm O_2, 7.5 mL acetic acid.
[b] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Based on cyclododecane **3** reacted.
[d] Alcohol **5** + ester **7**.

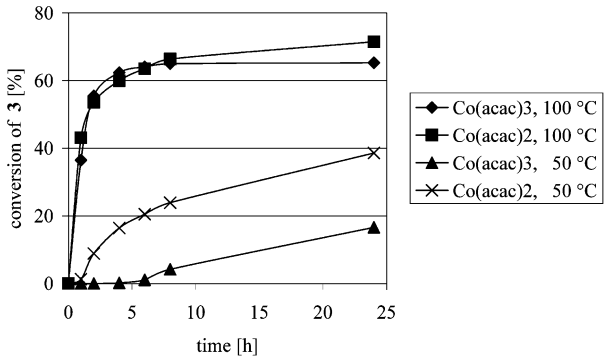


Figure 1. Oxidation of cyclododecane **3**, in the presence of NHS and $Co(acac)_3$ or $Co(acac)_2$, in AcOH at different temperatures.

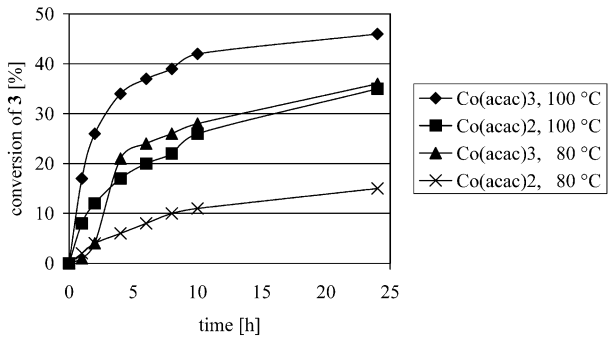


Figure 2. Oxidation of cyclododecane **3**, in the presence of NHS and $Co(acac)_3$ or $Co(acac)_2$, in $PhCF_3$ at different temperatures.

different solvents (Table 3). In acetonitrile and benzonitrile (runs 22 and 23) conversions were lower than in acetic acid, under comparable conditions, and selectivities were poor to moderate. Since ionic liquids are attracting increasing attention as media for catalytic processes,[13] we tested 1-butyl-3-methylimidazolium and 1-hexyl-3-methylimidazolium tetrafluoroborates, [bmim][BF_4] and [hmim][BF_4], respectively, as solvent. However, relatively low conversions were observed (runs 24 and 25).

A reasonable activity (24% conversion in 8 h at 100 °C) together with good selectivity to cyclododecanone (53%) + cyclododecanol (26%) was observed in chlorobenzene (run 26). Good results were also observed in α,α,α-trifluorotoluene (runs 27 and 28), a solvent that is often used for aerobic oxidations.[14] At 100 °C, 35% conversion was observed in 24 h, affording cyclododecanone and cyclododecanol in 54% and 20% selectivity, respectively (run 28). Similar results were obtained when the $Co(acac)_2$ was replaced by $Co(OAc)_2$ (run 29). Replacement of $Co(acac)_2$ with $Co(acac)_3$, in contrast, led to a higher reaction rate (35% conversion in 4 h) and a selectivity to ketone and alcohol of 64% and 16%, respectively (run 30). The best result (90% selectivity for a 4:1 mixture of ketone and alcohol at 24% conversion) was observed with $Co(acac)_3$/NHS in $PhCF_3$ at 80 °C (run 32).

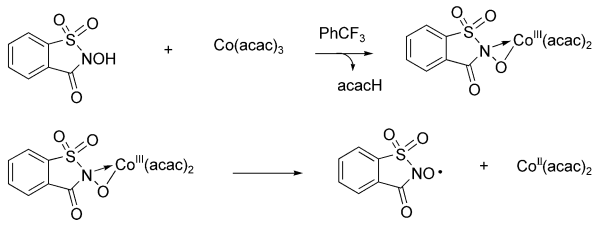
The course of cyclododecane oxidation in the presence of NHS and $Co(acac)_2$ or $Co(acac)_3$ at 80 °C and 100 °C is shown in Figure 2. It is interesting to note that, depending on the solvent, acetic acid or $PhCF_3$, either $Co(acac)_2$ or $Co(acac)_3$, respectively, displays the higher activity in combination with NHS (compare Figures 1 and 2).

We propose that this can be explained by assuming that, in $PhCF_3$, NHS displaces an acac ligand in $Co(acac)_3$ *via* nucleophilic substitution at cobalt, to form a Co^{III}-NHS complex (Scheme 3). Decomposition

Table 3. Oxidation of cyclododecane **3** with oxygen in the presence of NHS in different solvents.[a]

Run	Solvent	Co-catalyst	T [°C]	Time [h]	Conv.[b] [%]	Ketone[b, c] **4** [%]	Alcohol[b, c] **5** [%]
22	CH_3CN	$Co(acac)_2$	85	24	28	35	14
23	PhCN	$Co(acac)_2$	100	24	16	18	24
24	[C_4mim][BF_4]	$Co(acac)_2$	100	24	7	traces	traces
25	[C_6mim][BF_4]	$Co(acac)_2$	100	24	11	45	5
26	PhCl	$Co(acac)_2$	100	8	24	53	26
27	$PhCF_3$	*n*-$Bu_4N^+Br^-$	80	24	9	41	33
28	$PhCF_3$	$Co(acac)_2$	80	24	16	69	28
29	$PhCF_3$	$Co(acac)_2$	100	24	35	54	20
30	$PhCF_3$	$Co(OAc)_2$	100	24	26	49	30
31	$PhCF_3$	$Co(acac)_3$	100	4	35	64	16
32	$PhCF_3$	$Co(acac)_3$	80	10	24	72	18
33	$PhCF_3$	$Cu(acac)_2$	100	8	32	61	9
34	$PhCF_3$	$Fe(acac)_3$	100	8	20	59	37
35	$PhCF_3$	$(py)_2Cr_2O_7$	100	6	18	40	21
36	$PhCF_3$	$Cr(acac)_3$	100	24	36	50	6

[a] Experimental conditions, 0.5 mol % co-catalyst, 10 mol % NHS (0.3 mmol), 3 mmol **3**, 9 mL solvent.
[b] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Based on cyclododecane **3** reacted.

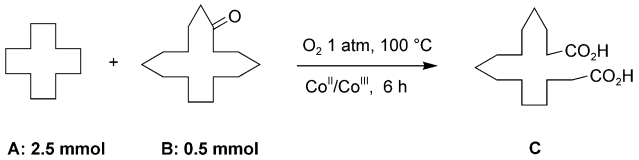


Scheme 3.

of the latter, *via* one-electron transfer, affords the *N*-oxyl radical and $Co(acac)_2$. This ligand substitution reaction is much less favourable in the protic solvent, acetic acid, than in the apolar $PhCF_3$.

The optimum conditions developed for cyclododecane oxidation – NHS/$Co(acac)_3$ in $PhCF_3$ at 80 °C – were subsequently applied to the oxidation of cyclododecane and cyclooctane (Table 4). In the oxidation of cyclododecane (run 37) no oxidative cleavage leading to dodecanedioic acid was observed. The only by-products observed were a result of transannular hydrogen abstraction (see earlier). As a result of ring strain, caused by transannular interactions, cyclodecane and cyclooctane are more reactive than cyclododecane towards autoxidation. Thus, cyclodecane gave 31% conversion in 5 h at 100 °C, affording cyclodecanone (61%), cyclodecanol (24%) and 2% of 1,10-decanedioic acid (run 38). The oxidation of cyclooctane was even faster (run 39): 30% conversion in 1.5 h, affording cyclooctanone (55%), cyclooctanol (22%) and 1,8-octanedioic (20%). It is interesting to note that in the case of oxidation of cyclododecane in $PhCF_3$ – as opposed to acetic acid as solvent – no oxidative cleavage leading to dodecanedioic acid was observed.

The stability of *N*-hydroxysaccharin was determined in a separate experiment, by heating NHS in either acetic acid or trifluorotoluene up to 100 °C for 6 hours under 1 atm O_2. No loss of NHS occurred and the identity was verified by NMR. To study the stability of NHS under the reaction conditions, two reaction mixtures (in either acetic acid or trifluorotoluene)



solvent/co-catalyst	addition time [h]	% of B decomposed	% diacid C formed
$PhCF_3/Co(acac)_3$	0	25	0
	1	12	0
$AcOH/Co(acac)_2$	0	43	< 5
	1	24	0

Figure 3. Competition experiments with cyclododecane and cyclopentadecanone.

were separately analysed by HPLC. The NHS was found largely unchanged (at least 75% could be recovered) which suggests the possibility of recycling of NHS as a catalyst.

By-Product Formation in Cycloalkane Oxidation

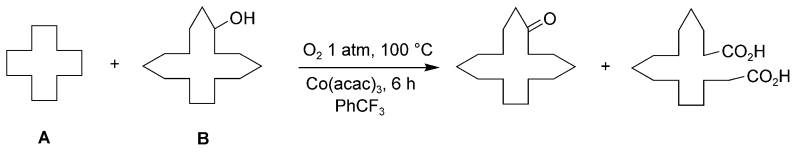
An interesting question with regard to cycloalkane oxidation is how dicarboxylic acids are formed *via* oxidative cleavage of the ring. It is generally assumed that they are formed *via* consecutive oxidation of the cycloalkanone product.[1a] We tested this hypothesis by performing competition experiments in which a mixture of cyclododecane and cyclopentadecanone, in a molar ratio of 5:1 (corresponding to *ca.* 17% conversion in a cycloalkane oxidation) was subjected to aerobic oxidation (see Figure 3). The ketone was added either at $t = 0$ or after the cyclododecane had been allowed to react for 1 h, and the oxidation was allowed to proceed for a total of 6 h.

When the oxidation was conducted with NHS/$Co(acac)_3$ in $PhCF_3$, the conversions of cyclopentadecanone were 25% and 12% when it was added at $t = 0$ or $t = 1$ h, respectively. In neither case was any formation

Table 4. Oxidation of cycloalkanes in the presence of NHS.[a]

Run	Substrate	Time [h]	Conv.[b] [%]	Selectivity [%][b, c]			
				Ketone[d]	Alcohol	Diacid[e]	Total
37	Cyclododecane	10	24	72	18	0	90
38	Cyclodecane	5	31	61	24	2	87
39	Cyclooctane	1.5	30	55 (0)	22	20	99

[a] Cycloalkanes (3 mmol), NHS (0.3 mmol), $Co(acac)_3$ (0.015 mmol), $PhCF_3$ (9 mL), 80 °C, O_2 1 atm.
[b] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Based on cycloalkane reacted.
[d] Between brackets 1,3-cyclooctadione.
[e] Determined by HPLC.

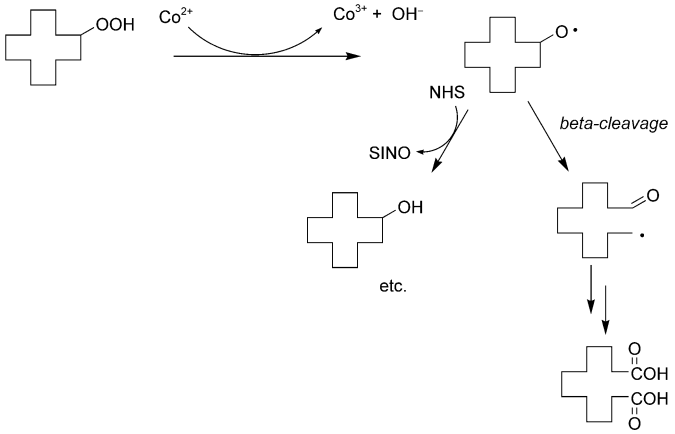


substrates [mmol]	conv. B [%]	sel. for ketone [%]	sel. for diacid [%]
B (3)	94	91	0
A (2.5) / **B** (0.5)	98	87	9

Figure 4. Competition experiments with cyclododecane and cyclopentanedecanol.

of 1,15-pentadecanedioic acid observed, consistent with the observation of no 1,12-dodecanedioc acid in the oxidation of cyclododecane (see above). When the oxidation was performed with NHS/$Co(acac)_2$ in acetic acid the ketone conversions were 43% and 24%, respectively. No formation of the dicarboxylic acid was observed in the latter case while in the former a small amount ($< 5\%$) was observed. We conclude from these results that consecutive oxidation of the ketone product is not the (primary) source of ring-opened by-products. The observed disappearance of the ketone in the competition experiments probably involves oxidation at other C–H bonds in the ring than those adjacent to the ketone group.

We subsequently performed competition experiments with a mixture of cyclododecane and cyclopentadecanol (see Figure 4). When cyclopentadecanol alone was subjected to aerobic oxidation in the presence of NHS/$Co(acac)_3$ in $PhCF_3$ at 100 °C for 6 h, cyclopentadecanone was obtained in 91% selectivity at 94% conversion. When a 5:1 mixture of cyclododecane/cyclopentadecanol was subjected to the same conditions 98% of the cyclopentadecanol was converted, affording cyclopentadecanone in 87% selectivity, together with 9% of 1,15-pentadecanedioic acid. We propose that, in cycloalkane oxidations, ring-opened products are formed *via* β-cleavage of intermediate cycloalkoxy radicals formed *via* (metal-catalysed) decomposition of the corresponding hydroperoxide (Scheme 4). The formation of carbonyl compounds *via* β-cleavage is a well-documented reaction of alkoxy radicals,[15] which in the case of cyclic alkoxy radicals leads to ring opening. In the presence of NHS (or NHPI) efficient scavenging of alkoxy radicals suppresses β-cleavage in favour of alcohol formation leading to a higher selectivity to alcohol + ketone (Scheme 4). In contrast, alcohol autoxidation does not proceed *via* intermediate alkoxy radicals but primarily *via* α-hydroxyalkyl radicals, formed *via* hydrogen abstraction from the α-C–H bond. Hence, alcohols are selectively oxidised to the corresponding ketone with little or no oxidative cleavage. The promising results obtained in the oxidation of cyclopentadecanol led us to explore the NHS/$Co(acac)_3$ catalysed aerobic oxidation of a range of alcohols.



Scheme 4.

Alcohol Oxidation

The selective oxidation of alcohols to the corresponding carbonyl compounds is one of the most frequently used transformations in organic synthesis. In recent years, increasing attention has been focused on the selective aerobic oxidation of alcohols to carbonyl compounds under mild conditions.[16] The use of *N*-hydroxyphthalimide (NHPI) in combination with $Co(acac)_3$ as a catalyst for the aerobic oxidation of alcohols in acetonitrile at 75 °C was described by Ishii.[17] The same group subsequently reported that the $Co(acac)_3$ could be replaced by $Co(OAc)_2$ in the presence of various substituted benzoic acids in ethyl acetate at room temperature.[18] The NHPI-catalysed oxidation of 2-octanol under these two different conditions gave, in our hands, 93% and 70% yield respectively (Table 5, runs 41 and 43). The substitution of NHPI by NHS under the conditions developed by Ishii gave disappointing results (10 and 12% yield respectively, runs 42 and 44). An increase of the temperature to 75 °C, however, allowed the NHS-catalysed oxidation of 2-octanol in EtOAc in the presence of $Co(OAc)_2$ and benzoic acid to take place efficiently, and 2-octanone was obtained with 80% yield (run 45). Moreover, the oxidation of 2-octanol could be successfully carried out under the conditions previously described for the oxidation of cycloalkanes, e.g., NHS,

Table 5. Oxidation of 2-octanol catalysed by NHPI or NHS at various temperatures in different solvents.[a]

Run	Conditions	Co-catalyst	T [°C]	Time [h]	Conv.[b] [%]	Sel. to ketone[b] [%]
40	$Co(acac)_3$, $PhCF_3$	NHS	100	24	84	94
41	$Co(acac)_3$, CH_3CN	NHPI	75	24	93	100
42	$Co(acac)_3$, CH_3CN	NHS	75	24	11	91
43	$Co(OAc)_2$, $PhCO_2H$, EtOAc	NHPI	25	24	70	100
44	$Co(OAc)_2$, $PhCO_2H$, EtOAc	NHS	25	24	12	100
45	$Co(OAc)_2$, $PhCO_2H$, EtOAc	NHS	75	24	85	94
46[c]	$Co(OAc)_2$, $PhCO_2H$, EtOAc	NHS	75	24	94	95

[a] Experimental conditions: 2-octanol (4.5 mmol), NHS or NHPI (0.45 mmol), Co-complex (0.022 mmol), $PhCO_2H$ (0.22 mmol), solvent (7.5 mL), O_2 1 atm.
[b] Conversions and selectivities towards ketone are determined by GC using 1,2,4-trichlorobenzene (200 mg) as internal standard.
[c] No stirring.

Table 6. Oxidation of 2-octanol in EtOAc catalysed by Co/NHS and additives.[a]

Run	Metal salt	Additive[b]	T [°C]	Time [h]	Conv.[c] [%]	Sel. To ketone[c] [%]
47	$Co(OAc)_2$	none	75	24	57	95
48		$PhCO_2H$	75	24	85	94
49		$PhCO_2H$	100	2	89	89
50		MCBA	75	24	94	93
51		PMBA	75	24	45	98
52	$Co(acac)_3$	none	75	24	90	92
53		$PhCO_2H$	75	24	97	95
54		$PhCO_2H$	100	5	93	99
56		PMBA	75	24	78	95

[a] Experimental conditions, see Table 5.
[b] MCBA: 3-chlorobenzoic acid, PMBA: 4-methoxybenzoic acid.
[c] Conversions and selectivities are determined by GC using 1,2,4-trichlorobenzene as internal standard.

$Co(acac)_3$ in $PhCF_3$ at 100 °C, resulting in 2-octanone in 94% selectivity at 84% conversion (run 40).

We subsequently studied the effect of different combinations of metal salt, additive and temperature on the aerobic oxidation of 2-octanol in the presence of NHS (see Table 6). The best result was obtained at 75 °C in EtOAc, with benzoic acid and $Co(acac)_3$ (97% conversion at 24 h, 92% selectivity to octanone, run 53). Raising the temperature to 100 °C (run 54) resulted in 93% conversion in 5 h (selectivity 92%). The superior results obtained in the presence of benzoic acid can be explained as follows. The benzoic acid can protonate the acetate ligand to give the weak, labile acetic acid ligand:

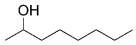
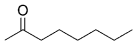
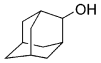
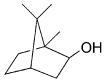
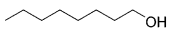
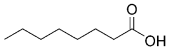
$$[Co(OAc)_2(H_2O)_4] + PhCOOH \longrightarrow [Co(OAc)(HOAc)(H_2O)_4] + PhCOO^-$$

One might expect, therefore, to see an increased activity with increasing acidity of the benzoic acid, which is what we observed: conversions decreased in the order 3-chlorobenzoic acid > benzoic acid > 4-methoxybenzoic acid (Table 6).

Different secondary alcohols were oxidised following the procedure developed for 2-octanol [NHS 10 mol %, $Co(acac)_3$ 0.5 mol %, $PhCO_2H$ 5 mol %, in EtOAc at 100 °C] and the results are summarised in Table 7. Cyclic aliphatic alcohols gave good to excellent results (runs 58 – 64). The oxidation of 2-adamantanol (entry 60) and D,L-borneol (entry 61) was very efficient: both adamantanone and camphor were obtained with 94 and 92% yield, respectively, the latter needing a longer reaction time (10 h *vs.* 3 h for adamantanone) (runs 60 and 61). Cyclohexanol and cyclododecanol were at first oxidised at 100 °C leading to a fast reaction and 90 – 94% conversion after 5 to 6 hours of reaction (runs 58 and 59), but the corresponding ketones were obtained with less than 80% yield (75 and 78%, respectively, for cyclohexanone and cyclododecanone). The oxidation was then performed at lower temperature (75 °C) leading to a slower reaction rate but still very efficiently and much more selectively. Cyclohexanol was oxidised with 90% conversion leading to cyclohexanone with 87% yield (97% selectivity).

As expected the oxidation of secondary benzylic alcohols (at 100 °C) gave excellent results (runs 62 – 64). 1-Phenylethanol and benzhydrol were oxidised within

Table 7. Oxidation of different alcohols catalysed by NHS.[a]

Run	Alcohol	Time [h]	Conversion [%]	Product	Yield[b] [%]
57		5	93		92
58		6 8[c]	94 90		75 87
59		5	90		78
60		3	96		94
61		10	96		92
62		2	100		98
63		2	100		100
64		4	97		86
65		8[d]	86		67
66		4[d]	100		100

[a] Experimental conditions: 2-octanol (4.5 mmol), NHS or NHPI (0.45 mmol), $Co(acac)_3$ (0.022 mmol), $PhCO_2H$ (0.22 mmol), butyl acetate (7.5 mL), 100 °C, O_2 1 atm.
[b] Conversions and yields are determined by GC using 1,2,4-trichlorobenzene (200 mg) as internal standard.
[c] Using 0.5 mol % $Co(OAc)_2$ and 5 mol % MCBA in EtOAc as solvent at 75 °C.
[d] Using 0.5 mol % $Co(OAc)_2$ and 5 mol % *m*-CPBA(*m*-chloroperbenzoic acid) in EtOAc as solvent at 75 °C.

2 hours with complete conversion and almost complete selectivity (runs 62 and 63). The oxidation of 1,2,3,4-tetrahydro-1-naphthol gave α-tetralone in 86% yield at almost complete conversion (run 64). Finally, 1-octanol and benzyl alcohol were oxidised under slightly different conditions [NHS 10 mol %, $Co(OAc)_2 \cdot 4\,H_2O$ 0.5 mol %, *m*-CPBA (*m*-chloroperbenzoic acid) 5 mol %, EtOAc, 75 °C] (runs 65 and 66). Oxidation of 1-octanol led to the formation of octanoic acid in 67% yield at 86% conversion. Benzyl alcohol gave very good results with complete conversion after 4 hours, benzoic acid being formed in 100% yield.

Ethylbenzene Oxidation

We also applied our new catalytic system to the oxidation of ethylbenzene. In our hands oxidation of ethylbenzene under optimised Ishii's conditions, namely $Co(acac)_2$/NHPI, in acetic acid at 100 °C under 1 atm of molecular oxygen, gave 82% conversion in 6 hours, affording acetophenone in 90% selectivity (Table 8, run 67). Substitution of NHPI by NHS led to a decrease in activity. The conversion reached 55% and acetophenone was formed in only 66% selectivity (run 68). When performed in CH_3CN at 85 °C, the difference of reactivity between NHPI and NHS was even larger (runs 69 and 70). These results are comparable to those obtained in alcohol oxidations, NHPI showing a higher catalytic activity than NHS. The protocols developed for the oxidation of cycloalkanes [e.g., $Co(acac)_3$/NHS in $PhCF_3$ at 100 °C] and alcohols [$Co(OAc)_2$/NHS, $PhCO_2H$ in BuOAc at 100 °C] were applied to the oxidation of ethylbenzene. The former conditions were not successful: conversion remained below 50% even after 24 hours (Table 8, run 71). When the second set of conditions was applied, the conversion reached 71% after 12 hours with high selectivity toward the formation of acetophenone (96%) along with a small amount (3%) of phenylethanol (run 72).

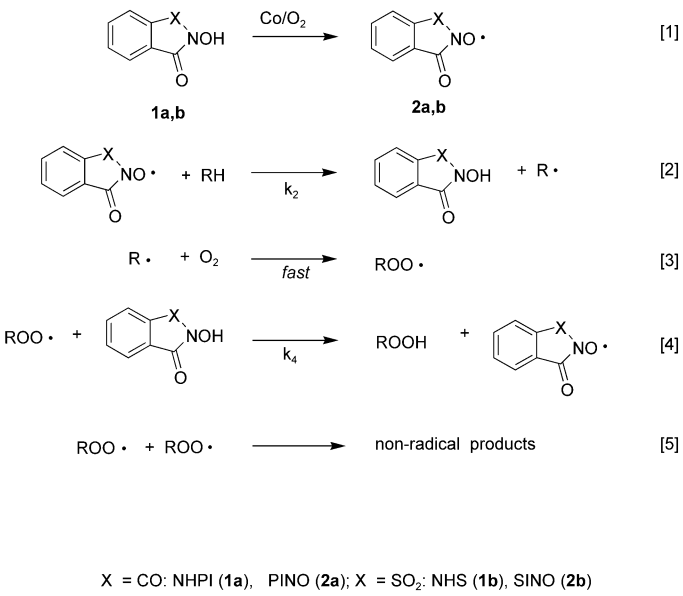
Mechanistic Considerations: NHS *vs.* NHPI

In accordance with the mechanism proposed by Ishii and co-workers[5] the carbon radical chain promoter (NHPI or NHS) is involved in two chain propagation steps (see Scheme 5).

Table 8. Oxidation of ethylbenzene catalysed by Co/NHS or Co/NHPI.[a]

Run	Catalytic system	Solvent	T [°C]	Time [h]	Conv.[b] [%]	Sel. to acetophenone[b, c] [%]
67	$Co(acac)_2$/NHPI	AcOH	100	6	82	90
68	$Co(acac)_2$/NHS	AcOH	100	6	55	66
69	$Co(OAc)_2$/NHPI	CH_3CN	85	8	85	80
70	$Co(OAc)_2$/NHS	CH_3CN	85	8	27	42
71	$Co(acac)_3$/NHS	$PhCF_3$	100	24	46	76
72	$Co(OAc)_2$/NHS, $PhCO_2H$	BuOAc	100	12	71	96

[a] Experimental conditions: 10 mol % NHPI or NHS, 0.5 mol % Co-complex, 5 mol % $PhCO_2H$ (when added).
[b] Conversions and yields are determined by GC using 1,2,4-trichlorobenzene as internal standard.
[c] Selectivity based on ethylbenzene reacted.



Scheme 5.

In the first step the *N*-oxyl radical, PINO (**2a)** or SINO (**2b**), generated by reaction of Co^{II}/O_2 with NHPI (**1a**) or NHS (**1b**) (see also Scheme 2), abstracts a hydrogen atom from the substrate [Eq. (2)]. The resulting alkyl radical reacts with dioxygen, in a diffusion-controlled step, to produce the corresponding alkylperoxy radical [Eq. (3)]. The alkylperoxy radical subsequently reacts with **1a** or **1b** to afford the alkyl hydroperoxide, as the primary oxidation product, and regenerate the *N*-oxyl radical **2a** or **2b** [Eq. (4)].

The intervention of NHPI or NHS in the radical chain process results in an increase in both the rate and selectivity of the autoxidation.[8] In previous studies it was shown that for the autoxidation of cyclohexylbenzene – in the presence of NHPI – a higher intrinsic selectivity towards the main product of the reaction was observed. This increase of both the rate and selectivity of product formation could be explained by the fact that NHPI increased the rate of propagation and/or decreased the rate of termination. Efficient scavenging of alkylperoxy radicals by **1a** or **1b** [Eq. (4)] results in a decrease in the rate of bimolecular termination [Eq. (5)], thereby affording an increase in the overall rate. An increase in selectivity in cycloalkane oxidation could be a consequence of the fact that efficient scavenging of alkoxy and alkylperoxy radicals (see Scheme 4) takes place in the presence of high concentrations of NHPI/NHS, thus suppressing cleavage and transannular hydrogen abstraction, respectively.

In this study we have shown that NHS (**1b**) is a more effective catalyst in the oxidation of cycloalkanes while NHPI is more effective in the oxidation of alcohols and alkylbenzenes. We suggest that a plausible explanation for this reversal of activity is that it is a consequence of a change in the relative rates of reactions (2) and (4). The rate of reaction (2) is largely determined by the bond dissociation enthalpy (BDE) of the substrate and NHPI (**1a**) or NHS (**1b**). The BDE of the C–H bond of cycloalkanes (95 kcal/mol) is significantly higher than that of α-C–H bond of alcohols or alkyl benzenes (*ca.* 85 kcal/mol). This difference will be reflected in a larger activation energy and lower rate for reaction (2) for cycloalkanes compared to alcohols or alkylbenzenes.

According to a recent study,[19] substitution of alkyl, aryl or vinyl groups, attached to the nitrogen atom of hydroxylamines, with acyl groups results in a large increase in the BDE of the OH bond (from 70 to 88 kcal/mol). This effect was rationalised on the basis of the resonance stabilisation energy derived from the extra mesomeric structures which are not possible for the dialkylhydroxylamines. Substitution of one of the carbonyl groups in NHPI by the more electron-withdrawing sulphonyl moiety is expected to lead to an even higher BDE of the NO–H bond. This translates to an *N*-oxyl radical which is more difficult to generate but, by the same token, is more reactive in the abstraction of a hydrogen atom of the substrate.

Hence, we propose that in the oxidation of the less reactive cycloalkane substrates reaction (2) is rate-limiting and is faster with SINO (**2b**) than with PINO (**2a**). In contrast, in the oxidation of the more reactive substrates – alcohols and alkylbenzenes – reaction (2) is much more favourable and reaction (4) can become rate-limiting. Based on the same BDE arguments this reaction is expected to be more favourable for NHPI *vs.* NHS.

In NHPI- and NHS-catalysed oxidations the metal co-catalyst, usually a cobalt compound, actually functions as an initiator, i.e., to generate the *N*-oxyl radical which then enters the catalytic cycle (Scheme 1). If the goal is to achieve a high yield of hydroperoxide the metal catalyst should be replaced with a radical initiator, such as a peroxide, to avoid metal-catalysed decomposition of the hydroperoxide.[8] When the desired product is the ketone the metal catalyst has a second function: to catalyse the decomposition of the alkyl hydroperoxide.

The overall catalytic activity of NHS and NHPI-based systems is very dependent on the choice of initiator (metal complex) and solvent. As noted earlier, depending on the solvent used, and the reaction temperature, either $Co(acac)_2$ or $Co(acac)_3$ is the better initiator. We believe that this is caused by a delicate balance of rates of ligand substitution reactions at cobalt (it is well-known that ligand substitution at Co^{III} is a rather slow process at lower temperatures) and one-electron transfer processes leading to the eventual formation of the actual catalyst, the *N*-oxyl radical. Thus, the latter can either be formed *via* reaction of NHS with an $acacO_2\cdot$ radical, formed by dissociation of $Co^{III}(acac)_3$ (Scheme 2) or by ligand substitution at $Co^{III}(acac)_2$ of NHS followed by one-electron transfer from the *N*-oxy ligand to Co^{III} (see Scheme 3).

Conclusions

The NHS/Co combination is an effective catalyst for the aerobic oxidation of cycloalkanes to the corresponding cycloalkanones, displaying higher activities than the previously reported NHPI/Co system. The system was also applied successfully to the autoxidation of ethylbenzene to acetophenone and of a variety of secondary and primary alcohols to the corresponding ketones and carboxylic acids, respectively. A mechanistic rationale is proposed to explain the activities of *N*-oxyl radicals as autoxidation catalysts and the different reactivities observed for NHS and NHPI.

Experimental Section

Safety Remarks

Aerobic oxidations should always be performed with caution. In our case with 100% molecular oxygen, we worked above the explosion limit, and monitored the oxygen uptake by a burette. Laboratory glassware was used behind safety screens, and the scale was limited to 10 mL solutions.

Chemicals

The chemicals were obtained from commercial sources and used as received. *N*-Hydroxysaccharin (NHS) was synthesised according to a seven-step synthesis published by Nagasawa et al.[5] in 1995 with an overall yield of 17%. ^{1}H NMR (DMSO): $\delta = 7.9-8.1$ (m, 4H, H_{arom}), 11.2 (b, 1H, NOH); ^{13}C NMR (DMSO): $\delta = 121.5$, 125.1, 125.8, 134.7, 135.2, 135.7 ($6C_{arom}$), 157.5 (C=O).

Typical Catalytic Run

Experiments were carried out in a two-necked 25-cm^3 round-bottom flask containing a magnetic stirrer, equipped with a condenser and connected to a gas burette filled with molecular oxygen. In a typical experiment 504 mg (3 mmol) of cyclododecane, 60 mg (0.3 mmol) of *N*-hydroxysaccharin, 5.3 mg (0.015 mmol) of $Co(acac)_3$ and 200 mg of 1,2,4-trichlorobenzene were weighed in the flask before addition of 7.5 mL acetic acid or 9 mL of acetic acid. A series of vacuum/molecular oxygen purges were applied before the reaction was started. The resultant mixture was stirred at a temperature of 80 °C for 10 hours.

For 2-octanol oxidation in a typical experiment 585 mg 2-octanol (4.5 mmol), 90 mg (0.45 mmol) of *N*-hydroxysaccharin, 8 mg (0.022 mmol) $Co(acac)_3$, 27.5 mg (0.022 mmol) of benzoic acid and 200 mg of 1,2,4-trichlorobenzene were dissolved in 7.5 mL solvent, followed by oxygen purges. The resultant mixture was stirred at a temperature of 100 °C for 5 h. For other substrates conditions are listed with the tables.

Analysis

The reactions were monitored by gas chromatography using a CP-WAX 52 CB column (50 m × 0.53 mm). A typical temperature program starts at 50 °C (5 min) with a ramp of 8 °C/min up to 220 °C. The reported yields are thus GC yields and are determined using 1,2,4-trichlorobenzene as the internal standard. Molar responses were obtained by calibration of pure samples against this internal standard. 1,15-Pentadecanoic acid, 1,12-dodecanedioic acid, 1,10-decanedioic acid and 1,8-octanedioic acid were analysed by HPLC (Waters Symmetry C18 reversed phase column, eluent: water/methanol, 50:50, 0.1% TFA) using octanoic acid as an internal standard. The products reported in the tables, plus the two isomeric hydroxycyclododecanones and two isomeric cyclododecadienones which have been identified, together account for more than 90% of the substrate converted.

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