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Selective catalytic oxidation of cyclohexylbenzene to cyclohexylbenzene-1-hydroperoxide: a coproduct-free route to phenol

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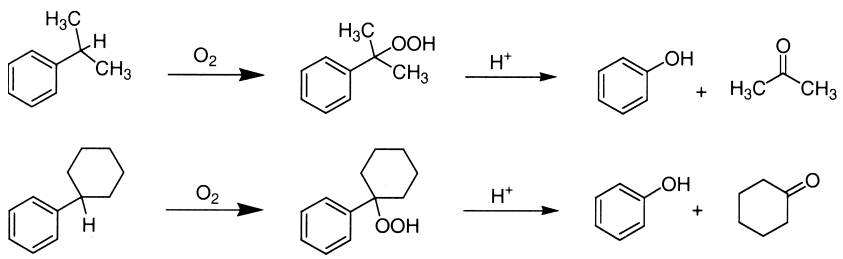
Abstract—A method is described for the highly selective oxidation of cyclohexylbenzene to cyclohexylbenzene-1-hydroperoxide. In the presence of 0.5 mol% *N*-hydroxyphthalimide (NHPI) and 2 mol% of the hydroperoxide product, without solvent, a selectivity of ca. 98% to the desired product was obtained at 32% conversion. The use of NHPI increases the selectivity for initial H-abstraction from the 1-position, vs the other positions in the cyclohexyl ring, suppresses byproduct formation via transannular hydrogen abstraction and increases the overall rate of reaction.

1. Introduction

The production of phenol via the Hock process is a well-established commercial process that accounts for >1 million tons of phenol production annually on a world-wide basis.[1,2] Cumene, which is prepared by reaction of benzene with propylene, is oxidized with molecular oxygen to give the corresponding hydroperoxide (Scheme 1). Acid-catalyzed decomposition of the latter affords one equivalent of both phenol and acetone. Herein lies the disadvantage of the Hock-process: coproduction of acetone. A coproduct-free route to phenol would, therefore, be an economically attractive alternative.

One possible alternative involves the use of cyclohexylbenzene (CHB) (see Scheme 1). Analogous to cumene, the corresponding tertiary hydroperoxide can be easily converted into phenol and cyclohexanone.[3] However, in this case, the cyclohexanone coproduct can be dehydrogenated to give a second molecule of phenol,[4] thus providing an overall coproduct-free route to phenol. The complete process scheme is depicted in Scheme 2. CHB can be made from benzene via two possible routes (Scheme 2): (a) selective hydrogenation of benzene to cyclohexene over a ruthenium catalyst[5] followed by Friedel–Crafts alkylation of a second molecule of benzene or (b) oxidative coupling of benzene to biphenyl[6] followed by selective hydrogenation of the latter.[7] Route (a) requires no net consumption of hydrogen and is 100% atom efficient.[8] Route (b), on the other hand, involves the consumption of one equivalent of hydrogen and the formation of one equivalent of water. Recently a palladium based catalytic system was described,



Scheme 1. Production of phenol via cumene hydroperoxide and cyclohexylbenzene-1-hydroperoxide, respectively.

Keywords: autoxidation; cyclohexylbenzene; phenol; *N*-hydroxyphthalimide.
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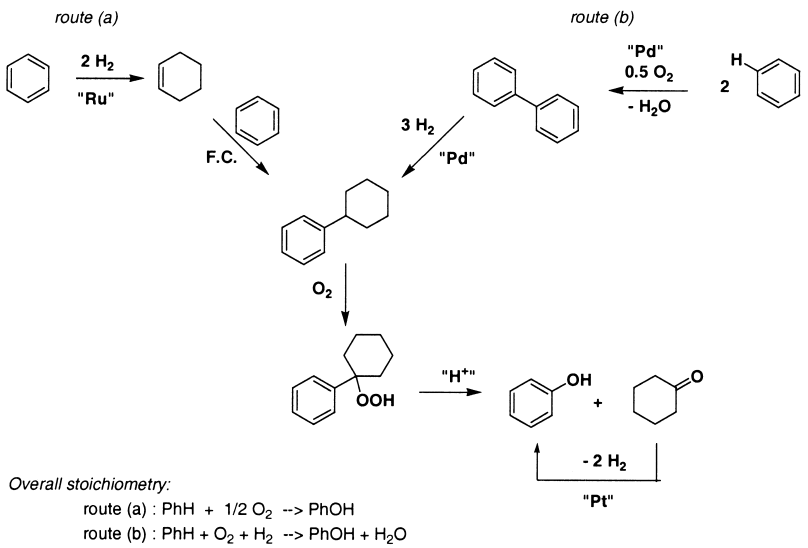
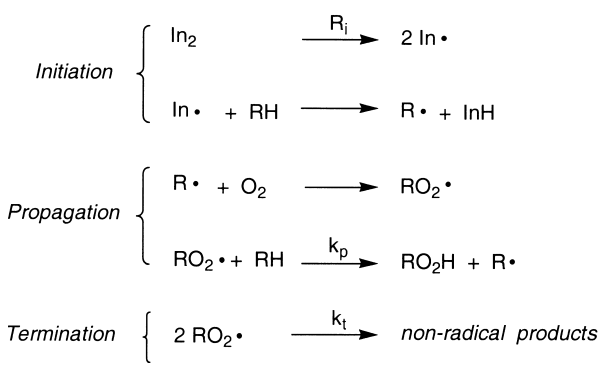


Scheme 2. Process scheme for the production of phenol.

which performs this oxidative coupling of benzene at 105°C under moderate oxygen pressure.[6]

Compared to cumene, which has only one reactive tertiary C–H position to be oxidized, cyclohexylbenzene has 1 tertiary position and 10 secondary C–H positions.[9] Earlier reports[10] from patents indicated, however, that in the presence of azo-initiators air oxidation of cyclohexylbenzene resulted in a selectivity for cyclohexylbenzene-1-hydroperoxide (CHBHP) as high as 90% albeit at low conversion levels of 3–5%. This encouraged us to embark on the study of the selective autoxidation of cyclohexylbenzene. In order to have practical utility the autoxidation of CHB should afford CHBHP in >90% selectivity at conversions of ca. 30%.

The free radical chain mechanism of hydrocarbon autoxidation is well documented.[2,11] The susceptibility of any substrate to autoxidation is determined by the ratio $k_p/(2k_t)^{1/2}$-referred to as the oxidizability[12]-which determines the length of the propagating chain and thus the rate of the reaction (see Scheme 3). A vital role is played by alkylperoxy radicals, which are the active propagating species. In order to improve the performance in autoxidation processes, a large variety of additives have been demonstrated to exhibit (minor) advantages, among which HBr/Br^- is probably most well understood.[13] This

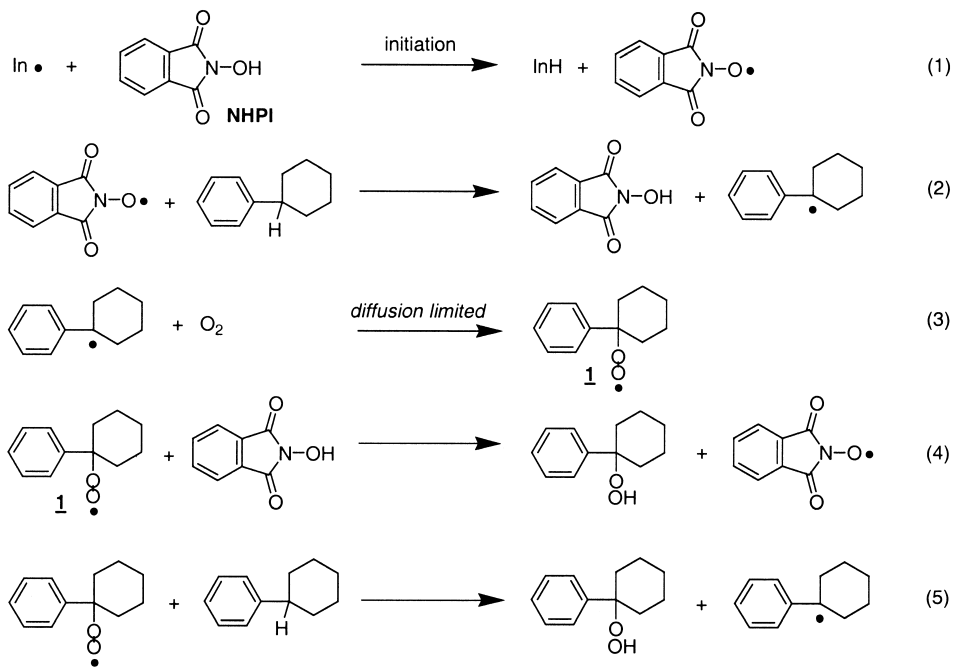


Scheme 3. Standard mechanism autoxidation.

effect was ascribed to the replacement of the chain carrying alkylperoxy radicals by bromine atoms. Bromine atoms exhibit higher selectivity and retard the termination process thereby accelerating the rate of oxidation.

Recently Ishii has described the selective oxidation of a large variety of substrates by the combination of *N*-hydroxyphthalimide (NHPI) and metal salts.[14] Under these conditions, alcohols and ketones are the main products. The use of NHPI/metal resulted in high yields and selectivities under mild conditions. For example, using NHPI (10 mol%) and $Co(OAc)_2$ (0.5 mol%) the oxidation of toluene in acetic acid for 20 h afforded benzoic acid and benzaldehyde in 81% and 3% yield, respectively.[15] The metal salt functions as an initiator for the autoxidation reaction, but also catalyzes the decomposition of the intermediate hydroperoxides. Since the metal salt acts only as an initiator we envisaged that it could be replaced by organic initiators leading to an NHPI catalyzed oxidation that would afford the hydroperoxide in high selectivity. The validity of this idea was given support by a recent publication of the group of Ishii, which described the preparation of hydroperoxides in 75% yield, using 10 mol% NHPI as the catalyst.[16] This publication prompted us to report our results on the selective oxidation of CHB, using NHPI as a catalyst.[17] We will show that when using NHPI concentrations as low as 0.1 mol%, CHBHP can be prepared in 97% yield.

The role of NHPI is analogous to that of HBr in metal-catalyzed autoxidation processes. However, HBr could not be used for our purposes, as it would lead to acid-catalyzed decomposition of the hydroperoxide product. Although this is the final goal, in situ formation of phenol would even inhibit the autoxidation reaction. The proposed reaction sequence is shown in Scheme 4. NHPI efficiently traps the intermediate alkylperoxy radicals (reaction 4) thereby suppressing competing termination. The thus formed phthalimide *N*-oxy radical (PINO) abstracts a hydrogen from the substrate to regenerate NHPI (reaction 2). Obviously the ratio of propagation to termination and hence the hydroperoxide selectivity will be directly



Scheme 4. Reaction scheme for the NHPI catalyzed oxidation of cyclohexylbenzene.

dependent on the NHPI concentration. A decrease in NHPI concentration should lead to a decrease in both rate and selectivity of RO_2H formation.

2. Results and discussion

Oxidation reactions were performed using neat CHB with 1 bar of pure oxygen. In initial experiments we investigated the oxidation of CHB in the presence of 1.5–2 mol% of *tert*-butyl hydroperoxide (TBHP) or CHBHP and commercially available azo compounds as initiators at different temperatures. The results are given in Table 1. The selectivity decreased rapidly with increasing conversion. At 100°C and 5% conversion, a selectivity of 87% was achieved, while at 9% conversion the selectivity for the 1-hydroperoxide decreased to 65%. The main byproducts were the cyclohexylbenzene-4-hydroperoxide (around 8% selectivity) and the 1,3-disubstituted products **A** and **B** (total selectivity ranging from 4 to 15%, for structures see Scheme 5 and Experimental). The latter two products arise from transannular abstraction of hydrogen from the 3 position of the cyclohexane ring in the intermediate alkylperoxy radical **1** as depicted in Scheme 5. Mass spectral data (see Experimental) are in accordance with the assigned structures of **A** and **B**. Furthermore, molecular mechanics calculations showed that for the 1-phenylcyclohexylperoxy radical (**1**) the interatomic distance between the distal

Table 1. Autoxidation of cyclohexylbenzene using azo-initiators and hydroperoxide

Initiator	Temperature (°C)	Conv.% CHB	Selectivity products (%)[a]					Ratio[b] attack at 1 vs 4-position
			1-ROOH	2-ROOH	4-ROOH	**A**	**B**	
AMDN[c]	40	0.96	94.8	–	2.4	0.50	–	40
AMDN[c]	50	1.9	94.0	–	2.5	0.65	–	39
ADVN[d]	60	3.1	87.5	–	4.0	1.8	1.0	23
ACCN[e,f]	95	5.1	86.7	–	8.0	10	5.0	10
AIBN[g]	95	6.0	76.2	–	8.3	6.8	3.6	9.2
ACCN[e]	95	9.5	65.0	–	8.0	10	5.0	10
No[h]	100	3.2	86.0	0.9	7.4	5.1	0.7	11
No[h]	110	13	78.7	0.5	9.4	7.7	1.2	8.8
No[h]	120	20	72.2	0.5	9.1	12	1.0	8.8

Conditions: no solvent, 60 mmol CHB, 0.19 mmol initiator, 0.9 mmol TBHP, 8 h reaction time, 1 atm O_2, hydroperoxide determined by GC as well as iodometric titration.

[a] Selectivity of products formed, missing balance is accounted for by several unidentified products in low quantities.

[b] Ratio of initial attack at 1-position vs attack at 4-position. Calculated as {[1-ROOH]+[**A**]+[**B**]}/{[2-ROOH+[4-ROOH]}.

[c] Initiator is=2,2′-azobis(4-methoxy,2,4-dimethylvaleronitrile)=AMDN, $t_{1/2}$=150 min at 60°C and 37 min at 50°C.

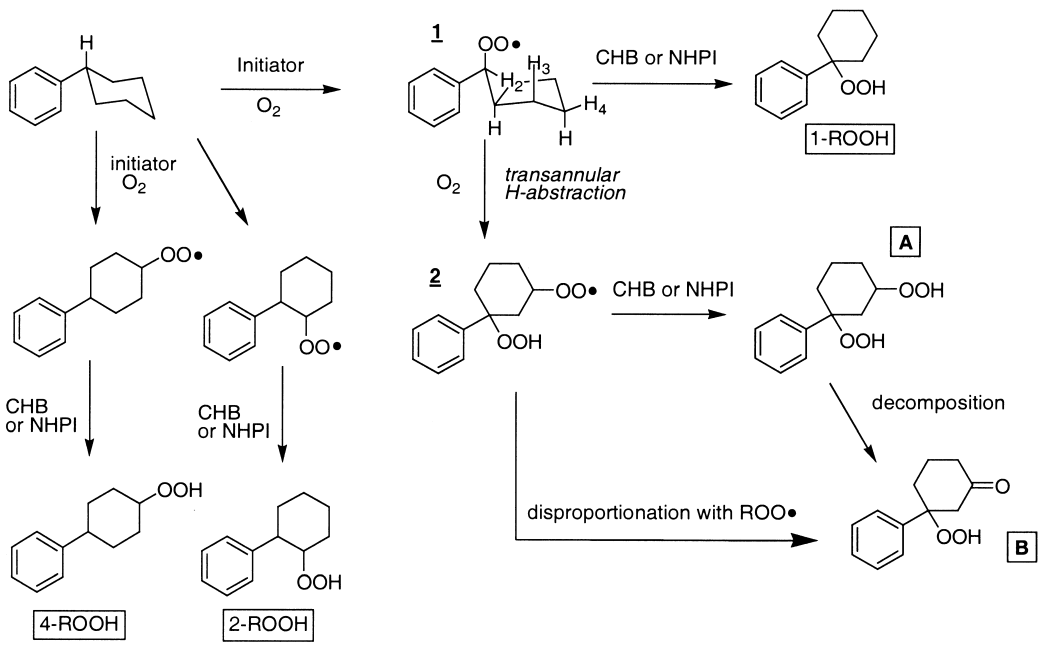
[d] Initiator is 2,2′-azobis(2,4-dimethyl valeronitrile)=ADVN, $t_{1/2}$=200 min at 60°C.

[e] 1,1′-azobis(cyclohexane carbonitrile) (ACCN) was used as initiator, $t_{1/2}$=150 min at 100°C.

[f] No TBHP was added.

[g] 2,2′-azobis(2-methylpropionitrile) (AIBN) was used as initiator, $t_{1/2}$=10 min at 100°C.

[h] No azo-initiator and 1.2 mmol CHBHP was used.



Scheme 5. Formation of products in the radical oxidation of cyclohexylbenzene.

peroxy oxygen and the H-atom at the 3-position is substantially shorter (2.4 Å) than for the 2- (3.0 Å) or the 4-position (4.0 Å). We conclude, therefore, that transannular hydrogen abstraction in **1** occurs from the 3-position, resulting in the formation of **A** and **B**.

The other byproducts—the 2- and 4-hydroperoxides were identified by comparison with authentic samples of the corresponding alcohols (after reduction with triphenylphosphine). Hence, lower selectivities result from two competing processes: oxidation at the 1 vs other positions in the cyclohexane ring and transannular hydrogen abstraction in the intermediate alkylperoxy radical. Competition from both processes increased with increasing temperature.

The oxidations were also performed in the presence of 1 mol% NHPI. The results are shown in Table 2. Our first attempts using a combination of azo-initiator and NHPI did not give satisfactory results. However, the combination of CHBHP and NHPI between 100 and 110°C gave a selectivity as high as 96% at 29% conversion, which remained 94% at 37% conversion. In the presence of NHPI but without extra CHBHP (entries 1–3, Table 2) the selectivity for oxidation at the 1-position was improved but the transannular hydrogen abstraction was still significant. Apparently the presence of high concentrations of CHBHP in the beginning of the reaction instead of azo-initiator is essential to prevent the latter rearrangement. Thus, only in the presence of both NHPI and CHBHP, was the selectivity for oxidation at the 1-position improved and the rearrangement of the intermediate alkylperoxy radical suppressed.

A possible explanation for this effect may be that CHBHP undergoes homolytic decomposition at an optimum rate under these conditions (100–110°C) during the early stages of reaction. It is well known[2] that in order to achieve smooth autoxidations the rate of initiation should have an optimum value. If the rate is too low, little or no reaction occurs while if it is too fast the selectivity decreases owing to higher

Table 2. Oxidation of cyclohexylbenzene catalyzed by NHPI

Entry	Temperature (°C)	Initiator	Conv.% CHB	Selectivity products (%)[a]					Ratio[b] attack at 1 vs 4-position
				1-ROOH	2-ROOH	4-ROOH	**A**	**B**	
1	60	ADVN[c]	2.3	96.9	–	1.1	1.3	0.7	90
2	95	AIBN[d]	9.5	65.2	0.4	2.9	13	8.0	25
3	95	ACCN[e]	17	58.1	1.0	0.8	9.8	12	44
4	95	CHBHP	8.4	98.0	0.2	1.8	–	–	49
5	100	CHBHP	29	96.2	–	2.1	1.6	0.1	47
6	110	CHBHP	37	93.9	0.2	2.5	2.7	0.2	36

Conditions: no solvent, 60 mmol CHB, 0.6 mmol NHPI (1 mol%), 0.03 mmol azo-initiator (0.05%) or 1.2 mmol CHBHP (2 mol%), 8 h reaction time,1 atm O_2, internal standard used is naphthalene; hydroperoxide determined by GC as well as iodometric titration.

[a] Selectivity of products formed, missing balance is accounted for by several unidentified products in low quantities.

[b] Ratio of initial attack at 1-position vs attack at 4-position. Calculated as {[1-ROOH]+[**A**]+[**B**]}/{[2-ROOH+[4-ROOH]}.

[c] See footnote d Table 1.

[d] See footnote g Table 1.

[e] See footnote e Table 1.

Table 3. Oxidation of cyclohexylbenzene at 100°C using CHBHP as initiator: dependence on NHPI concentration

Entry	Ratio CHB/NHPI	Conv.% CHB	Selectivity products (%)[a]			
			1-ROOH	2-ROOH	4-ROOH	**A**
1	No NHPI	3.2	86.0	0.9	6.0	2.9
2	2000	14	94.1	0.3	4.0	1.7
3	1000	19	96.7	0.1	3.2	–
4	200	32	97.6	–	1.2	0.4
5	100	29	96.2	–	2.1	1.6

Conditions: no solvent, 60 mmol CHB, 0.6 mmol NHPI (1 mol%), 1.2 mmol CHBHP (2 mol%), 8 h reaction time, 1 atm O_2, internal standard used is naphthalene; hydroperoxide determined by GC as well as iodometric titration.
[a] See note a, Table 2. Yield of product **B**, was <0.5% in all cases.

concentrations of alkylperoxy radicals resulting in more termination vs propagation (which can also lead to a decrease in overall rate).

The results of studies of selectivity and conversion as a function of NHPI concentration are presented in Table 3. Without NHPI the conversion after 8 h was as low as 3%, with 86% selectivity for cyclohexylbenzene-1-hydroperoxide. However, the presence of even 0.05% NHPI was sufficient to increase conversion to 13%, with 94% selectivity for CHBHP. The optimum result (32% CHB conversion and 97.6% selectivity to CHBHP) was achieved using 0.5% of NHPI and 2 mol% of the CHBHP product as the initiator. The use of 1 mol% NHPI did not lead to further improvements. This is most likely due to the limited solubility of NHPI in cyclohexylbenzene, which is close to 0.5 mol% at 100°C.[18] Fig. 1 summarizes all the results obtained, by depicting the selectivity obtained as a function of conversion. It shows that only in the presence of both NHPI and CHBHP does the selectivity remain constantly high with conversions of up to 37%. These results clearly demonstrate the validity of our idea that NHPI should increase both the *rate* and *selectivity* of alkyl hydroperoxide formation by increasing the rate of propagation and/or decreasing the rate of termination.

3. Conclusions

We have developed a highly efficient method for the selective autoxidation of cyclohexylbenzene to cyclohexylbenzene-1-hydroperoxide using NHPI as the catalyst and the CHBHP product as the initiator. Commercially attractive results (ca. 98% selectivity at 20–30% conversion) were obtained with CHB/NHPI molar ratios as high as 200–1000. These results provide the basis for a new coproduct-free route to phenol. We are currently investigating the use of this methodology for the synthesis of other industrially useful alkyl hydroperoxides and will report our results in due course.

4. Experimental

4.1. Safety caution

The production of hydroperoxides 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, making sure that the conversion stayed below 40%. Laboratory glassware was used behind safety screens, and the scale was

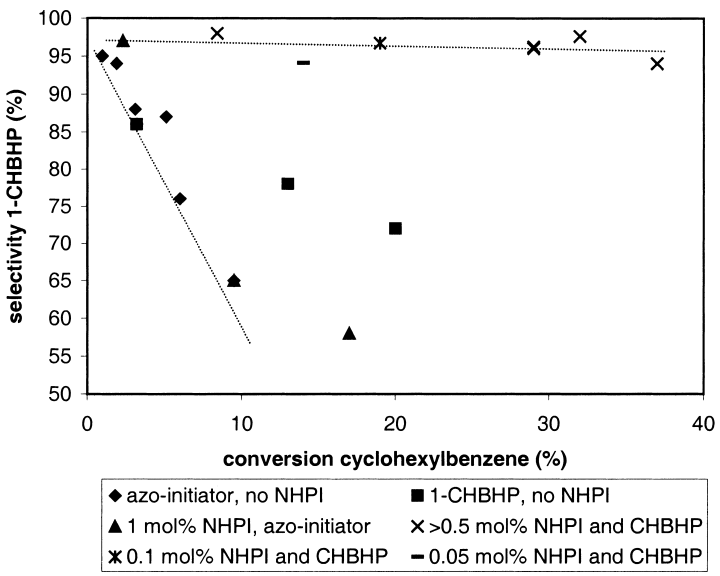


Figure 1. Conversion vs selectivity plot for all data reported in Tables 1–3.

limited to 10 ml solutions. Hydroperoxides were stored at 4°C as dilute solutions, with the corresponding alkylbenzenes as solvent.

4.2. Materials

AMDN (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) and ADVN (2,2′-azobis(2,4-dimethyl valeronitrile) were purchased from WACO, Pure Chemical Industries Ltd, Japan (trade names V-65 and V-70, respectively). Cyclohexylbenzene-1-hydroperoxide was prepared from the corresponding alcohol using H_2O_2 and H_2SO_4, adopting a similar reported procedure.[19] All other chemicals were from commercial sources. Cyclohexylbenzene was distilled before use.

4.3. Typical experimental procedure

(For variations in amount of reagents etc. see footnotes in tables.) Reactions were performed in a stirred three-necked flask equipped with a condenser. A typical reaction mixture consisted of 60 mmol cyclohexylbenzene (10.1 ml), 0.6 mmol of NHPI, 1.2 mmol of the cyclohexylbenzene-1-hydroperoxide, and 4 mmol of naphthalene as internal standard (quantities for specific experiments can be found in the tables). 1 atm of oxygen was applied by first purging the reaction mixture and protecting the reaction atmosphere with a gas-burette filled with water. In this way the oxygen uptake could be followed in time. After this the reaction was brought to the reaction temperature and run for 8 h. Samples were taken during and after the reaction. Samples were cooled down, diluted with dichloromethane and enough triphenylphosphine was added to reduce all the alkylhydroperoxides present in the liquid to the corresponding alcohols. Analysis followed with the GC. Iodometric titration was performed to determine the amount of hydroperoxide present in the reaction mixture. The amounts of hydroperoxides given in Tables 1–3 correspond to the total amount of the alcohols produced after reduction. A close correspondence of the amount of hydroperoxide, determined by iodometric titration, with the amount of alcohols determined by GC, after reduction with triphenylphosphine, was taken as evidence that only minor amounts of alcohols are formed as primary products in reactions in the presence of NHPI.

4.4. Analysis

Products were analyzed after reduction with triphenylphosphine by GC, using naphthalene as an internal standard and a CP-Sil-5 CB (50 m×0.53 mm) column. Qualitative and quantitative analysis of 1-phenylcyclohexanol, 2-phenylcyclohexanol and 4-phenylcyclohexanol (obtained by reduction of 1-, 2- and 4-substituted cyclohexylbenzene hydroperoxide) was achieved by comparison with authentic samples. 1- and 2-phenylcyclohexanol were obtained from commercial sources, while 4-phenylcyclohexanol was synthesized by catalytic reduction of 4-phenylcyclohexanone. The retention times of cyclohexylbenzene, 1-, 2- and 4-phenylcyclohexanol were 13.7, 16.0, 16.7 and 16.9 min, respectively (temp. program: init. temp 100°C. for 5 min, followed by 5°/min to 220°C). The molar responses R_f (defined as $(A_{substr}/A_{IS})/(C_{substr}/C_{IS})$) determined for cyclohexylbenzene and phenylcyclohexanol were 1.03 and 1.09 with respect to naphthalene, respectively.

The structures of products **A** and **B** (after reduction with triphenylphosphine) were assigned qualitatively on the basis of GC/MS data. Product **B** (rt was 18.2 min in the gas chromatogram, see above) showed a molecular ion peak at Mz 190 (1% relative intensity). The NIST MS database gave a good match for the spectrum of 3-hydroxy-3-phenylcyclohexanone (CAS: 25444-79-5; NIST entry 8202). Major peaks: Mz 51 (19.5%); Mz 77 (55%); Mz 105 (100%); Mz 106 (9%); Mz 120 (38%); Mz 133 (6.5%); 146 (6%); Mz 172 (5%). The product **A** (rt was 19.3 in the in the GC) gave a MI peak of 192 (2%) and as major peaks Mz 51 (16%); Mz 77 (53%); Mz 105 (100%); Mz 106 (11%); 120 (64%); 133 (4.5%); 174 (8.5%). Based on the fact that this fragmentation pattern is very close to that of product **B** (M+2), we assigned the spectrum of **B** to 3-hydroxy-3-phenylcyclohexanol (although this could not be verified due to the absence of this compound in the NIST database). For qualitative analysis of products **A** and **B** a R_f of 1.0 with respect to naphthalene was used.

Given the fact that products **A** and **B** were analyzed after reduction with triphenylphosphine, and that they were most likely formed via intramolecular H-abstraction (see text) in the 1-phenyl-cyclohexylperoxy radical (see structure **1** in Scheme 5), their structure corresponds to 1,3-dihydroperoxy-1-phenylcyclohexane (**A**) and 1-hydroperoxy-1-phenyl-3-cyclohexanone (**B**). To rationalize the formation and substitution pattern (1,3 vs e.g. 1,2 or 1,4) of products **A** and **B**, we performed a molecular mechanics calculation using HyperChem® 7 (see also text).

Acknowledgements

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