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# The Formation of Byproducts in the Autoxidation of Cyclohexane

**Ive Hermans,*[a] Pierre Jacobs,[a] and Jozef Peeters[b]**

**Abstract:** In this work, a complementary experimental and theoretical approach is used to unravel the formation of byproducts in the autoxidation of cyclohexane. The widely accepted vision that cyclohexanone would be the most important precursor of undesired products was found inconsistent with several experimental observations. However, the propagation reaction of cyclohexyl hydroperoxide, which we recently put forward as the missing source of cyclohexanol and cyclohexanone, is now unambiguously identified also as the dominant path leading to byproducts. Indeed, this overlooked reaction produces large amounts of cyclohexoxy radicals, able to ring-open via a β-C–C cleavage to ω-formyl radicals. The pathway by which these radicals are converted into the observed and quantified byproducts is derived in this work. In this liquid-phase reaction, solvent cages were found very important, steering the fate of nascent species.

**Keywords:** autoxidation · kinetics · radicals · reaction mechanisms · selectivity

## Introduction

The liquid-phase autoxidation of cyclohexane (415–435 K) is an important process in the chemical industry, producing cyclohexanone and cyclohexanol (KA-oil, $\approx 6\times10^6$ Tons/y).[1,5] Both products are precursors for caprolactam and adipic acid, building blocks for the important polyamides nylon-6 and nylon-6,6, respectively.[5] The reaction is known to proceed through a complex radical-chain mechanism in which cyclohexylperoxyl radicals (CyOO•) are the main chain propagators.[1–3] The conversion is usually kept below 5% in order to avoid large amounts of ring-opened byproducts (e.g. 6-hydroxyhexanoic acid and adipic acid).

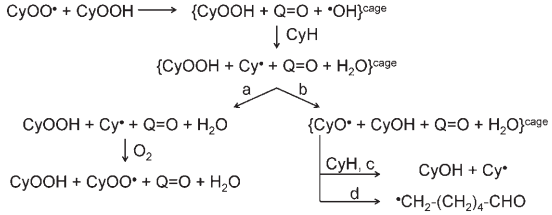
Whereas cyclohexyl hydroperoxide (CyOOH) was known to be produced in fast propagation reactions [Eqs. (1) and (2)], the literature attributed the formation of both cyclohexanol (CyOH) and cyclohexanone (Q=O) to the slow mutual termination of two peroxyl radicals [Eq. (3)].[1–3]

$$CyOO^{\cdot} + CyH \rightarrow CyOOH + Cy^{\cdot} \quad (1)$$

$$Cy^{\cdot} + O_2 \rightarrow CyOO^{\cdot} \quad (2)$$

$$CyOO^{\cdot} + CyOO^{\cdot} \rightarrow CyOH + Q{=}O + O_2 \quad (3)$$

However, kinetic experiments and a detailed theoretical analysis provided solid evidence that the hitherto overlooked, though very fast subsequent propagation reaction of CyOOH (the propagation rate constant ratio $k^{CyOOH}/k^{CyH}$ being $\approx$55) is responsible for both the CyOH and Q=O formation.[6,7] In this reaction (Scheme 1), the weakly bonded αH-atom of CyOOH is abstracted by a CyOO• radical, producing the unstable $Cy_{-\alpha H}$•OOH radical,[8] which decomposes promptly to Q=O + •OH. The "hot" •OH co-product radical of this exothermic reaction[8] rapidly abstracts a hydrogen atom from one of the CyH molecules that form the wall of




Scheme 1. Propagation of cyclohexyl hydroperoxide.

[a] Dr. I. Hermans, Prof. Dr. P. Jacobs
K.U.Leuven, Department of Microbial and Molecular Systems ($M^2S$)
Centre for Surface Chemistry and Catalysis
Kasteelpark Arenberg 23, 3001 Heverlee (Belgium)
Fax (+32) 16-321-998
E-mail: ive.hermans@biw.kuleuven.be

[b] Prof. Dr. J. Peeters
K.U.Leuven, Department of Chemistry
Division for Quantum Chemistry and Physical Chemistry
Celestijnenlaan 200F, 3001 Heverlee (Belgium)

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the solvent cage, surrounding the $\{CyOOH + Q{=}O + {}^{\bullet}OH\}^{cage}$ products. The resulting reaction products $\{CyOOH + Cy^{\bullet} + Q{=}O + H_2O\}^{cage}$ can either diffuse out of the solvent cage (path a, Scheme 1), or react within their Franck–Rabinowitch solvent cage to give $\{CyO^{\bullet} + CyOH + Q{=}O + H_2O\}^{cage}$ (path b, Scheme 1).[6,7] This cage reaction contributes about 70% of the CyOOH propagation flux,[6,7] owing its high efficiency to the nanosized hot-spot generated by the large heat release ($>250\ kJ\,mol^{-1}$) in the αH-abstraction from CyOOH and the subsequent hydrogen abstraction from CyH by $^{\bullet}OH$.[6]

Prior to our work, above, the only role for CyOOH was thought to be the initiation of new radical chains, through its homolytic dissociation.[1–3] Recently, we demonstrated that such a unimolecular O–O scission is much slower and less efficient in generating radicals than a newly identified, concerted bimolecular reaction between CyOOH and Q=O,[9] in which the OH radical breaking away from the CyO–OH abstracts an αH-atom from the ketone, leaving a resonance stabilized ketonyl radical and a cyclohexoxy radical ($CyO^{\bullet}$), hydrogen-bonded to water. This reaction was shown to account for the autocatalytic nature of the process.[9]

The CyOOH propagation reaction in Scheme 1 also produces a large amount of $CyO^{\bullet}$ radicals, known to abstract hydrogen atoms from the CyH substrate and to undergo ring-opening through β-C–C cleavage[10] in a ≈1:1 ratio.[6] Therefore, we already suggested that CyOOH propagation could also produce (ring-opened) byproducts.[7] In the present work, we aim to elucidate the formation mechanism of these undesired products. The exact knowledge of the chemistry at issue is a prerequisite to a focused optimalization of the process and the design of appropriate catalysts.[11]

## Results and Discussion

**Cyclohexyl hydroperoxide—the true precursor of byproducts**: Up to now, it was mostly assumed that overoxidation of Q=O is the predominant source of byproducts.[1–3] In autoxidation experiments in which 1 mol% of Q=O was initially added to the CyH, more ring-opened byproducts were observed indeed, though their fractional increase becomes almost negligible at higher CyH conversions, as illustrated in Figure 1. This observation provides experimental evidence against the hypothesis of Q=O being responsible for the majority of the byproducts. Moreover, this view is entirely at odds with our measured and calculated reactivity of ketones towards $CyOO^{\bullet}$ radicals: Q=O reacts only ≈5 times as fast as CyH, making it an unlikely source for the bulk of the observed byproducts (see Figure 2).[6,7]

As the relative propagation rate of Q=O to CyH is known, namely, $k^{Q=O}/k^{CyH} \approx 5$,[6,7] the upper limit of the amount of byproducts which can possibly originate from Q=O can be evaluated by Equation (4).[12]

$$[\text{byproduct}]^{Q=O}(t) = \int (5 \cdot k^{CyH})\,[Q{=}O]\,[CyOO^{\cdot}]\,dt \qquad (4)$$

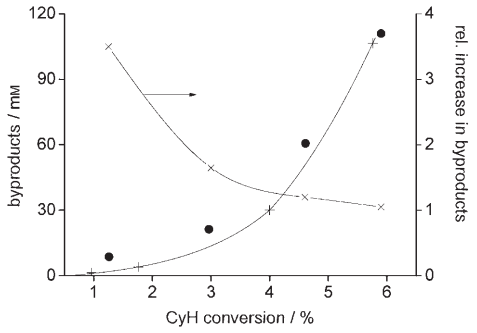



Figure 1. Byproducts produced during the pure 418 K autoxidation of cyclohexane (+), compared with the amount of byproducts produced upon initial addition of 1 mol% of Q=O (●); × represents the ratio of byproducts after initial addition of Q=O, over byproducts in the pure autoxidation.

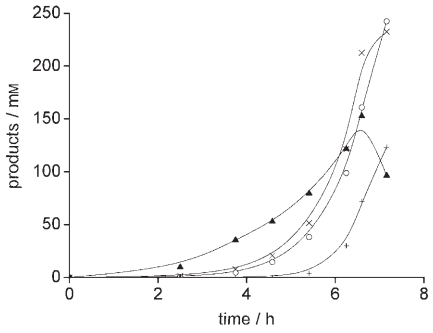



Figure 2. Concentrations as function of time of the oxidation products CyOOH (▲), CyOH (×), Q=O (o) and byproducts (+) during CyH autoxidation at 418 K.

Thus, it is found that the ketone route can only explain a minor fraction of the observed byproducts (Table 1). Studying the *N*-hydroxyimide/Co-catalyzed oxidation of cyclododecane, Sheldon and co-workers reached the same conclusion: the overoxidation of cyclododecanone can only account for a very small amount of ring-opened acids.[13]

Table 1. The experimentally observed and modeled byproduct formation: estimated contributions of Q=O and CyOOH.

| | CyH conversion | |
|---|---|---|
| | 4% | 6% |
| observed byproducts | 30 mM | 107 mM |
| modeled byproducts | | |
| ketone source | 4 mM | 17 mM |
| CyOOH source | 30 mM | 78 mM |
| sum of both sources | 34 mM | 95 mM |

To evaluate byproduct formation from CyOOH, the fraction of consumed CyOOH molecules that actually leads to ring-opened ω-formyl radicals (paths b and d, Scheme 1),[6,7] needs to be taken into account, putting the effective byproducts formation rate constant at $\{k^{CyOOH}/k^{CyH}\} \times b \times d = 20 \pm 10$, relative to the CyH rate constant. For a value of 12, the experimental amount of byproducts is in very good agreement

with this rough model calculation, taking the sum of both the Q=O and CyOOH sources (Table 1).

Both analyses thus show unequivocally that byproducts are formed predominantly from CyOOH and not from Q=O as assumed in the literature.

**From radicals to byproducts**

*Experimental observations*: Figure 3 displays the concentrations of the observed and quantified byproducts against their sum. The order by which the *relative contributions* of

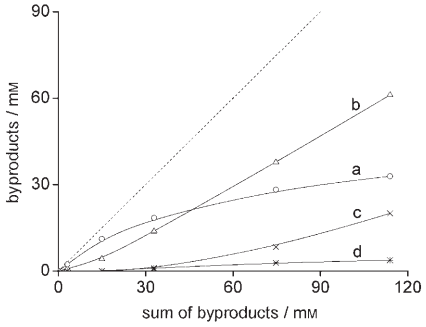



Figure 3. Evolution of the most important byproducts a) 6-hydroxyhexanoic acid, b) adipic acid, c) glutaric acid, and d) ε-caprolactone as a function of the total amount of byproducts. Data collected at 418 K, up to 7% cyclohexane conversion.

byproducts gain in relative importance reflects the sequence of their respective formation. Thus, Figure 3 identifies 6-hydroxyhexanoic acid ($HO(CH_2)_5C(=O)OH$) unequivocally as the predominant, if not exclusive, primary byproduct, whereas all other byproducts clearly exhibit a secondary character with respect to this compound. Up to 7% CyH conversion, adipic acid ($O=C(OH)(CH_2)_4C(=O)OH$) formation shows an induction period, whereas the appearance of glutaric acid ($O=C(OH)(CH_2)_3C(=O)OH$) and ε-caprolactone takes off even more slowly. It can be concluded that 6-hydroxyhexanoic acid cannot originate from hydration of ε-caprolactone, as the latter is a tertiary or even quaternary byproduct. At even higher conversions, one observes the formation of other (shorter) acids, not included in Figures 2 and 3. Up to now, the formation of the byproducts, especially the decarboxylated ones, remained rather enigmatic. Thermal decarboxylation can indeed be ruled out, due to the huge barrier: for example, the rate constant for the decomposition of propionic acid to ethane + $CO_2$ is $6.03 \times 10^9\ s^{-1} \exp(-49.28\ kcal\,mol^{-1}/RT)$.[14] Also the abstraction of an acidic hydrogen atom by peroxyl radicals is negligibly slow, due to the strong O–H bond.

*From ω-formyl radicals to 6-hydroxyhexanoic acid*: Firstly, we aimed to identify the fate of the ω-formyl radicals ($^{\bullet}CH_2$-$(CH_2)_4CHO$), produced in the ring-opening of CyO$^{\bullet}$ radicals[10] (path d, Scheme 1). ω-Formyl can either isomerize [Eq. (5)] in a unimolecular 1,6-H-shift, or it can add $O_2$ [Eq. (6)].

$$^{\bullet}CH_2\text{-}(CH_2)_4\text{-}CHO \rightarrow CH_3\text{-}(CH_2)_4\text{-}C^{\bullet}=O \quad (5)$$

$$^{\bullet}CH_2\text{-}(CH_2)_4\text{-}CHO + O_2 \rightarrow {}^{\bullet}OOCH_2\text{-}(CH_2)_4\text{-}CHO \quad (6)$$

The intramolecular hydrogen shift faces a computed energy barrier of 11.1 kcal mol$^{-1}$, making this reaction much slower than the diffusion controlled oxygen addition in our experimental conditions.[15] However, under conditions of oxygen starvation, often encountered under industrial conditions, isomerization [Eq. (5)][10b] may compete with the reaction given in Equation (6), causing monofunctionalized acids, namely, caproic and valeric acid, observed industrially.[16] When sufficient oxygen is present, a new peroxyl radical, $^{\bullet}OOCH_2$-$(CH_2)_4$-CHO, is formed, able to abstract a hydrogen atom, either from the CyH substrate [Eq. (7)] or from its own aldehyde functionality, in a 1,8-H-shift [Eq. (8)].

$$^{\bullet}OOCH_2\text{-}(CH_2)_4\text{-}CHO + CyH \rightarrow HOOCH_2\text{-}(CH_2)_4\text{-}CHO + Cy^{\bullet} \quad (7)$$

$$^{\bullet}OOCH_2\text{-}(CH_2)_4\text{-}CHO \rightarrow HOOCH_2\text{-}(CH_2)_4\text{-}C^{\bullet}=O \quad (8)$$

The unimolecular formation of $HOOCH_2$-$(CH_2)_4$-C$^{\bullet}$=O [Eq. (8)] proceeds through a cyclic transition state (TS) computed to lie 14.4 kcal mol$^{-1}$ above the reactant level, whereas the bimolecular H-abstraction [Eq. (7)] faces a barrier of 16.8 kcal mol$^{-1}$. Evidently, the formation of $HOOCH_2$-$(CH_2)_4$-C$^{\bullet}$=O will be favored.[17]

Next, the chemistry of the $HOOCH_2$-$(CH_2)_4$-C$^{\bullet}$=O radical is addressed. There will be a competition between the addition of $O_2$ [Eq. (9)][15] and the highly exothermic 1,7-OH-shift [Eq. (10); $\Delta_r H(0\ K) = -68$ kcal mol$^{-1}$], proposed here for the first time. The elimination of CO [Eq. (11)] is very slow, due to the high activation barrier, calculated to be 14.0 kcal mol$^{-1}$.[19] Nevertheless, CO is observed during the industrial process;[16] most probably it originates from $CH_3$-$(CH_2)_4$-C$^{\bullet}$=O decomposition at very small oxygen concentrations as explained above.

$$HOOCH_2\text{-}(CH_2)_4\text{-}C^{\bullet}=O + O_2 \rightarrow HOOCH_2\text{-}(CH_2)_4\text{-}C(=O)OO^{\bullet} \quad (9)$$

$$HOOCH_2\text{-}(CH_2)_4\text{-}C^{\bullet}=O \rightarrow {}^{\bullet}OCH_2\text{-}(CH_2)_4\text{-}C(=O)OH \quad (10)$$

$$HOOCH_2\text{-}(CH_2)_4\text{-}C^{\bullet}=O \rightarrow HOOCH_2\text{-}(CH_2)_3\text{-}CH_2^{\bullet} + CO \quad (11)$$

Several loose TS conformers were identified for the reaction given in Equation (10), lying 7.9–10.5 kcal mol$^{-1}$ above the reactant at the UB3LYP/6–31G(d,p)-level of theory. However, B3LYP-DFT calculations are expected to give a rather incorrect prediction of the energy barrier for this

type of highly exothermic reaction, involving a very "early", reactant-like TS and drastic electronic rearrangements. In particular, the newly forming C···OH bond length in the TS is still large (2.14 Å, compared to a normal C–OH bond length of 1.43 Å), as shown in Figure 4. As the B3LYP-functional is optimized for "normal" covalent interactions,[20] B3LYP-DFT calculations will likely underestimate the new, long-range C···OH interaction, thus leading to an overestimation of the energy barrier. Unfortunately, the system at issue is too large for the use of high ab initio benchmark levels of theory. For the smaller analogous, though bimolecular, reaction $CH_3OOH + CH_3C^{\bullet}(=O) \rightarrow CH_3O^{\bullet} + CH_3C(=O)OH$, the state-of-the-art CCSD(T)/6–31G(d,p)//QCISD(T)/cc-pVDZ and CCSD(T)/6-31+G(d,p)//QCISD(T)/cc-pVDZ ab initio methods predict barriers of only 5.3 and 4.9 kcal mol$^{-1}$, respectively.[21] The O–O···C atoms in the loose TS of the reaction given in Equation (10) are nearly collinear ($\measuredangle COO = 158°$, see Figure 4), similar to the smaller bimolecular system (169°), while all other bond angles and bond lengths have near-normal values. This reflects a negligible-to-low ring strain in the TS at hand, supported furthermore by the low ring-strain energy of 0.7± 1.2 kcal mol$^{-1}$ in cyclooctanone,[22] a molecule that closely resembles the floppy TS structure. Therefore, the barrier of the reaction given in Equation (10) is expected to be close to the high-level result of ≈5 kcal mol$^{-1}$ for the smaller bimolecular system. Such a barrier, in combination with an estimated pre-exponential rate factor of $\approx 3 \times 10^{11}$ s$^{-1}$,[18] entails that Equation (10), proceeding through several loose TS conformers, should readily outrun the addition of oxygen [Eq. (9)].[15]

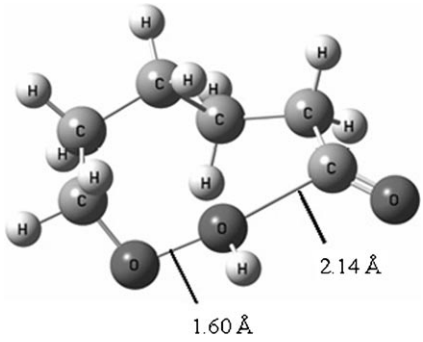


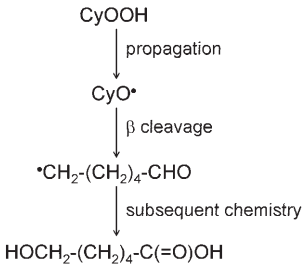

Figure 4. The lowest TS-conformer for the reaction given in Equation (10), optimized at the B3LYP/6–31G(d,p)-level of theory.

Once $^{\bullet}OCH_2$-$(CH_2)_4$-C(=O)OH is formed, fast hydrogen abstraction from the ubiquitous surrounding CyH molecules immediately yields 6-hydroxyhexanoic acid, the first major byproduct [Eq. (12)]. The competing β-cleavage of $^{\bullet}OCH_2$-$(CH_2)_4$-C(=O)OH [Eq. (13)] can be neglected, due to the higher energy barrier.[23]

$$^{\bullet}OCH_2\text{-}(CH_2)_4\text{-}C(=O)OH + CyH \rightarrow HOCH_2\text{-}(CH_2)_4\text{-}C(=O)OH + Cy^{\bullet} \quad (12)$$

$$^{\bullet}OCH_2\text{-}(CH_2)_4\text{-}C(=O)OH \rightarrow H_2C=O + {}^{\bullet}CH_2\text{-}(CH_2)_3\text{-}C(=O)OH \quad (13)$$

Thus, a fast, plausible and straightforward formation route of the major initial byproduct 6-hydroxyhexanoic acid, fully sustained by theoretical calculations and experimental observations, has been identified and characterized (Scheme 2).




Scheme 2. Schematic representation of the formation of 6-hydroxyhexanoic acid.

*Oxidation of 6-hydroxyhexanoic acid*: The oxidation of 6-hydroxyhexanoic acid proceeds preferentially by the abstraction of a weaker-bonded αH atom from the alcohol functionality by CyOO$^{\bullet}$ radicals [Eq. (14)].[6,7] The barrier for the analogous reaction between CyOO$^{\bullet}$ and $CH_3CH_2C\mathbf{H}_2OH$ was calculated to be 12.8 kcal mol$^{-1}$. As a consequence, this abstraction reaction takes place on a timescale of hours in the experimental conditions,[25] explaining the convex shape of the 6-hydroxyhexanoic acid contribution in Figure 3. The α-hydroxy-alkyl-peroxyl radical, $^{\bullet}OOC$-(OH)H-$(CH_2)_4$-C(=O)OH, resulting after $O_2$ addition, rapidly expels $HO_2^{\bullet}$, yielding OCH-$(CH_2)_4$-C(=O)OH, as shown by us to be the general fate of α-hydroxy-alkyl-peroxyl radicals.[26] Due to the energy barrier of only 9.0 kcal mol$^{-1}$, the abstraction of the aldehyde hydrogen atom from this product by peroxyl radicals [Eq. (15)] is fast (lifetime ≈1 minute),[27] explaining why this compound cannot be observed in significant concentrations. For the subsequent fate of the $\{O=C^{\bullet}\text{-}(CH_2)_4\text{-}C(=O)OH + CyOOH\}^{cage}$ products, one needs, again, to consider the competition between the in-cage OH abstraction from CyOOH [Eq. (16)] and the out-diffusion [Eq. (17)]. The elimination of CO can be neglected, just as for the $HOO\text{-}CH_2\text{-}(CH_2)_4\text{-}C^{\bullet}=O$ radical above.

$$HOCH_2\text{-}(CH_2)_4\text{-}C(=O)OH + CyOO^{\bullet} + O_2 \rightarrow OCH\text{-}(CH_2)_4\text{-}C(=O)OH + HO_2^{\bullet} + CyOOH \quad (14)$$

$$OCH\text{-}(CH_2)_4\text{-}C(=O)OH + CyOO^{\bullet} \rightarrow \{O=C^{\bullet}\text{-}(CH_2)_4\text{-}C(=O)OH + CyOOH\} \quad (15)$$

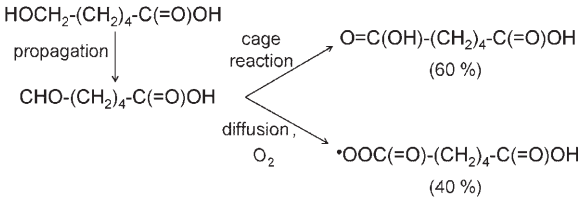
$$\{O=C^{\bullet}\text{-}(CH_2)_4\text{-}C(=O)OH + CyO\text{-}OH\} \rightarrow \{O=C(OH)\text{-}(CH_2)_4\text{-}C(=O)OH + CyO^{\bullet}\} \quad (16)$$

$$\{O{=}C^{\cdot}\text{-}(CH_2)_4\text{-}C(=O)OH + CyOOH\} \rightarrow O{=}C^{\cdot}\text{-}(CH_2)_4\text{-}C(=O)OH + CyOOH \quad (17)$$

The out-diffusion [Eq. (17)] is slowed down by the computed, 2.2 kcal mol$^{-1}$ strong hydrogen bond between the two nascent species, putting the rate of this diffusion process at $\approx 3.5\times10^9$ s$^{-1}$ at 418 K.[28] Given the UCCSD(T)/6–31G-(d,p)//UQCISD/cc-pVDZ and UCCSD(T)/6-31+G(d,p)//UQCISD/cc-pVDZ barriers for the analogous $CH_3OOH + CH_3C^{\cdot}{=}O \rightarrow CH_3O^{\cdot} + CH_3C(=O)OH$ reaction of 5.3 and 4.9 kcal mol$^{-1}$, respectively, a value of $\approx$4.5 kcal mol$^{-1}$ appears reasonable for the energy barrier for the reaction given in Equation (16).[21] The rate constant can thus be estimated at $\approx 5.5\times10^9$ s$^{-1}$.[30]

Thus, it is to be expected that about half of the OCH-$(CH_2)_4$-C(=O)OH will be converted to adipic acid O=C-(OH)-$(CH_2)_4$-C(=O)OH, whereas a somewhat smaller fraction yields the acylperoxyl radical $^{\cdot}$OOC(=O)-$(CH_2)_4$-C(=O)OH by the addition of $O_2$ to the O=C$^{\cdot}$-$(CH_2)_4$-C-(=O)OH acyl radical (Scheme 3).[31]




Scheme 3. Pathway from 6-hydroxyhexanoic acid to adipic acid and the $^{\cdot}$OOC(=O)-$(CH_2)_4$-C(=O)OH acylperoxyl radical.

*Formation of decarboxylated acids*: The most likely path for the $^{\cdot}$OOC(=O)-$(CH_2)_4$-C(=O)OH acylperoxyl radical is the abstraction of an H-atom from the surrounding cyclohexane substrate [Eq. (18)], facing a barrier of only 8.8 kcal mol$^{-1}$, that is, the calculated value for the analogous $CH_3CH_2C$-(=O)OO$^{\cdot}$ + CyH reaction. Again there will be a competition between the in-cage OH-abstraction from the peracid functionality [Eq. (19)] and the out-diffusion [Eq. (20)] freeing a peracid.

$$^{\cdot}OOC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + CyH \rightarrow \{HOOC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + Cy^{\cdot}\} \quad (18)$$

$$\{HO\text{-}OC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + Cy^{\cdot}\} \rightarrow \{^{\cdot}OC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + CyOH\} \quad (19)$$

$$\{HOOC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + Cy^{\cdot}\} \rightarrow HOOC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH + Cy^{\cdot} \quad (20)$$

As the computed barrier for the reaction given in Equation (19) is as low as 0.3 kcal mol$^{-1}$, owing to a strong hydrogen bond, nearly all $^{\cdot}$OOC(=O)-$(CH_2)_4$-C(=O)OH radicals will be converted to the resonance stabilized $^{\cdot}$OC(=O)-$(CH_2)_4$-C(=O)OH acyloxy radicals. The predominant fate of these radicals is the unimolecular elimination of $CO_2$ [Eq. (21)]. Indeed, the B3LYP/6–311++G(d,p) barrier for this process is only 4.1 kcal mol$^{-1}$, reducing the lifetime of this radical to $\approx$10 ps at 418 K, precluding any other competing processes. $^{\cdot}CH_2$-$(CH_2)_3$-C(=O)OH will react further according to the reactions given in Equations (22)–(24), the last reaction—similar to the CyOOH propagation in Scheme 1—yielding OCH-$(CH_2)_3$-C(=O)OH. This compound will react as OCH-$(CH_2)_4$-C(=O)OH above [Eq. (25)–(28)]. The reaction given in Equation (26) produces glutaric acid; the observed induction period (Figure 3) is due to, and consistent with the reaction given in Equation (24). Similar to the $C_6$ analogue (vide supra), the O=C(OH)-$(CH_2)_3$-C(=O)OH yield is expected to be somewhat larger than that of $^{\cdot}$OOC(=O)-$(CH_2)_3$-C(=O)OH. Therefore, this reaction scheme provides an elegant and straightforward explanation for the observed $C_5$ decarboxylated acids. Further shortened acids are generated *via* similar subsequent reactions.

$$^{\cdot}OC(=O)\text{-}(CH_2)_4\text{-}C(=O)OH \rightarrow {}^{\cdot}CH_2\text{-}(CH_2)_3\text{-}C(=O)OH + CO_2 \quad (21)$$

$$^{\cdot}CH_2\text{-}(CH_2)_3\text{-}C(=O)OH + O_2 \rightarrow {}^{\cdot}OOCH_2\text{-}(CH_2)_3\text{-}C(=O)OH \quad (22)$$

$$^{\cdot}OOCH_2\text{-}(CH_2)_3\text{-}C(=O)OH + CyH \rightarrow HOOCH_2\text{-}(CH_2)_3\text{-}C(=O)OH + Cy^{\cdot} \quad (23)$$

$$HOOCH_2\text{-}(CH_2)_3\text{-}C(=O)OH + CyOO^{\cdot} \rightarrow OCH\text{-}(CH_2)_3\text{-}C(=O)OH + {}^{\cdot}OH + CyOOH \quad (24)$$

$$OCH\text{-}(CH_2)_3\text{-}C(=O)OH + CyOO^{\cdot} \rightarrow \{O{=}C^{\cdot}\text{-}(CH_2)_3\text{-}C(=O)OH + CyOOH\} \quad (25)$$

$$\{O{=}C^{\cdot}\text{-}(CH_2)_3\text{-}C(=O)OH + CyO\text{-}OH\} \rightarrow \{O{=}C(OH)\text{-}(CH_2)_3\text{-}C(=O)OH + CyO^{\cdot}\} \quad (26)$$

$$\{O{=}C^{\cdot}\text{-}(CH_2)_3\text{-}C(=O)OH + CyOOH\} \rightarrow O{=}C^{\cdot}\text{-}(CH_2)_3\text{-}C(=O)OH + CyOOH \quad (27)$$

$$O{=}C^{\cdot}\text{-}(CH_2)_3\text{-}C(=O)OH + O_2 \rightarrow {}^{\cdot}OOC(=O)\text{-}(CH_2)_3\text{-}C(=O)OH \quad (28)$$

Additionally, this mechanism explains the relative amounts of adipic acid and glutaric acid (ratio $\approx$4:1). Indeed, according to the proposed mechanism, roughly 60% of the 6-hydroxyhexanoic acid is converted to adipic acid, whereas 40% is converted to $^{\cdot}$OOC(=O)-$(CH_2)_4$-C(=O)OH radicals which mainly form $^{\cdot}CH_2$-$(CH_2)_3$-C(=O)OH, by means of a cage reaction and subsequent decarboxylation. A large fraction of these radicals will react further to form glutaric acid, explaining the experimental adipic/glutaric acid ratio.

*Hypothetical routes to caprolactone*: One minor byproduct which needs yet to be discussed is ε-caprolactone. Although it is only formed in a very low yield, polymerization of this compound can cause clogging of the reactor. Its formation has been attributed in literature to a Baeyer–Villiger-like oxidation of cyclohexanone by CyOO• radicals.[2] This reaction was assumed to start with the addition of the peroxyl radicals to the C=O double bond, followed by a ring-expansion and elimination of CyO•. Though an increase of ε-caprolactone production was observed by us when 1 mol% Q=O was initially added (e.g. at 5% conversion ≈20 mM versus ≈5 mM without initial Q=O), the addition reaction of CyOO• to Q=O was computed to be endothermic for 11.1 kcal mol$^{-1}$ (B3LYP/6–31G(d,p) level), making such a reaction unrealistic under autoxidation conditions.

On the other hand, we found the analogous addition of acylperoxyl radicals (R-C(=O)OO•) to Q=O to be nearly thermoneutral ($\Delta_r H(0\,K) = +0.6$ kcal mol$^{-1}$; B3LYP/6–31G-(d,p)-level for R = $CH_3$). Yet this addition would face a B3LYP/6–31G(d,p) barrier of 13.1 kcal mol$^{-1}$, making this process [Eq. (29)] significantly slower than reaction 17. The resulting oxy radical decomposes through a fast β C-C cleavage [Eq. (30); B3LYP/6–31G(d,p) barrier of 5.85 kcal mol$^{-1}$] to a labile perester structure. For this radical, there will be a competition between the addition of $O_2$ and the unimolecular formation of ε-caprolactone [Eq. (31)], driven by the expulsion of the resonance stabilized acyloxy radical C(=O)OH-$(CH_2)_4$C(=O)O• (Figure 5). Likely, the B3LYP/6–31G(d,p) barrier of 13.8 kcal mol$^{-1}$ is an overestimation of the true barrier for this highly exothermic reaction, due to resonance stabilization. To make this reaction competitive with the addition of $O_2$, the barrier should indeed be less than 7 kcal mol$^{-1}$. So, although the reaction given in Equation (18) will be favored by far, a small fraction of the acylperoxyl radicals might add to Q=O and form small quantities of ε-caprolactone. The overall effect is a Baeyer–Villiger-like oxidation of cyclohexanone, not by peroxyl radicals, but by acylperoxyl radicals. It is of interest to note that ε-caprolactone indeed starts to appear simultaneously with glutaric acid (Figure 3), a product which is proposed here to originate from the same •OOC(=O)-$(CH_2)_4$-C(=O)OH radical.

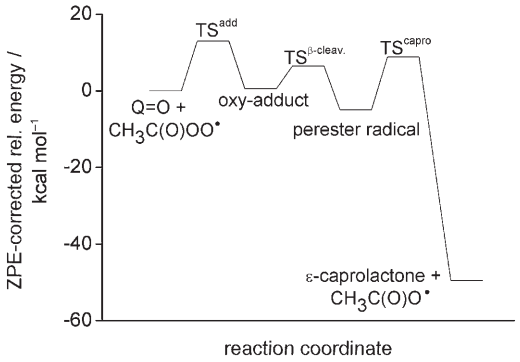
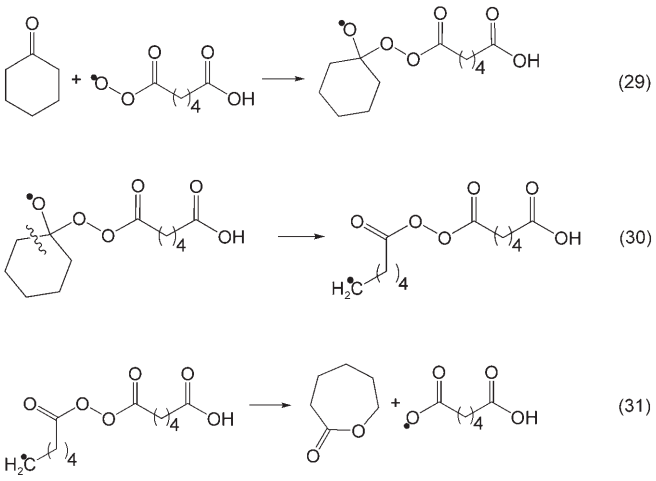



Figure 5. The reaction of $CH_3C(=O)OO•$ acyl peroxyl radicals with Q=O; PES at the B3LYP/6–31G(d,p)-level of theory.




However, the (acid-catalyzed) ring-closure of 6-hydroxyhexanoic acid must be considered as another likely source of ε-caprolactone.

## Conclusion

In this paper, compelling evidence is presented that cyclohexyl hydroperoxide is by far the most dominant source of byproducts in the autoxidation of cyclohexane. Cyclohexanone, to which this role was attributed up to now, can only account for a small fraction of the byproducts. It is demonstrated how the overlooked propagation of the hydroperoxide gives rise to cyclohexoxy radicals, able to form ring-opened ω-formyl radicals. New and straightforward chemistry is presented for their conversion into the first major byproduct, 6-hydroxyhexanoic acid. Radical conversion of this primary byproduct is rather slow and explains the initial build up of this compound. α-Hydrogen abstraction from the alcohol functionality produces OCH-$(CH_2)_4$-C(=O)OH, the concentration of which remains very low as it reacts rapidly with CyOO• radicals. A cage reaction subsequent to this hydrogen abstraction produces predominantly adipic acid. A small fraction will, however, also give rise to acylperoxyl radicals •OOC(=O)-$(CH_2)_4$-C(=O)OH, yielding the decarboxylated •$CH_2$-$(CH_2)_3$-C(=O)OH radical, through the intermediate stage of the •OC(=O)-$(CH_2)_4$-C(=O)OH acyloxy radical. This decarboxylation is the first step on the way to glutaric acid, and other shorter byproducts. Under conditions of oxygen starvation, even more byproducts can originate by means of an 1,6-isomerization of the ω-formyl radicals, leading to several monofunctionalized acids by analogous mechanisms as for the bifunctional acids. This contribution presents a leap forward in understanding the chemistry of autoxidations indeed. In the future, to improve the yield of useful products in cyclohexane autoxidation, one should aim for a nonradical, that is, catalytic, conversion of the hy-

droperoxide, preventing the formation of cyclohexoxy radicals. For the time being, working at sufficient oxygen pressures, and/or preventing oxygen mass transfer limitations, can already prevent the formation of monofunctional acids.

## Experimental Section

The autoxidation of cyclohexane (50 mL, HPLC-grade) was studied experimentally in a stirred (500 rpm) stainless steel high-pressure Parr reactor (100 mL) at an initial room-temperature pressure of 2.76 MPa of pure oxygen. Prior to each experiment, the reactor wall was passivated by means of a saturated sodium pyrophosphate (p.a.) solution.[6,32] Acetone (p.a.) was added to the reaction mixture to dissolve all products. The reaction products were quantified by GC-FID, after the addition of an external standard (1-heptanol, 99.9%) and the silylating agent *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (MSTFA); the injection port temperature was set to 150°C. Peak areas were corrected for sensitivity differences by calibration.

**Computational methods**: Quantum-chemical calculations were carried out with the GAUSSIAN03 program.[33] At the DFT level, the Becke three-parameter hybrid exchange functional was used, combined with the Lee–Yang–Parr nonlocal correlation functional B3LYP-DFT.[34] Unless stated otherwise in the text, the B3LYP/6–311++G(d,p)//B3LYP/6–31G(d,p) level of theory was used, which we earlier showed to agree within 0.5 kcal mol$^{-1}$ with state-of-the-art computational levels for H-abstractions by peroxyl radicals.[6] For other reactions, the accuracy of the calculated barriers is estimated at 2 kcal mol$^{-1}$.[20]

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[28] Following Benson,[29] the rate of diffusive separation of a "caged pair" {A···B} is given by $3D_{AB}/(r_{AB})^2\times\exp(-W_{AB}/RT)$, where $r_{AB}$ is the initial distance ($\approx3.5$ Å), $D_{AB}$ is the diffusion coefficient ($\approx2\times10^{-5}$ cm$^2$ s$^{-1}$) and $W_{AB}$ is the interaction energy between A and B in the solvent ($\approx2.2$ kcal mol$^{-1}$ for $CH_3OOH\cdots O{=}C^\bullet{-}CH_2CH_3$). This gives a diffusion rate constant of $\approx3.5\times10^9$ s$^{-1}$.
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[30] In the frame of TST, the geminate reaction [Eq. (16)] should be treated as a unimolecular reaction with a rate constant given by $k_BT/h\times Q^\bullet/Q^{react}\times\exp(-E^\bullet/k_BT)$ with $k_B$ Boltzmann's constant; $Q^\bullet$ and $Q^{react}$ the partition function of the TS and the caged reactants, respectively.[6] Though the ratio $Q^\bullet/Q^{react}$ is unknown, a value of 0.1 appears reasonable for this low energy TS, putting the value for the rate constant at $\approx5.5\times10^9$ s$^{-1}$.
[31] Given all the uncertainties in this estimation, the result is in good agreement with the experimental observations. For example, at 6.4% CyH conversion, the sum of byproducts equals ≈75 mM, from with 36.75 mM 6-hydroxyhexanoic acid and 27.45 mM adipic acid. As 6-hydroxyhexanoic acid was identified experimentally as the primary

  

byproduct from which nearly all other byproducts are formed, at this stage 38.25 mM of 6-hydroxyhexanoic acid was converted into other byproducts. The concentration of adipic acid is indeed ≈70% of this value, in good agreement with the predicted 60%.

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