A Rationale of the Baeyer–Villiger Oxidation of Cyclohexanone to ε-Caprolactone with Hydrogen Peroxide: Unprecedented Evidence for a Radical Mechanism Controlling Reactivity

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Abstract: We demonstrate, for the first time, in the Baeyer–Villiger oxidation of cyclohexanone with aqueous hydrogen peroxide under conditions aimed at obtaining ε-caprolactone, that a thermally activated radical reaction leads to the concurrent formation of adipic acid, even when a stoichiometric amount of the oxidant is used. In fact, ε-caprolactone is the primary reaction product, but it is more reactive than cyclohexanone, and quickly undergoes consecutive transformations. When titanium silicalite-1 (TS-1) is used as a catalyst, the high concentration of hydroxy radicals within its pores accelerates the reaction rates, and the consecutive formation of adipic acid (and of lighter diacids as well) becomes largely kinetically preferred. The proper choice of the solvent, which also may act as a radical scavenger, both without catalyst and with TS-1, is a powerful tool for controlling the rates of the various reactions involved.

Keywords: heterogeneous catalysis · lactones · oxidation · radical reactions · titanium silicalite

Introduction

The Baeyer–Villiger (BV) reaction has aroused great interest as a tool for the preparation of pharmaceuticals (e.g., antibiotics, steroids) and compounds for the fine chemicals and intermediates industry.[1–3] Various substrates have been considered as reagents for this reaction, the main interest being focused on cyclic ketones and aromatic aldehydes, with organic peracids and peroxides, and hydrogen peroxide (HP) as oxidants; HP appears to be the ideal oxidant for developing cleaner and more sustainable chemistry. Within this context, in recent years many studies have been devoted to the investigation of new heterogeneous systems that can selectively transform cyclohexanone to ε-caprolactone with HP as the oxidant,[4–20] because this lactone is a monomer of great industrial interest for the synthesis of polycaprolactone, a biodegradable polyester with a low melting point.

Active heterogeneous catalysts for the BV oxidation of cycloalkanones with HP may be divided into four different classes: a) Brønsted-type acid catalysts, such as zeolites (H-β and USY),[4,5] alumina,[6] and polyoxometalates;[7] b) Lewis-type acid catalysts, based on Sn^{IV} (Sn-β, Sn-hydrotalcite, Sn-clay),[8–12,20] Sb^V,[13,14] or supported Pt complexes;[2,15] c) basic oxides;[16,17] and d) catalysts based on elements that will allow the formation of Me−OOH species, such as Ti^{IV} incorporated into silicalite or β zeolite.[18,19] In general, catalysts belonging to classes a) and c) show limited preference for production of the lactone; this could be due either to subsequent lactone hydrolysis, possibly catalyzed by acid sites, or to the formation of unknown heavy compounds. An acidic functionality is regarded as most important for BV oxidation, according to the mechanism proposed by Criegee,[21] because an acid activation of the ketone enables nucleophilic oxidation by nonactivated HP.[1]

Outstanding results have been reported with class b) catalysts; for example, with the highly regioselective Sn-β catalyst developed by Corma and co-workers.[20,22,23] In this case, the key reason for the high selectivity is the interaction between the carbonyl group of the reactant and the Lewis acid sites (i.e., the Sn^{IV} atom incorporated in the zeolite lattice); this interaction activates the reactant to the HP attack.

Herein, we demonstrate, for the first time, that the thermally activated BV oxidation of cyclohexanone with HP leads fatally to the formation of adipic acid (AA), because of the concomitant occurrence of reactions involving radi-

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cals formed during HP decomposition. However, strict control of reaction conditions may enable a shift in favor of the intermediate product, ε-caprolactone. Even more remarkably, strong evidence was obtained that shows that the formation of lactone first, and adipic acid later, occurs through a radical mechanism, even when titanium silicalite (TS-1) is used as catalyst.

Results and Discussion

The thermal, uncatalyzed oxidation of cyclohexanone with HP: The results from the uncatalyzed, thermal oxidation ($T = 90\,°C$) of cyclohexanone with HP are shown in Figure 1. This behavior, usually overlooked in studies of the catalyzed BV oxidation to lactones, indeed proved to be the key to understanding the reaction mechanism and, subsequently, the role of the catalyst and reaction medium as well.

In a few hours, cyclohexanone conversion reached 40%. ε-Caprolactone was the only primary product, and was largely predominant at low cyclohexanone conversion; however, the ε-caprolactone was quite reactive. Secondary products observed were 6-hydroxyhexanoic acid and AA. Note that the secondary products were not kinetically related: this means that both compounds were formed by direct transformation of ε-caprolactone; the former possibly by hydrolysis, and the latter by direct oxidation. Moreover, we observed that at these conditions the hydroxy acid was stable, and was not extensively transformed into AA. Glutaric and succinic acids were apparently formed as the final products in the reaction (the initial level of their formation was nil or very low at up to 1 h reaction time), which means that these compounds were formed by subsequent reactions on a secondary product, either 6-hydroxyhexanoic or adipic acid. A small amount of 6-oxohexanoic acid was also formed.

Figure 1 also shows the corresponding variation in HP concentration with time for the thermally activated oxidation of cyclohexanone, and for the decomposition of HP without cyclohexanone. The decomposition of HP in the absence of cyclohexanone was only slightly less rapid than it was in the presence of cyclohexanone. This means that the presence of cyclohexanone in the solution did not have additional effects on HP conversion that occurred regardless of the presence of cyclohexanone. This supports the hypothesis that, in the absence of catalyst (i.e., without any specific catalytic activation of the ketone) the formation of lactone, and then of AA, occurs by reaction with the radical species formed by HP decomposition. Considering the amount of HP required to produce the oxidation products and the HP conversion, we can deduce that HP was partially (ca. 50%) decomposed into water and oxygen.
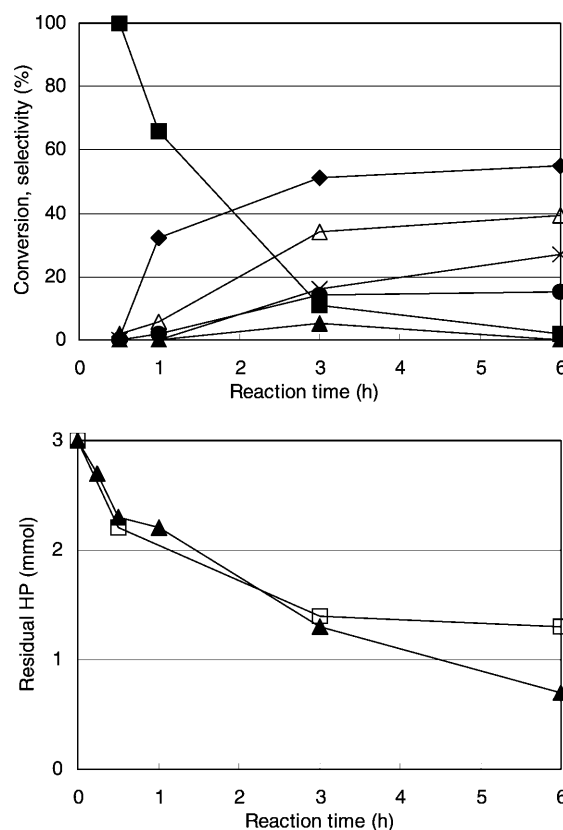

Figure 1. Top: Cyclohexanone conversion (△); proportional yields of caprolactone (■), 6-hydroxyhexanoic acid (●), 6-oxohexanoic acid (▲), AA (◆), and to glutaric+succinic acids (✕), all calculated with respect to amount of cyclohexanone converted, versus reaction time, in the absence of a catalyst. Reaction conditions: $T = 90\,°C$, 1 mmol cyclohexanone (0.103 mL), 3 mmol HP (30% aqueous solution; overall volume 0.304 mL); solvent = water (0.100 mL). Bottom: Residual HP versus reaction time for the tests shown in the top part (▲), and for tests carried out without cyclohexanone (□).

Reactivity tests made in the presence of radical scavengers confirmed our hypothesis (Table 1). Both cyclohexanone conversion and the product distribution were greatly affected by the type and amount of radical scavenger added. First, an experiment was carried out under the same conditions as for the tests in Figure 1, but in the presence of *tert*-butanol. The amount of *tert*-butanol added was in a molar ratio of 1:1 with cyclohexanone. We chose this compound because 1) it is soluble in water, 2) it generates *tert*-butyl hydroperoxide by reaction with HP, a hydroperoxide that is stable and does not react with cyclohexanone in the absence of a

Table 1. Comparison of reactivity tests made without catalyst, and either with or without radical scavenger.[a]

Radical scavenger	Cyclohexanone conversion [%]	AA	ε-CL[b]	6-HHA[c]	6-OHA[d]	GA+SA[e]
			Proportional yield [mol%]			
–	34	51	11	14	5	16
tert-butanol	18	51	23	9	–	17
dioxane	6	18	71	–	–	10

[a] Reaction time = 3 h. Cyclohexanone/*tert*-butanol and cyclohexanone/dioxane 1:1 (molar ratios). No catalyst. Other conditions as in Figure 1. [b] ε-CL = ε-caprolactone. [c] 6-HHA: 6-hydroxyhexanoic acid. [d] 6-OHA: 6-oxohexanoic acid. [e] GA+SA: glutaric acid+succinic acid.

proper catalyst, and 3) *tert*-butanol may diffuse into the TS-1 pores (see experiments with TS-1 catalyst, below). After 3 h reaction time, the conversion of cyclohexanone was 18% (versus 34% without *tert*-butanol), of which 51% (versus 51%) was converted to AA, 23% to caprolactone (versus 11%), and 9% to 6-hydroxyhexanoic acid (versus 14%). Thus, the distribution of products was slightly different from that achieved in the absence of *tert*-butanol; however, the main effect was on the reaction rate at which cyclohexanone was transformed into ε-caprolactone (the only primary reaction, see Figure 1), which was definitely lower than without *tert*-butanol. These results were confirmed by using dioxane (molar ratio dioxane/cyclohexanone = 1:1), an efficient radical scavenger that is also soluble in water.[24] In this case, the effect was even more pronounced, because the conversion of cyclohexanone was only 6%, but with a high proportional yield (71%) of lactone, and a low yield (18%) of AA. Furthermore, when a large excess of dioxane was used (molar ratio dioxane/cyclohexanone 34:1, cyclohexanone/HP 1.5:1), the conversion was nil. In conclusion, these results confirm the hypothesis that the radical species formed by HP decomposition is involved in the noncatalyzed transformation of cyclohexanone into lactone and of the latter into AA.

Tests made with a cyclohexanone/HP 1:1 molar ratio (stoichiometric for lactone formation) showed that even in these conditions it is possible to achieve both a remarkable cyclohexanone conversion (30% after 6 h reaction time) and a high proportional yield of AA (see Table 2). The pro-

Table 2. Comparison of reactivity tests made without catalyst, at different cyclohexanone/HP feed ratio.[a]

Cyclohexanone/HP molar feed ratio	Cyclohexanone conversion [%]	Proportional yield [mol%]			
		AA	ε-CL	6-HHA[b]	GA+SA[c]
1:3	40	55	2	15	28
1:1	30	43	7	37	13

[a] Reaction time = 6 h. No catalyst. Other conditions as in Figure 1. [b] 6-HHA: 6-hydroxyhexanoic acid. [c] GA+SA: glutaric acid+succinic acid.

portion of 6-hydroxyhexanoic acid produced (37%)was higher than that achieved with excess HP (15%), whereas the proportion of AA produced was lower (43% versus 55%), as was that of the lighter diacids (13% versus 28%). This means that under conditions of excess HP (cyclohexanone/HP 1:3, molar ratio, as seen in Figure 1), the consecutive degradation into glutaric and succinic acids is kinetically more probable. With a cyclohexanone/HP 1:1 molar ratio, the yield with respect to the converted HP was around 75% for an HP conversion of 87% after 6 h reaction time (yield 80% after 1 h, for an HP conversion of 38%). Therefore, when the cyclohexanone/HP molar ratio was increased, the majority of the radicals generated by HP transformation reacted with the ketone.

The role of molecular oxygen as a possible reactant for radical autoxidation was ruled out by carrying out an experiment in a nitrogen atmosphere. Cyclohexanone conversion after 6 h reaction time and under continuous feeding of nitrogen was 42% (40% in air), with 58% proportional yield of AA (55% in air).

We could also rule out the possible role of metals present in traces in cyclohexanone for two reasons. First, the overall content of transition metals in the cyclohexanone used was less than 0.2 ppm (see Experimental Section for details). Second, we carried out reactivity tests by measuring the HP decomposition after 1 h without a catalyst at 90°C, and by using cyclohexanone of two different purities, either ≥99.5 or ≥99.9%. The same extent of HP decomposition was observed in each case.

Experiments were also carried out by directly reacting ε-caprolactone or 6-hydroxyhexanoic acid, which are postulated to be reaction intermediates in the formation of AA; the results of these experiments are reported in Table 3. The lactone was much more reactive than cyclohexanone under the

Table 3. Reactivity of ε-caprolactone (ε-CL) and of 6-hydroxyhexanoic acid (6-HHA) without catalyst.[a]

Reactant	Conversion [%]	Proportional yield [mol%]			
		AA	6-HHA[b]	6-OHA[c]	GA+SA[d]
ε-CL	78	28	44	trace	28
ε-CL[e]	99	56	9	trace	35
6-HHA	13	62	–	4	34

[a] Reaction time = 3 h, except [e]. No catalyst. Other conditions as in Figure 1 (ε-CL or 6-HHA replacing cyclohexanone). [b] 6-HHA: 6-hydroxyhexanoic acid. [c] 6-OHA: 6-oxohexanoic acid. [d] GA+SA: glutaric acid+succinic acid. [e] 6 h.

conditions examined, conversion being 78% after 3 h, and almost complete after 6 h reaction time; this supports the view that in the uncatalyzed, thermally activated oxidation of the ketone, stopping the reaction at the formation of the lactone intermediate is not an easy task. The main product of lactone transformation was 6-hydroxyhexanoic acid; however, the latter was converted into AA, and to a minor extent to lighter diacids, when the conversion of the lactone increased. In fact, when the reaction time was increased from 3 to 6 h, conversion to AA increased from 28 to 56%, whereas the proportional yield of 6-hydroxyhexanoic acid correspondingly decreased from 44 to 9%. This was confirmed in an experiment carried out by direct reaction of 6-hydroxyhexanoic acid (also reported in Table 3). This compound was less reactive than the lactone (conversion 13% after 3 h reaction time); it was converted to AA (proportional yield 62%) and to lighter diacids, with minor amounts of 6-oxohexanoic acid.

All of these experiments support the proposed reaction network for the noncatalyzed, thermally activated BV reaction depicted as shown in Scheme 1. It is worth noting that, while it has been proposed in the past,[25] this is the first reported experimental evidence of the reaction network connecting the various products formed in the oxidation of cyclohexanone with HP.
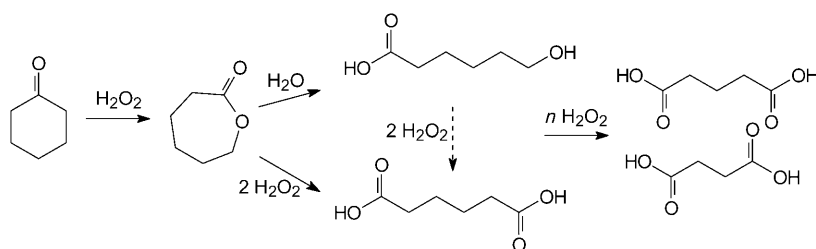
Scheme 1. Reaction network of cyclohexanone oxidation with HP.

Our results demonstrate that, even in the absence of a catalyst, under conditions typically used for the catalytic BV oxidation of ketones, cyclohexanone is converted to ε-caprolactone. Therefore, the radicals generated by HP decomposition, as shown in Equations (1) and (2) are also involved in the cyclohexanone transformation:

$$H_2O_2 \rightarrow 2\,HO^{\bullet} \tag{1}$$

$$HO^{\bullet} + H_2O_2 \rightarrow H_2O + HO_2^{\bullet} \tag{2}$$
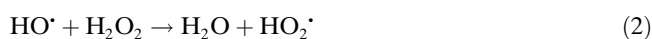
In other words, even though an acid-type activation of the ketone may accelerate the reaction, the carbonyl moiety in cyclohexanone does not need this chemical activation to react. The Criegee intermediate may indeed form either by the classical addition of HOOH, or by a two-step reaction with ·OH (Scheme 2). However, cyclohexanone activation by hydrogen bonding with water could also occur (also shown in Scheme 2).
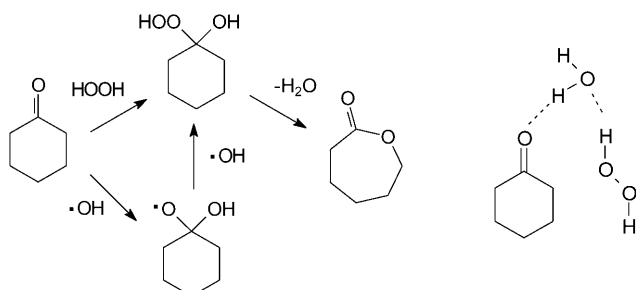
Scheme 2. Left: Conventional (upper route) and nonconventional radical (lower route) routes to ε-caprolactone, via the common Criegee intermediate. Right: Possible carbonyl activation by water through hydrogen bonding.
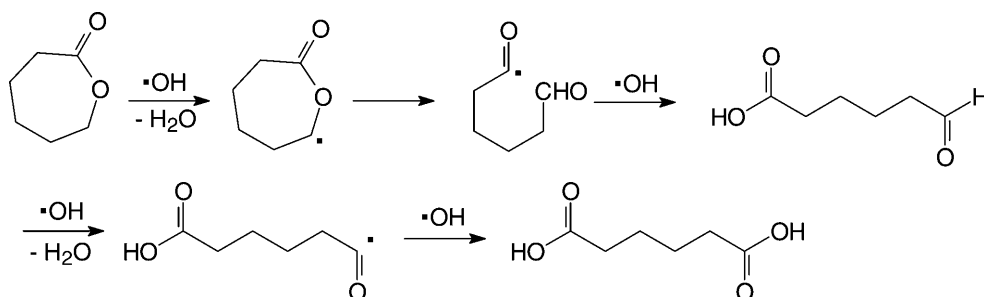
Lactone is then converted into various products by means of parallel reactions (Scheme 1): 1) hydrolysis to 6-hydroxyhexanoic acid, which appears to be not very reactive under the chosen conditions; or 2) radical reactions to generate either AA (Scheme 3), or lighter diacids, or, to a minor extent, 6-oxohexanoic acid.

Reactivity tests with TS-1 catalyst: Results of experiments carried out with TS-1 catalyst are shown in Figure 2; conditions were similar to those used for the thermally activated reaction. In contrast to the experiments carried out without catalyst, there was no formation of either the 6-hydroxyhexanoic or the 6-oxohexanoic acids, and only a very low amount of ε-caprolactone was formed. The main product over the entire range of cyclohexanone conversion was AA, but glutaric and succinic acids were also produced in significant quantities. The distribution of products was not affected by the conversion, thus supporting the hypothesis that AA is mainly formed by a direct, parallel reaction of cyclohexanone, or that the intermediate ε-caprolactone is very efficiently transformed into AA inside the pores of the silicalite before it diffuses out into the bulk liquid phase.

Figure 2 also depicts the effect of reaction time on HP conversion; the amount of unconverted HP is compared with that achieved under the same conditions but without a catalyst. The HP conversion was greatly enhanced in the presence of TS-1, but the initial proportional yield of oxygenated compounds still remained lower than 50%. This implies that Ti sites are able to activate HP and develop the TiOOH species, but that a large part of the latter then decomposes into radical species, and then to water and oxygen. However, it is also shown that, even though the conversion of cyclohexanone increased continuously over the entire range of reaction time (0–6 h), the amount of residual HP was already very low after 1 h reaction time. At the same time, the proportional yield of AA, calculated with respect to the converted HP, increased over time.

The only possible explanation for these observations is that the rate-determining step of the process is not the gen-
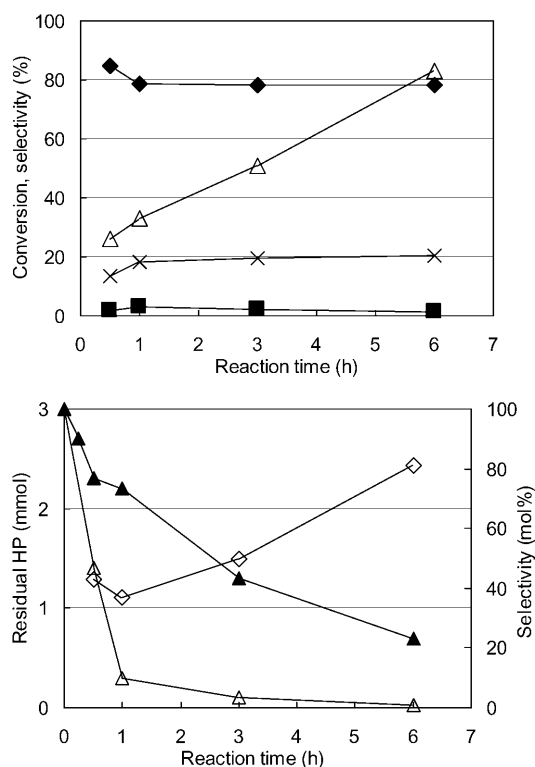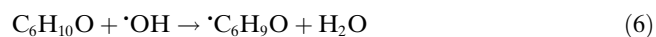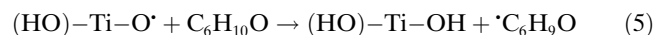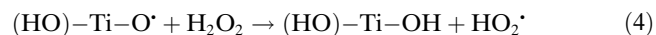

Scheme 3. Transformation of ε-caprolactone into AA through a radical mechanism.

Figure 2. Top: Cyclohexanone conversion ($\triangle$); proportional yield of caprolactone ($\blacksquare$), AA ($\blacklozenge$), and glutaric+succinic acids ($\times$), all calculated with respect to amount of cyclohexanone converted, versus reaction time. Reaction conditions: $T = 90\,°C$, 1 mmol cyclohexanone (0.103 mL), 3 mmol HP (30% aqueous solution; overall volume 0.304 mL); solvent = water (0.100 mL). Catalyst TS-1 (0.077 g; 0.032 mmol Ti). Bottom: Residual amount of HP, in the absence ($\blacktriangle$) and in the presence of TS-1 ($\triangle$), and proportional yield of diacids with respect to converted HP ($\diamond$), versus reaction time.

eration of the TiOOH species, but its subsequent reaction with cyclohexanone; in other words, the few Ti sites (the molar ratio Ti^{IV}/cyclohexanone was equal to 0.032) act as reservoirs for the oxidizing species, the hydroxy radicals, as shown in Equations (3) to (7):

$$H_2O_2 + -O-Ti^{IV} \rightarrow (HO)-Ti-OOH \rightleftharpoons (HO)-Ti-O^\bullet + {}^\bullet OH \quad (3)$$

$$(HO)-Ti-O^\bullet + H_2O_2 \rightarrow (HO)-Ti-OH + HO_2{}^\bullet \quad (4)$$

$$(HO)-Ti-O^\bullet + C_6H_{10}O \rightarrow (HO)-Ti-OH + {}^\bullet C_6H_9O \quad (5)$$

$$C_6H_{10}O + {}^\bullet OH \rightarrow {}^\bullet C_6H_9O + H_2O \quad (6)$$

$$(HO)-Ti-OH + H_2O_2 \rightarrow (HO)-Ti-OOH + H_2O \quad (7)$$
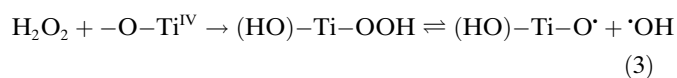
Due to both the higher reactivity of ε-caprolactone than cyclohexanone, and the very high local concentration of the $^\bullet OH$ (and $^\bullet O_2H$) radicals generated and trapped inside the TS-1 pores, lactone is very efficiently transformed into AA and lighter diacids.

When the reaction was carried out under the same experimental conditions as for Figure 2, but in the presence of tert-butanol (cyclohexanone/tert-butanol molar ratio 1:1), the conversion of cyclohexanone was only slightly lower than that observed during the same reaction time without tert-butanol (Figure 3). However, the main difference concerned
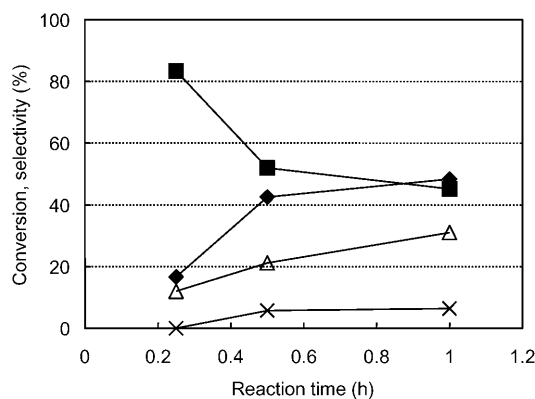

Figure 3. Cyclohexanone conversion ($\triangle$); proportional yield of caprolactone ($\blacksquare$), AA ($\blacklozenge$), and glutaric+succinic acids ($\times$), all calculated with respect to amount of cyclohexanone converted, versus reaction time. Reaction conditions as in Figure 2, but with tert-butanol as cosolvent (cyclohexanone/tert-butanol 1:1 molar ratio). Catalyst TS-1 (0.077 g; 0.032 mmol Ti).

the distribution of products. In the presence of tert-butanol, ε-caprolactone formed in higher proportions; in other words, its consecutive transformation into AA was much slower than it was in the absence of tert-butanol. It is also important to note that the HP conversion over time was exactly the same for tests carried out either with or without tert-butanol; a result that agrees with the assumption that the radical scavenger does not have any effect on the HP decomposition rate. On the other hand, when a large excess of tert-butanol was used (cyclohexanone/tert-butanol 1:6), while keeping the other reaction parameters constant, the cyclohexanone conversion was largely reduced (8% after 6 h reaction time), and once again the proportional yield of ε-caprolactone was relatively high (34 versus 42% for the proportional yield of AA). This means that tert-butanol has a major effect on the rate of oxidation of the lactone into AA, due to the higher reactivity of this compound than cyclohexanone, but when higher amounts of tert-butanol are used, the inhibitory effect also extends to the less reactive cyclohexanone. Note that the same detrimental effect was not observed when methanol was used as solvent.

Furthermore, similarly to what is observed in tests carried out without catalysts, with TS-1 an experiment conducted in a nitrogen atmosphere gave the same result as that obtained in the presence of air: cyclohexanone conversion was 51% after 3 h reaction time (versus 51% in air), with 82% proportional yield of AA (versus 78% in air).

Lastly, experiments were conducted by direct reaction of either ε-caprolactone or 6-hydroxyhexanoic acid (Table 4);

Table 4. Reactivity of ε-caprolactone (ε-CL) and of 6-hydroxyhexanoic acid (6-HHA) with TS-1 catalyst.[a]

Radical scavenger	Reactant	Conversion [%], t [h]	Proportional yield [mol%]			
			AA	6-HHA[b]	6-OHA[c]	GA+SA[d]
–	ε-CL	40, 0.5	93	3	2	2
–	ε-CL	84, 1	87	7	2	4
tert-butanol[e]	ε-CL	22, 1	59	27	–	14
–	6-HHA	17, 6	83	–	5	12

[a] Reaction conditions as in Figure 2 (ε-CL or 6-HHA replacing cyclohexanone). [b] 6-HHA: 6-hydroxyhexanoic acid. [c] 6-OHA: 6-oxohexanoic acid. [d] GA+SA: glutaric acid+succinic acid. [e] ε-caprolactone/tert-butanol 1:1 (molar ratio).

these tests were aimed at confirming the high reactivity of the lactone. The reaction conducted for 1 h, under the same conditions as for cyclohexanone (Figure 2, with the same molar ratio of reactant/Ti^{IV}/HP), led to 84% lactone conversion, with 87% proportional yield of AA. However, when the reaction was carried out in the presence of tert-butanol, ε-caprolactone conversion was only 22% after 1 h reaction time, with 59% proportional yield of AA and 27% 6-hydroxyhexanoic acid. This means that the presence of this alcohol inhibited the transformation of ε-caprolactone to AA, whereas the parallel route of lactone hydrolysis to 6-hydroxyhexanoic acid was left substantially untouched. 6-Hydroxyhexanoic acid was much less reactive than ε-caprolactone, which is similar to what is observed in experiments conducted without catalysts; after 6 h reaction time, conversion was only 17%, the main product of oxidation being AA.

Reactivity tests were carried out by using both greater amounts of TS-1 and reactants and solvent volumes, to evaluate the isolated yield of AA. Figure 4 shows a plot of the results of these experiments; the yield of the products and the conversion of HP are plotted as a function of reaction time for tests carried out either in water only, or in water+tert-butanol. During these experiments, all the reactants and catalyst weights loaded were 50 times higher than those
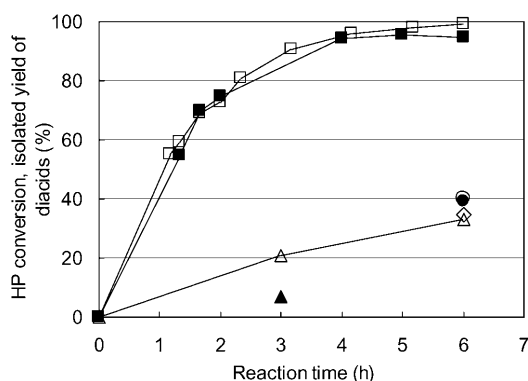

Figure 4. Isolated yield of (adipic+glutaric+succinic) acids (△,▲) and HP conversion (□,■) as a function of reaction time. Reaction conditions: Open symbols: 5 mL cyclohexanone, 5 mL H$_2$O, 15.2 mL H$_2$O$_2$ (35%) (molar ratio HP/cyclohexanone 3:1). Full symbols: 5 mL cyclohexanone, 5 mL H$_2$O, and 29 mL tert-butanol (molar ratio tert-butanol/cyclohexanone 6.3), 15.2 mL H$_2$O$_2$ (35%) (molar ratio HP/cyclohexanone 3:1), TS-1 3.83 g. $T = 90$°C. Isolated yield with filtered and reused TS-1 (◇); isolated yield with regenerated TS-1 catalyst: after regeneration of TS-1 by washing with water and acetone (●), and after regeneration of TS-1 by calcination at 450°C in air for 3 h (○).

used in the tests shown in Figures 2 and 3; under these conditions, we could not load all reactants from the very beginning, because the very rapid decomposition of HP led to the evolution of large amounts of oxygen, causing a sudden and very dangerous pressure increase in the reactor. Therefore, we slowly added HP over one hour, and then continued the reaction over the desired time. Because of this, the rates of transformation and extent of conversion of both HP and cyclohexanone were lower than those obtained for the same reaction times in the experiments shown in Figures 2 and 3.

The yield of the final solid product (which consisted of 75% AA, and 25% glutaric and succinic acids, with only traces of ε-caprolactone; see the Experimental Section for details of yield measurement) was 21% after 3 h reaction time, and 32% after 6 h reaction time. The experiment was repeated after the recovery of the spent TS-1, which was either reloaded as such for another experiment, or regenerated either by simply washing with water and acetone, or by a thermal treatment at 450°C in air for 3 h. In all cases, the isolated yield obtained after 6 h reaction time was very similar to that obtained with the fresh catalyst (results also shown in Figure 4).

Again, Figure 4 shows the results of experiments carried out in the presence of tert-butanol. The yield after 3 h reaction time was much lower than that obtained without tert-butanol, but the conversion of HP did not differ in the two cases; in fact, during tests carried out with tert-butanol, most of the HP decomposed into water and oxygen. This confirms the results obtained in tests carried out without a catalyst; the radical scavenger does not so much affect the conversion of HP, but it does affect the reaction pathway by which radicals generated by the HP conversion react further.

Our results highlight that the BV oxidation of cyclohexanone, and presumably of cyclic ketones in general, indeed comprises a complex network of reactions that have often been overlooked in the literature, such as the consecutive transformation of the very reactive ε-caprolactone into 6-hydroxyhexanoic acid, AA, and lighter diacids. This would suggest that it might not be possible to achieve both high conversion of cyclohexanone and high proportional yield of ε-caprolactone at the same time; a result which is in contrast with most reports on the catalyzed BV oxidation of cyclohexanone with HP. Remarkably, this reaction network is the same in both thermal and TS-1-catalyzed reactions, which strongly suggests that the same active oxidizing species are involved in the two cases. This supports the unprecedented view that the Ti-OOH hydroperoxo species does not act as an electrophile toward the activated carbonyl in the substrate, but acts as a sort of reservoir for the oxidant species through the controlled decomposition of the hydroperoxo into hydroxy radicals.

One possible explanation for discrepancies between our data and previously reported results is that the distribution of products, and therefore, the relative importance of each reaction rate in the mentioned network is dramatically affected by both the solvent used (because the solvent may act as a radical scavenger and thus slow down the consecutive transformation of the very reactive lactone) and by the characteristics of the catalyst used. For instance, we found that the Lewis-type Sn-β catalyst reported by Corma et al.[22,23] offers unique reactivity, and that its behavior is enormously affected by reaction conditions. When we used this catalyst under conditions similar to those reported in the present work (i.e., temperature 90 °C, reaction time 3 h, 0.06 g catalyst, H₂O (0.2 mL), cyclohexanone (2 mmol), HP (6 mmol)), the Sn-β afforded very low cyclohexanone conversion (0.9 %), with 20 % proportional yield of ε-caprolactone and 70 % AA. However, when the same catalyst was used under conditions closer to those described in papers by Corma et al.[22,23] (i.e., with dioxane as solvent, temperature 90 °C, reaction time 3 h, 0.06 g catalyst, 2 mmol cyclohexanone, 1.3 mmol HP, to achieve a cyclohexanone/HP molar ratio of 1.5 and a dioxane/cyclohexanone wt ratio of 30), cyclohexanone conversion was 19.4 %, with 98 % proportional yield of ε-caprolactone and only 2 % AA.

Conclusion

In the Baeyer–Villiger oxidation of cyclohexanone with aqueous hydrogen peroxide under conditions aimed at obtaining ε-caprolactone, an uncatalyzed, thermally activated radical reaction leads to the concurrent formation of adipic, succinic, and glutaric acids, even when a stoichiometric amount of the oxidant is used. ε-Caprolactone is the primary reaction product, but it is more reactive than cyclohexanone, and it quickly undergoes consecutive transformations by one of two different reaction pathways: 1) a hydrolytic pathway to 6-hydroxyhexanoic acid, which also is oxidized to AA, although more slowly than the concurrent ones, or 2) a direct oxidative scission to AA.

The relevant reaction rates are modified when TS-1 is used as catalyst. In this case, the high concentration of hydroxy radicals within pores accelerates the reaction rates, especially the consecutive formation of AA and of lighter diacids. The proper choice of solvent, which may also act as a radical scavenger, both without catalyst and with TS-1, is a powerful tool for controlling the rates of the various reactions involved. With either tert-butanol or dioxane, which are both efficient radical scavengers, all reaction rates are slowed down, especially the consecutive oxidation of the very reactive ε-caprolactone into diacids.

Experimental Section

General: Titanium-silicalite-1 (TS-1) was synthesized according to a previously described procedure.[27] The structural integrity of the sample and framework incorporation of Ti^{IV} were checked by means of XRD, FTIR, and UV/Vis diffuse reflectance spectroscopy. The amount of Ti incorporated was 2 wt %. The crystal size of this sample was <0.2 μm. The slurry containing TS-1 crystallites was spray dried after the addition of silica Ludox, by using a Lab-Spray drier (T of nebulization chamber 200 °C, nozzle diameter 2 mm). The final average size of agglomerated particles was about 25 μm. The agglomerated samples were then calcined in air at 550 °C.

Typical conditions for the thermal, uncatalyzed oxidation of cyclohexanone with HP: In a 10 mL pyrex reactor with screw stopper, a mixture of H₂O (0.1 mL), H₂O₂ (30 %, 3 mmol, 0.340 g, 0.304 mL; source Carlo Erba), and cyclohexanone (1 mmol, 0.098 mg, 0.103 mL; sources: 1) Aldrich, code 29140, ≥99.5 %, containing ≤0.1 ppm Fe; ≤0.02 ppm Co; ≤0.02 ppm Cr; ≤0.02 ppm Cu; 2) Aldrich code 02482, ≥99.9 %) were stirred at 90 °C for the required time. The reaction mixture was then cooled to room temperature and diluted with a 1:1 mixture of H₂O/CH₃CN to 50 mL. After addition of a known amount of benzoic acid as internal standard, subsequent dilutions were required to prepare samples for analysis, in particular 5 mM of internal standard for positive ion and 0.5 mM for negative ion mode. In TS-1-catalysed reactions, a mixture containing H₂O, 30 % H₂O₂, and TS-1 (0.077 g) was stirred at room temperature for 15 min. Cyclohexanone was then added, and the mixture was heated under stirring for the required time. After cooling the reaction mixture to room temperature, the catalyst was removed by Buchner filtration, and washed with H₂O (5 mL), then with CH₃CN (5 mL). The filtrate was diluted with a 1:1 mixture of H₂O/CH₃CN (10 mL). Hydrogen peroxide conversion was determined by iodometric titration.

Product concentration was determined by ultraperformance liquid chromatography (UPLC)–mass spectrometry (gas chromatography (GC) is not suitable for the identification of dicarboxylic acids).[26] Indeed, in most reports on the oxidation of cyclic ketones with hydrogen peroxide (with a few exceptions[4,10]), the analysis of the reaction products is carried out by means of GC, which does not allow the detection of diacids.[5–9,11–20]) UPLC analysis was performed by using an Acquity Ultra Performance Waters UPLC System equipped with autosampler. UPLC separation was conducted on a Acquity UPLC BEH C18 column (1.7 μm, 2.1 × 100 mm) at a flow rate of 0.3 mL min⁻¹ with an elution gradient: eluent A H₂O (0.2 % HCOOH), eluent B (0.2 % HCOOH); elution: 0–2 min isocratic 100 % A, 2–10 min linear gradient to 65 % A-35 % B, 10–10.5 min linear gradient to 100 % B, 10.5–13.5 min isocratic 100 % B, 13.5–14 min linear gradient to 100 % A, 14–19 min isocratic 100 % A; flow rate 0.3 mL min⁻¹. Both the column and the autosampler were maintained at 25 °C. Mass spectrometry conditions in positive ion mode: capillary voltage 3.0 kV, cone voltage 28.0 V, source temperature 100 °C, desolvation temperature 200 °C, cone gas flow (N₂) 100 L h⁻¹ desolvation gas flow (N₂) 600 L h⁻¹. Mass spectrometry conditions in negative ion mode: capillary voltage 2.8 kV, cone voltage 23.0 V, source temperature 100 °C, desolvation temperature 200 °C, cone gas flow (N₂) 100 L h⁻¹, desolvation gas flow (N₂) 600 L h⁻¹.

Experiments focused on the determination of the isolated yield were carried out by using cyclohexanone (5 mL), H₂O (5 mL), H₂O₂ (35 %, 15.2 mL, to give molar ratio HP/cyclohexanone 3:1), and TS-1 (3.83 g) with no tert-butanol or with 29 mL tert-butanol. In the latter case, the HP solution was slowly added over 1 h, and then the reaction was left to proceed for the desired time. Note that it was not possible to add all of the reactants at once, because the very rapid decomposition of HP leads to a sudden and very dangerous release of a large volume of oxygen. This causes a sudden pressure increase in the vessel, even when it is unsealed and exposed to air. The weight of the isolated yield was measured as follows: the hot slurry downloaded from the reactor was filtered to recover the TS-1 catalyst; then the filtrate was concentrated under vacuum at 80 °C to remove unconverted cyclohexanone and solvents (water and/or tert-butanol). The solid obtained was washed four times with cold water, dried overnight at 80 °C, and then weighed. Finally, a part of the solid was dissolved in hot water and analyzed to determine the relative amount of each product. These experiments were also aimed at determining the activity of the spent TS-1. The recovery of the spent catalyst always led to a loss of approximately 10 % of the original catalyst; the

amount lost was replaced with an analogous amount of catalyst recovered after another experiment. Then the catalyst was either reused as such, or regenerated by simply washing with water and acetone, or by washing and then by thermal treatment in air at 450 °C for 3 h.

In tests for isolated yield determination, the products were also analyzed by gas-chromatography (GC). Analysis of cyclohexanone and ε-caprolactone is possible by GC, but the analysis of diacids (adipic, succinic, and glutaric acids) is not; the latter need derivatization (e.g., by reaction with methanol) to be analyzable by GC.[26] The procedure for diacid derivatization was as follows: The reaction mixture was heated to 65 °C in a vacuum to remove both the unconverted cyclohexanone and the initial reaction solvent. The residual solid was mixed with an excess of methanol and BF_3 (dissolved in methanol) at 80 °C for 1 h in a sealed vessel. The esters were then extracted with *n*-hexane (this also led to the precipitation of BF_3 from the mixture); the extraction procedure was repeated several times. Lastly, the solution of diesters in *n*-hexane was analyzed by GC (internal standard *n*-decane). This method allowed the identification of acids in the form of methyl esters.

Acknowledgements

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