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ORGANIC SYNTHESIS AND INDUSTRIAL INORGANIC CHEMISTRY

Synthesis of ε-Caprolactone with Stable Hydrogen Peroxide Adducts

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Abstract—Oxidation of cyclohexanone to ε-caprolactone with stable industrially manufactured hydrogen peroxide derivatives: adduct with urea (urea hydrogen peroxide), sodium perborate, sodium percarbonate (Persol), magnesium monoperphthalate (Dismozon) was studied. Oxidation with urea hydrogen peroxide is the most efficient in hexafluoroisopropanol in the case of preliminary removal of urea in the form of an oxalate. Oxidation with sodium perborate and percarbonate provides high yields in trifluoroacetic acid. The lowest cost process consists in interaction with sodium monoperphthalate (Persol and phthalic anhydride) in an aqueous medium.

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ε-Caprolactone is a valuable monomer used to obtain biodegradable polymers for household and medicinal purposes. The manufactured amount of ε-caprolactone and its homo- and copolymers is steadily increasing in most of advanced countries. The demand for polymers of this kind also grows in our country primarily due to the replacement of the conventional surgical suture materials (silk, catgut) with synthetic bioabsorbable materials based on polyoxyalkanoates.

The conventional way to synthesize ε-caprolactone is via oxidation of cyclohexanone with peroxy acids or Caro's acid by the Bayer–Villiger reaction [1]. Also, various organic peroxy acids and catalytic systems with hydrogen peroxide have been suggested [2]. These processes, as a rule, require a high concentration of hydrogen peroxide whose solutions are not only unstable, but also dangerously explosive.

Use of H_2O_2 adducts is preferable owing to their higher stability and safety in transportation and storage. Adducts of this kind are widely used as bleaching and disinfectant agents and can serve as convenient and commercially available oxidants.

For example, it is known that oxidation of cyclohexanone with urea hydrogen peroxide [UHP, $H_2O_2 \cdot CO(NH_2)_2$] well occurs under heating in hexafluoroisopropanol in the presence of p-toluenesulfonyl acid. In this case, the yield of ε-caprolactone is 71% [3, 4]. Oxidation with sodium perborate in acetic acid must give ε-caprolactone in 91% yield [5]. Sodium percarbonate can also be used as oxidizing agent in an acid medium. In this case, the yield of ε-caprolactone in trifluoroacetic acid is in the range from 66% [6] to 81% [7]. Magnesium monoperphthalate is used to oxidize cyclohexanone in various media. For example, the yield of ε-caprolactone in DMFA is 66% [8], high yields of lactones (80–99%) are obtained in a water–methanol solution [9, 10].

In the present study, we compare stable industrially manufactured hydrogen peroxide adducts as cyclohexanone oxidants by the Bayer–Villiger reaction and optimize the conditions of oxidation reactions to give ε-caprolactone.

EXPERIMENTAL

UHP manufactured by Lugansky chemical-pharmaceutical factory was used without additional purification. Sodium perborate ($NaBO_2 \cdot H_2O_2 \cdot 4H_2O$) of specialpurity grade was manufactured by Kuibyshev chemical factory GUP. Sodium percarbonate ($Na_2CO_3 \cdot 1.5H_2O_2$) was purchased as a Persol Super commercial product (Supinsky chemical factory ZAO) or synthesized by the patented technique [11]. Magnesium perphthalate [$Mg(OCOC_6H_4COOOH)_2$], Dismozon Pur disinfectant from Bode Chemie GmbH & Co (Germany), was also synthesized by the method described in [12]. All the inorganic adducts were analyzed for the content of H_2O_2 by titration with potassium permanganate [13], and magnesium monoperphthalate, by titration with sodium thiosulfate with addition of potassium iodide [13].

To quantitatively estimate the content of reaction products, we analyzed the reaction mixtures with a Shimadzu 17A gas chromatograph (Japan) with a flame-ionization detector (GC-FID), ZB-5 quartz capillary column (polydimethylsiloxane, 5% phenyl groups, length 30 m, diameter 0.25 mm, film thickness 0.25 μm); initial column temperature 40°C (holding duration 3 min), heating at a rate of 10 deg min–1 to 300°C (holding duration 30 min), evaporator temperature 280°C, detector temperature 300°C, carrier-gas nitrogen, flow division 1 : 30, column flow rate 1.0 mL min^{-1}. Calculations were made by the internal normalization over peak areas in the chromatograms.

The products formed were identified with an Agilent GC 7890A MSD 5975C inert XL EI/CI gas chromatograph/mass spectrometer (United States) with a quadrupole mass-spectrometric detector operating under ionization with 70 eV electrons (GC-MSD), HP5-MS quartz capillary column (polydimethylsiloxane, 5% phenyl groups, length 30 m, diameter 0.25 mm, film thickness 0.25 μm); initial column temperature 40°C (holding duration 3 min); heating at a rate of 10 deg min^{-1} to 290°C (holding duration 30 min); temperature (°C): evaporator 250, intermediate chamber 280, mass-spectrometric source 230, quadrupole 250; carrier-gas helium; flow division 1 : 50; column flow rate 1.0 mL min^{-1}. Chromatograms were recorded by the full ionic current, with scanning in the mass range 20–1000 a.m.u. The identification was based on the mass-spectrum database NIST05 and analysis of individual substances.

A C,H,N analysis was made on a Perkin Elmer automated analyzer. ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer.

Oxidation of cyclohexanone by UHP. A flask was charged with 0.5 g (5.1 mmol) of cyclohexanone, 4.03 mL of a solvent, and 0.62 g (6.6 mmol) of UHP and then 0.01 *p*-toluenesulfonic acid monohydrate was added to the solution. The mixture was kept at 55°C for 10 h. The solvent was removed in a rotary vacuum evaporator with a liquid nitrogen trap (solvent recycling was 92–93%). A mixture of urea and raw ε-caprolactone was dissolved in water, and ε-caprolactone was extracted with chloroform (3 × 8 mL). A combined organic phase was washed with a saturated sodium chloride solution and dried with sodium sulfate. After chloroform was evaporated, the residue was analyzed and, when necessary, distilled in a vacuum (Table 1).

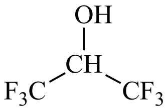
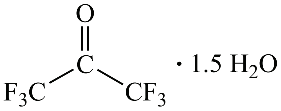
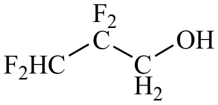
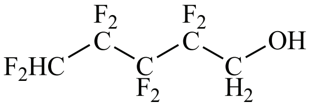
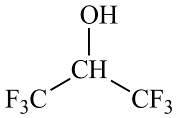
Oxidation of cyclohexanone by sodium perborate. A flask was charged with 0.5 g (5.1 mmol) of cyclohexanone, 5 mL of a solvent, and sodium perborate (7.65 mmol in terms of H_2O_2). The mixture was agitated at 55°C for 4 h. Then, 5 mL of methylene chloride was added to the reaction mass, the mixture was filtered, and the filtrate was evaporated and analyzed (Table 2).

Oxidation of cyclohexanone by sodium percarbonate. A flask was charged with 0.5 g (5.1 mmol) of cyclohexanone and 10 mL of the corresponding acid. Then, the mixture was cooled to 0°C and sodium percarbonate was added (10.2 mmol in terms of H_2O_2). The mixture was agitated at room temperature for 2 h, diluted with 20 mL f water, and extracted with methylene chloride (3 × 15 mL). A combined organic phase was washed with a sodium carbonate solution, dried with sodium sulfate, evaporated, and analyzed (Table 2).

Oxidation of cyclohexanone by magnesium monoperphthalate. A 0.5-g portion (5.1 mmol) of cyclohexanone was dissolved in a mixture of 20.4 mL of water and 20.4 mL methanol, and 0.86 g of sodium bicarbonate and 2.56 g (6.63 mmol) of magnesium monoperphthalate was added. The mixture was agitated at room temperature for 20 h. Then the precipitate was filtered off and the filtrate was extracted with methylene chloride (3 × 12 mL). A combined organic phase was dried with sodium sulfate and evaporated, and the concentrate was analyzed. The syntheses were performed by varying the molar ratio between the ketone and perphthalate (Table 3).

Oxidation of cyclohexanone by sodium perphthalate (Persol and phthalic anhydride). A vessel was charged with 6.04 g of ethyl acetate, 0.4 mL of water, and sodium percarbonate (10.71 mmol in terms of H_2O_2). The solution was cooled to 10°C and 1.51 g (10.2 mmol) of phthalic anhydride was introduced in portions under vigorous agitation. After that the mixture

Table 1. Results of cyclohexanone oxidation by UHP in fluorinated solvents at cyclohexanone concentrations of (1) 1.26 and (2) 0.63 M according to GLC data, 55°C, 10 h

Solvent	$C_6H_{10}O$ conversion, %		ε-$C_6H_{10}O_2$ content, %	
	1	2	1	2
	84	94	77	85
	16	89	23	39
	29	60	85	34
	24	27	49	54
	–	100[b]	–	33[a]
	–	99[b]	–	74[b]

[a] 30% hydrogen peroxide solution as oxidizing agent, instead of UHP.

[b] Sodium percarbonate as oxidizing agent, instead of UHP.

was agitated at room temperature for 1.5 h. A 0.25-g portion (2.55 mmol) of cyclohexanone and 20 mL of water was added to the mixture. The resulting diphase system was vigorously agitated at room temperature for 20 h. Ethyl acetate was distilled-off in the form of an azeotrope with water, ε-caprolactone was extracted from the aqueous solution with methylene chloride.

For comparison, the mixture was acidified, prior to introduction of cyclohexanone, with an additional amount of phthalic anhydride to pH ~4.5, which corresponds to the pH value of the aqueous reaction medium containing magnesium monoperphthalate. After ethyl acetate was removed, the precipitate of *o*-phthalic acid, formed in this case, was separated by filtration, with further isolation of ε-caprolactone performed as described above. Phthalic acid was 99% regenerated. The synthesis was also carried out in an aqueous medium without ethyl acetate (Table 3).

Table 2. Results of cyclohexanone oxidation by sodium perborate and percarbonate in an acid medium according to GLC data

Solvent	Sodium perborate[a]		Sodium percarbonate[b]	
	$C_6H_{10}O$ conversion, %	ε-$C_6H_{10}O_2$ content, %	$C_6H_{10}O$ conversion, %	ε-$C_6H_{10}O_2$ content, %
H_3CCOOH	21	100	1	72
$(H_3CCH_2CO)_2O$	22	100	13	1
F_3CCOOH	100	3	100	2
$(H_3CCH_2CO)_2O$ + F_3CCOOH	39	82	75	58

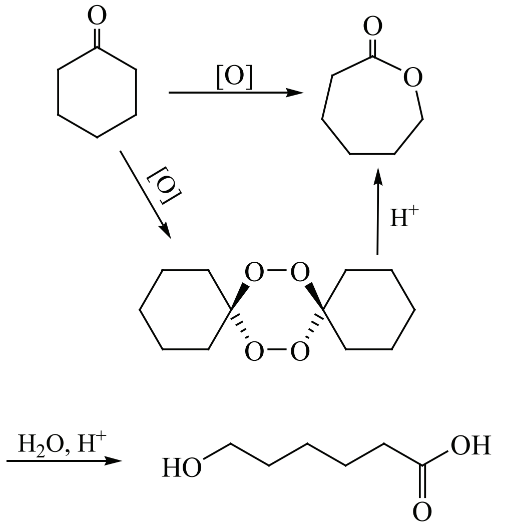
[a] 55°C, 4 h.

[b] 25°C, 2 h.

Cyclohexanone was acidified with H_2O_2 clathrate with urea (UHP), sodium perborate, sodium percarbonate (Persol), and magnesium (Dismozon) or sodium monoperphthalate.

Cyclohexanone was oxidized with UHP by using fluorinated solvents: hexafluoroisopropanol, tetra- and octafluoropropanol, and hexafluoroacetone hydrate (Table 1).

Presence of water in hexafluoroacetone leads to oxidative hydrolysis of ε-caprolactone to give 6-hydroxycaproic acid, whose content in reaction products is 60% according to GLC data, irrespective of the cyclohexanone concentration:



(1)

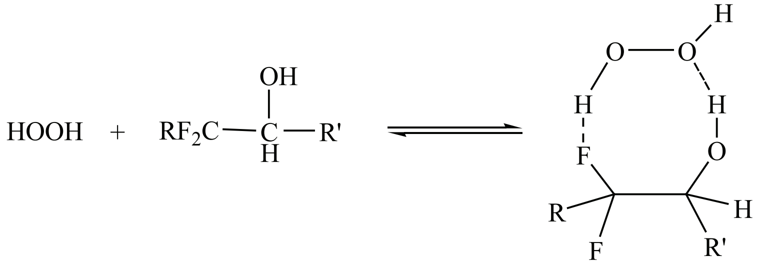
Table 3. Results of cyclohexanone oxidation by magnesium (Mg-MPP) and sodium (Na-MPP) monoperphthalates according to GLC data, 25°C, 24 h

Oxidizing agent	Solvent	pH	$C_6H_{10}O$ conversion, %	ε-$C_6H_{10}O_2$ content, %
Mg-MPP	$H_2O–H_3COH$[a]	6.9	46	84
	$H_2O–H_3COH$[b]	5.4	100	40
	$H_2O–H_3CCN$[b]	5.0	92	100
	H_2O[b]	4.5	95	100
Na-MPP	H_2O[b]	6.0	23	100
	H_2O[b]	4.5	100	100
	H_2O[c]	4.5	76	94

[a] Monoperphthalate : ketone ratio = 1 : 1.3.
[b] Monoperphthalate : ketone ratio = 1 : 4.
[c] Monoperphthalate : ketone ratio = 1 : 4 without ethyl acetate.

Use of a 30% H_2O_2 solution instead of UHP provides a 100% conversion of cyclohexanone; however, the presence of water results in that 6-hydroxycaproic acid is formed in an amount of 67% according to GLC data. Use of sodium percarbonate also provides a high cyclohexanone conversion, with the fraction of acid in the reaction products being small: ~5% according to GLC data.

It should be noted that the yield of ε-caprolactone in hexafluoroisopropanol considerably more than that with other solvents. The effect of the solvent on the reaction course becomes understandable if an eight-membered electrophilically active intermediate of the H_2O_2 molecule with the solvent molecule, rather than the hydrogen peroxide molecule itself, is regarded as the acting oxidizing agent [14]:


(2)

In this case, the process efficiency is determined by the formation energy of an intermediate of this kind. In the case of hexafluoroacetone [14], the role of the oxidizing agent is, in all probability, played by the semiacetal. Comparison of the results obtained with the calculated values of the intermediate formation energy for various solvents provides understanding of how the cyclohexanone conversion varies with the structure and amount of the solvent. For example: $F_3CCH(OH)CF_3 >> F_3CCF_2CH_2OH$, $E = 7.7$ and 8.3 kcal mol^{-1}, respectively (calculated using HyperChem 8.08 software package with STO-3G basis).

A preparative recovery of ε-caprolactone from the reaction mixture demonstrated that, in addition to the main product (lactone), cyclohexanone diperoxide (7,8,15,16-tetraoxodispyro[5,2,5,2]hexadecane) is formed, which is an intermediate product of ε-caprolactone synthesis [scheme (1)] and forms white needle-like crystals in solvent evaporation and(or) distillation of the reaction mixture. According to the results of an elemental analysis, the composition of the product is close to the calculated values; the compound is unambiguously identified by ^{13}C NMR spectroscopy ($CDCl_3$), δ, ppm: 25.2, 27.2, 42.0, 110 [3]. If the reaction is performed in a twofold volume of hexafluoroisopropanol (cyclohexanone concentration

0.63 M), the content of the diperoxide in the reaction products is up to 90 wt %.

According to published data [4], the diperoxide must decompose on being heated in an acid medium to give a lactone and(or) a hydroxy acid. Raising the content of p-toluenesulfonyl acid in the reaction medium from 1 to 5 mol % results in that the content of the diperoxide in the reaction products decreases to 12 wt %. Use of trifluoroacetic acid in the same amount yields 55 wt % diperoxide, use of perchloric acid yields 35 wt % of diperoxide, and use of trifluoromethanesulfonic acid yields 18 wt % of diperoxide.. Thus, the degree of diperoxide decomposition depends on the strength of an acid.

It was found that cyclohexanone diperoxide isolated in pure form decomposes faster in the presence of *p*-toluenesulfonic acid, compared with the reaction medium. In the latter case, the decomposition of the diperoxide is hindered by urea introduced in the form of UHP because urea is a weak base and inhibits the action of p-toluenesulfonyl acid due to the formation of a salt. It is known [16] that urea forms insoluble salts with nitric and oxalic acids. Addition, upon oxidation of cyclohexanone with UHP, of an equimolar amount of nitric acid or oxalic acid dehydrate makes it possible to remove 86 and 100% of urea; in this case, however, the diperoxide decomposition time is 5 and 7 days, respectively. Attempts to use salts (calcium sulfate or nitrate) to bind urea failed.

Methods for oxidation of cyclohexanone with UHP have been developed, in which urea is removed from the reaction medium before the beginning of the reaction and in its course. The first method produces ε-caprolactone in 100% yield according to GLC data. In the process, a solution of UHP in hexafluoroisopropanol is mixed in the course of 3 h with anhydrous oxalic acid taken in an equimolar, with respect to urea, amount. Then, urea oxalate is filtered off, cyclohexanone and 5 mol % *p*-toluenesulfonic acid are introduced into the filtrate, and the mixture is kept at 55°C for 10 h.

The second method consists in introducing paraformaldehyde into the reaction medium after 5 h of synthesis and performing the reaction for 10 h, which results in that the insoluble polymethyleneurea is formed and ε-caprolactone is produced in 81% yield. The polymer formed can be used as a filler for rubbers and plastics.

Cyclohexanone was oxidized with sodium perborate and percarbonate, with carboxylic acids as solvents. For both the oxidizing agents, use of trifluoroacetic acid leads to a quantitative conversion of cyclohexanone, but the main reaction product in this case is 6-hydroxycaproic acid. Its content in reaction products is, according to GLC data, 82 and 87% in oxidation with sodium perborate and percarbonate, respectively (Table 2).

The oxidation with magnesium and sodium monoperphthalates was performed at a fourfold excess of an oxidizing agent because its smaller amount fails to provide the necessary reaction rate. In this case, it is preferable to use the aqueous reaction medium because a water–methanol medium leads to formation of 6-hydroxycaproic and adipic acids and their methyl esters. The formation of the esters can be precluded by replacing methanol with acetonitrile. Use of sodium monoperphthalate leads to the higher pH value of the reaction medium (pH 6.0) than use of magnesium salt. The data in Table 3 show that the pH value strongly affects the reaction rate. A high conversion of cyclohexanone was reached with the magnesium salt, which corresponds to pH 4.5 of the reaction medium. Performing the reaction in an aqueous medium is only acceptable at room temperature, with 6-hydroxycaproic acid formed otherwise.

Thus, a method was developed for synthesis of ε-caprolactone by oxidation of cyclohexanone with sodium monoperphthalate in an aqueous medium, with a preparative yield of 75% and product purity of 99.6% (according to GLC data).

On the whole, the procedures developed use the readily available raw materials and are convenient for practical use, including that at small enterprises.

CONCLUSIONS

(1) Conditions of cyclohexanone oxidation to ε-caprolactone were studied and it was shown that a quantitative yield is achieved in the hexafluoroisopropanol medium in the case of preliminary removal of urea as an oxalate.

(2) Trifluoroacetic acid is the most acceptable solvent in oxidation of cyclohexanone with sodium perborate and percarbonate. However, 6-oxycaproic acid is formed in this case as the main product.

(3) Magnesium monoperphthalate can be successfully used to oxidize cyclohexanone. However, oxidation in an aqueous medium in the sodium percarbonate–phthalic anhydride system is the most convenient and

least expensive type of the process.

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