

Process Intensification for the Production of Cyclic Macrolactones: Identification of Safe Operating Conditions in Tubular Reactors

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In this work, the possibility to shift from a batch to a continuous production of 16-hexadecanolide, one of the main components of the white musk essence, was theoretically studied. The selected synthesis was an upgraded version of that proposed by Story in 1968, who obtained macrocyclic compounds from the decomposition of ketone peroxides (in this case the involved peroxide was tricyclohexylidene triperoxide). But such reaction presents some huge criticalities: 1) high exothermicity and, 2) production of carbon dioxide, which are known to both modify the kinetics of the desired reaction and lead to a pressure increase inside the reactor whether the gases are not vented. For such reasons, to implement any safe continuous production of this chemical compound, two main points must be addressed: 1) determination of the system runaway boundaries and 2) identification of the optimal operating conditions to make sustainable the production of 16-hexadecanolide (that is, the theoretical design of a tubular reactor capable of continuously discharging the produced incoercible gases). For what concerns the first point, a sensitivity analysis was carried out to determine the safe operating range of the most important operating variables (that is, coolant temperature and reactant inlet temperature) possibly taking into account the effect of radial dispersion; for the second point, as carbon dioxide is produced over the decomposition and needs to be continuously vented to avoid reactor pressurization, a Teflon tube, highly permeable with respect to carbon dioxide, was proposed and its theoretical performances was investigated trying to maximize 16-hexadecanolide productivity also maintaining safe operating conditions. Results showed the theoretical possibility of developing a continuous production process capable of being also commercially sustainable.

1. Introduction

16-hexadecanolide is a cyclic macrolactone used in both cosmetic and perfume industry for the synthetic production of the white musk fragrance. Originally, white musk aroma was available as a natural derivative, a secretion produced by the musk deer. Hence, due to high costs, environmental issues and scarce availability of this substance, the chemical industry was forced to develop synthetic productions. In the current literature, several studies have been proposed discussing different synthetic paths to obtain 16-hexadecanolide (Shono et al., 1986). However, one of the most interesting applications remains the solution presented by Story (Story et al., 1968). Story showed the possibility of obtaining macrocyclic lactones and high value hydrocarbons using common and easily available compounds such as cyclohexanone and hydrogen peroxide. Through the decomposition of the reaction intermediate, that is tricyclohexylidene triperoxide (TCTP), 16-hexadecanolide is obtained among various products. Despite both the simplicity and the relatively low costs, the process proposed by Story exhibits a series of critical issues. In fact, the decomposition of TCTP is a very fast and highly exothermic reaction (around 1861 [kJ/kg of TCTP] (Ferrer et al., 2018)). In addition, carbon dioxide is released

as a product of the decomposition. Currently, this process is carried out inside discontinuous reactors (batch type), within which, despite the exothermicity of the reaction, it is possible to produce 16-hexadecanolide with a selectivity ranging from a minimum of 15 to a maximum of 28% (Ferrer et al., 2018). Moreover, due to the presence of gaseous product, a proper continuous venting is also needed.

In the framework of shifting to the continuous the production of 16-hexadecanolide, some intensification attempts on other potentially runaway processes can be traced in the scientific literature (Copelli et al., 2017, 2022), including also kinetic-free models (Maestri et al., 2020), but, in those cases, the shifts have been done passing from batch to series of continuously stirred tank reactors. In this way, a non-negligible residual risk remained, due to the start-up of the continuous tank reactors and their criticalities in the maintenance of the level control.

In this work, the batch to continuous shift of 16-hexadecanolide potentially runaway synthesis was theoretically investigated. Particularly, basing on the current literature (Copelli et al., 2016), a lab-scale tubular reactor made of perfluorinated linear polymers, such as Teflon AF 1600® and Teflon AF 2400® (which exhibit both high gas permeability and high melting temperatures) was proposed. The optimization of the most important operating and design parameters (that is, coolant temperature and inlet reactant temperature together with tubular reactor length) was carried out by identifying the system runaway boundaries through a sensitivity analysis on the maximum local temperatures reached along the tubular reactor coordinate (Varma et al., 1999). In order to account for diffusive phenomena (thermal and material diffusion in both axial and radial directions), the sensitivity study was performed using initially a 1-D tubular reactor model and then, a 2-D one (operating in laminar conditions). Different reactant inlet flowrates were tested for all the models to assess their influence on the runaway boundaries. Once the runaway boundaries were identified, optimal operating conditions were proposed, together with a hypothetical process layout.

2. Case Study

The synthesis of 16-hexadecanolide developed by Story is basically made of two steps. The first one includes the synthesis of the cyclohexanone peroxides; the second one is about their decomposition.

The first procedure reported in literature (Story et al., 1970) provides 70% concentrated perchloric acid in acetonitrile as catalyst and 90% concentrated hydrogen peroxide, in 2:1 molar ratio to cyclohexanone, at 70 °C. The scale-up of this reaction is difficult because of its safety issues. Concentrated H₂O₂ is highly reactive and could lead to uncontrolled oxidations followed by a large generation of heat. A corrosive reaction mixture due to the presence of concentrated perchloric acid also increases the risks connected to this reaction.

The second step of the Story synthesis basically consists of the thermal (or photochemical) decomposition of the previously synthesized cyclohexanone peroxides.

TCTP decomposition leads to the formation of 16-hexadecanolide (15-28%), cyclopentadecane (28-34%) and cyclohexanone (Ferrer et al., 2018). Whenever the reaction path leads to the formation of 16-hexadecanolide also carbon dioxide is produced.

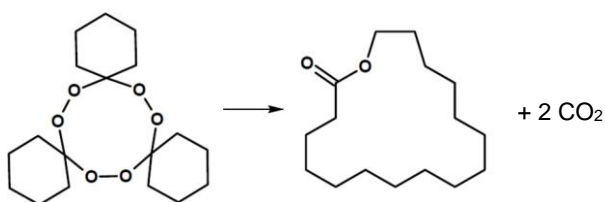


Figure 1: TCTP decomposition and formation of 16-hexadecanolide

Given the high exothermicity of the overall decomposition, TCTP must be diluted into a suitable solvent capable of decreasing the potential adiabatic temperature increase in case of thermal loss of control. According to literature, a 4% w/w solution of TCTP in dodecane has been proved to be stable in a wide range of temperatures (De Armas, 2015), therefore its physical properties together with the kinetics already proposed will be considered for this theoretical study.

3. Methods and Mathematical Models

A Plug Flow Reactor (PFR) model, with both presence (2-D model) and absence (1-D model) of radial heat and mass dispersions, was developed to identify the runaway boundaries for the system by implementing a suitable MATLAB® code solved using the Methods of Lines.

Equations for the 1-D model are reported in Eq. (1) and based on the following hypotheses: 1) no radial changes in reactant concentration (C_i), temperatures (T) and velocities (v); 2) perfect mixing in the radial direction (r) and no mixing in the axial direction (z); 3) constant inlet velocity (v_0) also equal to the axial one; 4) steady-state operation ($d/dt = 0$); 5) constant reacting mixture density (ρ_{mix}) and specific heat ($c_{p,mix}$); 6) presence of an external static cooling system at constant temperature (this means, constant reactor wall temperature T_w).

$$v_0 \cdot \frac{dC_i}{dz} = -r$$

$$v_0 \cdot \frac{dT}{dz} = -\frac{\Delta H}{\rho_{mix} \cdot c_{p,mix}} \cdot r - \frac{4U}{2 \cdot R \cdot \rho_{mix} \cdot c_{p,mix}} (T - T_w) \quad (1)$$

$$BC: C_i(z=0) = C_{IN}; \quad T(z=0) = T_{IN}$$

where the overall decomposition reaction rate can be expressed as (Ferrer et al., 2018):

$$r = 1.97 \cdot 10^8 \cdot e^{\left(-\frac{1.09 \cdot 10^4}{T}\right)} \cdot [(1-x)^{0.853} \cdot x^{1.405} + 0.228 \cdot (1-x)] \left[\frac{kmol}{m^3s}\right] \quad x = C_{IN} - \frac{C_i}{C_{IN}} \quad (2)$$

On the contrary, equations for the 2-D model are reported in Eq. (3) and based on the following hypotheses: 1) radial changes in reactant concentration (C_i), temperatures (T) and axial velocity (v_z) due to the presence of both radial material (D_i) and thermal (k_{mix}) diffusivity; 2) no mixing in the axial direction (z); 3) constant inlet velocity (v_0); 4) steady-state operation ($d/dt = 0$); 5) constant reacting mixture density (ρ_{mix}) and specific heat ($c_{p,mix}$); 6) presence of an external static cooling system at constant temperature (this means, constant reactor wall temperature T_w).

$$v_z \cdot \frac{\partial C_i}{\partial z} = \frac{D_i}{r} \cdot \frac{\partial C_i}{\partial r} + D_i \cdot \frac{\partial^2 C_i}{\partial r^2} - r$$

$$v_z \cdot \frac{\partial T}{\partial z} = \frac{k_{mix}}{\rho_{mix} \cdot c_{p,mix}} \left(\frac{1}{r} \cdot \frac{\partial T}{\partial r} + \frac{\partial^2 T}{\partial r^2} \right) - \frac{\Delta H}{\rho_{mix} \cdot c_{p,mix}} \cdot r \quad (3)$$

$$IC \ \& \ BC: \begin{cases} C_i(t=0) = C_{IN}; \quad T(t=0) = T_{IN} \\ \frac{\partial C_i}{\partial r} \Big|_{r=0} = 0; \quad \frac{\partial T}{\partial r} \Big|_{r=0} = 0 \\ \frac{\partial C_i}{\partial r} \Big|_{r=R} = 0; \quad \frac{\partial T}{\partial r} \Big|_{r=R} = -\frac{4U}{2 \cdot R \cdot \rho_{mix} \cdot c_{p,mix}} (T - T_w) \end{cases}$$

The laminar axial velocity was calculated as:

$$v_z = 2 \cdot v_0 \cdot \left(1 - \left(\frac{r}{R}\right)^2\right) \quad (4)$$

All parameters involved in the calculations are reported in Table 1.

Table 1: Values of all constitutive parameters involved in the study

| Parameter | Value | Parameter | Value | Parameter | Value |
|------------|--------------------------|--------------|-------------|---------------|-----------------------|
| k_{mix} | 0.14 [W/mK] | μ_{mix} | 1.34 [cP] | ρ_{cool} | 920 kg/m ³ |
| k_r | 0.25 [W/mK] | μ_{cool} | 1.50 [cP] | $c_{p,cool}$ | 1370 [J/kg K] |
| k_e | 0.12 [W/mK] | μ_w | 1.00 [cP] | ρ_{mix} | 750 kg/m ³ |
| D_i | 1e-8 [m ² /s] | v_{cool} | 0.001 [m/s] | $c_{p,mix}$ | 2207 [J/kg K] |
| ΔH | 6.706e9 [J/kmol] | | | s | 0.1 [mm] |

The overall heat transfer coefficient was calculated, case by case, considering the presence of an external bath of static silicon oil at a temperature equal to T_w (which is variable in the simulations but always considering that dodecane boils at 216.3 °C, and this is a limit for the operating temperatures) according to Eq. (5).

$$\frac{1}{U} = \frac{1}{h_i} + s \cdot \frac{A_i}{k_r A_{ln}} + \frac{A_i}{h_e A_e} \quad (5)$$

where:

$$A_i = \pi 2RL; \quad A_e = \pi 2(R+s)L; \quad A_{ln} = (A_i - A_e) / \ln(A_i - A_e); \quad h_{i/e} = \frac{Nu_{i/e} \cdot k_{i/e}}{2R \text{ (or } R+s)} \quad (6)$$

$$Nu_{i/e} = 3.66 \cdot 0.85 \cdot Gr_{i/e} \cdot \frac{\left(\frac{\mu_{mix/cool}}{\mu_w}\right)^{0.14}}{1+0.045 \cdot Gr_{i/e}^{0.66}} \quad Gr_{i/e} = Re_{i/e} \cdot Pr_{i/e} \cdot \frac{2R(or R+s)}{L} \quad Pr_{i/e} = c_{p,(mix,cool)} \cdot \frac{\mu_{mix/cool}}{k_{mix/cool}} \quad (7)$$

$$Re_{i/e} = \rho_{mix/cool} \cdot v_{0/cool} \cdot \frac{2R(or R+s)}{\mu_{mix/cool}} \quad (8)$$

It was chosen to simulate a mini-tubular reactor because it is safer than a classical tank due to the smaller reactive volumes and the high surface-volume ratio, which gives an optimal exchange with the external jacket. As carbon dioxide produced over the decomposition needs to be continuously vented to avoid reactor pressurization, a Teflon AF 2400® tube, highly permeable with respect to carbon dioxide, was simulated. The tubes commercially available have diameters ($2R$) of 0.8, 3 and 6 mm and a thickness (s) of 0.1 mm. Inlet flowrates (F_{max}) used for the simulated were 1, 4 and 10 mL/min because laminar conditions are required by Eq. (3).

4. Results and discussion

Table 2 reports the calculated values of Reynolds numbers and heat transfer coefficients for all the different diameter/flowrate combinations simulated in this work.

Table 2: Heat transfer values and Reynolds numbers used for the different diameter/flow combinations

| F_{max} [mL/min] | | D=0.8 mm | D=3 mm | D=6 mm |
|--------------------|---------------------------|----------|--------|--------|
| 1 | Re | 14.85 | 3.95 | 1.98 |
| | U [W/(m ² ·K)] | 267.43 | 76.51 | 38.72 |
| 4 | Re | 14.85 | 15.83 | 7.92 |
| | U [W/(m ² ·K)] | 267.63 | 76.54 | 38.82 |
| 10 | Re | 148.46 | 9.59 | 9.80 |
| | U [W/(m ² ·K)] | 267.73 | 76.60 | 38.90 |

Parametric sensitivity criterion was used to identify the runaway boundaries (RB) of the system as a function of both the reactor wall temperature T_w and the inlet reacting mixture temperature T_{in} . First, we investigated the RB with respect to the wall temperatures (considering T_{in} equal to 25 °C); particularly, temperatures below 200 °C were selected because of the solvent boiling point. Then, after the identification of the RB with respect to T_w , using a value of T_w lower than its detected boundary, the parametric sensitivity with respect to T_{in} was investigated. Table 3 shows all the results obtained for the one-dimensional model (1-D). According to the generalized parametric sensitivity criterion, the critical value of a parameter is that one in correspondence of which the parametric sensitivity function $S(\theta^*, \Phi)$, calculated using Eq. (12), exhibits a maximum.

$$S(\theta^*, \Phi) = \frac{\Phi}{\theta^*} \cdot \frac{\partial \theta^* (\Phi)}{\partial \theta^*} \quad (12)$$

where θ^* is the objective function and Φ is the parameter with respect to $S(\theta^*, \Phi)$ is calculated.

Table 3: Values of $T_{w,cr}$ and $T_{in,cr}$ obtained for different configurations (1-D)

| | Reactor Diameter [mm] | $F_{max}=1$ mL/min | $F_{max}=4$ mL/min | $F_{max}=10$ mL/min |
|-------------|-----------------------|--------------------|--------------------|---------------------|
| $T_{w,cr}$ | 0.8 | 176.15 °C | 176.15 °C | 176.15 °C |
| | 3 | 129.15 °C | 129.15 °C | 129.15 °C |
| | 6 | 107.15 °C | 107.15 °C | 107.15 °C |
| $T_{in,cr}$ | 0.8 | 222 °C | 221 °C | 222 °C |
| | 3 | 167 °C | 168 °C | 168 °C |
| | 6 | 145 °C | 145 °C | 145 °C |

As the sake of example, Figure 2 and Figure 3 report the sensitivity $S(\theta^* = T_{max}, \Phi = T_w)$ as a function of T_w and T_{in} , respectively. Figure 2 was calculated using: D=3 mm, $F_{max}=4$ mL/min, $T_{in}=25$ °C, and $v_0=0.0094$ m/s; while Figure 3 was calculated using: D=3 mm, $F_{max}=4$ mL/min, $T_w=115$ °C, and $v_0=0.0094$ m/s.

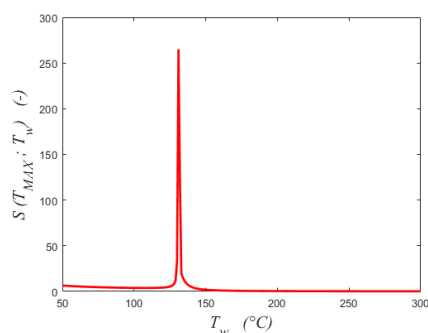


Figure 2: Sensitivity with respect to T_w

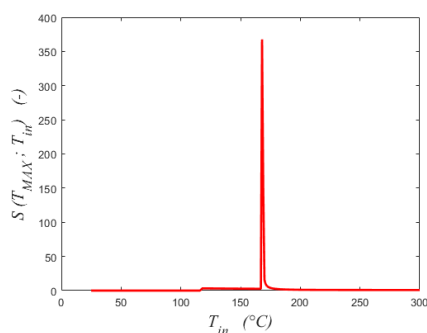


Figure 3: Sensitivity with respect to T_{in}

Once RB were calculated, it was decided to use 25 °C (ambient temperature) as inlet temperature and the maximum safe T_w for each diameter and flowrate to calculate the reactor lengths necessary to obtain conversions equal to 90% and 95%. The results obtained are shown in Table 4.

Table 4: Reactor lengths for 90-95 % conversions using different configurations (1-D)

| Diameter [mm] | T_w [°C] | $F_{max}=1$ mL/min | | $F_{max}=4$ mL/min | | $F_{max}=10$ mL/min | |
|------------------|---------------|--------------------|-----|--------------------|------|---------------------|------|
| | | 90% | 95% | 90% | 95% | 90% | 95% |
| 0.8 | 160 | 4.5 | 5 | 16.5 | 18.5 | 40.5 | 46 |
| 3 | 115 | 6 | 6.5 | 22 | 25 | 54.5 | 62.5 |
| 8.5 | 92 | 8.5 | 10 | 33.5 | 38.5 | 84.5 | 95.5 |

As it is possible to see from Table 4, the lower the diameter of the reactor the higher the wall temperature could be, also minimizing the reactor length required to obtain commercially sustainable conversions. The minimum reactor length was obtained for the combination: $F_{max}=1$ mL/min and $D=0.8$ mm. Such a set of operating conditions corresponded to a contact time within the reactor equal to 140-150 s, which is the same for all reactors having an internal diameter of 0.8 mm. The procedure performed for the 1-D model was then repeated using a two-dimensional (2-D) model. Table 5 shows the results obtained.

Table 5: Values of $T_{w,cr}$ and $T_{in,cr}$ obtained for different configurations (2-D)

| | Reactor Diameter [mm] | $F_{max}=1$ mL/min | $F_{max}=4$ mL/min | $F_{max}=10$ mL/min |
|-------------|--------------------------|--------------------|--------------------|---------------------|
| | | $T_{w,cr}$ | 0.8 | 158.65 °C |
| | 3 | 115.15 °C | 118.65 °C | 115.15 °C |
| | 6 | 95.15 °C | 96.65 °C | 95.65 °C |
| $T_{in,cr}$ | 0.8 | 223.15 °C | 223.15 °C | 223.15 °C |
| | 3 | 167.15 °C | 167.15 °C | 167.15 °C |
| | 6 | 141 °C | 141 °C | 141 °C |

As observed with the 1-D model sensitivity analysis, increasing the diameter of the reactor implied a shift of the RB towards less conservative values. This trend is justified by the values of the overall heat transfer coefficient, which were reported in Table 2. Larger diameter values corresponded to lower heat exchange efficiency, due to the reduced surface-to-volume ratio. This result suggests the choice of reactors with smaller diameters because they can tolerate safely higher wall temperatures. It is worth to notice that all the temperatures considered are compatible with the use of silicone oil as heat transfer fluid and Teflon AF 2400® material has reactor material. Moreover, concerning the absolute values of the critical wall temperature, it is possible to observe that the presence of radial heat and material dispersion leads to more conservative estimation of the RB; consequently, optimal and safe operating conditions must be chosen considering the possible presence of such dispersions. The trends obtained for the sensitivity analysis with respect to the wall temperature were also confirmed for the inlet temperature. It was also confirmed the general trend according to which the 2-D model is more conservative with respect to the 1-D model. As previously done for the 1-D model, it was decided to use 25 °C (ambient temperature) as inlet temperature and the maximum safe T_w for each diameter and flowrate to calculate the reactor lengths necessary to obtain conversions equal to 90% and 95%. The results obtained are shown in Table 6.

Table 6: Reactor lengths for 90-95% conversions using different configurations (2-D)

| Diameter [mm] | T _w [°C] | F _{max} =1 mL/min | | F _{max} =4 mL/min | | F _{max} =10 mL/min | |
|------------------|------------------------|----------------------------|-----|----------------------------|-----|-----------------------------|-----|
| | | 90% | 95% | 90% | 95% | 90% | 95% |
| 0.8 | 160 | 8 | 9.5 | 32 | 38 | 79 | 90 |
| 3 | 115 | 9 | 10 | 35 | 39 | 88 | 97 |
| 8.5 | 92 | 10 | 11 | 40.5 | 45 | 98 | 112 |

The two-dimensional model predicts greater reactor lengths than the 1-D model due to the lower wall temperatures necessary to operate outside the runaway region. A modest difference is observed between the lengths of the reactors needed to have a conversion of 90% and 95%, forcing to choose a desired final conversion of 95 % for guaranteeing less waste of reactant. The reactor lengths varied between 9 m and 112 m, depending on the flowrates and diameters chosen. So, it is possible to have both very long reactors and a shorter multi-tubular reactor. However, all predicted lengths can be used industrially because they can guarantee the production of 2 to 20 kg of pure 16-hexadecanolide (4% w/w TCTP in dodecane and 16% of maximum selectivity were considered), using from 1 mL/min to 10 mL/min of reacting mixture flowrate.

5. Conclusions

In this work a configuration for the continuous production of 16-hexadecanolide has been proposed. Specifically, Story's synthesis was chosen, based on the decomposition of tricyclohexylidene triperoxide. A tubular reactor composed of Teflon AF 2400® was chosen. As the reaction produces carbon dioxide, this material was chosen as it is permeable to gas, allowing CO₂ to be vented. Safe and optimal operating conditions were determined using the generalized parametric sensitivity criterion applied to the maximum reactor temperature with respect to the main process variables (wall and inlet temperature). Sensitivity analysis showed that safe optimum wall temperatures ranged between 95 °C and 160 °C, depending on the model (1-D, considering axial dispersion, or 2-D, to consider radial dispersion too) and the diameter of reactor chosen.

Results highlighted how, using a 2-D model, the runaway boundaries shifted significantly towards more conservative values of the operating temperatures, highlighting the limitations of simple 1-D tubular reactor models without radial dispersions. Knowing the critical temperatures from the 2-D model, it was possible to select the best reactor layout given a desired productivity. Particularly, a reactor diameter of 0.8 mm could be selected to have the sufficient contact time experimentally observed to reach the full TCTP conversion. Selecting an inline flowrate of 10 mL/min (corresponding to an overall annual productivity of 20 kg of 16-hexadecanolide), a coolant temperature of 158 °C should not be exceeded. In correspondence of these process parameters and operating conditions, the length of the reactor resulted to be around 90 m.

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