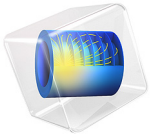


Ibuprofen Synthesis

Introduction

Kinetic analysis of catalytic reactions is essential for understanding rate behavior as well as the reaction mechanism. Developing knowledge of intrinsic reaction kinetics and of rate equations is central to reaction engineering studies aimed at improving reactor design.

This example illustrates the reaction kinetics of a complex chemistry occurring in a perfectly stirred tank reactor. The homogeneous catalysis of 1-(4-isobutylphenyl) ethanol into the anti-inflammatory drug ibuprofen serves as the example chemistry. The model determines concentrations of reactants, intermediates, and products as functions of time for the network of chemical reactions.

The chemistry in this example involves homogeneous catalysis. As this terminology suggests, the catalyst and the reacting species are in the same phase. Most commonly, a liquid reaction mixture contains a soluble metalorganic complex that affects the catalysis. Organometallic catalysts can often be fine-tuned with respect to reaction activity and selectivity. Because these relatively expensive catalysts produce highly-refined reaction products, they commonly find application in fine chemicals or pharmaceutics.

The model focuses on the use of the Chemical Reaction Engineering Module for a kinetics investigation. You easily enter chemical reaction formulas from the keyboard, then the Reaction Engineering interface automatically generates rate expressions and material balances. It solves the equations, and you postprocess results directly in the COMSOL Desktop.

Model Description

Analyzing chemical kinetics involves solving the set of ordinary differential equations corresponding to individual steps in a network of reactions. This example illustrates the

kinetics of ibuprofen synthesis. Figure 1 shows the reaction steps displayed in a catalytic cycle (Ref. 1).

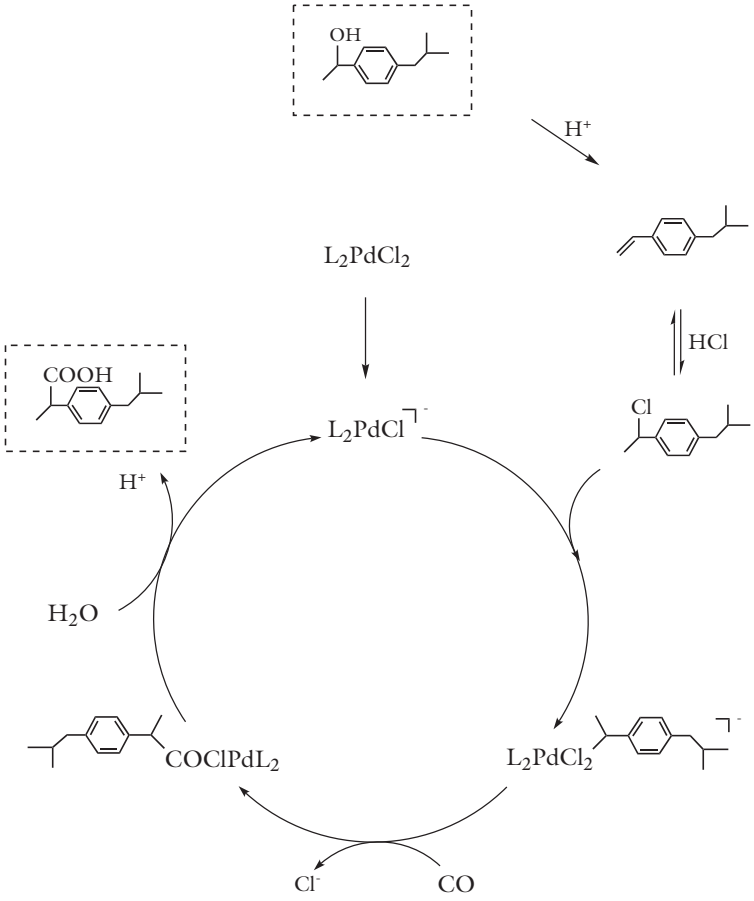
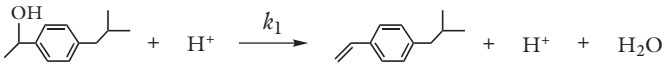


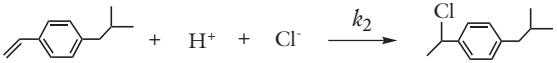
Figure 1: Catalytic cycle of ibuprofen synthesis.

Prior to entering the cycle, the starting material, 1-(4-isobutylphenyl)ethanol, is first dehydrated to form 4-isobutylstyrene. This species subsequently undergoes the addition of HCl to produce the active substrate 1-(4-isobutylphenyl)ethyl chloride. The palladium catalyst must also go through an initial transformation, from L_2PdCl_2 (L=triphenylphosphine) to anionic L_2PdCl, before becoming active. The activated catalyst then assists in the carbonylation and hydrolysis of 1-(4-isobutylphenyl)ethyl chloride, producing ibuprofen.

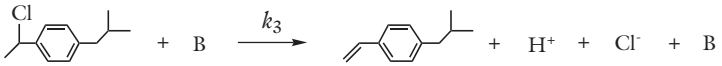
The following reactions represent the catalytic cycle:



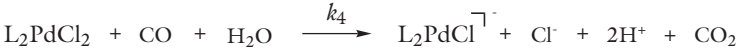
(1)



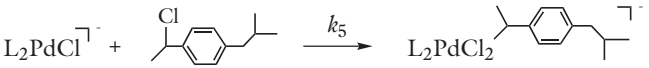
(2)



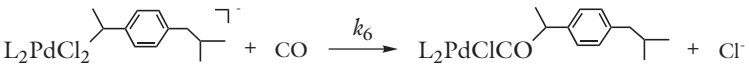
(3)



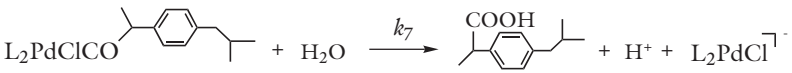
(4)



(5)



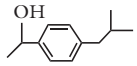
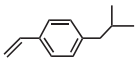
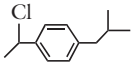
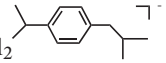
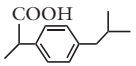
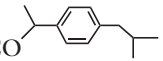
(6)



(7)

Reaction 1 involves the dehydration of the reactant alcohol to form the corresponding alkene. Reaction 2 describes the hydrohalogenation of alkene, resulting in the active substrate 1-(4-isobutylphenyl)ethyl chloride. Reaction 3 shows the dehydrohalogenation of the active substrate, assisted by a base, B. Reaction 4 describes the transformation of the precatalytic species L_2PdCl_2 into the active anionic catalyst L_2PdCl. In Reaction 5 the active substrate undergoes oxidative addition to the L_2PdCl catalyst. Reaction 6 summarizes the carbonylation, and Reaction 7 describes the hydrolysis of the metalorganic species, leading to the formation of ibuprofen and regeneration of the catalyst.

In order to make species notation more manageable, this example uses the following labels:

species	abbreviation	species	abbreviation
	roh	L_2PdCl_2	pd1
	ren	L_2PdCl^-	pd2
	rhcl		pd3
	ibu		pd4

Making use of these notations, the reaction rates corresponding to Reaction 1 through Reaction 7 are:

$$r_1 = k_1 c_{\mathrm{roh}} c_H \tag{8}$$

$$r_2 = k_2 c_{\mathrm{ren}} c_H c_{\mathrm{Cl}} \tag{9}$$

$$r_3 = k_3 c_{\mathrm{rhcl}} c_B \tag{10}$$

$$r_4 = k_4 c_{\mathrm{pd1}} c_{CO} c_{H_2O} \tag{11}$$

$$r_5 = k_5 c_{\mathrm{pd2}} c_{\mathrm{rhcl}} \tag{12}$$

$$r_6 = k_6 c_{\mathrm{pd3}} c_{CO} \tag{13}$$

$$r_7 = k_7 c_{\mathrm{pd4}} c_{H_2O} \tag{14}$$

The Reaction Engineering interface automatically generates these expressions and displays them immediately when you enter the chemical reaction formulas. By default, the software assumes that the chemistry takes place isothermally in a perfectly stirred batch reactor.

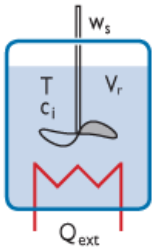


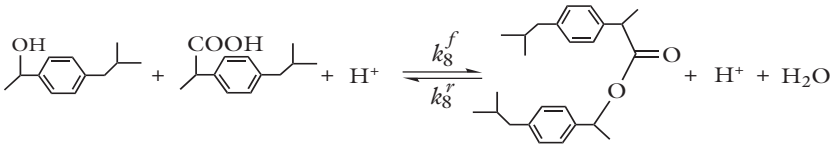
Figure 2: A perfectly stirred batch reactor where the reactant alcohol is carbonylated to form ibuprofen by means of palladium catalysis.

With no inflow or outflow from the reactor, the change of species concentrations with time is a function only of the reaction rates:

$$\frac{dc_i}{dt} = \sum_{j=1}^{n_r} \nu_{ij} r_j \tag{15}$$

The Reaction Engineering automatically generates the mass balance in Equation 15 for each of the species, i, in the reactions, j, accounting for the stoichiometry in the reaction formulas, ν, and solves these equations.

The model investigates two reaction conditions. The first simulation (Case 1) solves for the seven reaction displayed previously. In Case 2 you modify the reaction network with an additional reaction, altering the simulation results. Assume that the reactant alcohol and product ibuprofen (a carboxylic acid) react reversibly, forming an ester:



The results of the two simulations are compared to gain insight in the process implications.

CASE I

Figure 3 shows the concentration profiles for reactants and products over time.

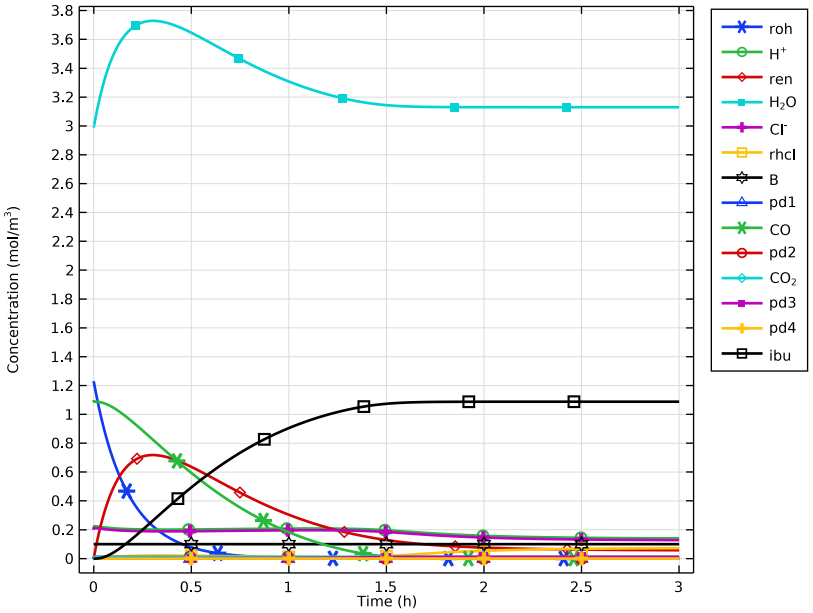


Figure 3: Species concentrations (mol/m^3) as a function of time (s).

Clearly, after approximately two hours the process has run to completion.

CASE 2

This expansion of the original case adds a reversible reaction between the reactant alcohol and the product ibuprofen to form an ester. Figure 4 shows the concentration transients.

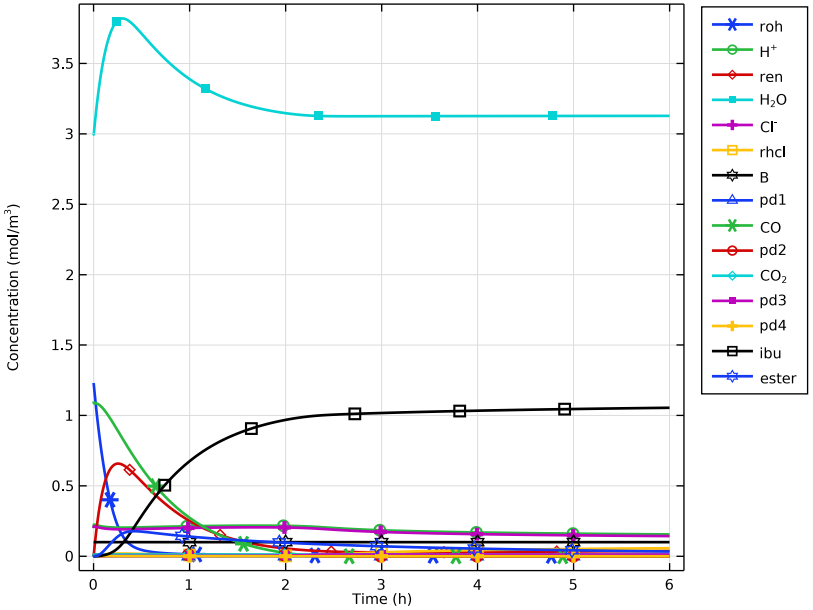


Figure 4: Species concentrations (mol/m^3) as a function of time (s).

In the course of the reaction, ester forms as an intermediary product. In order to achieve the same final concentration of ibuprofen for Case 2 as in Case 1, the process must run for at least 12 hours.

In conclusion, this example illustrates the use of the Chemical Reaction Engineering Module for analyzing the kinetics of a complex reaction network. When you enter the chemical-reaction formulas into the physics interface, the Reaction Engineering interface automatically sets up the corresponding rate expressions and material balances. You can modify simulation conditions effortlessly, for instance by activating/deactivating individual reactions or by changing initial conditions.

Reference

1. R.V. Chaudhari, A. Seayad, and S. Jayasree, "Kinetic modeling of homogeneous catalytic processes," *Catalysis Today*, vol. 66, pp. 371–380, 2001.

Application Library path: `Chemical_Reaction_Engineering_Module/Ideal_Tank_Reactors/ibuprofen_synthesis`

Modeling Instructions

From the **File** menu, choose **New**.

NEW

In the **New** window, click **Model Wizard**.

MODEL WIZARD

1 In the **Model Wizard** window, click **0D**.

2 In the **Select Physics** tree, select **Chemical Species Transport>Reaction Engineering (re)**.

3 Click **Add**.

4 Click **Study**.

5 In the **Select Study** tree, select **General Studies>Time Dependent**.

6 Click **Done**.

GLOBAL DEFINITIONS

Start by reading in a set of global parameters.

Parameters 1

1 In the **Model Builder** window, under **Global Definitions** click **Parameters 1**.

2 In the **Settings** window for **Parameters**, locate the **Parameters** section.

3 Click **Load from File**.

4 Browse to the model's Application Libraries folder and double-click the file `ibuprofen_synthesis_parameters.txt`.

First, set up the model for the first case.

REACTION ENGINEERING (RE)

1 In the **Model Builder** window, under **Component 1 (comp1)** click **Reaction Engineering (re)**.

2 In the **Settings** window for **Reaction Engineering**, click to expand the **Mixture Properties** section.

3 From the **Phase** list, choose **Liquid**.

Reaction 1

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `roh+H+=>ren+H2O+H+`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_1`.

Reaction 2

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `ren+H++Cl-=>rhcl`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_2`.

Reaction 3

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `rhcl+B=>ren+H++Cl-+B`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_3`.

Reaction 4

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `pd1+CO+H2O=>pd2+Cl-+2H++CO2`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_4`.

Reaction 5

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `pd2+rhcl=>pd3`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_5`.

Reaction 6

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `pd3+CO=>pd4+Cl-`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_6`.

Reaction 7

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `pd4+H2O=>pd2+H++ibu`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `kreac_7`.

Reaction 8

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `ibu+roh+H+<=>ester+H2O+H+`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `kfreac_8`.

6 In the k^{r} text field, type `krreac_8`.

Initial Values 1

1 In the **Model Builder** window, click **Initial Values 1**.

2 In the **Settings** window for **Initial Values**, locate the **Volumetric Species Initial Values** section.

3 In the table, enter the following settings:

Species	Concentration (mol/m^3)
B	`cB_0`
CO	`cCO_0`
Cl-	`cClion_0`
H+	`cHion_0`
H2O	`cH2O_0`
pd1	`cpd1_0`
roh	`croh_0`

STUDY - CASE 1

Run case 1, which only includes reactions 1-7, for three hours.

1 In the **Model Builder** window, click **Study 1**.

2 In the **Settings** window for **Study**, type `Study - Case 1` in the **Label** text field.

Step 1: Time Dependent

1 In the **Model Builder** window, under **Study - Case 1** click **Step 1: Time Dependent**.

2 In the **Settings** window for **Time Dependent**, locate the **Study Settings** section.

3 From the **Time unit** list, choose **h**.

4 In the **Output times** text field, type `range(0,0.1,3)`.

Now, disable reaction 8 and the participating ester.

5 Locate the **Physics and Variables Selection** section. Select the **Modify model configuration for study step** check box.

6 In the tree, select **Component 1 (comp1)>Reaction Engineering (re)>8: ibu+roh+H+<=> ester+H2O+H+**.

7 Right-click and choose **Disable**.

8 In the tree, select **Component 1 (comp1)>Reaction Engineering (re)>Species: ester**.

9 Right-click and choose **Disable**.

10 In the **Home** toolbar, click = **Compute**.

RESULTS

Concentration - Case 1

1 In the **Settings** window for **1D Plot Group**, type `Concentration - Case 1` in the **Label** text field.

2 Click to expand the **Title** section. From the **Title type** list, choose **None**.

3 Locate the **Legend** section. From the **Layout** list, choose **Outside graph axis area**.

Global 1

1 In the **Model Builder** window, expand the **Concentration - Case 1** node, then click **Global 1**.

2 In the **Settings** window for **Global**, click to expand the **Coloring and Style** section.

3 From the **Width** list, choose **2**.

4 Find the **Line markers** subsection. From the **Marker** list, choose **Cycle (reset)**.

5 In the **Number** text field, type `5`.

6 Click to expand the **Legends** section. From the **Legends** list, choose **Manual**.

7 In the table, enter the following settings:

Legends
`roh`
`H<sup>+</sup>`
`ren`

Legends
H₂O
Cl⁻
rhcl
B
pd1
CO
pd2
CO₂
pd3
pd4
ibu

8 In the **Concentration - Case 1** toolbar, click **Plot**.

The plot in the **Graphics** window should look like that in Figure 3.

Continue with the model for case 2.

ADD STUDY

Run case 2 for six hours, now including reaction 8.

1 In the **Home** toolbar, click **Add Study** to open the **Add Study** window.

2 Go to the **Add Study** window.

3 Find the **Studies** subsection. In the **Select Study** tree, select **General Studies> Time Dependent**.

4 Click **Add Study** in the window toolbar.

STUDY - CASE 2

1 In the **Model Builder** window, click **Study 2**.

2 In the **Settings** window for **Study**, type `Study - Case 2` in the **Label** text field.

Step 1: Time Dependent

1 In the **Model Builder** window, under **Study - Case 2** click **Step 1: Time Dependent**.

2 In the **Settings** window for **Time Dependent**, locate the **Study Settings** section.

3 From the **Time unit** list, choose **h**.

4 In the **Output times** text field, type `range(0,0.1,6)`.

5 In the **Home** toolbar, click **Compute**.

RESULTS

Concentration - Case 2

1. In the **Settings** window for **1D Plot Group**, type `Concentration - Case 2` in the **Label** text field.
2. Locate the **Data** section. From the **Dataset** list, choose **Study - Case 2/Solution 2 (sol2)**.
3. Locate the **Title** section. From the **Title type** list, choose **None**.
4. Locate the **Legend** section. From the **Layout** list, choose **Outside graph axis area**.

Global 1

1. In the **Model Builder** window, expand the **Concentration - Case 2** node, then click **Global 1**.
2. In the **Settings** window for **Global**, locate the **Coloring and Style** section.
3. From the **Width** list, choose **2**.
4. Find the **Line markers** subsection. From the **Marker** list, choose **Cycle (reset)**.
5. In the **Number** text field, type `5`.
6. Locate the **Legends** section. From the **Legends** list, choose **Manual**.
7. In the table, enter the following settings:

Legends
roh
H⁺
ren
H₂O
Cl⁻
rhcl
B
pd1
CO
pd2
CO₂
pd3
pd4
ibu
ester

8 In the **Concentration - Case 2** toolbar, click  **Plot**.

Compare the plot in the **Graphics** window with that in Figure 4.