



Model created in COMSOL Multiphysics 6.4

# Ibuprofen Synthesis

## *Introduction*

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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 pharmaceuticals.

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*

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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).

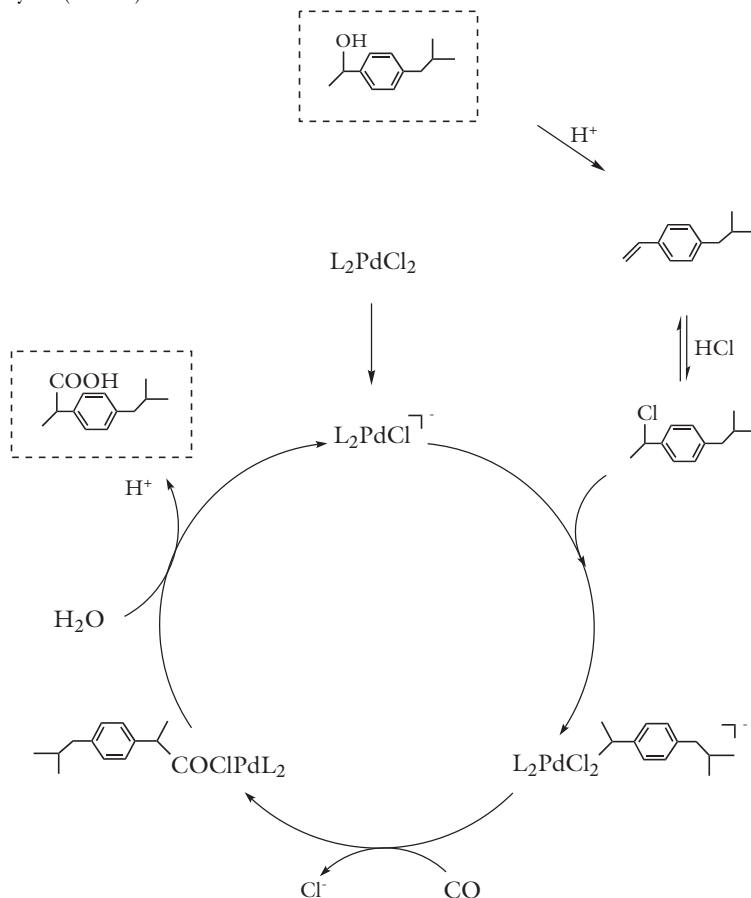
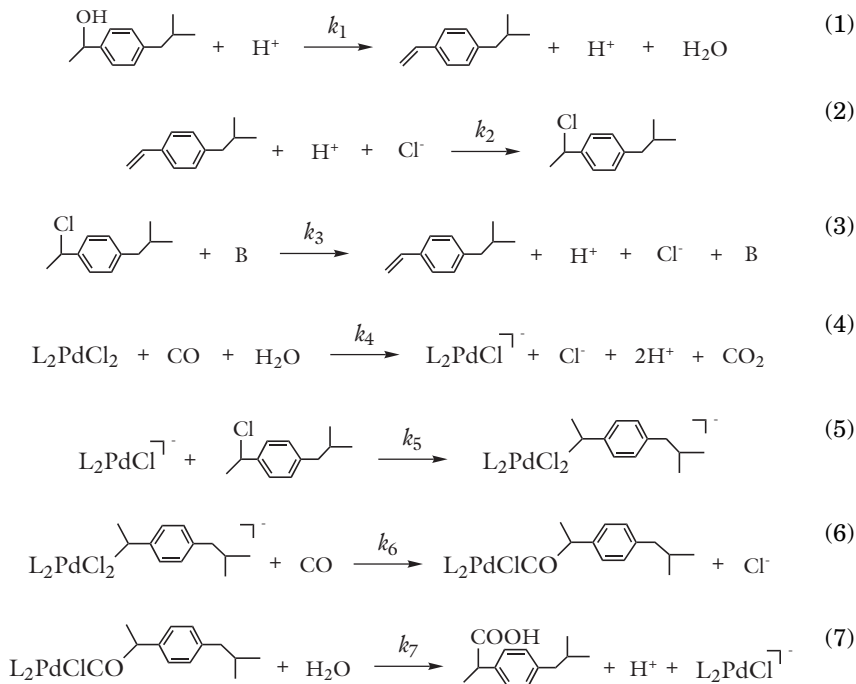


Figure 1: Catalytic cycle of ibuprofen synthesis.

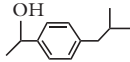
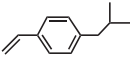
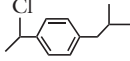
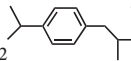
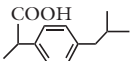
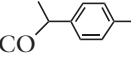
Prior to entering the cycle, the starting material, 1-(4-isobutylphenyl)ethanol, is first dehydrated to form 4-isobutylstyrene. This species subsequently undergoes the addition of HCl to produce the active substrate 1-(4-isobutylphenyl)ethyl chloride. The palladium catalyst must also go through an initial transformation, from L<sub>2</sub>PdCl<sub>2</sub> (L=triphenylphosphine) to anionic L<sub>2</sub>PdCl<sup>-</sup>, 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:



**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  $\text{L}_2\text{PdCl}_2$  into the active anionic catalyst  $\text{L}_2\text{PdCl}^{\ominus}$ . In **Reaction 5** the active substrate undergoes oxidative addition to the  $\text{L}_2\text{PdCl}$  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	$L_2PdCl^{\ominus}$	pd2
	rhcl	$L_2PdCl_2$ 	pd3
	ibu	$L_2PdClCO$ 	pd4

Making use of these notations, the reaction rates corresponding to [Reaction 1](#) through [Reaction 7](#) are:

$$r_1 = k_1 c_{roh} c_H \quad (8)$$

$$r_2 = k_2 c_{ren} c_H c_{Cl} \quad (9)$$

$$r_3 = k_3 c_{rhcl} c_B \quad (10)$$

$$r_4 = k_4 c_{pd1} c_{CO} c_{H_2O} \quad (11)$$

$$r_5 = k_5 c_{pd2} c_{rhcl} \quad (12)$$

$$r_6 = k_6 c_{pd3} c_{CO} \quad (13)$$

$$r_7 = k_7 c_{pd4} c_{H_2O} \quad (14)$$

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.

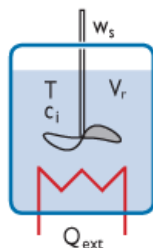


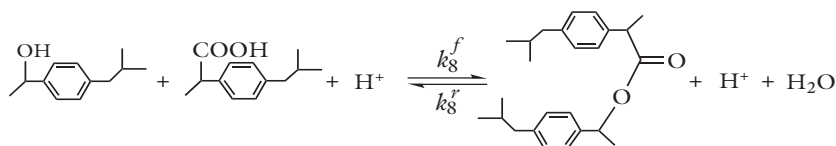
Figure 2: A perfectly stirred batch reactor where the reactant alcohol is carbonylated to form ibuprofen by means of palladium catalysis.

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

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

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,  $\nu$ , and solves these equations.

The model investigates two reaction conditions. The first simulation (Case 1) solves for the seven reactions 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.

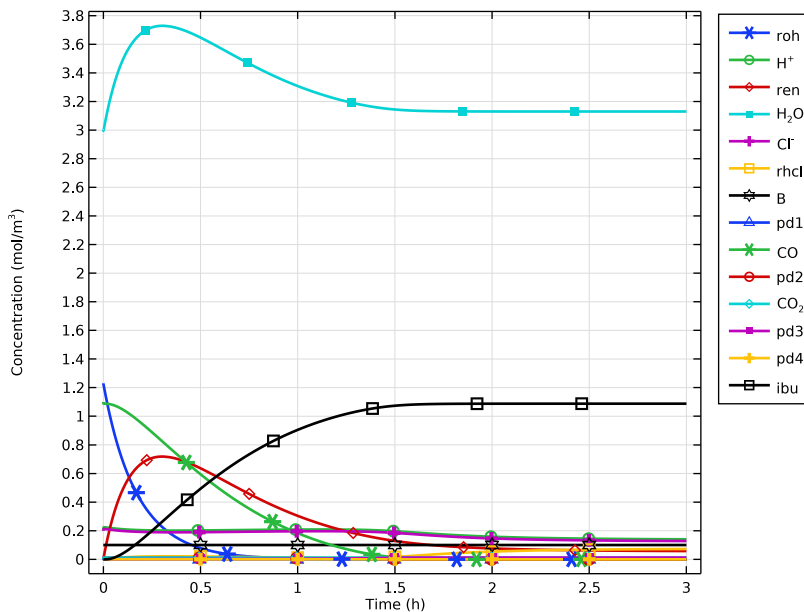


Figure 3: Species concentrations ( $\text{mol}/\text{m}^3$ ) as a function of time (s).

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.

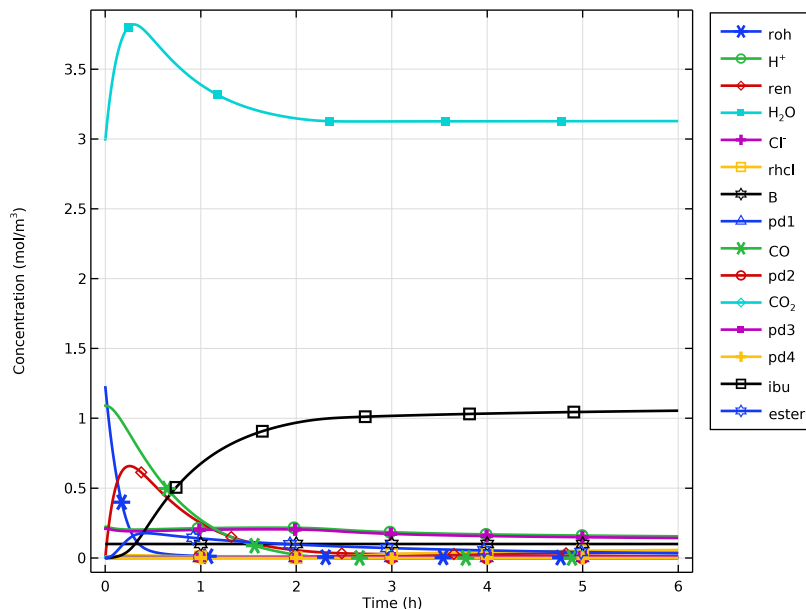


Figure 4: Species concentrations ( $\text{mol}/\text{m}^3$ ) as a function of time (s).

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.

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**Application Library path:** Chemical\_Reaction\_Engineering\_Module/  
Ideal\_Tank\_Reactors/ibuprofen\_synthesis


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### *Modeling Instructions*




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

#### **NEW**

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


#### **MODEL WIZARD**

- 1 In the **Model Wizard** window, click  **OD**.
- 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  $\text{roh}+\text{H}+\Rightarrow\text{ren}+\text{H}_2\text{O}+\text{H}+$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_1}}$ .


#### 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  $\text{ren}+\text{H}++\text{Cl}-\Rightarrow\text{rhc1}$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_2}}$ .


#### 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  $\text{rhc1}+\text{B}\Rightarrow\text{ren}+\text{H}++\text{Cl}-+\text{B}$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_3}}$ .


#### 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  $\text{pd1}+\text{CO}+\text{H}_2\text{O}\Rightarrow\text{pd2}+\text{Cl}-+2\text{H}++\text{CO}_2$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_4}}$ .


#### 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  $\text{pd2}+\text{rhc1}\Rightarrow\text{pd3}$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_5}}$ .


#### 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  $\text{pd3}+\text{CO}\Rightarrow\text{pd4}+\text{Cl}-$ .
- 4 Locate the **Rate Constants** section. In the  $k^f$  text field, type  $k_{\text{reac\_6}}$ .

### 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 <sup>3</sup> )
B	cB_0
CO	cCO_0
Cl-	cClion_0
H+	cHion_0
H <sub>2</sub> O	cH <sub>2</sub> O_0
pdI	cpd1_0
roh	croh_0


### 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 Case 1 in the **Label** text field.

### Step 1: Time Dependent

- 1 In the **Model Builder** window, under **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** checkbox.
- 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 **Study** toolbar, click  **Compute**.

## RESULTS

### *Case 1 - Concentrations*

- 1 In the **Settings** window for **ID Plot Group**, type Case 1 - Concentrations 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 **Case 1 - Concentrations** 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
H <sub>2</sub> O
C <sup>1</sup>
rhcl
B
pd1
C0
pd2
C <sub>2</sub>
pd3
pd4
ibu

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



The plot in the **Graphics** window should look like that in [Figure 3](#).

Next, create a plot that only includes the product, starting material, and intermediate species.

*Case 1 - Concentrations, Product and Intermediates*

- 1** In the **Home** toolbar, click  **Add Plot Group** and choose **ID Plot Group**.
- 2** In the **Settings** window for **ID Plot Group**, type **Case 1 - Concentrations, Product and Intermediates** in the **Label** text field.
- 3** Locate the **Title** section. From the **Title type** list, choose **None**.
- 4** Locate the **Plot Settings** section. Select the **Two y-axes** checkbox.
- 5** Locate the **Legend** section. From the **Position** list, choose **Middle right**.

*Global 1*

- 1** In the **Case 1 - Concentrations, Product and Intermediates** toolbar, click  **Global**.
- 2** In the **Settings** window for **Global**, locate the **y-Axis Data** section.
- 3** Click  **Clear Table**.
- 4** In the table, enter the following settings:

Expression	Unit	Description
re.c_roh	mol/m <sup>3</sup>	Concentration
re.c_ren	mol/m <sup>3</sup>	Concentration

Expression	Unit	Description
re.c_rhc1	mol/m <sup>3</sup>	Concentration
re.c_ibu	mol/m <sup>3</sup>	Concentration

5 Locate the **Coloring and Style** section. From the **Width** list, choose **2**.

6 Locate the **Legends** section. From the **Legends** list, choose **Manual**.

7 In the table, enter the following settings:

Legends
roh
ren
rhc1
ibu

*Case 1 - Concentrations, Product and Intermediates*

In the **Case 1 - Concentrations, Product and Intermediates** toolbar, click  **Global**.

*Global 2*

1 In the **Settings** window for **Global**, locate the **y-Axis Data** section.

2 Click  **Clear Table**.

3 In the table, enter the following settings:

Expression	Unit	Description
re.c_pd3	mol/m <sup>3</sup>	Concentration
re.c_pd4	mol/m <sup>3</sup>	Concentration

4 Locate the **Coloring and Style** section. From the **Width** list, choose **2**.

5 Locate the **Legends** section. From the **Legends** list, choose **Manual**.

6 In the table, enter the following settings:


Legends
pd3
pd4

*Case 1 - Concentrations, Product and Intermediates*

1 In the **Model Builder** window, click **Case 1 - Concentrations, Product and Intermediates**.

2 In the **Settings** window for **ID Plot Group**, locate the **Plot Settings** section.



3 In the table, select the **Plot on secondary y-axis** checkbox for **Global 2**.

4 In the **Case 1 - Concentrations, Product and Intermediates** toolbar, click  **Plot**.

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 the **Add Study** button in the window toolbar.
- 5 In the **Home** toolbar, click  **Add Study** to close the **Add Study** window.

### CASE 2

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

#### *Step 1: Time Dependent*

- 1 In the **Model Builder** window, under **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 **Study** toolbar, click  **Compute**.

### RESULTS

#### *Case 2 - Concentrations*

- 1 In the **Settings** window for **ID Plot Group**, type Case 2 - Concentrations in the **Label** text field.
- 2 Locate the **Data** section. From the **Dataset** list, choose **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 **Case 2 - Concentrations** 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
$H_2O$
$Cl^{-}$
rhcl
B
pd1
CO
pd2
$CO_2$
pd3
pd4
ibu
ester

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

Compare the plot in the **Graphics** window with that in [Figure 4](#).

Again, create a new plot with the product, starting material, and intermediate species for Case 2.

#### *Case 2 - Concentrations, Product and Intermediates*

1 In the **Model Builder** window, right-click **Case 1 - Concentrations, Product and Intermediates** and choose **Duplicate**.

2 In the **Settings** window for **ID Plot Group**, type Case 2 - Concentrations, Product and Intermediates in the **Label** text field.

3 Locate the **Data** section. From the **Dataset** list, choose **Case 2/Solution 2 (sol2)**.

#### *Global 1*

1 In the **Model Builder** window, expand the **Case 2 - Concentrations, Product and Intermediates** node, then click **Global 1**.


2 In the **Settings** window for **Global**, locate the **y-Axis Data** section.

3 In the table, enter the following settings:

Expression	Unit	Description
re.c_ester	mol/m <sup>3</sup>	Concentration

4 Locate the **Legends** section. In the table, enter the following settings:

Legends
roh
ren
rhcl
ibu
ester

5 In the **Case 2 - Concentrations, Product and Intermediates** toolbar, click  **Plot**.