

# "Phosphine Imide" Reaction on Peracetylated $\beta$ -Cyclodextrins: Comparison between Supercritical CO<sub>2</sub> and Organic Solvent Processes

Danielle Barth<sup>a\*</sup>, Alexandre SCONDO<sup>b</sup>, Florence Dumarcay<sup>c</sup> and Alain Marsura<sup>c</sup>

<sup>a</sup>Laboratoire des Sciences du Génie Chimique, Nancy-Université, 1 rue Grandville, BP20451, 54001, Nancy, France. e-mail: [Danielle.Barth@ensic.inpl-nancy.fr](mailto:Danielle.Barth@ensic.inpl-nancy.fr)

Fax: +33 3 83 32 29 75 (D.Barth)

<sup>b</sup>Laboratoire de Thermodynamique des Milieux Polyphasés, Nancy-Université, 1 rue Grandville, BP20451, 54001, Nancy, France.

<sup>c</sup>Laboratoire Structure et réactivité des Systèmes Moléculaires Complexes, Nancy-Université, 5 Rue Albert Lebrun, BP 80403, 54001 Nancy France.

## ABSTRACT

This work deals with three sets of experiments. Two sets of experiments were designed, both at a pressure of 200 bars, in a 100 mL reactor which is stirred by impeller at 1400 rpm and temperature between 20°C and 55°C. The first set was commonly carried at low reactants concentrations (1 mg of reactive cyclodextrins for 1 mL of reactor) in order to follow the kinetic without transport limitations. The second set was carried at high reactants concentrations (5 mg of reactive cyclodextrins for 1 mL of reactor) in order to observe the behavior of the reaction in these non conventional conditions. An additional experiment was carried out in DMF at 33°C to compare organic solvent and supercritical solvent performances. In DMF, the kinetic of the reaction is well fitted by a model where  $A \xrightarrow{r_1} B \xrightarrow{r_2} C$ , where  $r_1$  and  $r_2$  follow first order kinetic. The reaction in scCO<sub>2</sub> showed a first order kinetic at low concentrations with yields from 75% up to 86%. The behavior is widely different at high concentration: a lag-time is observed and yields are lower.

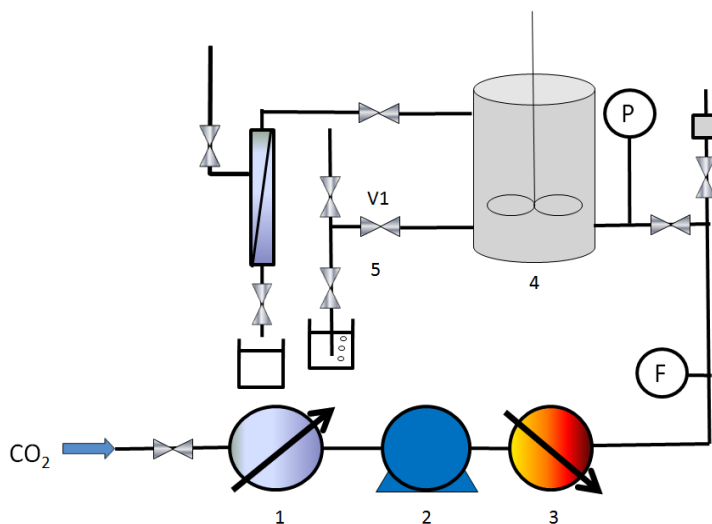
## Introduction

The literature devoted to supercritical carbon dioxide (scCO<sub>2</sub>) for extraction and material applications is vast in comparison with that for chemical reaction. This field however is fast growing, mainly for fine and solvent free products. Ureas have a large range of uses including dyes for cellulose fibers, intermediates in carbamate synthesis, agrochemistry and wide sets of pharmaceuticals and have been traditionally synthesized by methodologies based on the use of hazardous reagents such as phosgene. The 'phosphine imide' strategy have been developed to achieve a rapid and easy access to sophisticated cyclodextrin derivatives (urea, carbodiimides, and isocyanates) from azides.

The aim of this research was to investigate the capability of using scCO<sub>2</sub> as reagent and solvent in the syntheses of ureas and other sensitive compounds (e.g., carbamates, isocyanate carbodiimides ... ) in smooth reaction conditions and to follow the kinetics of this reaction in near critical media and to compare the performances with those of classical organic solvent like DMF.

## Reactor

A schematic flow-sheet of the equipment is given in Figure 1. Since it was previously described [1], only a short description is reported here. The compression module consists in a CO<sub>2</sub> cylinder, a chiller 1 (3 °C), a piston pump 2 (LEWA EK-M-210V1), a heat exchanger 3 and a Coriolis mass flow-meter (Rheonik REH 07, 0.01 g accuracy). The reaction module consists in a 100 mL vessel 4 (Top Industrie) of internal diameter and height of 40 and 80 mm, respectively. Its temperature is regulated at 0.1 °C by a water circulation.



**Figure 1: 100 ml high pressure reactor flow sheet**

The stirring is provided by a magnetically coupled stirrer with a Rushton-type impeller of 16 mm in diameter located at 5 mm from the vessel bottom; for these experiments, the stirring rate was settled at 1400 rpm. The pressure is measured by a sensor accurate at 0.1 MPa (Touzard et Matignon). The sampling module 5 consists in three valves (Top Industrie) and a pre-calibrated sampling loop of 1 mL; all lines are thermostated by heating strips. Sampling tests conducted using triphenylphosphine at 200bars, 33°C with the stirring device working and concentration between 0.25 and 2.0 g per/liters show good agreements between composition of the sample and composition attempted with a maximal differences of 10% for the lowest concentration.

## MATERIALS AND METHODS

The cyclodextrine derivatives were previously produced and characterized [2]. Triphenylphosphine and benzylamine were from Aldrich. The carbon dioxide from Messer exhibited a purity of 99.995%. The dichloromethane, dimethylformamide and methanol used were HPLC grade from VWR ProLabo.

### *Procedure for reaction in supercritical CO<sub>2</sub>*

A determined amount of reactants was introduced into the reactor previously heated at the desired temperature (from 20 up to 45°C). For 1 mole of monoazido-peroacetyl- $\beta$ -cyclodextrin, we add 10 equivalents of benzylamine and 40 equivalents of triphenylphosphine. Once the reactor was sealed, CO<sub>2</sub> was added at tank pressure (6MPa). When the pressure is stabilized, liquefied CO<sub>2</sub> (3°C) was delivered to the vessel by the Lewa pump after a pre-heating up to desired pressure and temperature. This pressure is then maintained constant using an electric control system. Once the operational pressure was attained, the stirring was started. Samples (1mL) were regularly taken via the sampling system using the following protocol. By opening valve V1, sample of the fluid phase flew into the sampling loop, which was further slowly depressurized and rinsed with dichloromethane. The volume of the dichloromethane rinsing solution  $V_{\text{dichloromethane}}$  was

measured by pipette taking and the content in the sampling was immediately analyzed by HPLC. Samples were collected every 15 minutes but after 1h30 a sample was collected every 30 minutes. The sampling operation continued until that a constant reaction rate in the fluid phase was obtained.

### ***HPLC Analysis***

The HPLC system consists of a SpectraSystem P1000Xr quaternary pump (Finningan,USA), a SpectraSystem SCM 1000 vacuum membrane degasser, a DDL 21 evaporative light-scattering detector (Eurosep, Fr), and a Rheodyne 7125 sample injector with a constant volume loop  $V_{\text{sample loop}} = 10\mu\text{l}$ . Chromatograms were acquired with a WINI 10 acquisition card and recorded on a computer by using WINILAB 2 software (Perichrom, Fr). The analytical column was an unbounded silica Polaris Si-A column (150 mm\*4 mm, Varian, USA ) ; to increase the column life a Polaris Metaguard guard column (Si-A 5u, Varian, USA) was used. The thermostat used herein was a Gecko 2000 (Cluzeau,Fr) to set the column temperature at 33°C. The ELSD was set at 100°C for evaporation temperature. Compressed air was used as nebulization gas at 2 bars of working pressure. The HPLC flow rate was 1 ml/min. A binary gradient of methanol in dichloromethane was used as eluent and permit analysis in 15 minutes.

## **RESULTS**

### ***Experimental design and statistical analysis***

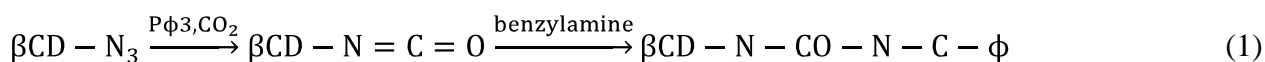
The objective was to follow the kinetic of the reaction we have chosen as standard phosphine imide reaction in supercritical carbon dioxide and its dependency to operational parameters, mainly temperature and concentration of the reactants. Because of the poor solubility of cyclodextrines in low density  $\text{scCO}_2$  [3], we decided to manage all the experiments at the maximal working pressure of the vessel, 200 bars and thus no studying pressure effect. Three sets of experiments were designed at different levels of temperature, initial amount of reactants and in a classical organic solvent in order to get a comparison point between supercritical process and classical process.

The first set was carried at low reactants concentrations (100 mg of CD in 100 mL, corresponding amount of other reactants as explained in Procedure). The procedure was repeated for a temperature range compatible with sensitive compounds wich was 20°C up to 45°C. The second set was carried at high reactants concentrations (500 mg of CD in 100 mL, corresponding amount ..). The procedure was repeated for a temperature range wich was 20°C up to 45°C.

The third set was carried in 100 mL of DMF saturated by  $\text{CO}_2$  bubbling at 33°C. The same quantity of reactant as in the first set was introduced in a stirred glass reactor. Samples were taken every 15 minutes during 2 hours and then every hour during 6 hours. Each sample was frozen before being cool-evaporated and formerly analysed using HPLC.

Regular samplings over time and fast analysis allowed monitoring the conversion rate; when the conversion rate became constant, it was considered that the reaction was completed. Values of conversion rate on the plateau were averaged, and the mean value was further compared to the corresponding rate issued from the first set.

The standard reaction, assumed irreversible, can be schematically written as in (1):



Which can be simplified by (2) for kinetic analysis  $\text{azide} \xrightarrow{r_1} \text{isocyanate} \xrightarrow{r_2} \text{urea}$  (2)

### Composition and kinetic calculations

The compositional analysis was performed using HPLC-ELSD because this method offers a relatively fast separation of the reaction mixture into P $\phi$ 3, azide, isocyanate and urea by high performance liquid chromatography (HPLC) followed by quantification by electrovaporative light-scattering detector (ELSD). Such detection method is reliable and well adapted for cyclodextrins detection [4]. We didn't try to evaluate the concentration of the triphenylphosphine by this method, because it's used in wide excess (40eq.) and very well separated from other compounds.

Kinetic data were calculated using equation (2), the best values for the rate constant  $k$  and final yield were obtained using the last squares method where the differences between the experimental and model conversion rates were minimized. When needed, the two consecutive reactions model was simplified to a first order model to better fit the experimental points. This simplification can be explained by a promotion in scCO<sub>2</sub> of  $r_2$  that consume isocyanate to produce urea.

### Temperature effect

All of our experiments at low concentrations didn't permit to observe the intermediate, what reflects that its quantity was widely below those of the others compounds during all the reaction, perhaps due to its reactivity with benzylamine. The evolution of the conversion rate at 200 bars in function of the temperature was modeled using a first order model justified by the observations of experimental conversion rate as shown in Figures 2 and 3 which are representative for all experiments. This model shows a good accuracy for estimating the conversion rate, the maximal error in all the cases was about 9%. As expected, rate constant and yield increase with the temperature, but it clearly appears that the kinetic in liquid carbon dioxide (20°C) is very different from those near and beyond critical point. The activation energy is about 34.32kJ/mol and pre-exponential factor around 311 s<sup>-1</sup>. This data permit to predict  $k$  with a satisfactory as shown in Table 1.

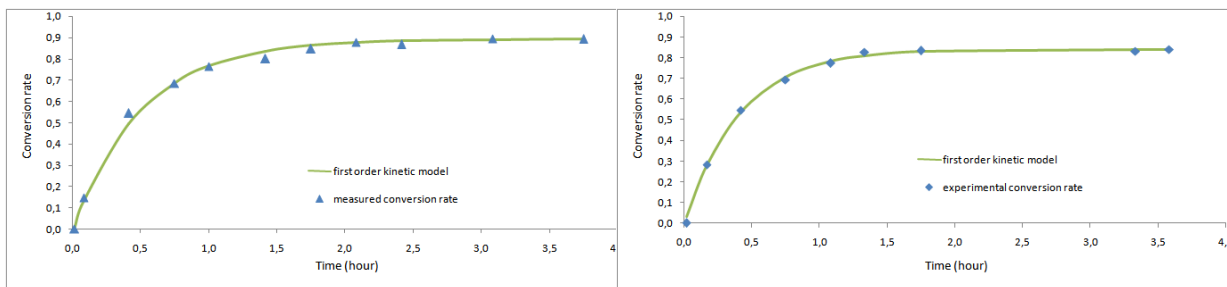


Figure 2: Experimental vs model conversion rate at 45°C Figure 3: Experimental vs model conversion rate at 20°C

It appears that it's mainly the kinetic of the reaction that is affected by the evolution of the CO<sub>2</sub> behavior, the yield seems less sensible to this change and is very good even at low temperature. This increase of the reaction kinetic when passing from liquid to supercritical behavior can be explained by the increase of the CO<sub>2</sub> activity [5].

|                               |       |       |       |       |       |
|-------------------------------|-------|-------|-------|-------|-------|
| temperature (°C)              | 33    | 40    | 30    | 35    | 45    |
| k exp (s-1) *10 <sup>4</sup>  | 4.39  | 6.26  | 3.51  | 5.13  | 6.72  |
| k calc (s-1) *10 <sup>4</sup> | 4.34  | 5.87  | 3.80  | 4.74  | 7.22  |
| error %                       | 0.97% | 6.25% | 8.34% | 7.59% | 7.54% |

Table 1: kinetic constant for low concentration of reactants

### Effect of initial reagent concentration

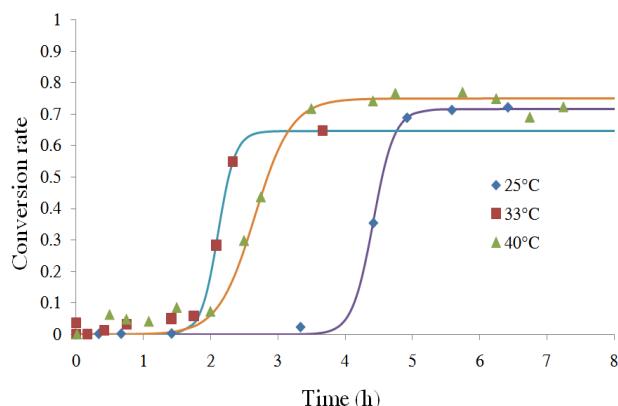


Figure 4 : Conversion rate in scCO<sub>2</sub> at high concentrations

Most studies in supercritical fluids deals with low compounds concentrations, and the effect of a concentration increase is not well known, while very important for improving the productivity of an apparatus with its industrial usefulness. We decided to increase the initial amounts of all the reactants by a 5 factor in the second set of experiment in order to monitor the reaction in this "concentrated" conditions. We observe a lag time with no evolution of the conversion rate followed by a growing step as shown in Figure 4.

This lag time seems to be dependent with the phase behavior of the carbon dioxide (liquid or near-critical). In all the cases, it appears that even at equilibrium a larger amount of azide remains unreacted than in less concentrated experiments, what may reflect an effect of the saturation of the media with some of the compounds.

### Comparison with DMF

We follow the kinetic of the same reaction in DMF in order to get a comparison point for the supercritical process. The same amount of reactant as in first set was introduced in a glass reactor with 100 mL of DMF at a temperature of 30°C saturated by a bubble flow of gaseous CO<sub>2</sub>. The evolution of the concentrations of azide, isocyanate and urea are shown in Figure 5. The kinetic of this reaction was fitted using this scheme were  $r_1$  and  $r_2$  follows first order kinetic model with good agreement with experimental measurements as shown in Figure 5.

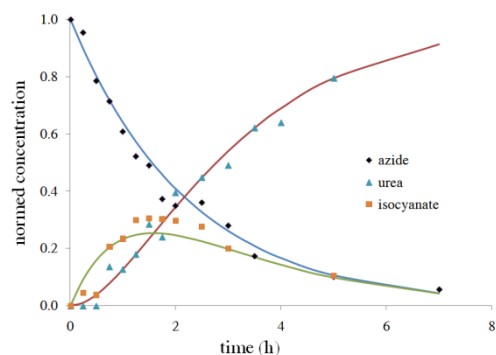


Figure 5: concentrations in DMF at 33°C

We observe that in DMF the final conversion rate, obtain in approx 8h, is near total, what was never observed in scCO<sub>2</sub>. To compare supercritical process with those based on organic solvent, we can observe the Figure 6 that shows the evolution of the conversion rate for the temperature of 33°C in low concentrated scCO<sub>2</sub>, in high concentrated scCO<sub>2</sub> and DMF. It clearly appears that reaction in low-c scCO<sub>2</sub> is faster than in DMF and that reaction in DMF as a higher reaction rate.

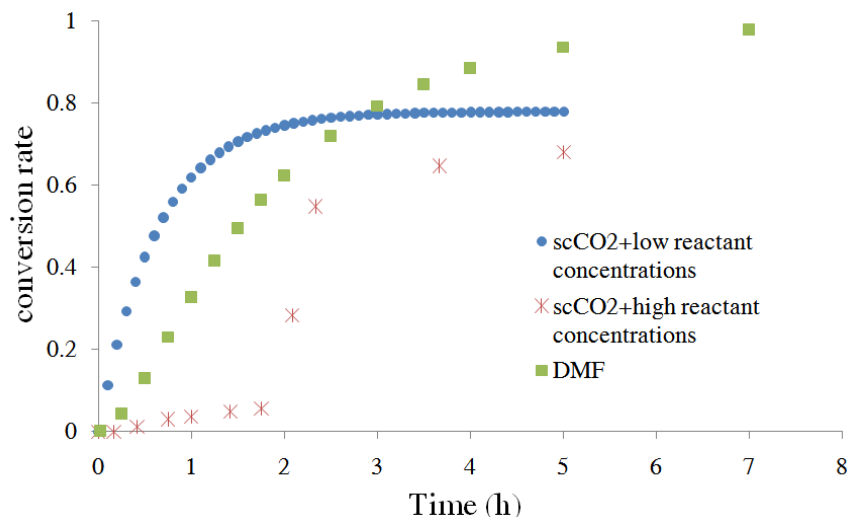


Figure 6: conversion rate in scCO<sub>2</sub> and DMF at 33°C

## CONCLUSION

Our procedure allows following efficiently the kinetic of the reaction in both scCO<sub>2</sub> and organic solvent, and a pseudo first-order was calculated in scCO<sub>2</sub> at low concentration. As expected, the rate constant increase with the temperature independently of the solvent media, even if differences appears between liquid and near critical CO<sub>2</sub>. The activation energy in pure scCO<sub>2</sub> was 34 kJ/mol.

Supercritical carbon dioxide as a solvent medium permit a significant improvement of the reaction kinetic compared with organic solvent. The use of dense carbon dioxide as media for this reaction shows a good efficiency with yield above 78% and reaction in less than 6 hours. Moreover, the use of CO<sub>2</sub> avoids the time-lasting solvent purification and de-watering step due to the highly hydrophilic isocyanates intermediates.

## REFERENCES

- [1] T. Dumont, D. Barth, G. Branlant and M. Perrut, *Biotechnol. Bioeng.*, Vol. 40, 1992, 329-333.
- [2] Stephane Menuel, Michel Wagner, Danielle Barth, Alain Marsura., *Tetrahedron Letters*. Vol. 46, 2005, 3307-3309.
- [3] V. Potluri, A. Hamilton, C. Karanikas, S. Bane, J. Xu, E. Beckman and R. Enick, *Fluid Phase Equilibria.*, Vol. 211, 2003, 211-217.
- [4] M. Agüeros, M.A. Campanero and J.M. Irache., *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 39, 2005, pp. 495-502.
- [5] P. Moquin, F. Temelli, H. Sovová and M. Saldaña., *The Journal of Supercritical Fluids*, Vol. 37, 2006, 417-424.