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Thorough Examination of a Wittig−Horner Reaction Using Reaction Calorimetry (RC-1), LabMax, and ReactIR

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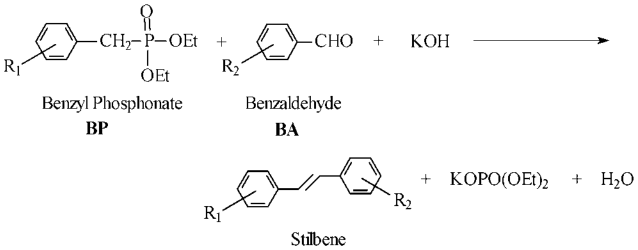
Abstract:

The kinetics and thermodynamics of a Wittig−Horner reaction was investigated, together with side reactions such as the hydrolysis of benzyl phosphonate. It was found that the water content in the reaction mass has a crucial effect on the rates both of the unwanted hydrolysis of the phosphonate and of the main reaction. The reaction was found to be fourth-order. That means that the reaction is very fast at the start but tails off towards the end. On the basis of the kinetic and thermodynamic parameters, a simulation of the whole process was made, including the expected concentrations of the product under the required conditions (temperature, reactor characteristics, etc.). The experimental values of the concentrations were obtained from spectra collected via a *rapid reaction mode* in the *ReactIR* (a spectrum was collected every ∼3 s). Exact agreement between experimental and theoretical values confirms the correctness of the mathematical model and enables right planning of the industrial process.

Introduction

From early 1950, when Wittig and co-workers published a new method for olefin synthesis from aldehydes or ketones and phosphonium ylides, the Wittig reaction with some modifications (for example, as shown below) has become widely used and discussed in numerous reviews.[1]



The mechanism of the Wittig reaction is commonly presented showing formation of a four-membered cycle of oxaphosphetane that is irreversibly decomposed to the reaction products. In this work we consider kinetic peculiarities, differences in the reaction mechanism, process optimization, and industrial usage of the Wittig−Horner reaction.

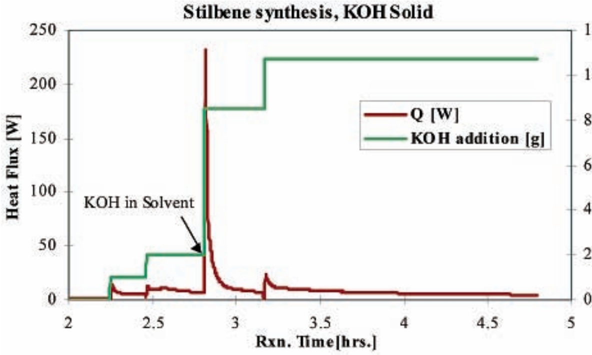


Figure 1. **Heat flow during stilbene synthesis with solid KOH additions (the third portion of KOH was suspended in solvent after high-shear mixing).**

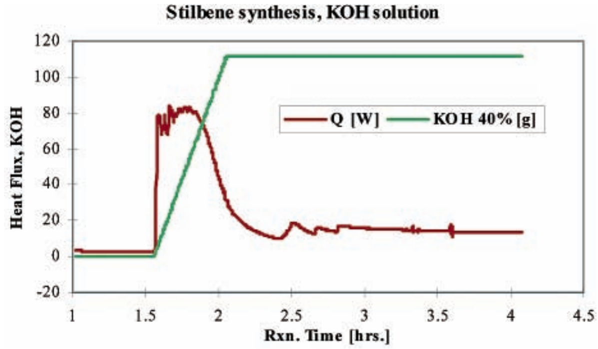


Figure 2. **Heat flow during stilbene synthesis with aqueous KOH solution.**

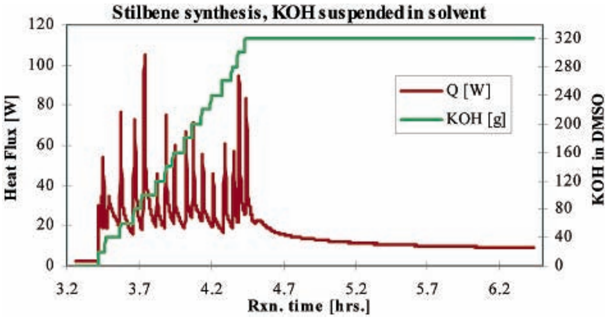


Figure 3. **Heat flow during stilbene synthesis with solid KOH suspended in solvent.**

RC-1 Experiments and Process Optimization by DOE. Preliminary experiments that were carried out in the ***RC-1*** reactor showed that the stilbene-producing reaction is very

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[1] For example: Maryanoff B. E.; Reitz A. B. *Chem. Rev.* **1989**, *89*, 863−927.

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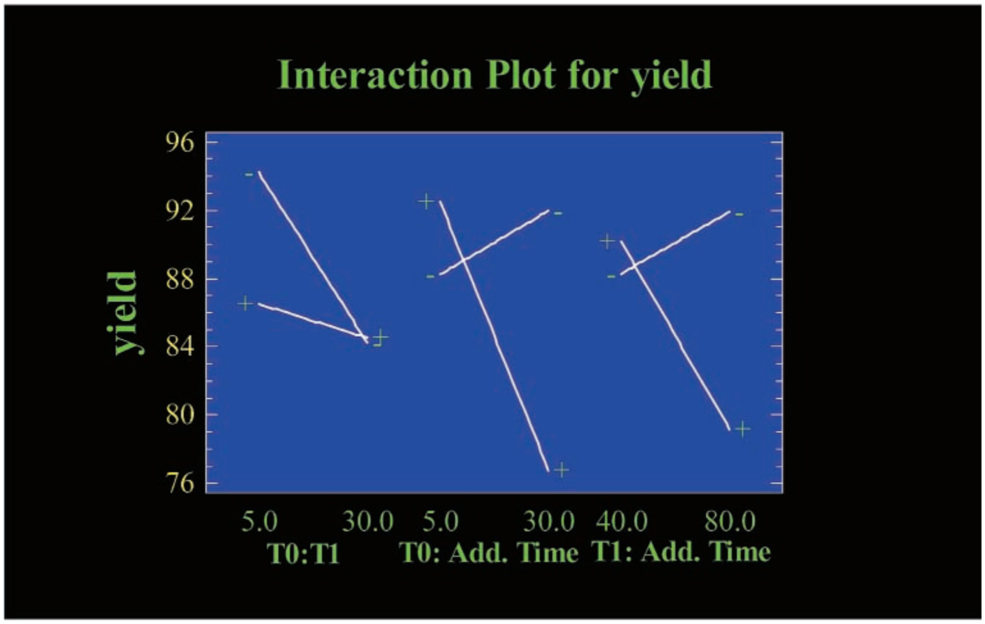

Figure 4. **Interaction plot of the three factors.**

fast and that the yield is sensitive to the way the base is added to the reaction media. The lowest yield was obtained when solid KOH was added in four portions (Figure 1). It can be seen that when the KOH was added suspended in the solvent using a high-shear mixer (i.e. high availability of the base), the heat flow was much higher. KOH addition in aqueous solution (Figure 2) or suspended in the solvent (Figure 3) gave better results.

Since preliminary experiments had shown that the base addition time is the important factor to the reaction, we included it as a parameter (parameter (c) 10 and 20 min) in the process development by design of experiment (DOE). Two additional factors that were examined were (a) starting temperature: $T0$ (5 and 30 °C) and (b) final temperature: $T1$ (40 and 80 °C). To all of these factors repeated center-point values were added (17.5 °C, 60 °C, and 15 min, respectively). All the experiments were performed with KOH suspended in solvent.

Calculation of results was carried out using the STATGRAPHICS Plus program.[4] Figure 4 shows the interaction plot of the three factors. It can be seen that the influence of both the starting temperature and the final temperature on the yield are in opposition when interacting with the addition time (factor c). It means that a high yield is obtained both when the starting temperature is low and the addition time is long, and when the starting temperature is high and the addition time is short. The same tendency was obtained with the final temperature.

The following results were obtained from the ANOVA (analysis of variance) Table of the DOE from the STATGRAPHICS program. It can be seen that all the parameters are significant from the statistical point of view (p values are less than 0.05), and that the model is adequate to the real process (p value of lack-of-fit test is greater than 0.05).

Reaction Kinetics. The prediction ability of this statistical model is restricted usually both by the number of parameters

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Analysis of Variance for yield
--------------------------------------------------------------------------------
Source                Sum of Squares     Df    Mean Square    F-Ratio    P-Value
--------------------------------------------------------------------------------
A:T0                          40.272      1         40.272     635.87      .  16
B:T1                         15.3624      1        15.3624     242.56      .  41
C:Time add                   33.3104      1        33.3104     525.95      .  19
AB                            17.952      1         17.952     283.45      .  35
AC                           106.392      1        106.392    1679.87      .   6
BC                            60.564      1         60.564     956.27      .  10
Lack-of-fit                  1.12012      1        1.12012      17.69      . 522
Pure error                   .126667      2       .0633333
--------------------------------------------------------------------------------
Total (corr.)                484.009      9

R-squared = 99.7424 percent
R-squared (adjusted for d.f.) = 99.2272 percent
Standard Error of Est. = .644667
Mean absolute error = .277143
Durbin-Watson statistic = .901307
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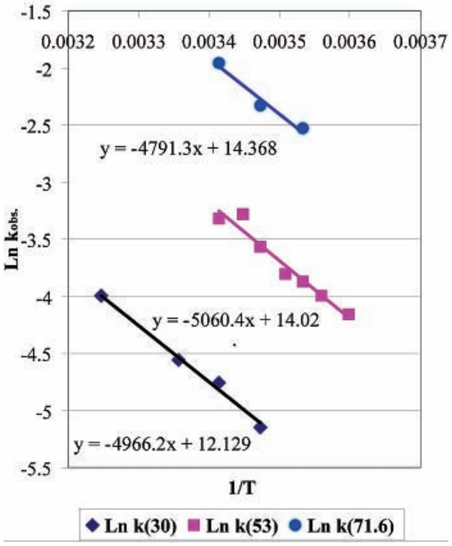


Figure 5. **Activation parameters as a function of water content.**

and by the limits of the changes of the parameters during DOE performance. Although the results of the DOE prediction were of high quality, we must carry out at least one additional set of DOE to obtain the optimal parameters of the process.

Another method of process optimization is based on the kinetic investigation of the desired reaction and of the main side reactions. Kinetic data enable us to understand the mechanism of the chemical reaction, to define the limiting reaction step, to create a mathematical model of the process, and as a result, to find the optimal parameters. As a rule, this method needs more experiments and more calculations but allows more precise and less limited predictions to be made.

Kinetic measurements of the main process were carried out under pseudo-first-order conditions by means of HPLC analysis of the samples. We used not less than 30-times excess of KOH and BA, and to avoid quantitative analysis of the reaction mass samples we used an internal standard. The constants (k_{obs}) of the reaction were calculated by linear regression in coordinates $-\ln(S_{BP}/S_{IS}) - \tau$. Here S_{BP} is the peak area of benzyl phosphonate, S_{IS} is the peak area of the internal standard, and τ is the reaction time. The straight lines that were obtained in these coordinates demonstrate that the Wittig−Horner reaction is first-order with respect to BP.

To find the reaction order with respect to KOH and BA we measured k_{obs} at different concentrations of these reagents in the reaction mass. We obtained first-order with respect to KOH, but surprisingly the reaction order with respect to BA was two! In other words, the order of the Wittig−Horner reaction under the considered conditions is four.

We checked also the influence of water on the reaction rate at different temperatures. Changing the water content in the reaction mass was done by the dilution of KOH. It is evident that increasing the water concentration in the reaction mass (reducing the KOH concentration in the water solution) decreases the reaction rate (Figure 5).

At the same time the activation energy is not changed, which means that this reaction series is isoenthalpic and that the activation entropy determines the change in the reaction rate. It was found that a linear relationship exists between ln k_0 and water concentration in the reaction mass, where k_0 is the preexponential factor of the reaction constant of the fourth order.

Our knowledge of the reaction order and the influence of temperature and water content on the reaction rate make it possible to calculate the real reaction constant and the real rate of the reaction in wide intervals of the temperature and the reagent concentrations. Comparison of the pseudo-first-order constants that were calculated and measured in the new

Scheme 1

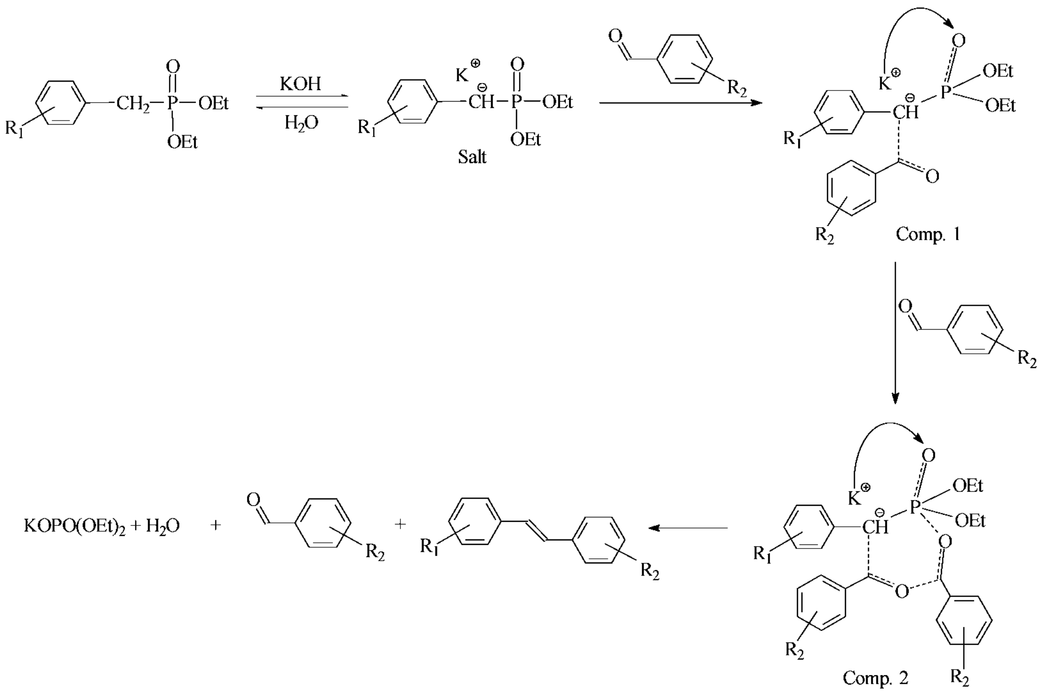


Table 1. **Calculated and measured pseudo-first-order constants**

BA concn, mol/L	KOH concn, mol/L	water concn, mol/L	temperature, °C	k_{obs}, s^{-1}	k_{calc}, s^{-1}
0.766	0.894	1.742	10	3.55×10^{-2}	3.66×10^{-2}
0.766	0.894	1.742	15	4.78×10^{-2}	4.96×10^{-2}

conditions does validate the mathematical model (Table 1).

From the theoretical viewpoint it is important to understand, what is the mechanism of the Wittig–Horner reaction, what is the rate-limiting step of the reaction, why do we have a second-order kinetics of the reaction with respect to BA—what is the role of the second molecule of BA?

It seems trivial that the first stage of the reaction is a rapid equilibrium between CH-acid (BP) and its potassium salt (Scheme 1). Because of the high nucleophility of the anion, synthesis of the activated complex 1 may also be very rapid. The next reaction step must be oxygen transfer from carbonyl carbon to phosphor and decomposition of the activated complex to the reaction products. The problem is that an oxygen transfer by a four-membered cyclic transition state is very difficult! For this transfer, we probably need a second molecule of BA. It enables the synthesis of the six-membered cyclic activated complex **2**. Producing this complex or its decomposition to the reaction products with release of a molecule of BA may be the rate-limiting step of the reaction. We believe that the second case is more probable, because the activation energy is too low for typical nucleophilic reactions (about 41 kJ/mol). Apart from it, activation energy is not changed with changing solvating ability of the solvent (increasing water concentration in the solution). An increase of the water content in the reaction mass due to the hydration of complex **2** tends to increase the activation entropy (about 20 J/(mol·K) more negative).[2]

We investigated the hydrolysis of BP by a similar method without BA addition. Again, the straight lines that were obtained in coordinates $-\ln(S_{BP}/S_{IS}) - \tau$ demonstrates first-order kinetics of this reaction with respect to BP. Measurements of k_{obs} at the different concentrations of KOH lead us to a conclusion that the reaction is also first-order with respect to KOH.

As in the case of the Wittig–Horner reaction, we investigated the hydrolysis of BP at different temperatures and in solutions at different water concentrations. It is interesting to note that the activation energy of the BP hydrolysis is essentially higher than in the Wittig–Horner reaction and is changed, depending on the water content, from 63 up to 82 kJ/mol (Figure 6).

In these experiments we have an ideal isokinetic relationship.[3] This means that the reaction mechanism is the same in all reaction series. Water addition leads to reduction of the reaction rate and activation entropy owing to the hydration effect. At the same time activation enthalpy is increased. According to our calculations, at a temperature of about 100 °C (isokinetic temperature) the influence of water concentration is negligible, and at higher temperatures the influence should be the opposite.

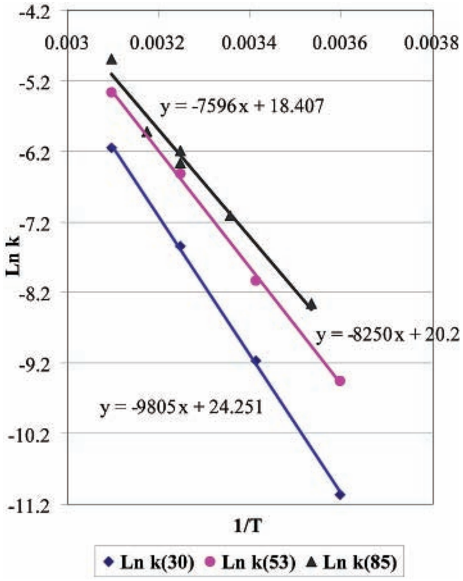
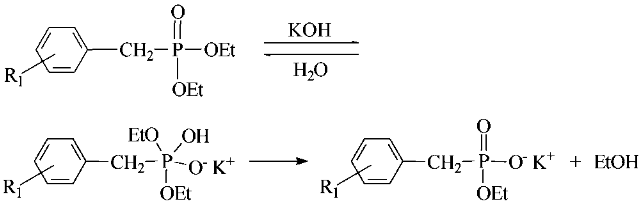


Figure 6. **Activation parameters as a function of water content.**

Scheme 2



We have found that in the investigated intervals, linear relationships exist both between water concentration and the preexponential factor of the second-order reaction rate constant, and between water concentration and the activation energy of hydrolysis. These facts make it possible to calculate the real reaction constant and the real rate of BP hydrolysis at different temperature and reagent concentrations. In other words, we now have a full mathematical model of the BP hydrolysis.

Second-order kinetics (first with respect to BP and to KOH) and activation parameters allow us to conclude that the hydrolysis of BP is carried out according to the classical (addition − elimination) (A − E) mechanism and that probably the rate-limiting step is nucleophilic attack by the hydroxide ion (Scheme 2). In this case a higher concentration of water leads to higher hydration of the hydroxide ion. Respectively, on one hand, activation enthalpy of the nucleophilic attack rises up, and on the other hand, the difference between hydration entropy of the hydroxide ion and of the activated complex decreases (activation entropy becomes less negative).

Comparison of the kinetic and thermodynamic parameters of the main process of the stilbene synthesis (Wittig–Horner reaction) and the side reaction (hydrolysis of BP) permits us to note some important conclusions about the possibilities

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(2) Gordon A. J.; Ford R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*; John Wiley: New York, 1972.

(3) Palm, V. A. *The Base of the Quantitative Theory of Organic Reactions*; Khimiya: Leningrad (SU), 1977.

(4) *SGWIN Software: STATGRAPHICS Plus for windows*; Manugistics Inc.: Rockville, MD.

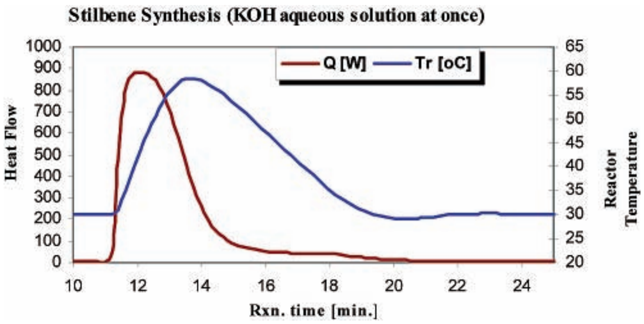

Figure 7. **Heat flow and reactor temperature in the stilbene synthesis.**

to improve the selectivity of the stilbene synthesis.

(1) Because the activation energy of the BP hydrolysis is higher than that of the Wittig–Horner reaction, ***the stilbene synthesis should be performed at the lowest temperature as possible***.

(2) Sensitivity of the Wittig–Horner reaction to water addition (reduction of the reaction rate constant) is higher than that of the BP hydrolysis. Consequently, ***stilbene synthesis should be carried out with the water content as low as possible***.

(3) Second-order reaction kinetics of the Wittig–Horner reaction with respect to BA makes the rate of this reaction very sensitive to the BA concentration. Therefore, ***stilbene synthesis should be done with the concentration and excess of BA as high as possible***.

(4) Real decisions about process realization in industrial conditions should be made on the basis of process simulation, after a compulsory test of the mathematical model in pilot reactors.

Measurement of the stilbene synthesis reaction heat was carried out under the recommended conditions (Figure 7). It can be seen that the reaction heat flow corresponds with the kinetics of the high-order reaction—it is very high at the beginning and remains low for a long time.

Process Simulation. Process simulations were carried out by numeric integration in Excel. The integration constant of time was 1 s. At every integration step we calculated the temperature of the reaction mass, water content, and reagent concentrations at the beginning of the second. On the basis of these data, constants of the main and side processes were determined, and changes of all reagents and all product concentrations up to end of the second step were calculated. After evaluating the change of the product concentration we calculated the heat of reaction during the second step. Using the reactor parameters and temperature of the cooling agent we defined the heat flow to the jacket during the time interval and the amount of heat accumulated in the reaction mass. From the C_p of the reaction mass we calculated the temperature change during the second step.

Now we have all the information to go to the next step and to calculate the temperature of the reaction mass, water content, and the reagent concentrations at the beginning of the new interval. This procedure was repeated for the reaction

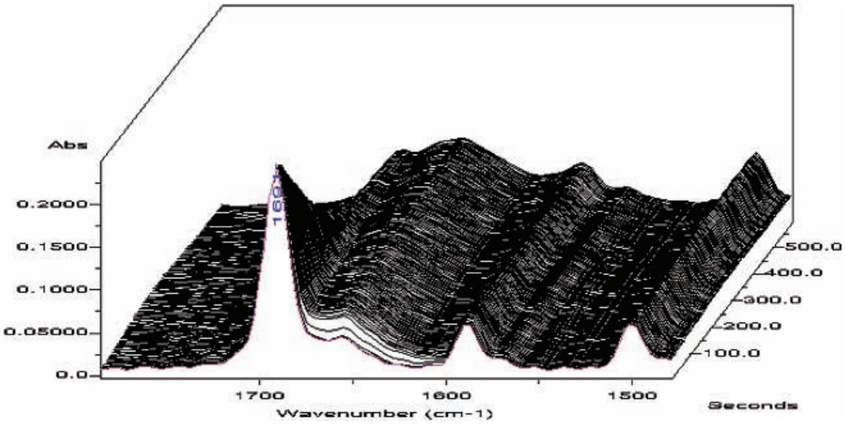

Figure 8. **Three-dimensional plot of the reactant (BA) at 1691 cm^{-1} during 600 s.**

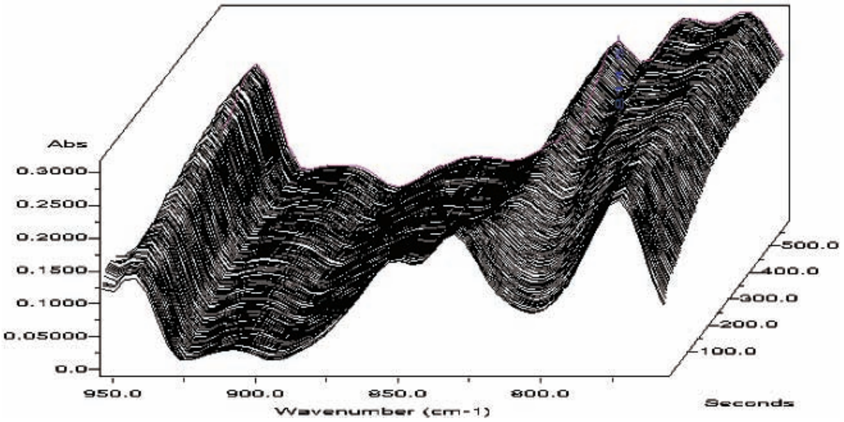

Figure 9. **Three-dimensional plot of the product formation (stilbene) at 942 cm^{-1} during 600 s.**

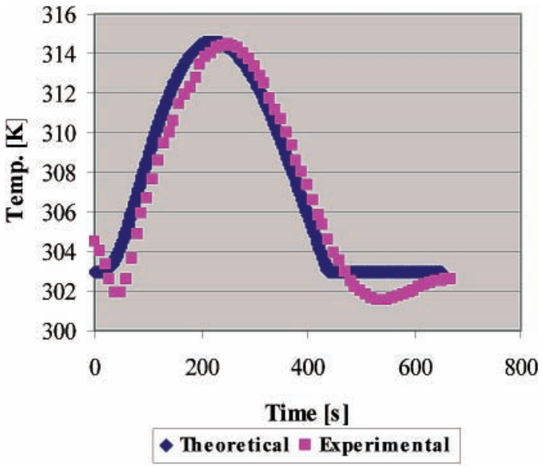

Figure 10. **Reactor temperature, theoretical − from simulation; experimental − from LabMax.**

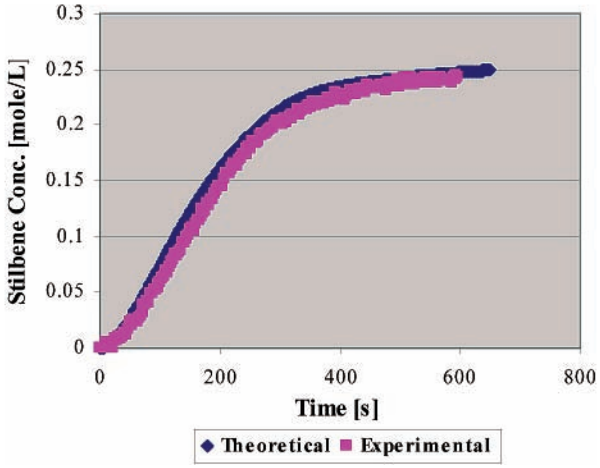

Figure 11. **Product concentration, theoretical − from simulation; experimental − from ReactIR profile.**

time of 1 h; after that, the yield of the desired stilbene was calculated.

Validation of the Simulation Process with the ReactIR and the LabMax. To validate the simulation results we carried out few experiments in the LabMax 1-L reactor equipped with the ReactIR Dicomp probe. We have followed the reaction temperature and the profiles of the reactant and the product during the reaction. These values were compared to the simulated values.

The reactants were dissolved in the reaction solvent at 50 °C, without the KOH solution, and then we cooled the jacket temperature to ∼−10 °C as rapidly as possible. When the reactor temperature reached the desired value (30 or 40 °C), we added the KOH solution all at once. When the reactor temperature reached the maximal value, we set the temperature to the starting value (in the reactor). At that time we collected spectra in the rapid mode (eight scans at a resolution of 8 cm^{-1}, 2.8 s between the spectra). At the end of the reaction, a sample for the final stilbene concentration was analyzed for calculation of the yield. Figures 8 and 9 show the 3D plots of the reactant and the product, respectively.

The following figures (10−12) show the degree of fit of the simulated values to the experimental values of a sample experiment (at 30 °C). The values that were obtained from the IR profiles were fitted to the concentration by multiplication of these values by a constant (extinction coefficient) that was the same for all the experimental values that were obtained (but different for the reactant and for the product).

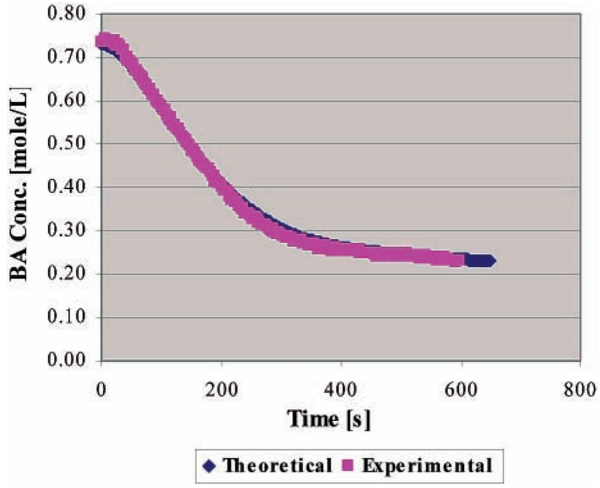

Figure 12. **Reactant concentration, theoretical − from simulation; experimental − from ReactIR profile.**

The yield that was obtained in this experiment was 94%, whilst the calculated yield was 95%.

The same accordance was obtained in other experiments at different temperatures and reagent concentrations.

The model was also tested on a large-scale production reactor (8 m^3). It was calculated that performing the process in this reactor under adiabatic conditions would lead to a temperature rise of up to 70 °C and thus to a decrease of the yield to 80%. Exactly these results were obtained during preparation of the first industrial samples of the stilbene. To achieve a higher yield of the product, an industrial reactor will be equipped by a more effective heat exchanger.•

Conclusions

• In this study the mechanism of a Wittig−Horner reaction was found after a thorough kinetic and thermodynamic research.

• The optimal conditions for the reaction were obtained.

• A mathematical model that enables the planning of the industrial equipment was prepared.

Experimental Section

Materials. Solvents and reagents were obtained from commercial sources and used without further purification.

Analytics. HPLC analysis was performed using Varian 9012 with Autosampler 9300 and UV−vis detector 9050.

Kinetic Measurements of the Stilbene Synthesis. The solvent (between 200 and 500 mL) was added to a triple-jacket reactor of 1 L (with thermostatic unit CC 250 of Huber). The following materials were then added: benzaldehyde (from 0.2 up to 0.4 mol), benzyl phosphonate (about 0.005−0.01 mol), water (if needed), and internal standard; at that time the mixture was then heated to 40 °C to dissolve the components. After a clear solution was obtained, the reaction mass was cooled to the desired temperature, and with a high agitation rate (turbine agitator at about 1000 rpm) an excess of the KOH was added. Sampling was begun immediately, and for these, the reaction was stopped by a dilution with a mixture of a 1:1 ratio of acetonitrile:phosphate buffer, pH = 7.

Kinetic Measurements of the Benzyl Phosphonate Hydrolysis. In this case the same procedure was used, but without adding the benzaldehyde.

RC-1: Automatic Calorimetric Reactor (2 L) of Mettler-Toledo.

LabMax: Automatic Reactor (1 L) of Mettler-Toledo.

ReactIR 1000: For collecting FTIR spectra in-situ through **Dicomp** probe (diamond wafer used as a multiple reflection attenuated total reflectance (ATR), C-276 super alloy body, MCT detector) of Applied Systems. The probe was immersed in the LabMax reactor during all the experiments. The solvent of the reaction was used as the blank for the IR spectra.

Acknowledgment

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