

## Kinetic and safety assessment for salicylic acid nitration by nitric acid/acetic acid system

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### Abstract

The nitration process of salicylic acid for the production of the important intermediate 5-nitrosalicylic acid is studied from thermokinetic and safety points of view. Investigations carried out by considering, as process deviations, the loss of the thermal control point out the possibility of runaway phenomena due to the occurrence of polynitration reactions. Isothermal experiments are carried out in various conditions to assess the involved reaction network and reaction kinetics.

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### 1. Introduction

5-Nitrosalicylic acid is an important intermediate for chemical and pharmaceutical industries. The corresponding 5-amine (mesalazine) is currently used as active species for the treatment of various pathologies such as ulcerative colitis and Crohn's disease [1,2]. Its production through nitration processes, using the classic mixed acid, results into yields lower than 50% and in some difficulties with the separation of the reaction mixture. Even in recent years patents appeared claiming the possibility of producing this species from salicylic acid with interesting yields [3,4]. However, a literature survey indicated that there is still a need to find new nitrating systems to overcome the difficulties associated with current production processes of 5-nitrosalicylic acid. An alternative system with respect to the classic "mixed acid" could be represented by the mixture nitric acid/acetic acid/acetic anhydride which has been found in the past to give good results with the nitration of phenol and the esterification of carnitine [5,6]. Nevertheless, one has to consider that this system is not free of explosion hazards arising from the formation of intermediate acetylnitrate. This species has been reported to undergo thermal decomposition even during the

storage at ambient temperature [7,8]. Moreover, recently some authors investigated the tendency of the system nitric acid/acetic anhydride/acetic acid to decompose, from kinetic and thermal point of view [9], thus concluding that it can give rise to runaway phenomena which are sustained by the violent decomposition of intermediate acetylnitrate.

On the basis of these indications it could be argued that if the formation of acetylnitrate would be inhibited or reduced, a more inherently safe system could be found. A first attempt to move in this direction could be done by using the system nitric acid/acetic acid, in which a reduced formation – if any – of acetylnitrate could be expected. Previous investigations confirmed the possibility of using the system  $\text{HNO}_3/\text{CH}_3\text{COOH}$  for the nitration of salicylic acid with yields to 5-nitrosalicylic acid significantly higher than those found with a classic mixed acid.

Therefore, the present work aims at studying the kinetics and the safety aspects of the nitration process of salicylic acid by means of the system nitric acid/acetic acid.

### 2. Experimental

The investigations have been carried out under adiabatic and isothermal conditions. For adiabatic experiments ARC (Columbia Scientific Industries, USA) and Phi-Tec (Hazard Evaluation Laboratory, UK) calorimeters have been used.

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### Nomenclature

$C_i$	concentration of <i>i</i> th species ( $\text{mol l}^{-1}$ )
$C_{\text{org}}$	concentration of generic organic ( $\text{mol l}^{-1}$ )
$C_p$	mean specific heat of reacting mixture ( $\text{J K}^{-1} \text{g}^{-1}$ )
$E_i$	activation energy of reaction for <i>i</i> th species ( $\text{kJ mol}^{-1}$ )
$\Delta H_i$	heat of reaction for <i>i</i> th species ( $\text{kJ mol}^{-1}$ )
$k_i^0$	pre-exponential factor of reaction for <i>i</i> th species (rate expression depending)
$m_s$	sample mass (mixture) (g)
$n, m$	reaction orders (dimensionless)
$\varphi$	thermal inertia (dimensionless)
$r_i$	rate of reaction for <i>i</i> th species ( $\text{mol (l min)}^{-1}$ )
$R$	universal constant of gas ( $\text{J mol}^{-1} \text{K}^{-1}$ )
$t$	time (min)
$T$	temperature (K)
$T_0$	initial temperature (K)
$\Delta T_{\text{ad}}$	adiabatic temperature rise (K)
$V$	sample volume (mixture) (l)
$z$	stoichiometric coefficient (dimensionless)

In all the runs performed in the ARC calorimeter, in the usual heat/wait/search mode [10] with a slope sensitivity of  $0.02 \text{ K min}^{-1}$ , samples of about 2 g of reacting mixtures ( $C_p = 2.1 \text{ J g}^{-1} \text{ K}^{-1}$ ) and Stainless Steel ARC bomb ( $C_{pb} = 0.4186 \text{ J g}^{-1} \text{ K}^{-1}$ ) were used. Phi-Tec calorimeter has been used in standard “closed can”. In these runs, the glass reactor (magnetically stirred,  $V = 0.048 \text{ l}$ ) was primarily charged with the substrate and assembled into the calorimeter, afterwards, by using a vacuum pump, it was partially purged (initial absolute pressure 0.2 bar) and the system allowed to stabilize at the initial temperature. Once the desired initial conditions were attained, a suitable pre-heated solution (to the same temperature as the reactor) of nitric acid/acetic acid was fed in batch mode into the reactor (a typical values of the total mass of the reacting mixture was of about 34 g). The last operation being achieved by suction using the standard connections of the device.

For isothermal experiments, a RADEX oven [11] equipped with a closed high pressure stainless steel reactor ( $V = 0.004 \text{ l}$ ) and driven by a PC Combilab (SystAG, CH) has been used. Since the reactors do not allow any external addition during the course of the reaction, chemical mixtures were prepared at ambient temperature outside the oven by dissolving a suitable amount of reagents (nitro-derivatives of the salicylic acid) in the proper solution  $\text{HNO}_3$ /acetic acid. Once the reactor was charged, it was transferred in the oven previously heated to the desired initial temperature and allowing the mixture to react for the desired reaction time.

Whenever necessary, after a preliminary thermal quenching at ambient temperature, samples collected in both types of experiments have been submitted to HPLC analysis by using a Hewlett-Packard model 1100 II equipped with an UV-vis detector and a Phenomenex Synergi  $4 \mu$  polar RP/80° column. The

following operating conditions have been adopted: column temperature, 298.16 K; mobile phase composition (vol/vol-%), 80% buffer solution [ $\text{CH}_3\text{OH}$  (5%),  $\text{H}_3\text{PO}_4$  (0.4%),  $\text{H}_2\text{O}$  (94.6%)] and 20% acetonitrile; flow rate,  $1 \text{ ml min}^{-1}$ ; the signals have been acquired at 240, 280, 350 nm.

### 3. Results and discussion

It is well known that, among possible chemical process deviations, the loss of the thermal control is one of the most frequent and dangerous one [12]. In fact, in this case, an initial positive drift of the reactor temperature may result first into a runaway event and in some cases into a thermal explosion with severe damages to people and plants.

Preliminary experiments of nitration of salicylic acid with the proposed system at ambient or near ambient temperature indicated that main products are 5-nitrosalicylic and 3-nitrosalicylic acid, with a minor occurrence of 2-nitrophenol. Since it is well known that an increase of the temperature favours polynitration reactions of aromatics with the formation of di- and trinitroderivatives [13], it can be expected that a complex reaction network can arise from the successive nitrations of three above-reported species. A set of experiments has been thus planned and performed to identify the reactions occurring when the temperature increases. The nitration of 5-nitrosalicylic and 3-nitrosalicylic acid has been separately investigated at respectively 353.16 and 333.16 K using the RADEX oven (initial system composition for 5-nitrosalicylic acid: 0.0194 g of substrate, 0.0267 g of  $\text{HNO}_3$ , 0.0021 of acetic acid; for 3-nitrosalicylic acid: 0.018 g of substrate, 0.0248 g of  $\text{HNO}_3$ , 0.0021 of acetic acid). Collected results are shown in the Figs. 1 and 2. Some gathered information point out that both the compounds are partially converted into 3,5-dinitrosalicylic acid (3,5-DNS), whereas 2,4-dinitrophenol (2,4-DNP) and 2,6-dinitrophenol (2,6-DNP) result, respectively, from 5-nitrosalicylic (5-NS) and 3-nitrosalicylic acid (3-NS).

In both the experiments, a minor occurrence of picric acid (PA) was observed. Similar experiments on 2-nitrophenol (2-NP) (initial system composition: 0.0013 g of 2-NP, 0.0267 g of  $\text{HNO}_3$ , 0.0021 of acetic acid) at 313.16 K showed the formation

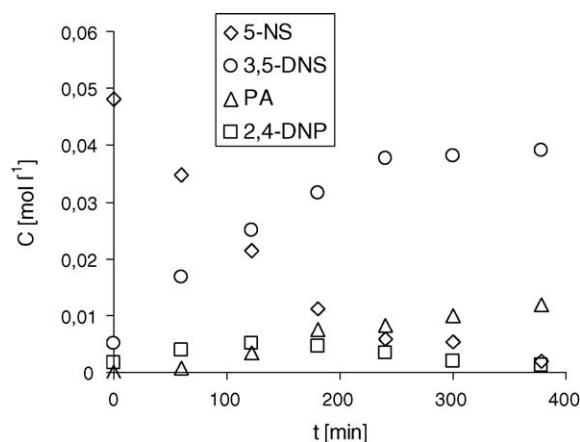


Fig. 1. Nitration of 5-nitrosalicylic acid at 353.16 K.

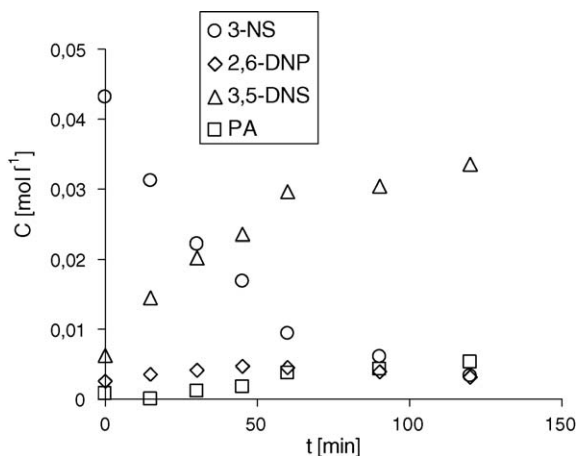


Fig. 2. Nitration of 3-nitrosalicylic acid at 333.16 K.

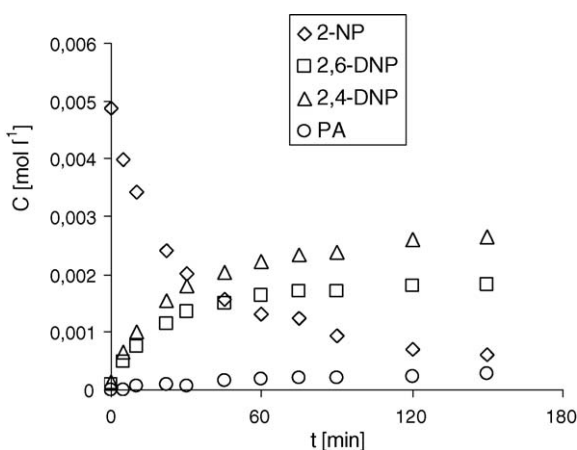


Fig. 3. Nitration of 2-nitrophenol at 313.16 K.

of both 2,4-dinitro (2,4-DNP) and 2,6-dinitrophenol (2,6-DNP) with a small amount of PA (Fig. 3).

A further run carried out at 393.16 K on 3,5-DNS acid (initial system composition: 0.0186 g of 3,5-DNS, 0.0267 g of HNO<sub>3</sub>, 0.0021 of acetic acid) led only to the formation of PA (Fig. 4).

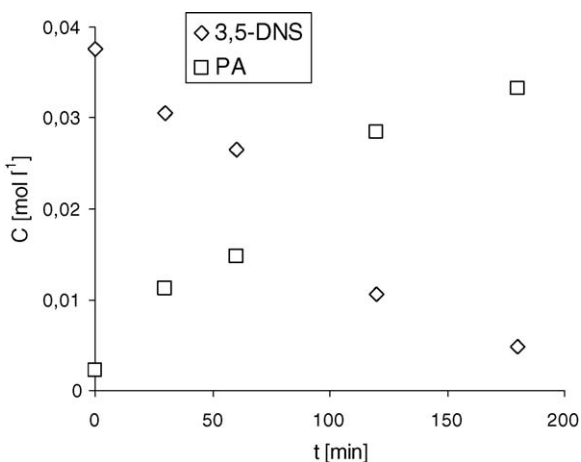


Fig. 4. Nitration of 3,5-dinitrosalicylic acid at 393.16 K.

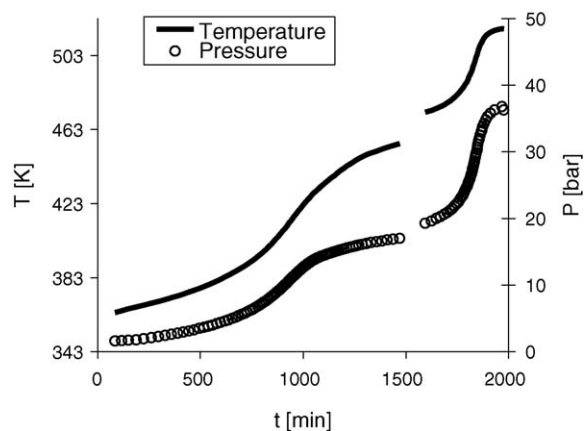


Fig. 5. Decomposition of picric acid under adiabatic conditions.

Although not evidenced by the results reported above, it is well known that PA can violently decompose with the formation of gaseous products [14]. Therefore, some experiments have been planned on the mixture PA/nitric acid/acetic acid (total sample mass: 1.898 g;  $\Phi = 1.852$ ; initial temperature: 364.21 K; system composition: 0.205 g of PA, 0.112 g of HNO<sub>3</sub>, 0.00151 of acetic acid) to investigate its decomposition in the conditions occurring during thermally uncontrolled nitration of salicylic acid.

In Fig. 5 the results collected when this mixture has been allowed to react under adiabatic conditions are shown. From these data, it is clear that the tested subsystem undergoes a complex decomposition reaction in which a great quantity of energy is released and a huge increase of the pressure is observed.

All the results gathered during the above-described experiments and those found in preliminary runs on salicylic acid nitration to obtain mononitroderivatives can be thus summarized in the Scheme 1.

### 3.1. Kinetic assessments

The results previously discussed clearly indicate that a loss of the thermal control of the nitration process of salicylic acid could give rise to a thermal explosion involving a complex reaction network. It is well known that a thermokinetic characterization of the investigated system is among the most important requirements for the adoption of safe operating conditions devoted to prevent the occurrence of unwanted events. Therefore, with the aim at estimating the kinetic parameters of the reactions involved when the nitration of salicylic acid is carried out with a loss of the thermal control (that is when a series of further transformation are triggered at highest temperature at the end of the mononitration of the salicylic acid) a new set of isothermal experiments at different temperatures has been performed.

As a general procedure, three subsystems obtained respectively by nitration and dinitration of 5-NS, 3-NS and 2-NP have been taken into account for further investigations. For each of them a series of isothermal runs (RADEX) have been performed considering different initial temperatures and system compositions.

It is noteworthy to observe that in adopted experimental conditions even at the highest temperatures and concentrations, PA does not undergo further chemical transformations, allowing to neglect at this stage its thermal decomposition.

For all the reactions whose kinetics have been investigated a simple second-order law has been used:

$$\frac{dC_{\text{org}}}{dt} = -k^0 \exp\left(\frac{-E_a}{RT}\right) C_{\text{org}} C_{\text{HNO}_3} \quad (1)$$

First of all, two runs with a mixture formed by 3,5-DNS/nitric acid and acetic acid have been performed at 388.16 and 393.16 K (and the concentration profile of the substrate and PA recorded). The two rate equations:

$$\frac{dC_{\text{PA}}}{dt} = k_{10}^0 \exp\left(\frac{-E_{10}}{RT}\right) C_{3,5\text{DNS}} C_{\text{HNO}_3} \quad (2)$$

$$\frac{dC_{3,5\text{DNS}}}{dt} = -\frac{dC_{\text{PA}}}{dt} = -k_{10}^0 \exp\left(\frac{-E_{10}}{RT}\right) C_{3,5\text{DNS}} C_{\text{HNO}_3} \quad (3)$$

have been numerically integrated with the initial conditions: for  $t=0$ ,  $C_{\text{DS}} = C_{\text{DS}}^0$  and  $C_{\text{P}}^0 = 0$ . The concentrations calculated in this way at different temperatures have been used in an optimization procedure in which they have been compared with the experimental data for both the runs. As a result of this calculation a value of  $1.83 \times 10^{10} \text{ l mol}^{-1} \text{ min}^{-1}$  and  $87.63 \text{ kJ mol}^{-1}$  for  $k_{10}$  and  $E_{10}$ , respectively have been found. Once the kinetic parameters for reaction (10) have been estimated, three experiments have been carried out starting from a mixture of 3-NS/nitric acid/acetic acid at 323.16, 333.16 and 343.16 K and three runs with a mixture of 5-NS/nitric acid/acetic acid performed at 353.16, 363.16 and 373.16 K.

According to the Scheme 1, different sets of mass-balance equations have been written to account for the evolution of each studied subsystem. The values of  $k_{10}$  and  $E_{10}$  previously estimated have been then inserted in these equations and by a similar procedure, kinetic parameters for the reactions (4), (5) and (11) evaluated from the data gathered for 5-NS nitration (see Table 1).

Table 1  
Kinetic parameters identified for reactions (4), (5) and (11)

$k_4^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$1.03 \times 10^{20}$
$E_4$ ( $\text{kJ mol}^{-1}$ )	145.38
$k_5^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$9.73 \times 10^{17}$
$E_5$ ( $\text{kJ mol}^{-1}$ )	136.21
$k_{11}^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$4.62 \times 10^{19}$
$E_{11}$ ( $\text{kJ mol}^{-1}$ )	142.45

Table 2  
Kinetic parameters identified for reactions (8), (9) and (12)

$k_8^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$3.95 \times 10^{21}$
$E_8$ ( $\text{kJ mol}^{-1}$ )	147.72
$k_9^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$1.79 \times 10^{23}$
$E_9$ ( $\text{kJ mol}^{-1}$ )	155.30
$k_{12}^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$1.68 \times 10^{19}$
$E_{12}$ ( $\text{kJ mol}^{-1}$ )	129.93

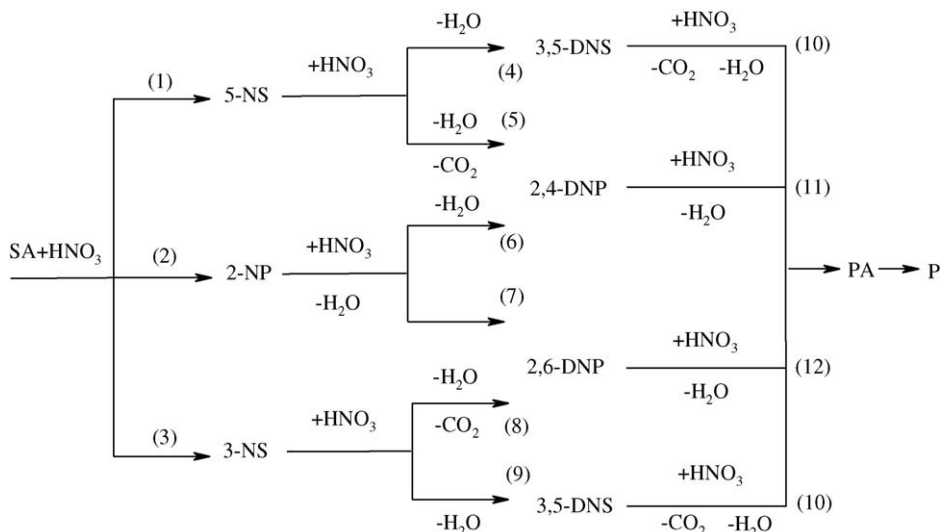
Table 3  
Kinetic parameters identified for reactions (6) and (7)

$k_6^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$1.15 \times 10^{20}$
$E_6$ ( $\text{kJ mol}^{-1}$ )	127.29
$k_7^0$ ( $\text{l mol}^{-1} \text{ min}^{-1}$ )	$5.89 \times 10^{20}$
$E_7$ ( $\text{kJ mol}^{-1}$ )	132.15

Similarly kinetic parameters for the reactions (8), (9) and (12) have been derived from the data collected during 3-NS nitration (see Table 2).

With the same procedure used above, kinetic parameters for the reactions (6), (7) have been estimated by using the data recorded during two experiments of nitration of 2-NP in presence of nitric acid and acetic acid at 303.16 and 313.16 K (see Table 3).

Some examples of comparison of experimental and calculated results are given in Figs. 6 and 7.



Scheme 1. SA Salicylic acid, 5-NS: 5-nitrosalicylic acid, 2-NP: 2-nitrophenol, 3-NS: 3-nitrosalicylic acid, 3,5-DNS: 3,5-dinitrosalicylic acid, 2,4-DNP: 2,4-dinitrophenol, 2,6-DNP: 2,6-dinitrophenol, PA: picric acid, P: decomposition products.

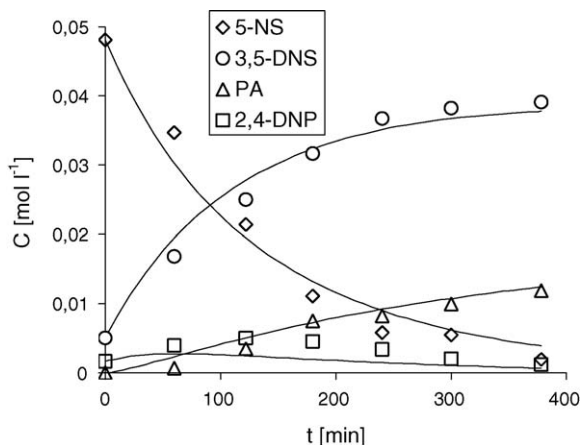


Fig. 6. Experimental and calculated results for nitration of 5-nitrosalicylic acid at 353.16 K.

To validate kinetic data which were collected, two additional nitration runs have been performed on 3-nitrosalicylic and 5-nitrosalicylic acid, respectively at 333.16 and 363.16 K, starting from initial concentrations different from those used in previous experiments (for 5-nitrosalicylic acid:  $C_{5NSA}^{(0)} = 0.09 \text{ mol l}^{-1}$ ,  $C_{HNO_3}^{(0)} = 0.36 \text{ mol l}^{-1}$ ; for 3-nitrosalicylic acid:  $C_{3NSA}^{(0)} = 0.08 \text{ mol l}^{-1}$ ,  $C_{HNO_3}^{(0)} = 0.32 \text{ mol l}^{-1}$ ). Figs. 8 and 9 show the experimental data collected during these two runs in comparison with those predicted by the model using kinetic constants previously estimated. Satisfactory results are obtained in both cases.

To complete the kinetic analysis of the studied system, the process through which PA decomposition develops in the presence of nitric and acetic acid has been also investigated. As previously shown, this decomposition process is characterized by more than one single exothermic event (Fig. 5).

To throw light on the mechanism of decomposition, a second adiabatic run has been carried out, starting from 363.16 K and quenched when the reactor reached 456.16 K. Chemical analysis of the reactor content showed that a reduction of about 30% of PA concentration occurred up to this temperature. Moreover, an adiabatic run performed on the mixture nitric/acetic acid (mol  $(HNO_3)$ /mol  $(CH_3COOH) = 1/15$ ) allowed to observe the occur-

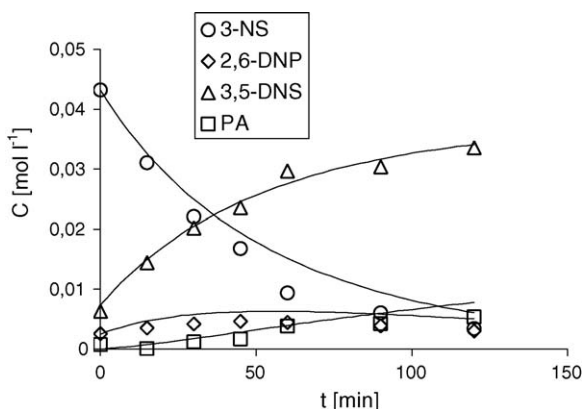


Fig. 7. Experimental and calculated results for nitration of 3-nitrosalicylic acid at 333.16 K.

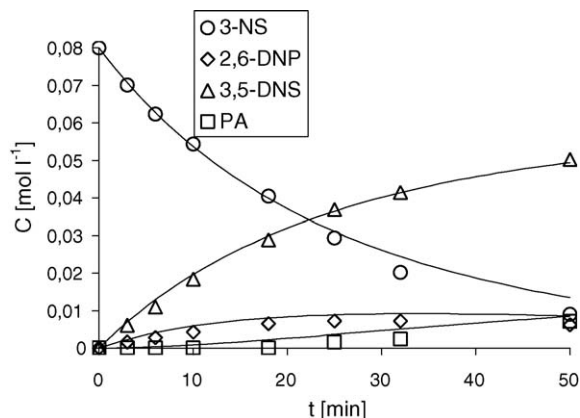


Fig. 8. Experimental and predicted results for nitration of 3-nitrosalicylic acid at 333.16 K.

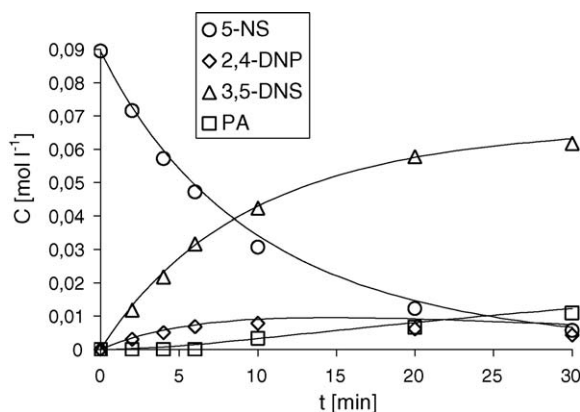


Fig. 9. Experimental and predicted results for nitration of 5-nitrosalicylic acid at 363.16 K.

rence of an exothermic process not previously reported in the literature (see Fig. 10).

Therefore, on the basis of these results, the first exothermic event in Fig. 5 can be ascribed to the contemporary occurrence of two exothermic reactions which have been put forward as:

Reaction 13

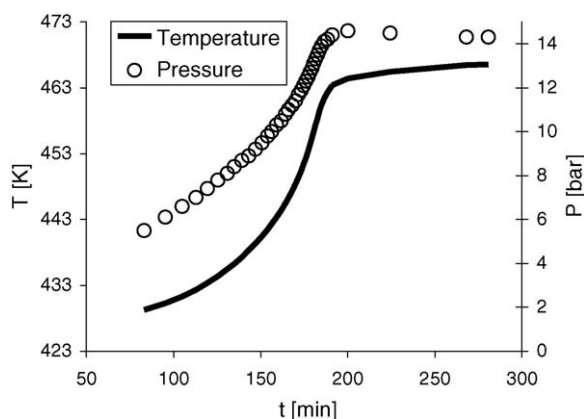
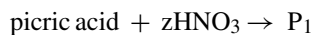
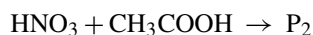


Fig. 10. Adiabatic run on the mixture nitric/acetic acid.

$$\text{rate} = k_{13} \cdot z \cdot C_{\text{HNO}_3}^n C_{\text{PA}} \quad (4)$$

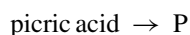
Reaction 14



$$\text{rate} = k_{14} C_{\text{HNO}_3}^m C_{\text{AcOH}} \quad (5)$$

On the other hand, the second event could be ascribed to the thermal decomposition of PA present at the end of the first phase:

Reaction 15



By assuming for this reaction a first-order kinetics:

$$\frac{dC_{\text{PA}}}{dt} = -k_{15}^0 \exp\left(\frac{-E_{15}}{RT}\right) C_{\text{PA}}$$

and making the assumption:

$$\frac{C_{\text{PA}}^0 - C_{\text{PA}}}{C_{\text{PA}}^0} = \frac{T - T_0}{\Delta T_{\text{ad}}}$$

the following equation is obtained:

$$\frac{dT}{dt} = k_{15}^0 \exp\left(\frac{-E_{15}}{RT}\right) (\Delta T_{\text{ad}} - T + T_0) \quad (6)$$

A first attempt to model these data has been done by putting forward a pseudo-first-order kinetics for reaction 15 and above-reported empirical equations for reactions 13 and 14. The following values have been estimated for unknown parameters:  $E_{13} = 84.72 \text{ kJ mol}^{-1}$ ,  $k_{13}^0 = 2.71 \times 10^8 \text{ l}^n \text{ mol}^{-n} \text{ min}^{-1}$ ,  $z = 1.99$ ,  $n = 2$ ,  $E_{14} = 270.92 \text{ kJ mol}^{-1}$ ,  $k_{14}^0 = 1.16 \times 10^{29} \text{ l}^m \text{ mol}^{-m} \text{ min}^{-1}$ ,  $m = 1.7167$ ,  $E_{15} = 270.58 \text{ kJ mol}^{-1}$ ,  $k_{15}^0 = 7.99 \times 10^{19} \text{ min}^{-1}$ .

### 3.2. Modelling of adiabatic runs

A set of mass-balance equations for each species included in Scheme 1 along with a thermal balance equation:

$$\frac{dT}{dt} = \frac{V}{\varphi \cdot m_s \cdot C_p} \sum_{i=1}^{15} r_i (-\Delta H_i) \quad (7)$$

may be written to account for the behaviour of the whole system under adiabatic conditions.

$\Delta H$ 's for all the nitration reactions have been evaluated by means of a group-contributing calculation [15], whereas for the reactions of PA and that between nitric and acetic acid the values derived from calorimetric data have been used. In Fig. 11 the data recorded during an adiabatic run (open circles) performed in a Phi-Tec calorimeter starting from  $C_{\text{SA}}^0 = 0.226 \text{ mol l}^{-1}$ ,  $C_{\text{HNO}_3}^0 = 1.28 \text{ mol l}^{-1}$ ,  $C_{\text{AcOH}}^0 = 16.13 \text{ mol l}^{-1}$ ,  $T_0 = 332.96 \text{ K}$ , are compared with those calculated (continuous line) by means of the developed model.

Although the calculated adiabatic temperature rise well agrees with that of experimentally recorded, it is evident that the model predicts a more reactive system than the real one. A more careful analysis of the results calculated by the model has

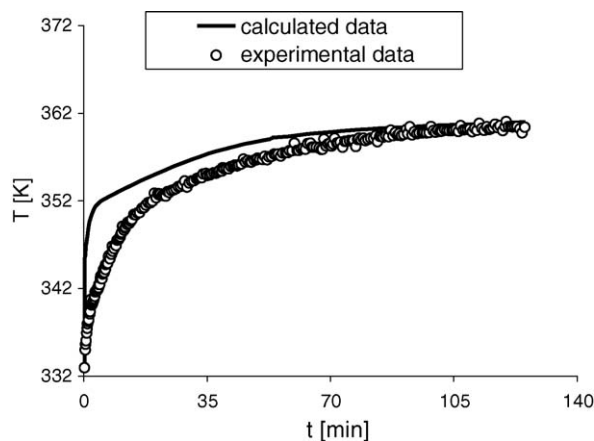


Fig. 11. Adiabatic run on mixture of reaction.

been thus carried out. A possible explanation of the higher reactivity foreseen by the model could be ascribed to the fact that it does not take into account the low solubility of the intermediates which could separate from the bulk solution during the process. This hypothesis is supported by the fact that some samples withdrawn from the reactor during the run showed the presence of suspended materials. Since no data of solubility were available in the literature, some efforts have been done to assess if, for the highest concentration values of 5-NS or 3-NS calculated by the model (at the temperature reached under adiabatic conditions), a homogeneous solution could be expected in the reactor. Unfortunately, solubility data collected in the present investigation indicate that during the process two mononitroderivatives separate from the solution. Therefore, to simulate the system behaviour a more complex model, which takes into account also the presence of a solid phase, is required.

### 4. Conclusions

The behaviour of the system salicylic acid/nitric acid/acetic acid has been studied when a loss of the thermal control happens. In these conditions, the possibility of occurrence of runaway phenomena and thermal explosion has been demonstrated as a result of a process development through a complex reaction network. A complete characterization of this network indicated that polynitration reactions occur when the temperature increases leading to the ultimate formation of PA, a highly reactive species which violently decomposes with the release of great quantity of energy and gaseous species. Kinetic assessments have been performed for each reaction of the network allowing the estimation of its kinetic parameters. Satisfactory results have been obtained in a validation procedure of estimated kinetic parameters, which have been used to simulate the data collected during additional nitration experiments under isothermal conditions. On the other hand, poor results have been observed in attempt to simulate the system behaviour recorded under adiabatic conditions.

Successive assessments revealed that for the concentration of the substrate adopted for the adiabatic run-formed mononitroderivatives are characterized by a poor solubility in the reacting medium for which they separate from the solution during the

process. A more complex model, which takes into account the presence of a second (solid) phase, is thus required to simulate the system behaviour for these conditions. Work is in progress to extend the investigation to kinetically characterize the heterogeneous resulting system and develop a more adequate model.

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