

Batch salicylic acid nitration by nitric acid/acetic acid mixture under isothermal, isoperibolic and adiabatic conditions

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Abstract

Runaway phenomena and thermal explosions can originate during the nitration of salicylic acid by means of a nitric acid/acetic acid mixture when the thermal control is lost, mainly as a result of the formation and thermal decomposition of picric acid. The prediction of the behaviour of this system is thus of great importance in view of possible industrial applications and the need to avoid the occurrence of unwanted dangerous events. During a previous investigation a model was developed to simulate its behaviour when the starting concentration of the substrate is too low, thus, preventing the precipitation of poor soluble intermediates. In this work this model is extended to deal with more concentrated systems even in case of a solid phase separating during the process. To this purpose the previously assessed dependence of the solubility of 3-nitro and 5-nitrosalicylic acids upon temperature and nitric acid concentration is included in the model. It is assumed that when 3-nitro and 5-nitrosalicylic acids are partially suspended in the reacting medium a kinetic regime of "dissolution with reaction" is established; that is, the redissolution of these species is a fast process compared to the successive nitration to give dinitroderivatives. Good results are obtained in the comparison of the experimental data with those calculated both in isoperibolic and adiabatic conditions when the revised model is used.

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1. Introduction

5-Nitrosalicylic acid is an important intermediate for the pharmaceutical industry. The derived amine (mesalazine) has been the elective drug for ulcerative colitis since many years [1]. The production of 5-nitrosalicylic acid is currently obtained through nitration processes of salicylic acid by means of different nitrating systems such as mixed acid (nitric acid/sulphuric acid, molar ratio = 3) or 70% nitric acid solutions [2,3]. Nitric acid/acetic acid mixtures have been demonstrated to be a suitable system for the nitration of salicylic acid showing interesting features in terms of yield and achievement of an easier separation of the product from the solution. In a previous investigation [4] the authors have shown that runaway phenomena can occur during the nitration process of salicylic acid by means of nitric acid/acetic acid mixtures as a result of polynitration reactions

which take place when the thermal control of the process is lost. In particular, successive nitration of 5-nitrosalicylic acid and of its side and by-product (3-nitrosalicylic acid and 2-nitrophenol) leads to the formation of explosive picric acid [5]. The reaction network through which the system evolves has been completely characterized from the thermokinetic point of view, although the previous study [4] has been carried out on diluted systems in which the substrate concentration was even two orders of magnitude lower than that which could be of interest in real applications. Since one of the most interesting features of nitric acid/acetic acid mixtures is represented by the capability of the product 5-nitrosalicylic acid to separate from the reacting solution by precipitating, an extension of the study to assess the behaviour of more concentrated systems is of great importance. Even though previous studies have demonstrated that the mixture of salicylic acid with nitric and acetic acid can give rise to runaway phenomena, no data are available for more concentrated heterogeneous systems. The present work thus aims to upgrade the model developed during previous investigations [4] to make it capable of simulating the nitration process starting

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Nomenclature

c_p	mean specific heat of reacting mixture ($\text{J K}^{-1} \text{g}^{-1}$)
C_j	concentration of j th species (mol l^{-1})
C^*	concentration (mol l^{-1})
E_i	activation energy of i th reaction (kJ mol^{-1})
$\Delta G_{\text{fus},j}^\circ$	Gibbs free energy of fusion for j th species (J g^{-1})
ΔH_i	heat of i th reaction (kJ mol^{-1})
k_i	kinetic constant of i th reaction ($\text{l mol}^{-1} \text{min}^{-1}$)
k_i^0	pre-exponential factor of i th reaction ($\text{l mol}^{-1} \text{min}^{-1}$)
m	sample mass (mixture) (g)
r_i	rate of i th reaction (mol (l t)^{-1})
R	universal constant of gas ($\text{J mol}^{-1} \text{K}^{-1}$)
t	time (min)
T	temperature (K)
T_0	cooling medium temperature (K)
ΔT_{mix}	mixing adiabatic temperature rise (K)
U_a	overall heat transfer coefficient ($\text{J K}^{-1} \text{min}^{-1}$)
V	sample volume (mixture) (l)
x_j	molar fraction of j th species
<i>Greek letters</i>	
γ_j	activity coefficient for j th species
φ	thermal inertia

from more concentrated salicylic acid solutions also when a solid phase is present. This is what is expected to occur in a possible application of the studied system. In fact, at an industrial level only concentrated systems are of interest and the prediction of their behaviour, as a result of different starting conditions, requires a proper model. It is worthwhile stressing that the availability of a reliable model may be of great help in the prevention of the occurrence of hazardous events such as runaway phenomena. This upgrading is done by inserting in the model the solubility correlations, for 5-nitro and 3-nitrosalicylic acid, upon temperature and nitric acid concentrations [6] and choosing a proper regime of “dissolution with reaction”. The resulting model may in principle account for the successive nitration of the two mononitroderivatives even when they are present as solids suspended in the reacting medium. A validation of the revised model is performed by means of the data collected during isoperibolic and adiabatic runs.

2. Experimental

All the isothermal and isoperibolic experiments have been carried out in a jacketed glass magnetically stirred (volume: 8.0×10^{-2} l) reactor. The temperature has been kept at the required value by using a Julabo F32 Refrigerated/Heating circulator (cooling fluid: water). In the nitration runs nitric acid has been added in batch mode to the solution of acetic acid and substrate previously charged in the reactor. The concentration of the involved species in the isothermal and isoperibolic runs

Table 1

Thermal inertia φ and overall heat transfer coefficient for the runs performed in isoperibolic and adiabatic conditions

	φ	U_a ($\text{J K}^{-1} \text{min}^{-1}$)
Isoperibolic runs	1.47	$97.6 + 0.88T$
Adiabatic runs	1.14	0

has been measured by submitting chemically quenched samples (with the addition of a methanol/urea solution) collected during the experiments to HPLC analysis using the Hewlett-Packard model 1100 II, equipped with an UV–VIS detector and a Phenomenex Synergi 4μ polar RP/80A column. The following operating conditions have been adopted: as mobile phase a mixture formed by 80% of a buffer solution (CH_3OH 5% (v/v), H_3PO_4 0.4% (v/v), H_2O 94.6% (v/v)) and 20% (v/v) of acetonitrile, the signals have been acquired at 240, 280, 350 nm, the column temperature has been kept at 298 K and the flow rate set at $10^{-3} \text{l min}^{-1}$. Adiabatic runs have been carried out in a PHITEC calorimeter equipped with a 70 ml glass reactor, used in standard mode. The thermal behaviour of both the reactors adopted has been evaluated by means of a suitable calibration procedure in which a preheated (or cooled) solution has been charged in batch mode and the cooling (or heating) curves have been recorded (Table 1). For all the experiments analytical grade reagents have been used (H_2SO_4 98% (v/v) by Fluka and the remaining ones by Sigma–Aldrich).

3. Results and discussion

3.1. Starting model

As found in the previous investigation the nitration of salicylic acid by means of the acetic/nitric acid system when the thermal control of the reaction is lost develops according to Scheme 1.

It is evident that the lost of control of the nitrating system may result in the development of a complex reaction network through which it is possible to explain the formation and the successive decomposition of picric acid.

On the basis of this reaction network a suitable mathematical model has been developed to simulate the system behaviour when all the species are soluble in the reacting medium (homogeneous system). The model has the form of a set of differential equations which describes the mass balance for each species of the network and (for adiabatic runs) the overall thermal balance:

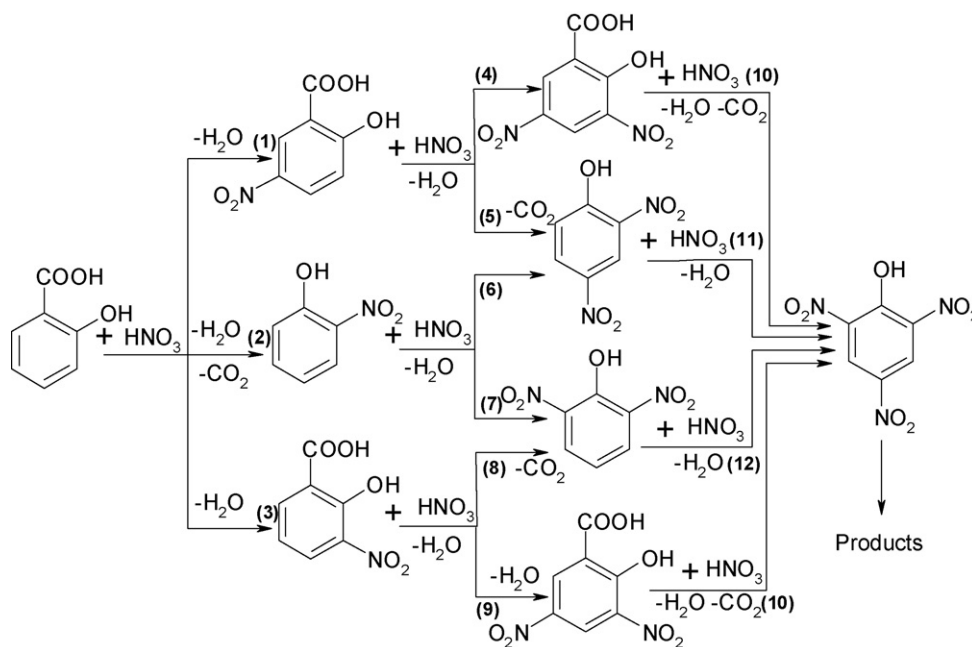
$$\frac{dC_j}{dt} = \sum r_i \quad (1)$$

$$(mc_p) \frac{\varphi}{V} \frac{dT}{dt} = \sum r_i (-\Delta H_i) \quad (2)$$

where r_i is the reactions in which the j th component is involved according to Scheme 1 and takes the form:

$$r_i = -k_i^0 \exp\left(-\frac{E_i}{RT}\right) C_j C_{\text{HNO}_3} \quad (3)$$

The results collected during the previous investigation enabled us to assess the values k_i^0 's and E_i 's reported in Table 2.



Scheme 1.

ΔH_i 's have been estimated by means of a group-contributing calculation [7].

3.2. Validation of the starting model

Initial runs with a salicylic acid concentration up to 18 times higher than those used in previous studies have revealed that the system was still homogeneous and that the above described model [4] well predicts its behaviours (data not shown). Good results have been obtained also in the modelling of isothermal nitration processes of salicylic acid (Fig. 1), 5-nitrosalicylic acid and 3-nitrosalicylic acid, starting from initial concentrations equal to 0.085, 0.09 and 0.08 mol l⁻¹, respectively (data not shown).

For further increases of the substrate concentration the cooling system failed to completely remove the power generated by the reaction. Therefore, to model the behaviour of the system, it has been necessary to add a thermal balance Eq. (4) to the

Table 2

Pre-exponential factors k_0 , activation energies E and heats of reaction ΔH for the reactions reported in Scheme 1

Reaction's n	k_0 (1 mol ⁻¹ min ⁻¹)	E (kJ mol ⁻¹)	ΔH (kJ mol ⁻¹)
1	$(2.53 \pm 0.10) \times 10^{+21}$	124.37 ± 0.17	-145.90
2	$(3.22 \pm 0.72) \times 10^{+20}$	124.66 ± 0.42	-115.45
3	$(8.28 \pm 0.66) \times 10^{+20}$	123.90 ± 0.17	-145.90
4	$(1.03 \pm 0.06) \times 10^{+20}$	145.38 ± 0.16	-149.89
5	$(9.73 \pm 1.49) \times 10^{+17}$	136.21 ± 0.46	-115.45
6	$(1.16 \pm 0.10) \times 10^{+20}$	127.29 ± 0.23	-145.90
7	$(5.89 \pm 0.62) \times 10^{+20}$	132.15 ± 0.27	-145.90
8	$(3.95 \pm 0.55) \times 10^{+21}$	147.72 ± 0.16	-115.45
9	$(1.79 \pm 0.10) \times 10^{+23}$	155.30 ± 0.38	-149.89
10	$(1.00 \pm 0.18) \times 10^{+18}$	145.47 ± 0.32	-115.45
11	$(4.62 \pm 0.12) \times 10^{+19}$	142.45 ± 0.76	-149.89
12	$(1.68 \pm 0.38) \times 10^{+19}$	129.93 ± 0.63	-149.89

material balances (1):

$$(mc_p)\varphi \frac{dT}{dt} = V \sum r_i(-\Delta H_i) - U_a(T - T_0) \quad (4)$$

$$\varphi = \frac{m_{RC}c_{pR} + mc_p}{mc_p} \quad (5)$$

where V is the volume of the reactor, φ the thermal inertia, m the sample mass, c_p the mean specific heat of the reacting mixture, $(m_{RC}c_{pR})$ the thermal mass of the reactor, ΔH_i 's the heats of reaction and U_a is the overall heat transfer coefficient.

In this way, two isoperibolic nitration runs with 5-nitrosalicylic acid and 3-nitrosalicylic acid respectively have been modelled starting from an initial concentration ten times higher than that used to develop the previous model (Table 3) (Figs. 2–5).

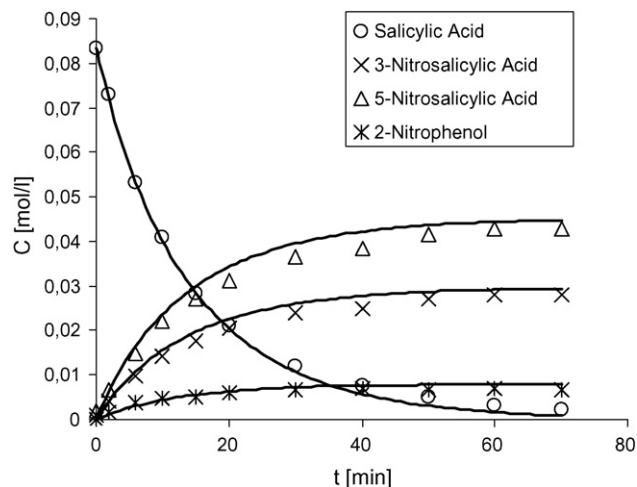


Fig. 1. Isothermal nitration of salicylic acid at 293.16 K—symbols: experimental data; curves: data calculated by the model.

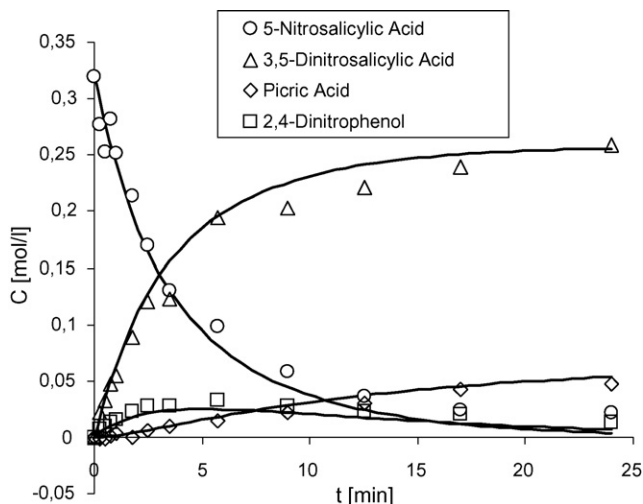


Fig. 2. Concentration profiles (isoperibolic nitration of 5-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

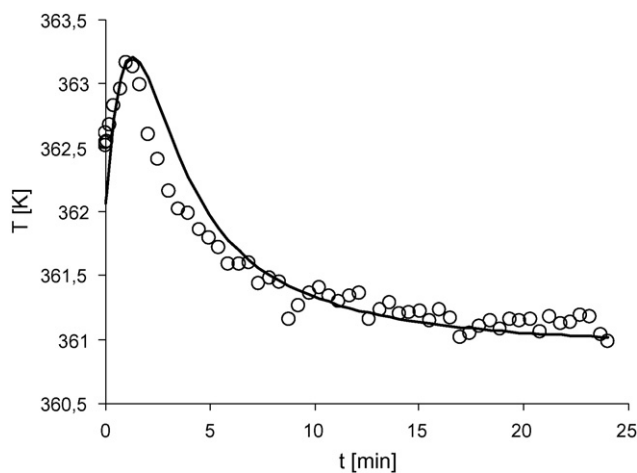


Fig. 3. Temperature profile (isoperibolic nitration of 5-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

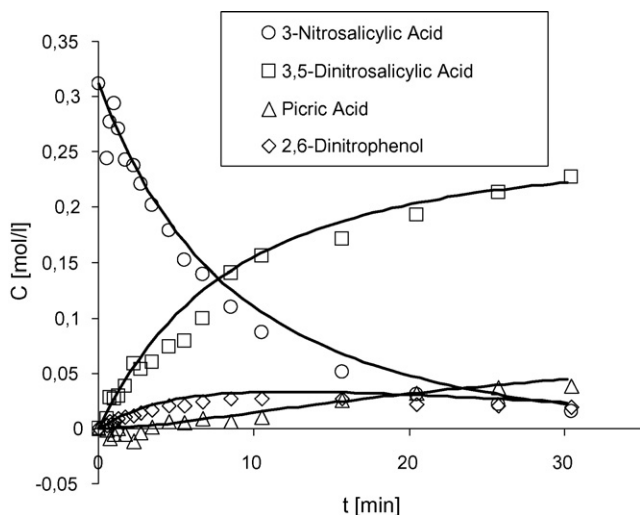


Fig. 4. Concentration profiles (isoperibolic nitration of 3-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

Table 3
Operating conditions adopted in the isoperibolic nitrations runs

Substrate	C_{sub}^0 (mol l ⁻¹)	$n_{\text{sub}}/n_{\text{HNO}_3}$	V_{AcOH} (ml)	$T_{\text{cooling fluid}}$ (K)
5-NSA	0.325	1/4	40	361.0
3-NSA	0.31	1/4	40	330.5

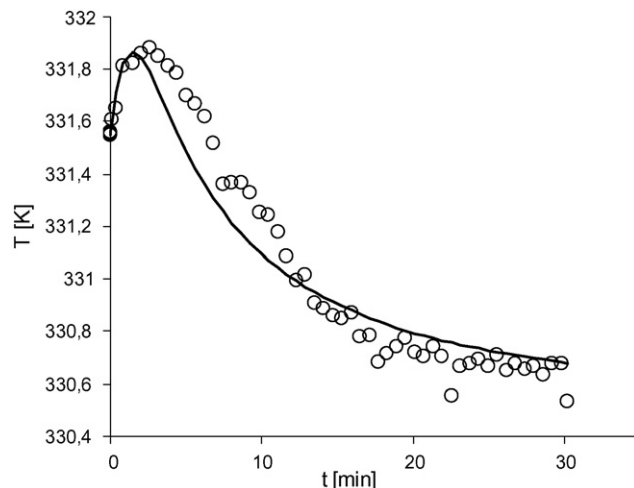


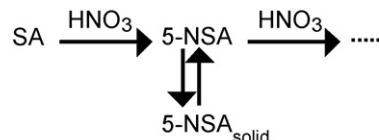
Fig. 5. Temperature profile (isoperibolic nitration of 3-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

Preliminary experiments starting from higher salicylic acid concentrations in reacting solutions, in which $n_{\text{SA}}/n_{\text{HNO}_3} = 1/5$, at a temperature in the range 288–308 K, have indicated the precipitation of the reaction products. In all the cases the solid phase obtained turned out to be a mixture of 5-nitrosalicylic and 3-nitrosalicylic acids.

Moreover, successive calorimetric runs, under adiabatic conditions, revealed that the precipitation of the two mononitroderivatives does not completely prevent their further nitration, thus, making still possible the occurrence of runaway phenomena whenever the thermal control of the reactor is lost (data not shown).

3.3. Upgraded model

A modified model is thus required to simulate the behaviour of this system in which some of the intermediates separate from the reacting solution. In fact, it is clear that to model the successive nitration of poorly soluble intermediates the regime of “dissolution with reaction” needs to be established; that is, the solid 5-nitrosalicylic acid which precipitates after its formation from salicylic acid needs to redissolve again to react with nitric acid (Scheme 2).



Scheme 2. SA: salicylic acid; 5-NSA: 5-nitrosalicylic acid.

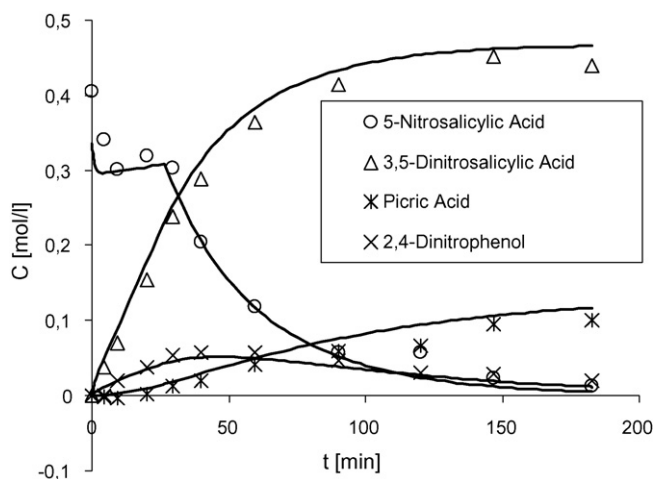


Fig. 6. Concentration profiles (isoperibolic heterogeneous nitration of 5-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

In principle, when one compares the rate of the solid dissolution with that of nitration no indications are available “a priori” to establish which of the two steps is rate-controlling. A practical approach consists in developing a suitable model according to the hypothesis on which step is rate-controlling and trying to validate it by means of experimental data. In the present case it has firstly put forward that the dissolution of the solid could be considered fast compared to the successive nitration step. In this perspective, the concentration of 5-nitrosalicylic acid and 3-nitrosalicylic acid in the solution kept at the solubility value until the solids were present. Fig. 6 shows the results collected during a nitration run on saturated 5-nitrosalicylic acid at a starting solution temperature (after the mixing) of 349.9 K and a cooling medium temperature of 343.2 K (Table 4). As expected, for the first 29.7 min, the 5-nitrosalicylic acid concentration keeps almost constant and equal to the solubility value. As it can be seen from Fig. 7, this experiment is not isothermal since a great heat of dissolution was almost instantaneously generated when nitric acid was fed to the reactor containing the solution of 5-nitrosalicylic acid in acetic acid.

The recorded temperature profile (Fig. 7, open circles) was thus the result of the heat generated by the dissolution of nitric acid, the heat of nitration reaction and that exchanged with the cooling medium at a constant temperature of 343.2 K.

For the substrate a fictitious concentration, C^* – as it was completely soluble – has been initially considered:

$$\frac{dC^*}{dt} = -k_{5\text{-NSA}}[\text{HNO}_3]S_{5\text{-NSA}} \quad (6a)$$

where $S_{5\text{-NSA}}$ was the solubility of 5-nitrosalicylic acid at the actual temperature and the nitric acid concentration calculated

Table 4

Operating conditions adopted in the isoperibolic heterogeneous nitration of 5-nitrosalicylic acid

$m_{5\text{-NSA}}^0$ (g)	4.944
$n_{5\text{-NSA}}/n_{\text{HNO}_3}$	1/4
V_{AcOH} (ml)	40
$T_{\text{cooling fluid}}$ (K)	343.16

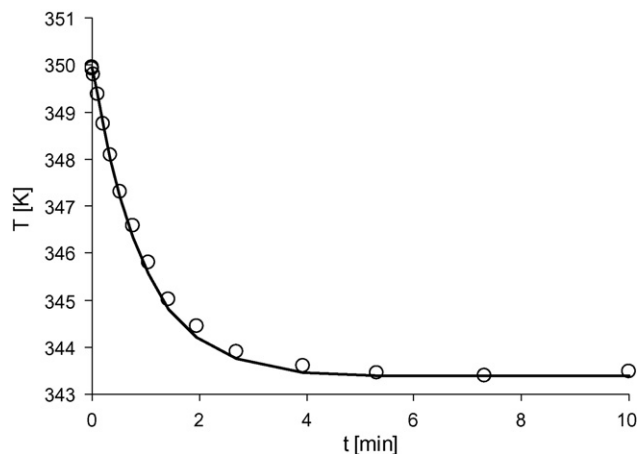


Fig. 7. Temperature profile (isoperibolic heterogeneous nitration of 5-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

by the model by means of the following relationship [8]:

$$\ln x_{5\text{-NSA}} = \frac{-\Delta G_{\text{fus}}^{\circ}}{RT} - (A + Bx_{\text{nitric acid}}) \quad (6b)$$

in which the values for the parameters, obtained in a previous investigation [6], are reported in Table 5.

When the concentration C^* became equal or lower than $S_{5\text{-NSA}}$ Eq. (6a) was replaced by

$$\frac{dC^*}{dt} = -k_{5\text{-NSA}}[\text{HNO}_3]C^* \quad (7a)$$

A numerical integration of the set of differential equations of the model by means of the following initial conditions

$$t = 0 \Rightarrow C_j = \begin{cases} C^* = 0.6 \text{ mol/l} & \text{for } j = 5\text{-NSA,} \\ 0 & \text{for } j = \text{other species,} \end{cases}$$

$$T = T_0 + \Delta T_{\text{mix}}$$

(where ΔT_{mix} is the instantaneous *quasi-adiabatic* temperature increase during the dissolution of 0.108 mol of nitric acid in 0.0451 of acetic acid, T_0 being the cooling medium temperature), enabled us to calculate the concentration profile of all the species shown in Fig. 6 (continuous lines). A good agreement was observed among the experimental data and those calculated by the model. It is worthwhile stressing that the kinetic parameters used in the model were those previously estimated [4] and reported in Table 1 without any adjustment. Similar results have been found by submitting to nitration (for initial conditions see Table 6) 3-nitrosalicylic acid (Figs. 8 and 9).

Table 5

Gibbs free energy of fusion $\Delta G_{\text{fus},5\text{-NSA}}^{\circ}$ and dimensionless parameters, A and B, in Eq. (6b)

$\Delta G_{\text{fus},5\text{-NSA}}^{\circ}$ (J g^{-1})	19898.9 ± 6.3
A	-4.344 ± 0.0045
B	3.845 ± 0.0815

Table 6
Operating conditions adopted in the isoperibolic heterogeneous nitration of 3-nitrosalicylic acid

$m_{3\text{-NSA}}^0$ (g)	4.834
$n_{3\text{-NSA}}/n_{\text{HNO}_3}$	1/4
V_{AcOH} (ml)	40
$T_{\text{cooling fluid}}$ (K)	318.2

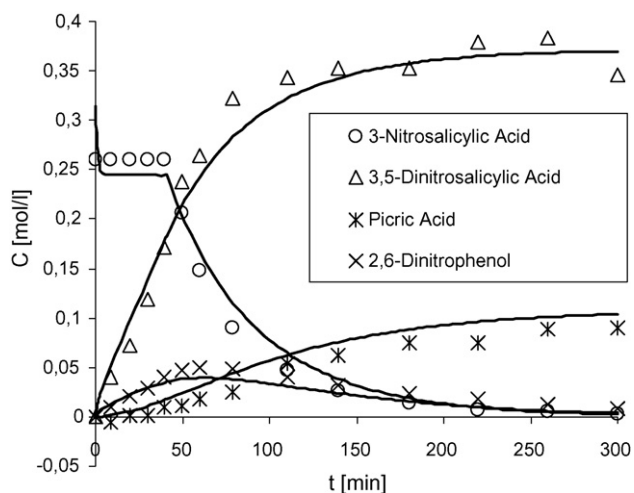


Fig. 8. Concentration profiles (isoperibolic heterogeneous nitration of 3-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

In this case, for the solubility of 3-nitrosalicylic acid the following relationship has been used:

$$\ln x_{3\text{-NSA}} = \frac{-\Delta G_{\text{fus}}^{\circ}}{RT} - \ln \gamma_{3\text{-NSA}} \quad (7b)$$

in which the values for the parameters, obtained in a previous investigation [6], are reported in Table 7.

Afterwards, the investigations have been extended to the modelling of a complete run starting from salicylic acid during which a part of 5-nitrosalicylic acid and 3-nitrosalicylic acid pre-

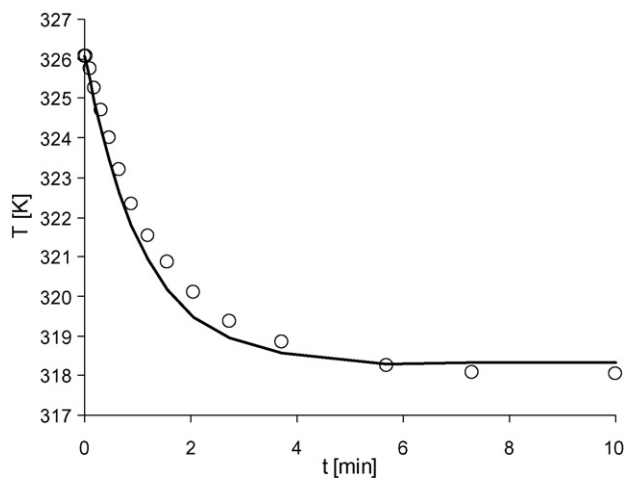


Fig. 9. Temperature profile (isoperibolic heterogeneous nitration of 3-nitrosalicylic acid)—symbols: experimental data; curves: data calculated by the model.

Table 7
Gibbs free energy of fusion $\Delta G_{\text{fus},3\text{-NSA}}^{\circ}$ and logarithm of the activity coefficient $\ln \gamma_{3\text{-NSA}}$ in Eq. (7b)

$\Delta G_{\text{fus},3\text{-NSA}}^{\circ}$ (J g^{-1})	26362.8 ± 23
$\ln \gamma_{3\text{-NSA}}$	-6.719 ± 0.0185

Table 8

C_{AS} (mol l^{-1})	0.45
$n_{\text{HNO}_3}/n_{\text{AS}}$	5
V_{AcOH} (ml)	40
T_0 (K)	293.16

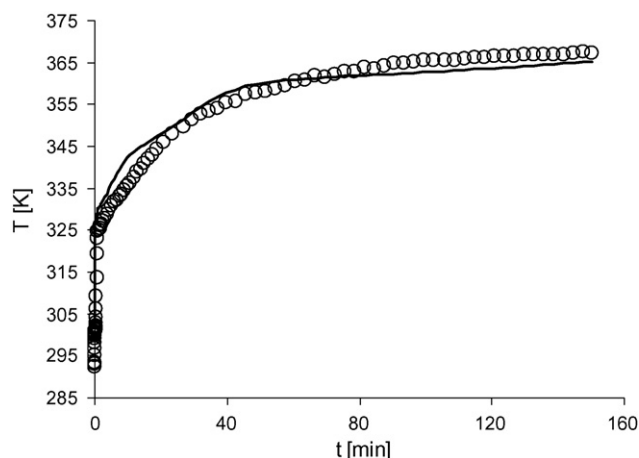


Fig. 10. Adiabatic run on the mixture nitric acid/acetic acid/salicylic acid.

cipitates (Table 8). In Fig. 10, the temperature profile recorded during one of these runs under adiabatic conditions (open circles) is compared with that calculated by the model (continuous lines).

A good agreement is observed in this case also, thus, confirming the capability of the model to simulate the system behaviour.

4. Conclusions

The nitration of salicylic acid by means of nitric and acetic acid mixture has been studied under isothermal, isoperibolic and adiabatic conditions starting from initial concentrations higher than those adopted in previous investigations. The model previously developed to simulate the nitrating homogeneous system behaviour has been upgraded to take into account the possibility that the two mononitroderivatives may be partially present as solid suspended on the reacting solution. It has been assessed that the successive nitration of these intermediates when they partially separate from the solution develops under a kinetic regime of dissolution with reaction. Good results have been obtained in the comparison with the experimental data and those calculated by means of this model in which the kinetic parameters estimated in previous studies have been used.

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