

(S)-Nitroxycarnitine nitrate production from (S)-carnitine by using acetic anhydride/nitric acid/acetic acid mixtures: safety assessment

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Abstract

The present work aims at assessing both thermodynamic and kinetic parameters of the esterification process of the (S)-carnitine, using calorimetric techniques. The use of the system acetic anhydride/nitric acid/acetic acid as esterifying agent and the explosive behaviour of nitric esters lead to safety considerations that have been investigated by hypothesizing some common process deviations. In particular, it has been investigated in adiabatic conditions both the batch addition of acetic anhydride and the effect of an initial temperature higher than those required by the process.

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1. Introduction

During last years, a growing interest has been recorded in developing industrial processes [1] for the (R)-carnitine production starting from the corresponding S enantiomer, a low cost raw material which is currently obtained as a side-product in the resolution of racemic mixtures of (R,S)-carnitine. Quoted processes are not free of drawbacks consisting mainly in the formation of large amounts of by-products and in the multiple steps production sequences.

A new process has been recently patented [2], in which the inversion of the S form is realized through the preparation of the corresponding carnitine nitric ester, with the same absolute configuration of the starting molecule (S), which gives rise, in alkaline medium, to the formation of (R)-carnitine with high yield (80%).

The success of this process seems to rely on the adoption of acetic anhydride/nitric acid/acetic acid as “esterifying” system instead of the classic mixed acid solutions. In fact, the milder conditions ensured by the former system seem to favour the obtainment of a nitroxycarnitine derivative at high yield, with a reduced occurrence of secondary reactions.

Although not completely elucidated, the mechanism of reaction through which the system $\text{Ac}_2\text{O}/\text{HNO}_3$ works is generally reported to involve the formation of acetyl nitrate as intermediate [3]. This species is known to undergo violent decomposition on heating [4], with spontaneous explosion of its solutions being reported also at ambient temperature during the storage [5].

The results of a recent investigation on the thermal behaviour of $\text{Ac}_2\text{O}/\text{HNO}_3$ mixtures indicate that this system can give rise to violent exothermic decomposition with the development of huge amount of gases with the released energy and heat rates strictly depending on the ratio (mol Ac_2O)/(mol HNO_3) [6].

The present work aims therefore at studying the safety aspects of the process for the preparation of nitrox-

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Nomenclature	
A	pre-exponential factor (rate expression depending)
E	activation energy (kJ mol^{-1})
R	universal constant of gas ($\text{J mol}^{-1} \text{K}^{-1}$)
t	time (min)
$[B]$ or	concentration of B ($\text{mol (dm}^{-3})$)
C_B	
n_B	moles of B (mol)
m_S	sample mass (mixture) (g)
V_S or V	sample volume (mixture) (dm^3)
$\bar{C}_{p,S}$	mean specific heat of reacting mixture ($\text{J K}^{-1} \text{g}^{-1}$)
MC_V	thermal capacity of the reactor (J K^{-1})
UA	global heat transfer coefficient ($\text{J K}^{-1} \text{min}^{-1}$)
Φ	thermal inertia (dimensionless)
ΔH_i	heat of reaction (kJ mol^{-1})
T	temperature (K)
T_E	external reactor temperature (K)
T_O	initial temperature (K)
ΔT_{ad}	adiabatic temperature rise (K)
AcOH	acetic acid
Ac ₂ O	acetic anhydride
S	substrate [(S)-carnitine–inner salt]
NC	(S)-nitroxycarnitine nitrate
x_B	molar fraction of component B (dimensionless)

ycarnitine nitrate (NC) ester by means of the system acetic anhydride/nitric acid/acetic acid with special attention devoted to the choice of the best operating conditions to counteract the effects of easily foreseeable process deviations.

2. Experimental

All experiments were performed using calorimetric devices. For scannig runs, a PC-Combilab (by Systag) equipped with a Radex oven [7] was used. In all the runs stainless steel reactors (100 bar) were used and the following operating parameters adopted: initial temperature 293 K, heat rate: 1.5 K min^{-1} . Adiabatic experiments were carried out either by means of a Sikarex oven (by Systag) [8,9] equipped with a mechanical stirring device running at 150 min^{-1} or an accelerating rate calorimeter (ARC) calorimeter (by Columbia Scientific Industries) [10]. The ARC runs were performed using stainless steel bombs with the following set parameters: wait time 10 min, heat step temperature 10 K, self-heating rate threshold value 0.02 K min^{-1} .

For sub-ambient temperature experiments, a quasi-adiabatic device was developed and characterized. The calorimeter (see Fig. 1) was built by wrapping a glass tube

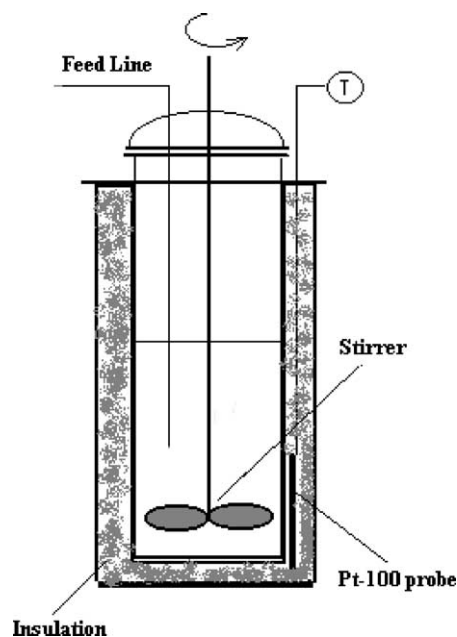


Fig. 1. Schematic representation of the quasi-adiabatic calorimeter used for the sub-ambient experiments.

with kaowool insulation (total volume: $9.5 \times 10^{-2} \text{ dm}^3$; glass tube i.d.: $2.2 \times 10^{-2} \text{ m}$; mean insulation thickness: $1.0 \times 10^{-2} \text{ m}$).

It was equipped with a feed line, a mechanical stirring device (a glass shaft coupled to an electric motor with stirring speed of 150 min^{-1} with a teflon impeller on it) and a Pt-100 probe (placed on the external side of the glass tube). The temperature signal was acquired using the same PC-Combilab system used to run the Radex and Sikarex ovens. The heat exchange coefficient (UA) and the vessel thermal capacity (MC_V) were estimated by means of a calibration procedure in which the reactor temperature was recorded immediately after the injection in the vessel of a known volume of pre-heated water and during the cooling. In particular for the evaluation of the term UA the following energy balance equation was used:

$$(m_{\text{H}_2\text{O}} \times c_{p,\text{H}_2\text{O}} + MC_V) \frac{dT}{dt} = -UA(T - T_E) \quad (\text{A})$$

where $m_{\text{H}_2\text{O}}$ is the mass of injected water, $c_{p,\text{H}_2\text{O}} = 4.186 \text{ J g}^{-1} \text{ K}^{-1}$ its specific heat, and T_E the external temperature.

A similar procedure was adopted to identify the MC_V of the Sikarex reactor (in this case $UA = 0$) for the estimation of the thermal inertia.

3. Results and discussion

3.1. Basic thermokinetic investigations

As reported in the patent [2], the preparation of 3-nitroxycarnitine nitrate (II) can be performed by mixing

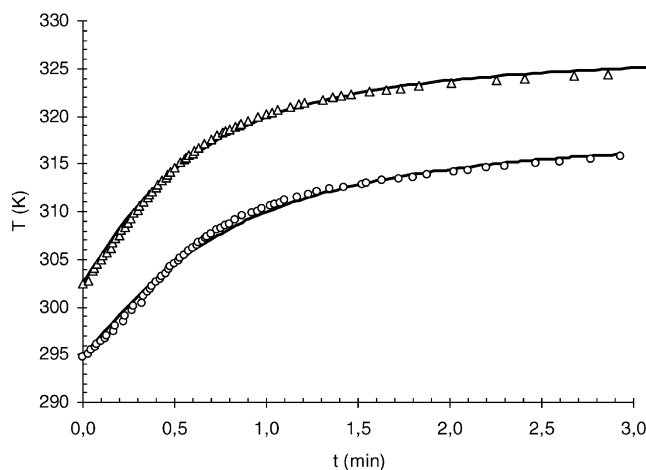
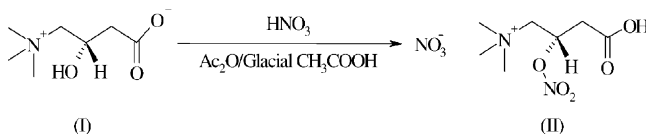


Fig. 2. Thermograms obtained in the Sikarex runs performed on the systems: Run no. 1 (Δ) and 2 (\circ) of Table 1. Solid lines: calculated curves.

0.62 mol of (*S*)-carnitine inner salt (I) in glacial CH_3COOH with 1.86 mol of 100% HNO_3 and 0.74 mol of acetic anhydride at 283 K.



Calorimetric measurements performed under adiabatic conditions in batch mode (Fig. 2), using the Sikarex oven and the experimental conditions reported on Table 1, indicate that the conversion of carnitine into its nitric ester proceeds through an exothermic reaction. The experiments were realized dissolving the substrate in glacial acetic acid (AcOH) previously charged in the reactor; afterwards the red fuming nitric acid (100%) was introduced slowly (since the salification of the (*S*)-carnitine inner salt is very exothermic), and cooled near the desired temperature. The reactor was then inserted in the Sikarex oven and brought to the initial temperature of the experiment. When the starting conditions were achieved, acetic anhydride (Ac_2O) previously charged in a syringe and kept at the same temperature of the reactor was rapidly injected in it.

From the data of Fig. 2, the heat of reaction is calculated:

$$\Phi m_S \bar{C}_{P,S} \Delta T_{\text{ad}} = (-\Delta H) n_C$$

where m_S is the total mass of the reacting mixture, $\bar{C}_{P,S} = 2.1 \text{ J g}^{-1} \text{ K}^{-1}$ its specific average heat, n_C the initial moles of (*S*)-carnitine inner salt, ΔH the enthalpy of reaction, and

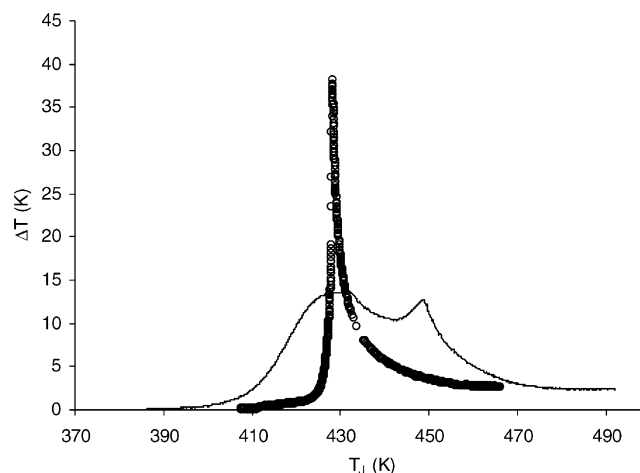


Fig. 3. Temperature difference ΔT (reactor-oven) vs. oven temperature (T_j): (\circ) pure nitroxycarnitine nitrate, (—) sample withdrawn at the end of the run no. 1 of Table 1.

$\Phi = 1 + MC_V/m_S \bar{C}_{P,S}$ the thermal inertia.

$\Delta H = -43.9 \text{ kJ mol}^{-1}$ of (*S*)-carnitine.

Since nitric esters are reported in the literature as energetic materials capable of violently decomposing [11], a set of experiments was performed to assess the thermal stability both of nitroxycarnitine and the final solutions in the reactor. In Fig. 3, the results of two scanning runs carried out on a pure nitroxycarnitine sample and on a solution collected at the end of an esterification run are shown.

From these thermograms, it is evident that the stability of the studied nitric ester is affected by the presence of the excess of nitric acid and/or acetic acid in the final mixture. In fact a marked decrease of the onset temperature, T_S , is observed between the two runs.

An attempt to better characterize the thermal behaviour of the final mixture which is relevant to the safety of the process has been also tried. To this purpose further investigations have been carried out by means of adiabatic calorimetry.

In Fig. 4, the results of an ARC run on a mixture at the end of the esterification are reported (run no. 1, in Table 1).

The above results have been confirmed also by considering two mixtures of nitroxycarnitine nitrate dissolved in pure glacial acetic acid. In Fig. 5 are reported the thermograms coming from two ARC runs carried out on the systems shown in Table 2.

Self-heat rate curves shown in Fig. 6 indicate that (*S*)-nitroxycarnitine nitrate decomposition is a complex process with the presence of different consecutive reaction steps.

Table 1
Experimental conditions used for the Sikarex runs reported in Fig. 2

Run	m_S (g)	V_S (dm^3)	Φ	n_{AcOH} (moles)	C_{AcOH} (moles (dm^3) $^{-1}$)	n_{HNO_3} (moles)	C_{HNO_3} (moles (dm^3) $^{-1}$)	$n_{\text{Ac}_2\text{O}}$ (moles)	$C_{\text{Ac}_2\text{O}}$ (moles (dm^3) $^{-1}$)	$n_{(S)\text{-carnitine}}$ (moles)	$C_{(S)\text{-carnitine}}$ (moles (dm^3) $^{-1}$)
1	15.9	14.0×10^{-2}	1.41	7.00×10^{-2}	5.0	4.95×10^{-2}	3.5	2.96×10^{-2}	2.1	2.49×10^{-2}	1.8
2	16.1	14.1×10^{-2}	1.41	7.35×10^{-2}	5.3	4.96×10^{-2}	3.5	2.96×10^{-2}	2.1	2.48×10^{-2}	1.8

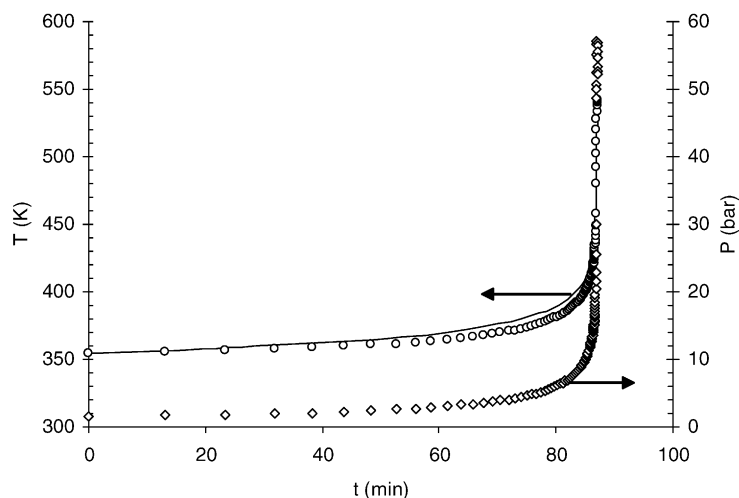


Fig. 4. ARC run performed on a sample withdrawn at the end of the run no. 1 of Table 1: (○) temperature, (◇) pressure.

Table 2

Experimental conditions used for the ARC runs reported in Fig. 5

Run	Φ	Sample mass (g)	m_{AcOH} (g)	m_{NC} (g)	n_{NC} (mol)	C_{NC} (mol (dm) ⁻³)
1	4.23	0.9362	0.5354	0.4008	1.49×10^{-3}	1.9
2	4.22	0.9370	0.6358	0.3012	1.12×10^{-3}	1.4

Moreover, it is worthy to stress that although the runs whose results are shown in Figs. 4 and 5 refer to different systems (with and without free nitric acid excess) measured heats of reactions are practically the same. By considering all the runs, a mean value of the heat of decomposition of $588.8 \pm 11.6 \text{ kJ mol}^{-1}$ of NC was then calculated.

3.2. Process deviations

Although for an industrial process a wide range of deviations can occur, the development under adiabatic condi-

tions is certainly one of the most frequent and important. According to the above-reported results, it can be stated that in adiabatic conditions, the primary reaction (esterification) and the secondary reaction (decomposition of the final mixture) of the studied process could combine to give a thermal explosion depending on the starting esterification temperature. In fact, at the adopted experimental conditions for the adiabatic ARC run performed on the sample withdrawn at the end of esterification step ($\Phi = 2.23$, $V_S/V_R = 0.15$ with V_S : sample volume, $V_R = 8.0 \times 10^{-3} \text{ dm}^3$: reactor volume) an exothermic decomposition is observed starting at $T_O = 354.5 \text{ K}$ with a $\Delta T_{\text{ad}} = 187.7 \text{ K}$ and a final pressure $P_F = 57.1 \text{ bar}$. For an extrapolation to real process conditions, a correction of T_O at $\Phi = 1.0$ is done by means of the following formula:

$$\frac{1}{T_{O2}} = \frac{1}{T_{O1}} + \frac{R}{E} \ln \left(\frac{\Phi_1}{\Phi_2} \right)$$

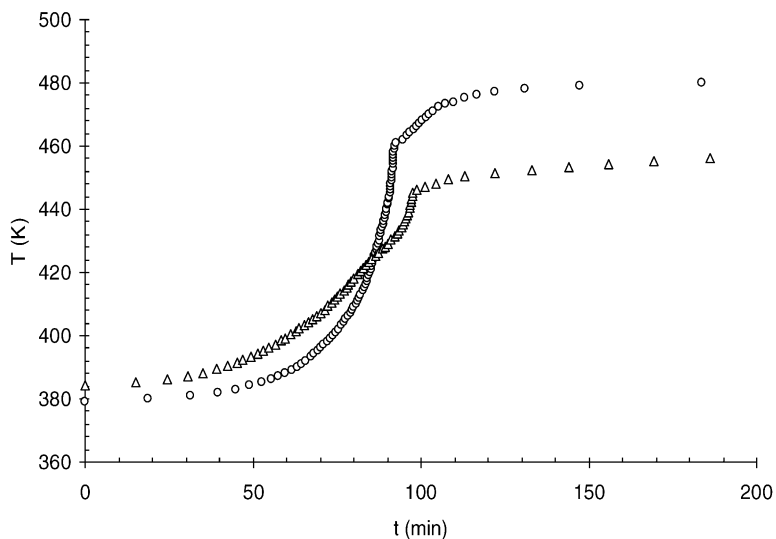


Fig. 5. Temperature vs. time obtained in adiabatic conditions during the ARC runs carried out on the systems reported in Table 2. Run no. 1 (○), and 2 (△)

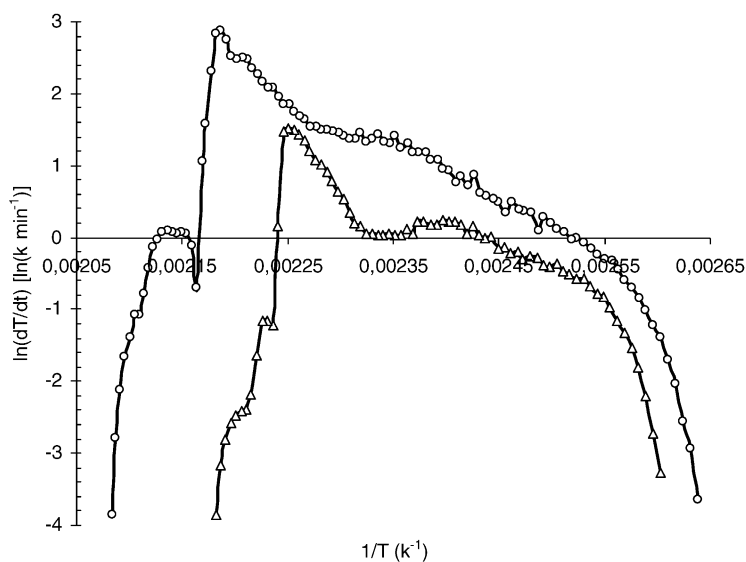


Fig. 6. Self heat rate vs. $1/T$ for the systems reported in Table 2. Run no. 1 (\circ), and 2 (Δ).

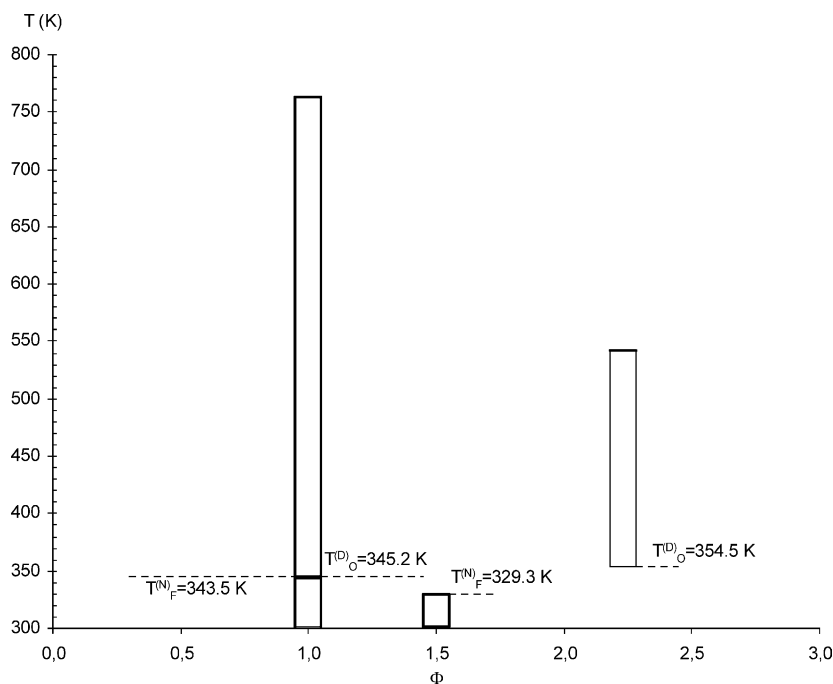


Fig. 7. Temperature changes due the effect of thermal inertia. $T_F^{(N)}$: final nitration temperature (Sikarex); $T_O^{(D)}$: Initial decomposition temperature (ARC) of the final mixture collected at the end of the run no. 1 in Table 1.

In which $T_{O1} = 354.5$ K, $\Phi_1 = 2.23$, $\Phi_2 = 1.0$ and the activation energy $E = 97.5$ kJ mol⁻¹ is derived from the slope of the plot of $\ln(dT/dt) = f(1/T)$.

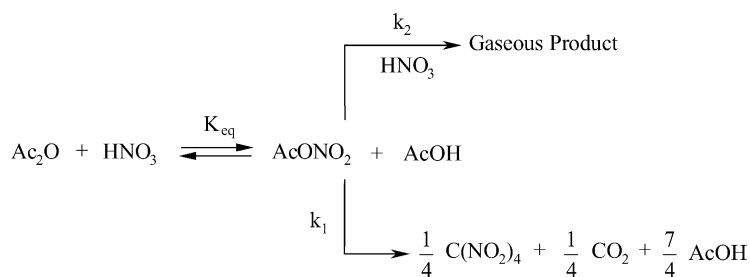
From these calculations, a value for the onset temperature of 345.3 K is obtained thus indicating a possible overlapping of the esterification and the thermal decomposition of the final mixture (Fig. 7).

Accident data-bank records indicate that often industrial explosions result from the simultaneous occurrence of more than one process deviation. In the following analysis it will be thus always considered the development under adiabatic

Table 3
Conditions used for thermograms reported in Fig. 8

Run	$n^{\circ}\text{HNO}_3$ (mol)	$n^{\circ}\text{Ac}_2\text{O}$ (mol)	$R =$ $n^{\circ}\text{Ac}_2\text{O}/n^{\circ}\text{HNO}_3$	$n^{\circ}\text{AcOH}$ (mol)	T_O (K)
1	0.18	0.09	0.5	0.40	323.1
2	0.22	0.09	0.4	0.40	323.8
3	0.22	0.09	0.4	0.40	308.9

conditions as a basic primary deviation to which others can combine. It can be, for example, taken into account the case in which, when no cooling power is available, an incorrect charge of the reagents occurs. The complete absence of car-



Scheme 1.

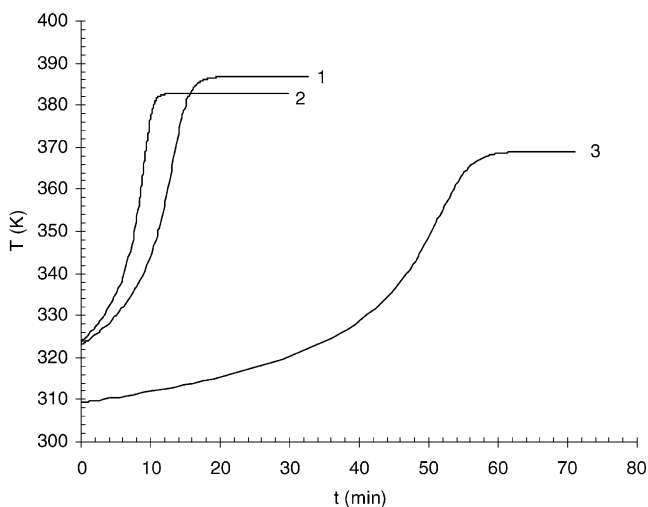


Fig. 8. Calculated temperature profiles for the decomposition of acetyl nitrate adopting the conditions reported in Table 3.

nitine in the reactor is a limiting example of this type of deviation. In these conditions, the relevant process is represented by the decomposition of the intermediate acetylnitrate, formed by mixing acetic anhydride and nitric acid. Accord-

Table 4

Experimental conditions used to simulate the overcharging of acetic anhydride ($\Phi = 1.4$)

Species	m (g)	n (mol)	C (mol (dm) ⁻³)
AcOH	4.410	7.35×10^{-2}	5.3
HNO ₃	3.133	4.97×10^{-2}	3.5
(Ac) ₂ O	4.536	4.45×10^{-2}	3.2
(S)-Carnitine	4.002	2.48×10^{-2}	1.8

ing to Andreozzi et al. [6], this species decomposes through a complex reaction network which could be lumped into two main reactions (Scheme 1), which are both responsible for the overpressurization of the reactor. Pressure and temperature profile during acetyl nitrate decomposition are strictly dependent on the initial molar ratio, acetic anhydride/nitric acid [6]. For example, the temperature profiles referring to the experimental condition reported in Table 3 are shown in Fig. 8.

Another example of uncorrect reagent charge is represented by an overcharging of acetic anhydride. In Fig. 9 are shown the results obtained in a Sikarex Run by adopting the conditions reported in Table 4.

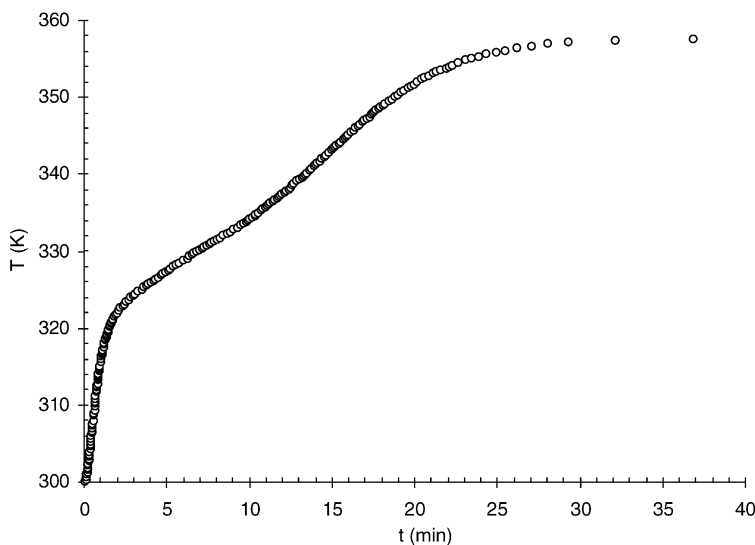


Fig. 9. Experimental data points collected during the Sikarex Run reported in Table 4.

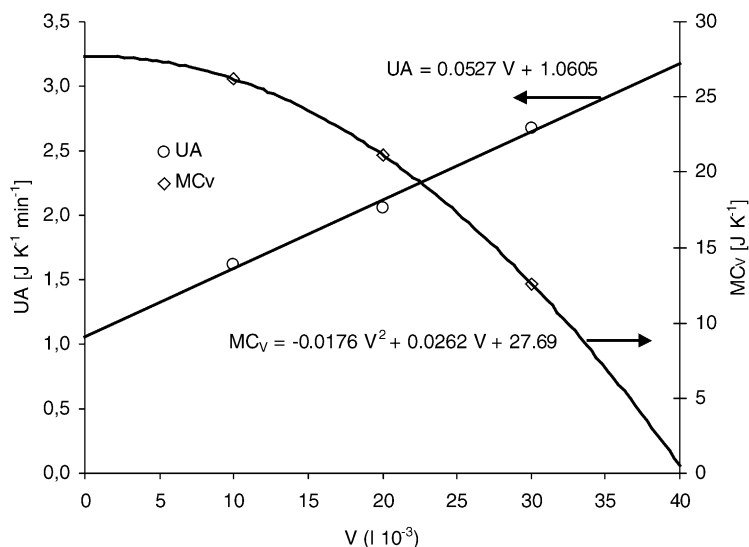


Fig. 10. Global Heat Transfer Coefficient, UA (○) and MC_V (◇) obtained for the reactor depicted in Fig. 11 as a function of volume of water injected into reactor. Solid Lines: curves obtained by fitting the experimental data using polynomial interpolation.

An adiabatic temperature rise higher than that recorded in normal conditions is observed during this run. In fact, the overcharging of anhydride allows the formation of an excess with respect to carnitine of acetyl nitrate which exothermically decomposes.

3.3. Kinetic modeling

The availability of a kinetic model which simulates the system behaviour may represent a useful tool for the evaluation of the consequence for safety of the process deviations.

Due to a lack of any literature information for the kinetics of the esterification process of the (*S*)-carnitine nitrate by means of acetic anhydride/nitric acid/acetic acid system, a set of runs was carried out to identify its rate law and kinetic parameters by using the quasi-adiabatic device described in the experimental section.

In Fig. 10, as a function of volume of pre-heated water injected into reactor, the estimated UA and MC_V values are shown.

To take into account the effects of viscosity and density on the parameters UA and MC_V , the values reported in the table were obtained by fitting for each run the cooling tract of the curves reported in Fig. 11 by using the Eq. (A).

Aiming at assessing the kinetic parameters of the esterification process, some experimental runs were then realized (Table 5).

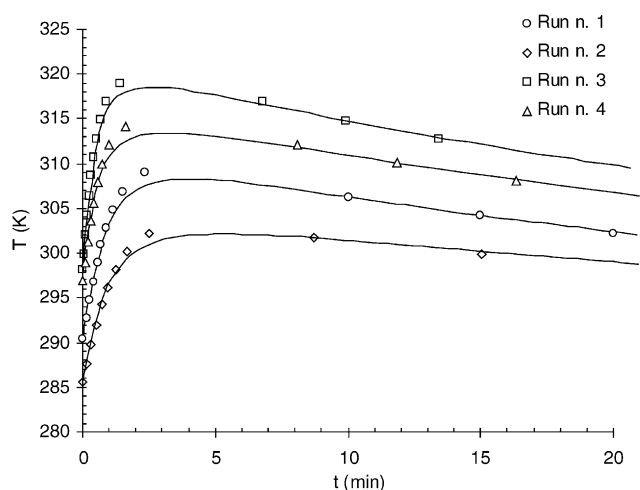


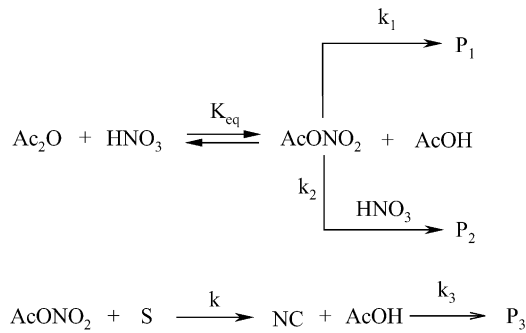
Fig. 11. Quasi-adiabatic runs carried out on the systems reported in Table 5. Run no. 1 (○), 2 (◇), 3 (□), and 4 (△). Calculated using the best estimated parameters A and E (—).

The results of these experiments are reported in Fig. 11. The heat of reaction derived by considering the above reported runs resulted equal to: $\Delta H_R = -44.8 \pm 1.7 \text{ kJ mol}^{-1}$ of *S*.

Simple calculations based on previously assessed kinetics for acetyl nitrate decomposition [6], indicate that in the adopted experimental conditions, even at the highest temper-

Table 5
Experimental Conditions used to perform the quasi-adiabatic runs reported in Fig. 11

Run	UA ($\text{JK}^{-1} \text{min}^{-1}$)	MC_V (JK^{-1})	ϕ	m_S (g)	V (dm^3)	$[\text{AcOH}]_i$ (moles (dm^3) $^{-1}$)	$[\text{Ac}_2\text{O}]_i$ (moles (dm^3) $^{-1}$)	$[\text{HNO}_3]_i$ (moles (dm^3) $^{-1}$)	$[\text{S}]_i$ (moles (dm^3) $^{-1}$)	T_O (K)
1	2.05	22.3	1.66	16.1	12.6×10^{-3}	5.83	2.35	3.93	1.97	290.5
2	2.05	22.3	1.66	16.1	12.6×10^{-3}	5.83	2.35	3.93	1.97	285.7
3	1.80	22.3	1.50	21.5	17.6×10^{-3}	5.55	2.27	3.73	1.88	298.3
4	1.97	23.1	1.54	20.6	16.9×10^{-3}	6.95	1.84	3.44	1.76	296.9



Scheme 2.

ature recorded during these runs (319.0 K), it is possible to neglect the thermal decomposition of acetylnitrate.

Therefore the following kinetic equation was written for the rate of esterification of the substrate:

$$\begin{aligned}
 -\frac{d[\text{S}]}{dt} &= k[\text{AcONO}_2][\text{S}] = \frac{kK_{\text{eq}}}{[\text{AcOH}]}[\text{Ac}_2\text{O}][\text{HNO}_3][\text{S}] \\
 &= \frac{k'}{[\text{AcOH}]}[\text{Ac}_2\text{O}][\text{HNO}_3][\text{S}] \quad (\text{B})
 \end{aligned}$$

As a result of single optimization procedure by means of a commercial software package (Matlab 5.3) [12] in which the Eq. (B) and the thermal balance (Eq. (C)):

$$\begin{aligned}
 \left(\phi \frac{mc_p}{V}\right) \frac{dT}{dt} &= \frac{k'}{[\text{AcOH}]}[\text{Ac}_2\text{O}][\text{HNO}_3][\text{S}](-\Delta H_R) \\
 &\quad - \frac{UA(T - T_E)}{V} \quad (\text{C})
 \end{aligned}$$

were used for the analysis of all the experimental data reported in Fig. 11.

Since:

$$k' = kK_{\text{eq}} = A \exp\left(-\frac{E}{RT}\right)$$

where

$$K_{\text{eq}} = \frac{[\text{AcONO}_2][\text{AcOH}]}{[\text{Ac}_2\text{O}][\text{HNO}_3]}$$

the following values for the parameters A and E were estimated

$$A = (8.90 \pm 0.10) \times 10^{+11} \text{ dm}^3 \text{ mol}^{-1} \text{ min}^{-1}$$

$$E = 72.4 \pm 12.3 \text{ kJ mol}^{-1}$$

In Fig. 11, the temperature profiles (solid line) predicted by adopting the above-reported values of A and E are compared with those experimentally found.

On the basis of the above reported experimental evidences, the following scheme was adopted to develop a possible global kinetic model: Scheme 2, where $\text{S} \equiv (\text{S})$ -carnitine-inner salt and $\text{NC} \equiv (\text{S})$ -nitroxcarnitine nitrate, for which the following balances and stoichiometric equations can be written:

$$\frac{d[\text{P}_1]}{dt} = \frac{k'_1}{[\text{AcOH}]}[\text{HNO}_3][\text{Ac}_2\text{O}] = r_1 \quad (1)$$

$$\frac{d[\text{P}_2]}{dt} = \frac{k'_2}{[\text{AcOH}]}[\text{HNO}_3]^2[\text{Ac}_2\text{O}] = r_2 \quad (2)$$

$$\frac{d[\text{P}_3]}{dt} = k_3[\text{NC}] = r_3 \quad (3)$$

$$\frac{d[\text{S}]}{dt} = -\frac{k'}{[\text{AcOH}]}[\text{HNO}_3][\text{Ac}_2\text{O}][\text{S}] = -r_R \quad (4)$$

$$\begin{aligned}
 \left(\frac{\phi m_S \bar{C}_{P,S}}{V}\right) \frac{dT}{dt} &= r_1(-\Delta H_1) + r_2(-\Delta H_2) + r_R(-\Delta H_R) \\
 &\quad + r_3(-\Delta H_3) + \frac{UA}{V}(T_E - T) \quad (5)
 \end{aligned}$$

$$[\text{Ac}_2\text{O}] = [\text{Ac}_2\text{O}]^{(0)} - ([\text{P}_1] + [\text{P}_2] + ([\text{S}]^{(0)} - [\text{S}])) \quad (6)$$

$$[\text{HNO}_3] = [\text{HNO}_3]^{(0)} - ([\text{P}_1] + 2[\text{P}_2] + ([\text{S}]^{(0)} - [\text{S}])) \quad (7)$$

$$[\text{NC}] = ([\text{S}]^{(0)} - [\text{S}]) - [\text{P}_3] \quad (8)$$

with for $t = 0$: $[\text{Ac}_2\text{O}] = [\text{Ac}_2\text{O}]^{(0)}$, $[\text{HNO}_3] = [\text{HNO}_3]^{(0)}$, $[\text{S}] = [\text{S}]^{(0)}$. In the above equations: $k'_i = k_i K_{\text{eq}} = A_i \exp(-E_i/RT)$ for $i = 1, 2$ and $k_3 = A_3 \exp(-E_3/RT)$.

This model has been used to simulate the temperature profile of the system when an overcharging of acetic anhydride happens along with a failure of the cooling. The integration of the Eqs. (1)–(8) with kinetic parameters already found in this paper and by using for the reactions 1 and 2 the kinetic parameters reported in Table 6 and the following values for the heat of reactions: $\Delta H_1 = -138.0 \text{ kJ mol}^{-1}$, $\Delta H_2 = -82.9 \text{ kJ mol}^{-1}$ [6], allowed the calculation of the temperature profile which is compared in Fig. 12 with that experimentally recorded.

As it is evident from the Fig. 12, a good agreement is obtained between experimental and calculated data for reaction temperatures lower than 353 K, although for higher values a discrepancy is observed, with a predicted adiabatic temperature rise greater than that measured at the end of the run.

A possible explanation of this result can be found considering that reported experimental data were collected in an open reactor and the recorded temperature rise could be lower

Table 6
Kinetic parameters used for the integration of the system of Eqs. (1)–(8)

A_1 (min^{-1})	E_1 (kJ mol^{-1})	A_2 ($\text{dm}^3 \text{ mol}^{-1} \text{ min}^{-1}$)	E_2 (kJ mol^{-1})
$(2.62 \pm 0.500) \times 10^{16}$	120 ± 0.837	$(2.06 \pm 0.600) \times 10^{17}$	127 ± 1.67

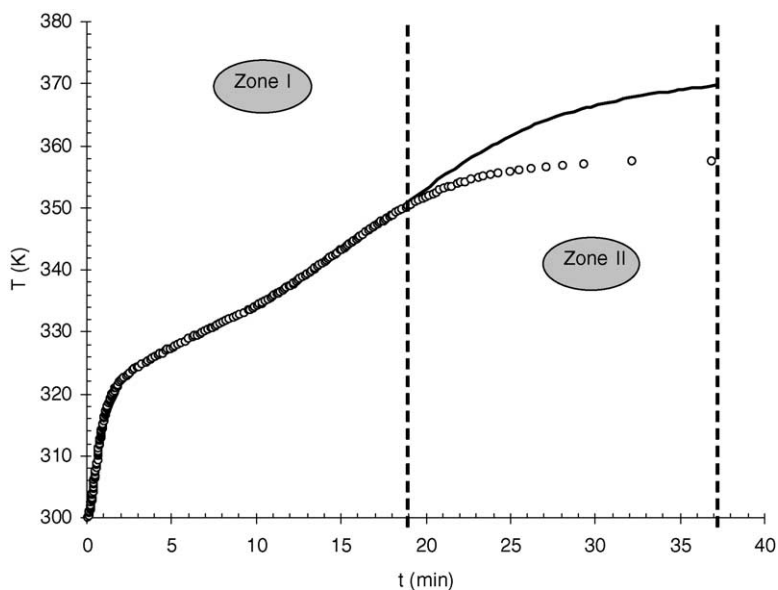


Fig. 12. Experimental data points (○) and calculated temperature profile (—) collected during the Sikarex run reported in Table 4.

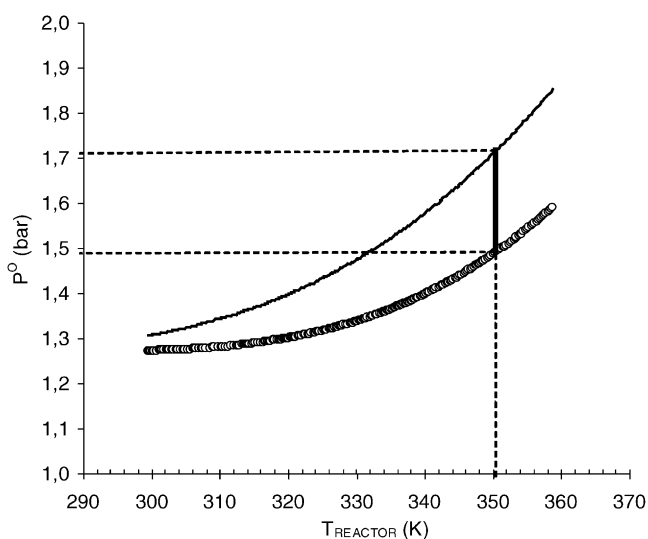


Fig. 13. Vapor pressure vs. temperature for pure acetic acid: (○) $x_{\text{AcOH}} = 1$, and a mixture AcOH/HNO_3 : (—) $x_{\text{AcOH}} = 0.68$.

than that obtainable in a closed reactor, due to a partial removal of evolved heat occurring at the highest temperature (zone II of Fig. 12). In fact, as shown in Fig. 13, a not negligible vapor pressure both of the acetic acid and a mixture HNO_3/AcOH with a molar fraction of acetic acid of 0.68 is recorded for temperature greater than 351 K (temperature for which the calculated curve deviates with respect to the experimental points).

4. Conclusions

The investigations carried out in the present work allowed to estimate, using calorimetric techniques both heat of reac-

tion and the kinetic parameters of the esterification process of the (*S*)-carnitine by using as esterifying system the mixture acetic anhydride/nitric acid/acetic acid. The analysis of some easily foreseeable process deviations point out that the system is not free of problems. A sequence of events could lead to a runaway scenario with a huge gas and heat evolution involving both acetyl nitrate decomposition and the thermal degradation of the nitric ester. This is possible in case of adiabatic batch addition of acetic anhydride and/or temperature highest than those required by the process. The same problems can occur if a batch reactor is involved in a fire. In this case, an internal temperature of the reactor's wall greater than 343 K has to be considered as a very dangerous event.

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