Solubility of 5-Nitro- and 3-Nitrosalicylic Acids in an Acetic Acid/Nitric Acid Mixture

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To better understand the batch production of 5-nitrosalicylic acid by means of the nitration of salicylic acid through the mixture nitric acid/acetic acid, the solubility of the two main mononitro derivatives of salicylic acid is investigated. For this purpose, the behavior of the two mononitro compounds in the ternary system organic/acetic acid/nitric acid is separately studied at different temperatures (288 to 303) K and nitric acid concentrations [(0 to 2) mol·L^{-1} for 5-nitrosalicylic acid, (0 to 1) mol·L^{-1} for 3-nitrosalicylic acid]. The solubility of these compounds increases with a rise in temperature, whereas only the solubility of 5-nitrosalicylic acid is dependent upon the nitric acid concentration. The mutual effect of each organic acid on the solubility of the other is also investigated. The observed dependencies are explained through simple thermodynamic relationships.

Introduction

5-Nitrosalicylic acid is the basic intermediate in the synthesis of mesalazine starting from salicylic acid.[1] Mesalazine is one of the most important active species used in the pharmaceutical field for the treatment of various pathologies such as ulcerative colitis and Crohn's disease.[2,3] In a recent study,[4] a novel method was proposed to obtain 5-nitrosalicylic acid using the system HNO_3/CH_3COOH for the nitration of salicylic acid. One of the most interesting features of this nitrating system is that the target product (5-nitrosalicylic acid) and its side product (3-nitrosalicylic acid) separate from the reacting solution by precipitation using particular operating conditions, thus simplifying the subsequent separation and purification steps.[5] However, there still exist some concerns related to the safety aspects of this nitrating system. In particular, although the authors provided in previous papers[4,5] a thermokinetic characterization of the reacting system that may be used to prevent the occurrence of runaway phenomena, at least in principle, the possibility of detonation of the mixture HNO_3/AcOH cannot be ruled out even if properly initiated and confined.[6] To refine the available kinetic model[4] with the view of a possible industrial application, an experimental work devoted to collect information on the solubility of the two mononitro derivatives in the ternary system organic/nitric acid/ acetic acid was carried out.

Therefore, the dependence of the solubility of both 5-nitro- and 3-nitrosalicylic acid with respect to temperature and nitric acid concentration was investigated. Some efforts were also undertaken to assess the influence of the presence of one compound on the solubility of the other.

Experimental Section

All the experiments were performed under isothermal conditions using a jacketed, magnetically stirred, glass reactor (volume: 2.0·10^{-2} L). The temperature was kept constant by using a Julabo F32 refrigerated/heating circulator (cooling fluid: water). The runs were performed by preparing the mixture of acetic acid and nitric acid directly in the reactor, and after a period of rest at the desired temperature to stabilize the mixture, the solid sample was fed in batch mode. The resulting system was kept under stirring for 6 h, then the stirrer was turned off, and the mixture was left to settle for 2 h. Samples of the liquid phase were withdrawn from the reactor by using a pipet equipped with an appropriate filter. The concentrations of the involved species were measured by means of an HPLC analysis using the Hewlett-Packard model 1100 II, equipped with an UV−VIS detector and a "Phenomenex Synergi 4 μ polar RP/80°" column. For the mobile phase, a mixture formed by 80 % v/v 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 was used. The signals were acquired at (240, 280, and 350) nm; the column temperature was kept at 298 K; and the flow rate set at 10^{-3} L·min^{-1}. For all the experiments, analytical grade reagents were used (H_2SO_4 98 % v/v by Fluka and the others by Sigma Aldrich).

Results and Discussions

The solubility of each nitroderivative in acetic acid/nitric acid media was investigated at five different values of the ratio $n_{HNO_3}/n_{substrate}$. For a fixed nitric acid concentration, the runs were performed at four different temperatures chosen in the range of (288 to 303) K, according to the procedure described in the Experimental Section. The operating conditions adopted in the runs performed on 5-nitro- and 3-nitrosalicylic acid are reported in Tables 1 and 2, respectively. Since the material balance is within the experimental error and no further peaks were detected in the chromatogram, it can be stated that even at the highest temperatures adopted for these experiments the substrates analyzed are stable species.

In Figure 1, the logarithm of the solubility of 5-nitrosalicylic acid, 5NS (as molar fraction $x^s_{5NS} = n^s_{5NS}/(n_{HNO_3} + n_{AcOH} + n^s_{5NS}))$ is reported against the reciprocal of absolute temperature for different values of the ratio R_5 = mol of nitric acid/mol of 5NS.

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Table 1. Operating Conditions Adopted in the Runs Performed on 5-Nitrosalicylic Acid[a]

R_5	m_{5NS}/g	V_{AcOH}/mL
0	0.5	5
1	0.5	5
2	0.5	5
3	0.5	5
4	0.5	5

[a] R_5, molar ratio n_{HNO_3}/n_{5NS}; m_{5NS}, 5-nitrosalicylic acid mass; V_{AcOH}, acetic acid volume.

Table 2. Operating Conditions Adopted in the Runs Performed on 3-Nitrosalicylic Acid[a]

R_3	m_{3NS}/g	V_{AcOH}/mL
0	0.13	3
1	0.13	3
2	0.13	3
3	0.13	3
4	0.13	3

[a] R_3, molar ratio n_{HNO_3}/n_{3NS}; m_{3NS}, 3-nitrosalicylic acid mass; V_{AcOH}, acetic acid volume.

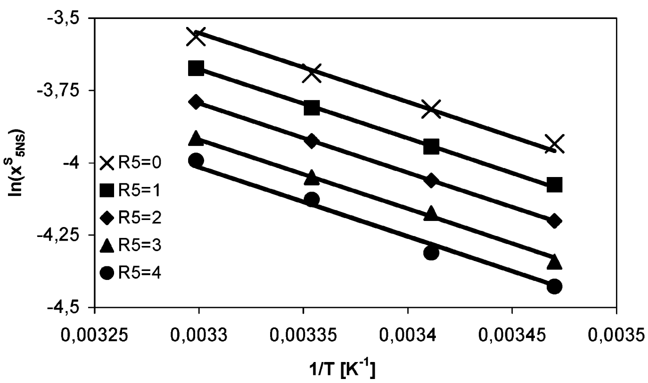

Figure 1. 5-Nitrosalicylic acid solubility dependence upon temperature for different values of the ratio $R_5 = n_{HNO_3}/n_{5NS}$.

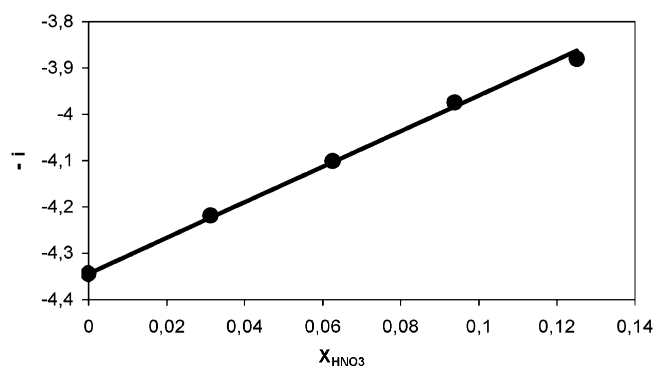

Figure 2. 5-Nitrosalicylic acid solubility dependence upon nitric acid concentration.

The diagrams reported in Figure 1 show that, when nitric acid concentration is kept constant, the logarithm of the solubility has a linear dependence on the reciprocal of the absolute temperature; in particular the logarithm of the solubility of 5-nitrosalicylic acid decreases with a rise in the reciprocal of temperature. Moreover, the lines that interpolate experimental data for different nitric acid concentrations have the same slope, and their intercepts (*i*) have a linear dependence upon nitric acid molar fraction x_{HNO_3}, as shown in Figure 2 in which negative *i* is plotted against x_{HNO_3}.

For 3-nitrosalicylic acid, a similar linear dependence of ln x_s on temperature is observed; also in this case the logarithm of the solubility increases linearly with temperature, but it seems

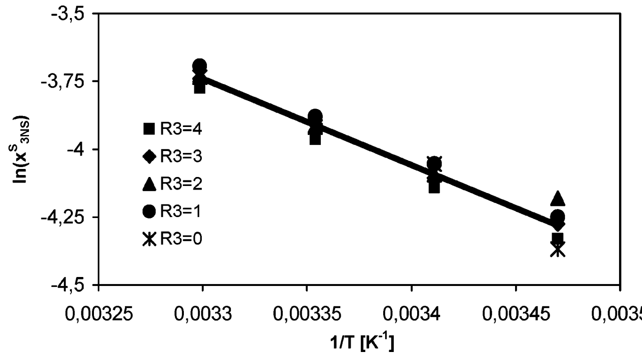

Figure 3. 3-Nitrosalicylic acid solubility dependence upon temperature for different values of the ratio $R_3 = n_{HNO_3}/n_{3NS}$.

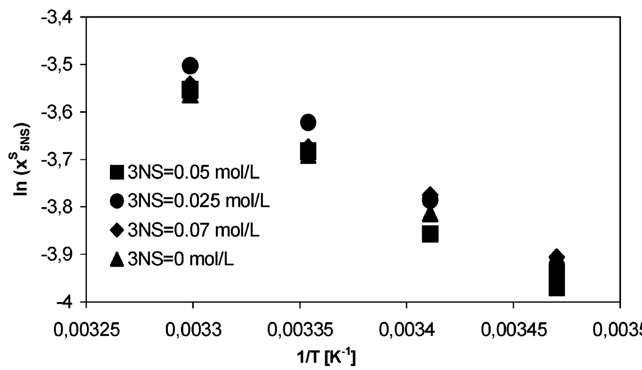

Figure 4. 5-Nitrosalicylic acid solubility dependence upon temperature for different 3-nitrosalicylic acid concentrations and for R_5 =0.

Table 3. Operating Conditions Adopted in the Runs Performed on 5-Nitrosalicylic Acid in the Presence of 3-Nitrosalicylic Acid[a]

m_{5NS}/g	V_{AcOH}/mL	R_5	C_{3NS}/mol·L^{-1}
0.5	5	0	0
0.5	5	0	0.025
0.5	5	0	0.05
0.5	5	0	0.07
0.5	5	4	0
0.5	5	4	0.025
0.5	5	4	0.05
0.5	5	4	0.07

[a] m_{5NS}, 5-nitrosalicylic acid mass; V_{AcOH}, acetic acid volume; R_5, molar ratio n_{HNO_3}/n_{5NS}; C_{3NS}, 3-nitrosalicylic acid concentration.

Table 4. Operating Conditions Adopted in the Runs Considered for the ANOVA Test[a]

m_{5NS}/g	V_{AcOH}/mL	R_5	T/K	C_{3NS}/mol·L^{-1}
0.5	5	0	288	0
0.5	5	0	288	0.025
0.5	5	0	288	0.05
0.5	5	0	288	0.07

[a] m_{5NS}, 5-nitrosalicylic acid mass; V_{AcOH}, acetic acid volume; R_5, molar ratio n_{HNO_3}/n_{5NS}; T, temperature; C_{3NS}, 3-nitrosalicylic acid concentration.

to be negligibly affected by a change in nitric acid concentration (Figure 3). The effect of 3-nitrosalicylic acid on the solubility of 5-nitrosalicylic acid was also studied. For this purpose, two different values of the molar ratio R_5 were chosen at fixed amounts of acetic acid and 5-nitrosalycilic acid. For two values of R_5, four experiments were carried out. For each experiment a different quantity of 3-nitrosalicylic acid was added to the mixture (see Table 3).

For each fixed composition of the system, four runs were performed at different temperatures (288, 293, 298, and 303) K. In Figure 4, the data gathered in the runs performed with a

Table 5. Calculations for the ANOVA Test[a]

source of variation	degrees of freedom	sum of square	mean square
between groups	$(r-1)=3$	$q_1=\sum_{j=1}^{r} g_j(\bar{\mu}_j-\bar{\mu})^2=2.28\cdot10^{-4}$	$q_1/(r-1)=9.37\cdot10^{-5}$
within groups	$(g-r)=16$	$q_2=\sum_{j=1}^{r}\sum_{k=1}^{gj}(\mu_{j,k}-\bar{\mu}_j)^2=3.91\cdot10^{-3}$	$q_2/(g-r)=2.25\cdot10^{-4}$
total	$(g-1)=19$	$q_1+q_2=4.19\cdot10^{-3}$	

[a] r, number of groups; g_j, size of each jth group; g, sum of g_j; $\mu_{j,k}$, kth sample of jth group; $\bar{\mu}$, mean of the entire sample; $\bar{\mu}_j$, mean of the jth group.

value of R_5 equal to zero are reported; similar results were obtained for $R_5 = 4$. On the basis of these results, it is assumed that the solubility of 5-nitrosalicylic acid is not significantly affected by the presence of 3-nitrosalicylic acid. To verify this hypothesis, an ANOVA test[7] was performed on the results of a set of experiments carried out using the initial condition reported in Table 4.

For each fixed value of 3-nitrosalicylic acid concentration, the solubility determination of 5NS was repeated five times. For each value of C_{3NS}, five values of the solubility of 5NS were also obtained; that is, four different groups of data were collected during all the experiments. These data were analyzed by calculating the mean values of 5NS solubility within a single group and over all the groups. The ANOVA test requires the calculation of the following ratio (see Table 5):

$$v_o = \frac{\text{mean square between groups}}{\text{mean square within groups}} = 0.383$$

and its comparison with a Fisher function value, $c = 3.24$, determined for a significance level α equal to 5 % from the Table of F distribution[7] with $((r - 1), (g - r))$ degrees of freedom (where r is the number of groups and g is the sum of the sizes of each group g_j). Since the calculated value of v_o is lower than 3.24, it is not possible to reject the hypothesis according to which the mean values of the solubility of all the groups are equal; therefore, the presence in the solution of 3NS does not affect the solubility of 5NS. The same procedure was successfully adopted to demonstrate that the solubility of 3-nitrosalicylic acid does not depend upon either the concentration of 5-nitrosalicylic acid or that of nitric acid (Figure 3).

Correlation

Simple thermodynamic considerations may be used to justify the observed dependence of the solubility upon temperature and (for 5-nitrosalicylic acid only) nitric acid concentration. In fact, if the thermodynamic constant for the solid−liquid equilibrium is written as the ratio between the activities (a_i) of the species in the liquid and the solid phases:

$$K_{eq,i} = \frac{a_i^s}{a_i^{solid}} \tag{1}$$

with $a_i^{solid} = 1.0$:

$$K_{eq,i} = a_i^s = \gamma_i^s \cdot x_i^s \tag{2}$$

Taking the logarithm of both members of eq 2 and considering the dependence of the equilibrium constant upon temperature:

$$\ln x_i^s = \ln K_{eq,i} - \ln \gamma_i^s = \frac{-\Delta G^0_{fus,i}}{R\cdot T} - \ln \gamma_i^s \tag{3}$$

At a fixed nitric acid concentration, if the change of γ_s in the investigated temperature range is negligible, then eq 3 is consistent with the data reported in Figures 1 and 3, which can be described by an equation of the following type:

$$\ln x_i^s = \frac{S}{T} + i \tag{4}$$

The comparison of eqs 3 and 4 gives $S = -\Delta G^0_{fus,i}/R$ and $i = -\ln \gamma_i^s$.

For the dependence of γ_i^s on nitric acid concentration observed in the case of 5-nitrosalicylic acid, the application of Wilson's equation[8] to the ternary acetic acid/nitric acid/5NS system gives rise to a linear relation:

$$\ln \gamma_i^s = A + B\cdot x_{nitric\ acid} \tag{5}$$

when x_i^s and $x_{nitric\ acid}$ are negligible as compared to $x_{acetic\ acid}$. This hypothesis is verified for all runs since the experiments were carried out with a large excess of acetic acid. Equations 3 and 5 were used for the analysis of the data collected for 5-nitrosalicylic acid shown in Figure 1 and 2, thus allowing an estimate of the parameters $\Delta G^0_{fus,3NS}$, A and B, through a least-square optimization procedure (Table 6).

To analyze the data found for 3-nitrosalicylic, only eq 3 was used. Also in this case, the optimization procedure allowed the determination of $\Delta G^0_{fus,3NS}$ and of $\ln \gamma^s_{3NS}$ (Table 7).

Table 6. Best Estimate of the Parameters for 5-Nitrosalicylic Acid[a]

$\Delta G^0_{fus,5NS}$/J·g^{-1}	A	B
19898.9 ± 6.3	−4.344 ± 0.0045	3.845 ± 0.0815

[a] $\Delta G^0_{fus,5NS}$, Gibbs free energy of fusion; A and B, dimensionless parameters in eq 2.

Table 7. Best Estimate of the Parameters for 3-Nitrosalicylic Acid[a]

$\Delta G^0_{fus,3NS}$/J·g^{-1}	$\ln \gamma^s_{3NS}$
26362.8 ± 23	−6.719 ± 0.0185

[a] $\Delta G^0_{fus,3NS}$, Gibbs free energy of fusion; $\ln \gamma^s_{3NS}$, logarithm of the activity coefficient.

Conclusions

The dependence of the solubility of 5-nitrosalicylic and 3-nitrosalicylic acids, in acetic acid/nitric acid mixtures, with respect to temperature and nitric acid concentration was assessed to simplify the 5-nitrosalicylic acid production process. The solubility of 5-nitrosalicylic acid was found to increase with a rise in temperature and decrease with increasing nitric acid concentration. In the case of 3-nitrosalicylic acid a similar dependence of solubility on temperature was observed but the solubility of this species appears not to be affected by a change in nitric acid concentration. The mutual effect of each organic acid on the solubility of the other was found to be negligible. The dependencies found were justified with simple thermodynamic considerations, and the parameters involved were assessed.

Glossary

a_i^{s}	activity of *i*th species in solution (mol·L^{-1})
a_i^{solid}	activity of *i*th species in solid phase (mol·L^{-1})
C_i	concentration of *i*th species (mol·L^{-1})
g	sum of g_j for the ANOVA test (dimensionless)
g_j	size of each group for the ANOVA test (dimensionless)
m_i	mass of *i*th species (g)
n_i	moles of *i*th species (mol)
n_i^{s}	moles of *i*th species in solution (mol)
R	universal costant of gas (J·mol^{-1}·K^{-1})
r	number of groups for the ANOVA test (dimensionless)
R_3	molar ratio between nitric acid and 3-nitrosalicylic acid (dimensionless)
R_5	molar ratio between nitric acid and 5-nitrosalicylic acid (dimensionless)
t	time (min)
T	temperature (K)
V_i	volume of *i*th species (L)
x_i	molar fraction of *i*th species (dimensionless)
x_i^{s}	molar fraction of *i*th species in solution (dimensionless)
$\Delta G^0_{\mathrm{fus},i}$	Gibbs free energy of fusion for *i*th species (J·g^{-1})
γ_i^{s}	activity coefficient of *i*th species (dimensionless)
$\bar{\mu}$	mean of the entire sample (dimensionless)
$\bar{\mu}_j$	mean of the *j*th group (dimensionless)
$\mu_{j,k}$	*k*th sample of *j*th group (dimensionless)

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