NITROSATION REACTION USING ISOTHERMAL POWER COMPENSATION CALORIMETRY
Kinetic and mechanistic study

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Abstract

Initial plant scale trials of the nitrosation of an amino acid revealed a number of issues:

- Much lower yield compared to laboratory scale
- Considerable loss of mass balance
- Large excess of nitrosating agent required for complete reaction
- Highly reactive off-gases produced causing fires in the carbon absorber
- Reaction sensitive to agitation speed
- The by-product produces an impurity in the next process stage which has high human toxicity

A kinetic and mechanistic study of the nitrosation reaction, using isothermal power compensation calorimetry and GC/mass spectrometry, has been undertaken in order to understand the above observations and to produce an improved manufacturing process – more robust, higher yielding, reduced effluent volumes and toxicity.

Keywords: aliphatic amine, nitrosation, pH-dependence, reaction calorimetry

Introduction

A hydroxyacid (**2**) is produced by the nitrosation of an O-substituted *L*-serine (**1**), along with a small amount of the nitrite ester of the hydroxyacid (**3**):
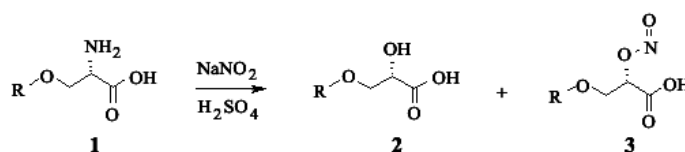
Scheme 1

In the current process, the serine is dissolved into aqueous sulphuric acid (pH ca 0) at 2°C and a solution of aqueous sodium nitrite is added at 2°C over 4 h using sub-surface addition. The reaction mixture is quenched with sulfamic acid and the product extracted into methyl-*t*-butyl ether. The isolated yield in the laboratory is approximately 55%.

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Initial reactions carried out on plant scale (25 kg input) revealed a number of issues:

- yield reduced to only 30% on plant scale
- considerable loss of mass balance
- $NaNO_2$ charge – reaction requires 3 equivalents to proceed to completion (i.e., complete conversion of serine)
- off-gases from the process are significantly more reactive (as measured by the exotherm on adsorption onto carbon) than expected for the generation of NO_x alone. The resulting problems in scrubbing the off-gases led to very long (30 h) addition time on plant scale
- the reaction is sensitive to stirring (low agitation rate=good), a problem for scale-up
- the nitrite ester impurity generates a highly toxic impurity (N-nitrosamine) in the following stage.

The paper describes a kinetic/mechanistic study of the nitrosation reaction using calorimetry, undertaken in order to understand the above observations and to produce an improved manufacturing process (more robust, higher yielding, reduced effluent problems).
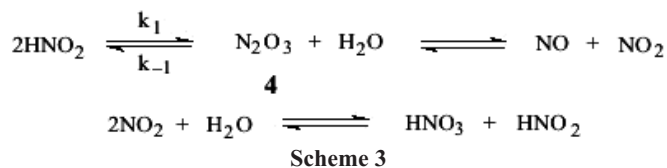
Background

The general mechanism of the nitrosation of α-amino acids, illustrated in Scheme 1 for alanine, is well established [1–3], with the rate-determining step being the diazotisation of the amino-group.
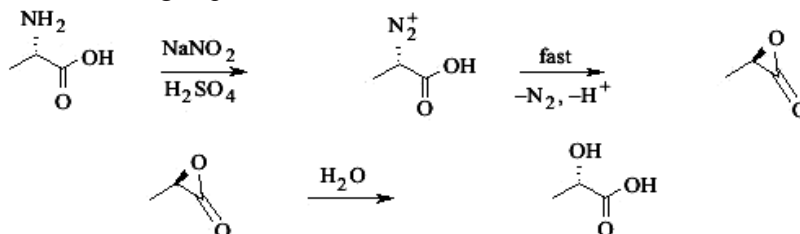
Scheme 2

A detailed analysis of literature data on the diazotisation of (aliphatic) amines lead to the following conclusions:

- the rate determining step in the diazotisation of amines in dilute to moderately concentrated acid is the reaction of the free (i.e., unprotonated) amine and N_2O_3 (**4**), formed from two moles of nitrous acid [1–3],
- competing with the diazotisation reaction is the decomposition of nitrous acid, the rate-determining step of which is the formation of N_2O_3 [4, 6, 7],
- for aromatic amines, the reaction of the (weakly basic) amine with N_2O_3, is very efficient [1–5]
- for aliphatic amines, the decomposition of nitrous acid via N_2O_3 is a serious issue at low pH due to a high degree of protonation, and hence low reactivity, of the

$$2HNO_2 \xrightleftharpoons[k_{-1}]{k_1} \underset{\mathbf{4}}{N_2O_3} + H_2O \rightleftharpoons NO + NO_2$$

$$2NO_2 + H_2O \rightleftharpoons HNO_3 + HNO_2$$

Scheme 3

amines; it is made worse by efficient stirring and the passage of inert gas (e.g., N_2 produced by decomposition of the diazo-compound) through the solution [4, 6, 7]

• the rate of the diazotisation initially increases with increasing pH from 0, due to an increased fraction of the unprotonated amino-group, but ultimately decreases again, due to the ionisation of nitrous acid into unreactive nitrite ions; for amino acids, the rate is at a maximum at pH ca 2.5 [3, 4, 7–10]

• the efficiency of the reaction with respect to nitrite usage continues to increase with pH beyond the point corresponding to the rate maximum [7–10]

• O-nitrosation of alcohols to give the corresponding nitrite esters occurs rapidly and reversibly, with a relatively low equilibrium constant [3].

The above conclusions suggest that effective control of the pH, optimised to give an appropriate compromise between reaction rate and efficiency with respect to nitrite usage, should be vital to the successful operation of the process. In addition, diazotisation reactions are very efficiently catalysed by thiourea [1–3, 11], which operates by converting nitrous acid to the S-nitrosothiouronium ion; the use of thiourea in the reactions has also been investigated.

Experimental

Nitrosation reactions

Process at pH 0, 2°C

The serine (**1**) was charged to a 500 mL jacketed reaction vessel, equipped with a glass pitched turbine agitator and o/h stirrer (140 rpm, ~0.04 W dm^{-3}), pH electrode, thermometer, reflux condenser and N_2 bubbler with a line off to a caustic scrubber. Water (80 mL) was then charged to the vessel and the temperature stabilised at 2°C (pH 4.8) before addition of conc. H_2SO_4 followed by a distilled water line wash (4 mL). An exotherm of ~15°C was observed upon addition of the acid. Subsurface addition of the nitrite solution over 4 h was performed using a syringe pump and PTFE needle. During the nitrite addition a blue/grey colour and gassing was observed (N_2 and NO_x). Stirring was continued for ca 80 min after completion of the nitrite charge before quenching remaining reagent by addition of sulfamic acid solution at a rate so as to control the resultant effervescence. Some colourless crystals of Na_2SO_4 were observed towards the end of the reaction. Samples were extracted periodically for analysis by HPLC during the reaction, upon preparation of which brown NO_2 gas was clearly visible.

The procedure was also carried out under the same experimental conditions using an agitation speed of ~430 rpm (0.6 W dm^{-3}).

Process at pH 2, 2°C; pH 4.5, 30°C

In the processes carried out using pH control, the sulphuric acid was charged to the vessel on demand, maintaining the required pH during the reaction.

The serine (**1**) was charged to a 500 mL jacketed reaction vessel, equipped with a glass pitched turbine agitator and o/h stirrer (140 rpm, ~0.04 W dm^{-3}), pH electrode and burette, thermometer, reflux condenser and N$_2$ bubbler with a line off to a caustic scrubber. Water (84 mL) was then charged to the vessel and the temperature stabilised at 2°C (pH 4.8) before adjusting the mixture to pH 2 by controlled addition of the acid via the GPD 751 Titrino (Stat Mode). Subsurface addition of the nitrite solution over ca 4 h was performed using a syringe pump and PTFE needle. No blue/grey colour was observed during the reaction, in which approx. 1 mol equivalent H$_2$SO$_4$ (0.3 mol equivalent, pH 4) was consumed. Stirring was continued for 80 min after completion of the nitrite charge before quenching remaining reagent by addition of sulfamic acid solution at a rate so as to control the resultant effervescence. Some colourless crystals of Na$_2$SO$_4$ were observed towards the end of the reaction. Samples were extracted periodically for analysis by HPLC during the reaction, upon preparation of which very little (if any) NO$_2$ was observed.

The same procedure was also carried out at high agitation power (as above, ~430 rpm; 0.6 W dm^{-3}).

The experiment was also carried out in the presence of thiourea (10 mol% on serine).

Calorimetric studies

All calorimetric experiments were performed using the same general procedure.

Power compensation calorimeters (Fig. 1) operate on the principle of applying a constant cooling load to the reaction mass in the calorimeter. Isothermal conditions are maintained by the application of heat from an electrical heater. Exothermic reactions produce heat and the rate of generation is determined by the reduction in the power supplied to the heater to maintain the isothermal conditions in the calorimeter.

Process at pH 2, 2°C; pH 4.5, 30°C

A slurry of the serine in water was charged to the calorimeter. The agitator was set at 250 rpm, the cooling bath temperature set ca 10 K below the desired batch temperature. The temperature and pH were stabilised as required before commencing addition of 2 mol equivalents NaNO$_2$, charged over 160 min via syringe pump and PTFE needle. The reaction pH was controlled as described above, by addition of H$_2$SO$_4$ to the vessel on demand. Gas evolution and heat output were monitored during the reaction. Analysis of the off gases was performed periodically using Thermolab Quadropole mass spectrome-
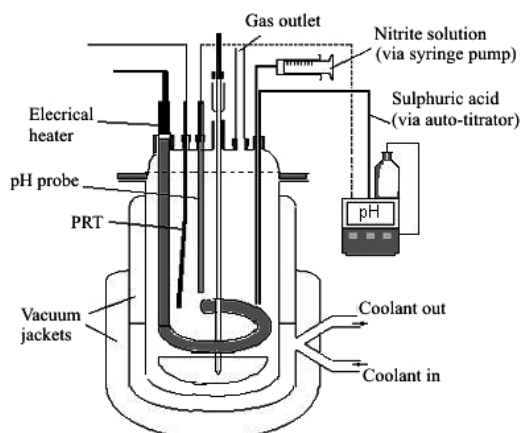
Fig. 1 Power compensation calorimeter – with pH control

try. No blue/grey colour or Na$_2$SO$_4$ precipitate was observed. The reaction was quenched with sulfamic acid and no further work up performed.

Process at pH 0

The reaction was performed as detailed above with the exception of the acid charge. The serine and H$_2$SO$_4$ solution (pH 0) was charged to the vessel and the temperature stabilised at 2°C before commencing the nitrite addition. The reaction was left overnight, during which time gas continued to evolve slowly. Remaining oxidant was quenched upon addition of sulfamic acid solution. No further workup was performed.

Results

Nitrosation reactions

The reaction showed an immediate benefit when the pH was increased from 0 to 2, or when carried out at pH 0 in the presence of 10 mol% thiourea. This is illustrated in the
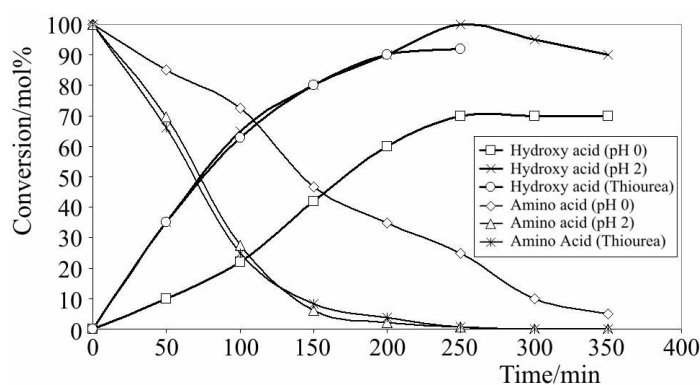

Fig. 2 Conversion *vs*. time of nitrosation reaction

Fig. 2, which shows extent of reaction with time, a total of 3 mol nitrite being added over 4 h (stirrer speed, 140 rpm except for pH 2, 240 rpm).

The absolute yields of product are uncertain, because of uncertainties in the strength of the analytical standard, but the following points may be noted:

• the yields and efficiency of nitrite uptake were considerably higher at pH 2 or in the presence of thiourea than in the standard process at pH 0

• pH 2 reaction was colourless, with no evidence of brown fumes during sampling until about 2 mol nitrite added; the standard pH 0 reaction was a blue/grey colour, typical of N_2O_3 and gave off brown fumes during sampling. Thiourea solutions were pale yellow/brown, with again no evidence of brown fumes.

A further series of reactions, covering the pH range 0 to 2.5 was carried out with standardized stirring conditions (140 rpm, ca 0.04 W dm^{-3}), with addition of 2 mol nitrite; reactions at pH 0 and pH 2 were repeated at considerably higher stirrer power (480 rpm, 0.6 W dm^{-3}). The results are illustrated in the Fig. 3.
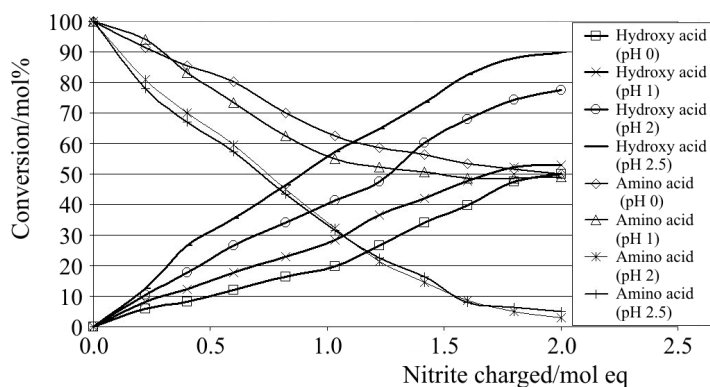

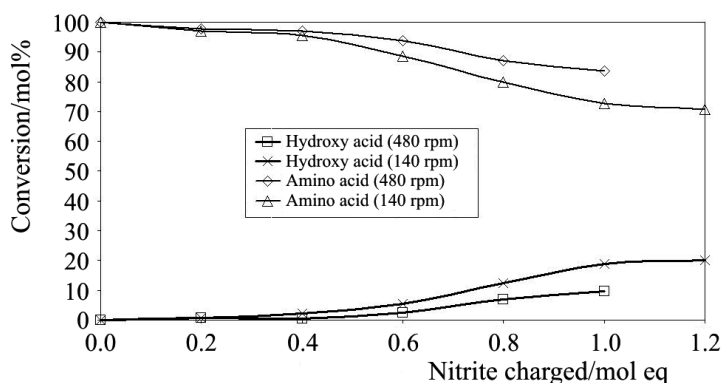**Fig. 3** Effect of pH (at slow agitation rate: 140 rpm, ca 0.4 W/litre)
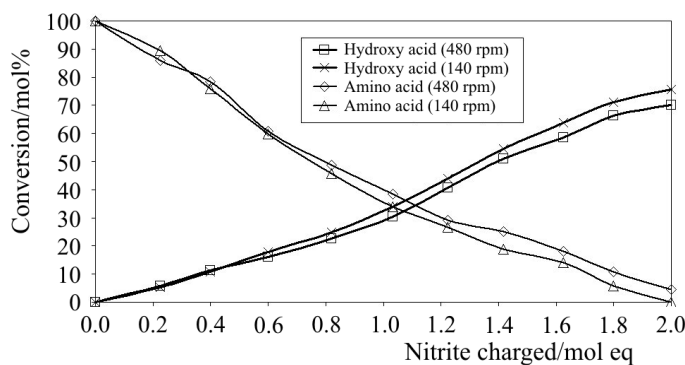

Fig. 4 Effect of agitation rate (pH 0)
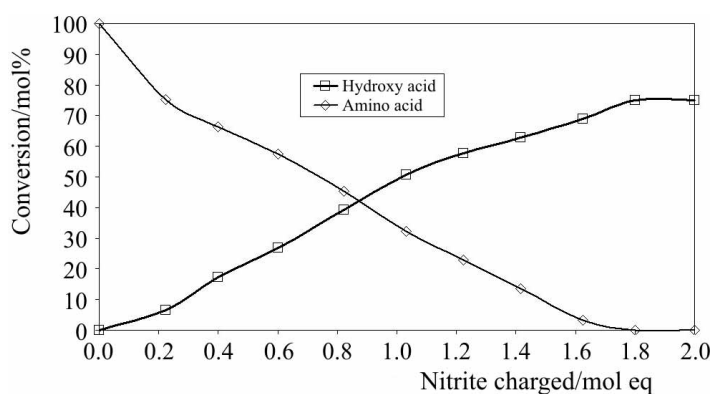
Fig. 5 Effect of agitation rate (pH 2)

Fig. 6 Process at pH 4, 25°C

The results confirm the trend to improved performance with increasing pH, and in particular show that the reaction is considerably less sensitive to agitator speed at pH 2. For the standard process at the higher agitation rate, less than 10% reaction has occurred after addition of 1 mol nitrite, whereas at pH 2 the higher agitation rate has only a very small, but probably real, effect towards the end of the reaction.

The above results, together with the O-substituent apparent high stability at the higher pH values, suggest the reaction could be carried out at even higher pH to reduce nitrite usage and NO$_x$ gas emission, using a higher temperature to compensate for an overall slower reaction rate. Results for the reaction performed at pH 4, 25°C were as follows:

The absolute yield is again uncertain, and the initial results are distorted by the incomplete dissolution of the serine, but complete loss of starting material has occurred on addition of 1.6–1.7 mol nitrite. The stoichiometry of nitrite usage is considered further in the discussion. There was no evidence of brown fuming occurring during sampling.

Calorimetric studies

Heat output and gas evolution measurements

Reaction were carried out under standard conditions as described above, with 2 mol mol^{-1} of nitrite added over ca 160 min, and the mixture quenched with excess sulfamic acid once gassing had ceased. The total heat during reaction and the volume of gas evolved was recorded. Periodically, gas samples were removed and analysed mass-spectrometrically. Two measurements (pH 0 and pH 2) were also carried out for comparison on *L*-serine. The results are listed in Table 1.

Table 1 Calorimetric results for serine nitrosation

Substrate	Conditions[a]	Heat output, ΔH/ kJ (mol serine)$^{-1}$	Gas evolution/ mol gas (mol serine)$^{-1}$
O-substituted serine	pH 0; 2°C	−126	1.5; 0.25 during quench
O-substituted serine	pH 2; 2°C	−326	1.5; 0.25 during quench
O-substituted serine	pH 2; 2°C; +thiourea (6 mol%)	−352	1.5; 0.25 during quench
O-substituted serine	pH 4.5; 30°C 1.7 mol nitrite	−356	1.2; 0.55 during quench
L-serine	pH 0; 2°C	−155	1.50; 0.08 during quench
L-serine	pH 2; 2°C	−423	1.3; 0.36 during quench

[a] 2 mol nitrite per mol serine, unless otherwise stated

Qualitatively, the results are similar for *L*-serine and the O-substituted serine, consistent with the reactivity and efficiency of the processes are controlled by the solution pH without any special effect of the side chain. Reactions at pH 0 were very inefficient in both cases, judging by the low overall heats of reaction compared with those at higher pH, confirming the earlier reaction profile studies. The relatively high agitation rates (250 rpm), necessitated by the heat-transfer requirements of the calorimeter, exacerbated the problem. Reactions of the serine at higher pH values suggest a heat of reaction of ca −334.9 kJ mol^{-1} (−80 kcal mol^{-1}) for complete consumption of the substrate (comparable with theory [12]. Reaction at pH 2, in the presence and absence of thiourea, appeared to be controlled essentially by the rate of addition of nitrite, with nitrogen and heat evolution ceasing within about 10 min of stopping nitrite addition. The reaction at pH 4.5, despite the higher temperature, was considerably slower, with about 40 min being required for completion of reaction after nitrite addition ceased. The results are considered further in the discussion.

Mass spectrometric analysis of evolved gas

One of the key issues was the potential presence of alkyl nitrite (from nitrosation of alcohols), alcohols, and alkenes, arising from the hydrolytic breakdown of the substrate dur-

ing reaction. Easily identified peaks from these products in the mass spectrometer are listed below (Table 2), and all gas samples were analysed for these peaks, as well as m/z 46 (NO_2) and 30 (NO from reaction mixture and breakdown of alkyl nitrite).

Table 2 Mass spectroscopic data of evolved gas

m/z values		
R–ONO	R–OH	R=
88	59	56
57	57	55
43	43	41

The most notable feature of the results was the presence of significant levels of m/z 88 in all samples for the reaction of the substituted serine at pH 0, as well as significant peaks corresponding to m/z in the region 55–59. Very high levels of m/z 46 and m/z 30 were also observed. *L*-serine showed similarly large m/z 46 and m/z 30, but as expected no peaks at $m/z>55$. The peak at m/z 88 was undetected in all reactions other than that of the substituted serine at pH 0. It was noticeable that m/z 30 (NO) levels (qualitative only) reduced by one order of magnitude for pH 2 relative to pH 0, and reduced by a further order of magnitude at pH 4.5; m/z 46 (NO_2) reduced by 1.5 orders of magnitude over the same pH range.

Discussion

The primary aims of the work were to address the issues of poor, stirrer-dependent yields, the high stoichiometry with respect to nitrite, and the reactive off-gases. The presence of the nitrite ester in the isolated product also has serious toxicological consequences for subsequent reaction stages. An analysis of literature reports on the nitrosation of aliphatic amines [1] shows that problems primarily arise from an unfavourable competition at low pH between the desired nitrosation reaction and the loss of nitrite as NO, through the decomposition of the nitrosating species, N_2O_3, The loss of NO is known to be highly dependent upon stirrer speed and particularly to the passage of an inert gas through the solution – inevitable in the present system because of the evolution of N_2 accompanying product formation. It is also clear that the use of pH values below 2–3, the point at which the rate and fraction of N_2O_3 formation is maximised, is counterproductive, serving only to reduce further the proportion of the amine in its reactive, unprotonated form. Low pH values also result in increased rates of the solvolysis of the side-chain linkage. Increased pH values above 2–3 decrease the overall reaction rate, because of a squared dependence upon the nitrous acid concentration, but the selectivity of the reaction with regard to nitrite usage continues to increase because of an overall increase in the fraction of the free amine. The optimum pH value should, therefore, be a compromise between an acceptable overall reaction rate and minimum loss of nitrite through decomposition.

All of the results obtained are consistent with the above comments. There was a significant increase in yield and a reduction in nitrite usage from 3 to 2 moles on increasing the pH from 0 to 2; the overall reaction rate at pH 2 was controlled by the rate of addition of nitrate and not the chemical reactivity. The calorimetric and gas-analysis studies also pointed to a much higher reaction efficiency, and the reaction was essentially independent of stirrer rate up to c. 0.6 W dm^{-3}, a stirrer rate of 480 rpm in our system. Thiourea was shown to be an effective catalyst, even at pH 0, but this option was not pursued further because of the difficulty of separating it from the product and the potential for slow release of H_2S from solvolysis of thiourea.

Detailed optimisation work was not carried out, but two further reaction conditions were tested: pH 4 at 25°C and pH 4.5 at 30°C, the latter by calorimeter only. The results at pH 4 showed that the reaction was still sufficiently fast to be controlled primarily by the rate of nitrite addition and that the nitrite consumption was reduced to c. 1.5–1.6 mol per mol of the serine. There was, in addition, no evidence of sodium sulphate precipitation, consistent with the much reduced requirements for sulphuric acid at this pH. The reaction at pH 4.5 was noticeably slower, requiring some 40 min to complete after nitrite addition ceased. A total of 1.7 mol nitrite was added and the reaction left to completion (as judged by gas evolution). The measured heat of reaction –356 kJ mol^{-1} (–85 kcal mol^{-1}) suggested near complete reaction of the substrate, and the sulfamic acid quench showed about 0.5 mol nitrite remaining. The slower reaction rates above pH ca 4 would necessitate optimisation through a process of adding known amounts of nitrite, allowing completion of reaction and analysing the subsequent reaction mixture. Isolated yields remain to be quantified for all of the reactions described. Note that the isolation pH should always be below 2, to prevent loss of the hydroxy acid through ionisation (pK_a=3.86).

The formation of nitrite ester would appear to be inevitable; however, the nitrosation of hydroxy groups is known to be reversible and so in principle it should all be retrievable as product. Literature reports [11] on the influence of hydroxy groups on amine nitrosation show that the rate of amine nitrosation is reduced because of nitrite consumption as the corresponding nitrite ester, but that the overall yield is unaffected because of the reversibility of nitrite ester formation under reaction conditions, e.g., the addition of 0.5 M *t*-butanol to aqueous morpholine reduces the nitrosation rate by a factor of 2. Reversion of the nitrite ester to hydroxyacid in the present case should occur in the quench provided there is excess sulfamic acid to remove the nitrite generated in the reverse reaction, but the timescale for this would need to be checked.

References

1 H. Zollinger, Diazo Chemistry I. Aromatic and Heteroaromatic Compounds, VCH, Weinheim 1994.
2 H. Zollinger, Diazo Chemistry II. Aliphatic, Inorganic and Organometallic Compounds, VCH, Weinheim 1995.
3 D. L. H. Williams, Nitrosation, CUP, Cambridge 1988.

4 E. D. Huges, C. K. Ingold and J. H. Ridd, J. Chem. Soc., 58 (1958) 65.

5 J. H. Ridd, Quart. Rev., 15 (1961) 418.

6 T. W. J. Taylor, E. W. Wignall and F. Cowley, J. Chem. Soc., (1928) 1922.

7 J-Y. Park and Y-N. Lee, J. Phys. Chem., 92 (1988) 6294.

8 E. J. King, J. Am. Chem. Soc., 82 (1960) 3575.

9 Handbook of Physics and Chemistry.

10 G. Y. Markovits, S. E. Schwartz and L. Newman, Inorg. Chem., 20 (1981) 445.

11 J. Casado, F. M. Lorenzo, M. Mosquera and M. F. R. Prieto, Can. J. Chem., 62 (1984) 136.

12 Bretherick 3rd Edition, 573.