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pH Control in Aqueous Processes: *N*-4-Methylsulfonylphenylguanidine

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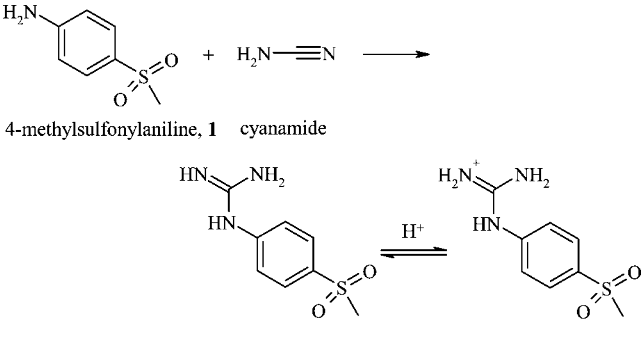
Abstract:

The kinetics and mechanism of the synthesis of the sulfonylguanidine 2 by reaction of the corresponding aniline, 1, with cyanamide have been investigated in aqueous acid solution. The reaction is acid-catalysed, but at low pH, where substantial protonation of 1 occurs, the dominant reaction occurring is a competing hydrolysis of cyanamide to urea. It is shown that reactions run under pH control in the region of pH 2 achieve close to maximum selectivity with respect to the desired guanidine formation, whilst still occurring at a practical rate.

Introduction

Synthetic/process chemists are often faced with the challenge of controlling competing reactions, and when one or more of the reactions is pH dependent, this can often be exploited to alter the selectivity of the reaction and increase the proportion of the desired product. One such case arises in the synthesis of *N*-4-methylsulfonylphenylguanidine, **2**, an intermediate for a potential preclinical oncology product. It can be prepared via the reaction between cyanamide, NH_2CN, with 4-methylsulfonylaniline, **1**, Scheme 1.

Scheme 1. **Formation of sulfonyl guanidine 2**

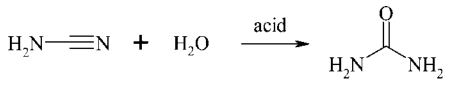


4-methylsulfonylaniline, **1** cyanamide

N-4-methylsulfonylphenylguanidine, **2**, **2**(H^+)

The reaction requires acid catalysis in order to proceed at a practical rate. Under acid conditions, however, the guanidine product, **2**, consumes 1 mol of acid to form the corresponding guanidinium cation, **2**(H^+) (pK_a of the guanidinium ion = 9.0),[1] and the reaction is therefore, in practice, stoichiometric in acid. Furthermore, in aqueous solution the synthesis is complicated by a competing acid-catalysed hydrolysis of cyanamide to urea, Scheme 2.

Scheme 2. **Hydrolysis of cyanamide**



An initial nonaqueous solvent screen, including 1,4-dioxane, sulfolane, tetrahydrofuran, and various alcohols, favoured dioxane as solvent. It was found, however, that ~4 equiv of cyanamide was required to achieve 60–85% yield (based on **1**) because of acid-catalysed polymerisation of cyanamide. Furthermore, there were a number of additional issues, such as irreproducible yields, poor product quality (<90% strength), low solubility and poor physical form of the resulting salt (hydrochloride) of **2** that caused operation issues such as difficulty in stirring due to balling effects, and the unfavourable environmental properties of dioxane. Most of these issues were also common to other nonaqueous solvents. We therefore decided to investigate the system in aqueous solution in more detail, with a view to avoiding many of the above issues and to developing a more environmentally benign aqueous manufacturing process. The use of water as solvent has the added advantage of allowing use of the cost-effective 50% w/w aqueous cyanamide solution as reagent.

Preliminary synthetic work in the presence of 1 equiv of HCl showed very inefficient usage of cyanamide: 55% conversion of **1** to **2** with 1 equiv of cyanamide, increasing to only 82% after 3 equiv, and thereafter very little further increase. We report in this paper that appropriate pH control during the reaction can lead to significantly improved performance and a successful synthetic and manufacturing process, despite the unavoidable limitations imposed by the inherent relative reactivity of cyanamide with water and sulfonyl aniline **1**. This problem of maximising the yield of reactions involving nucleophiles and hydrolysable electrophiles is commonly encountered, and King and co-workers have presented a general approach in an important paper.[2]

Results and Discussion

Reaction Kinetics. The detailed reaction system is presented in Scheme 3. It may be noted that the product guanidine, **2**, is always fully protonated under the acidic reaction conditions.

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(2) King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F *J. Am. Chem. Soc.* **1992**, *114*, 3028.

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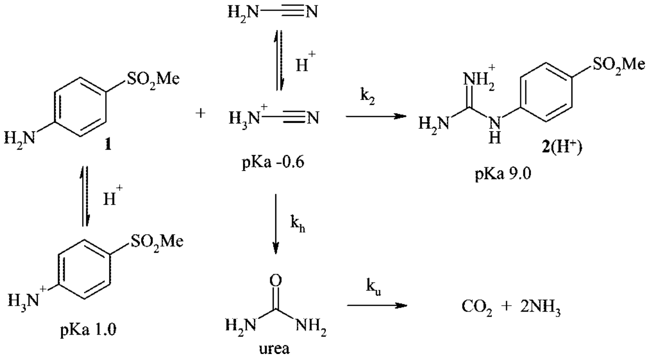
Scheme 3. **Species involved in the reaction between sulfonyl aniline 1 with cyanamide**



The corresponding reaction kinetics are shown below.

$$\mathrm{ArNH_3^+\ (\mathbf{1}(H^+))} \xrightleftharpoons{K_{a1}} \mathrm{ArNH_2\ (\mathbf{1}) + H^+} \tag{1}$$

$$\mathrm{NH_3^+CN} \xrightleftharpoons{K_{CA}} \mathrm{NH_2CN + H^+} \tag{2}$$

$$(\mathbf{1}) + \mathrm{NH_3^+CN} \xrightarrow{k_2} \text{product } (\mathbf{2}(\mathrm{H^+})) \tag{3}$$

$$\mathrm{NH_3^+CN + H_2O} \xrightarrow{k_h} \text{urea} \tag{4}$$

$$\text{urea} + \mathrm{H_2O} \xrightarrow{k_u} \mathrm{CO_2 + 2NH_3} \tag{5}$$

Equations 4 and 5 represent known literature reactions;[3–8] the latter does not directly affect the reaction outcome but is relevant because of the additional consumption of acid arising from the protonation of NH_3.

It follows that the rate law for the product sulfonyl guanidine, **2**, formation, d[P]/dt, is given by eqs 6 and 7, in which k_P is the observed rate constant, and $[NH_2CN]_T$ and $[ArNH_2]_T$ are the total concentrations of cyanamide and **1**, respectively.

$$\frac{d[P]}{dt} = k_p[NH_2CN]_T[ArNH_2]_T \tag{6}$$

where

$$k_p = \frac{k_2}{\left(1 + \frac{K_{CA}}{[H^+]}\right)\left(1 + \frac{[H^+]}{K_{a1}}\right)} \tag{7}$$

The denominator in eq 7 arises from the fractions of cyanamide and **1** protonated at equilibrium at the prevailing pH. In practice, because of the low pK_a of NH_3^+CN (p$K_{CA} = -0.6$ at 25 °C[1] and lower at higher temperatures[6]), the fraction of cyanamide protonated in the pH range studied (pH 1.5) is very small (<1%), i.e., $K_{CA}/[H^+] >> 1$, and so eq 7 simplifies to eq 8.

$$k_p = \left(\frac{k_2}{K_{CA}}\right)\frac{[H^+]}{1 + \frac{[H^+]}{K_{a1}}} \tag{8}$$

Similarly, the rate of loss of cyanamide to urea is given by eqs 9 and 10.[9]

$$\frac{-d[NH_2CN]_T}{dt} = k_{hyd}[NH_2CN]_T \tag{9}$$

where

$$k_{hyd} = \left(\frac{k_h}{K_{CA}}\right)[H^+] \tag{10}$$

Thus, it follows from eqs 6, 8, and 9 that the selectivity ratio for conversion of cyanamide product, **2**, relative to its hydrolysis to urea is given by eq 11.

$$\text{selectivity} = \frac{k_2}{k_h} \times \frac{[ArNH_2]_T}{1 + \frac{[H^+]}{K_{a1}}} \tag{11}$$

Equation 10 shows that the selectivity depends upon three factors: the ratio of the rate constants for reaction and hydrolysis, k_2/k_h; the total concentration of the aniline; and the fraction of the aniline in free base (reactive) form, $1/(1 + [H^+]/K_{a1})$. In order to maximise the guanidine yield for a given total aniline concentration, it is necessary to maximise the concentration of unprotonated aniline, i.e., to work at a pH significantly above pK_{a1}. At high pH values, however, the absolute rates of both hydrolysis and addition become very low because of the decreasing fraction of cyanamide existing as NH_3^+CN (eqs 8–10), and so a compromise may be required.

The reaction was monitored at 90 °C and at various fixed pH values by HPLC analysis for the loss of **1** and formation of **2**, combined with the measured rate of uptake of acid. HPLC data for reactions at pH 1.5, pH 2.0, pH 2.5 and pH 3.0 and initial concentrations of **1** and cyanamide of 1.06 and 2.12 M, respectively, were combined and analysed according to eqs 5–10. Data were fitted simultaneously using Micromaths Scientist. The results are shown in Figure 1, in which the points represent experimental measurements, and the solid lines are best-fit lines calculated using the following rate constants in eqs 8 and 10, combined with pK_a(**1**H$^+$) = 0.8:[1,6]

$$k_2 = 4.00 \times 10^{-2}\ M^{-1}\ s^{-1} \tag{12}$$

$$k_h = 1.31 \times 10^{-2}\ s^{-1} \tag{13}$$

The concentrations of the corresponding guanidine product, **2**, have been omitted for clarity but show an analogous increase.

The strong pH dependence of the rates is apparent. It is noticeable also that because of the competing hydrolysis of cyanamide the reactions do not go to completion with respect

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[9] Note that eqs 6 and 9 cannot be solved in isolation as both involve consumption of cyanamide.

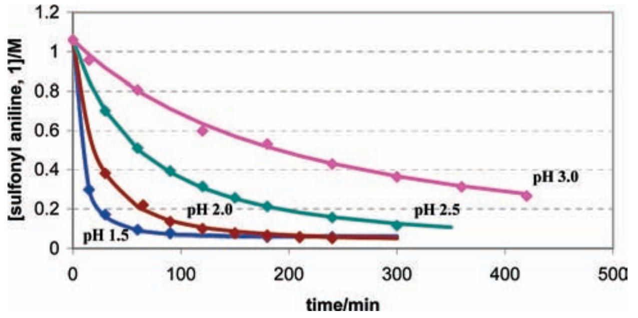

Figure 1. **Reaction of sulfonyl aniline, 1, with cyanamide at 90 °C at various pH values. Points represent concentrations measured by HPLC; solid lines are calculated from eqs 8 and 10 with pK_a(1H$^+$) = 0.8, $k_2 = 4.00 \times 10^{-2}$ M^{-1} s^{-1}, $k_h = 1.31 \times 10^{-2}$ s^{-1}.**

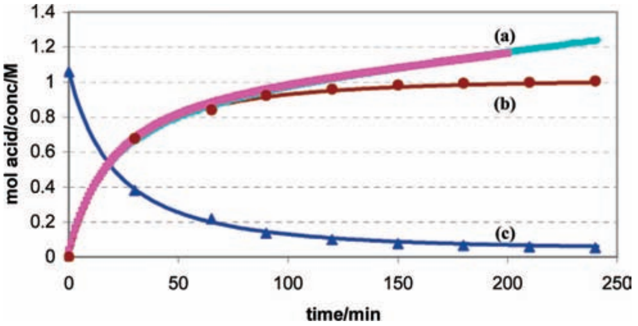

Figure 2. **Reaction of sulfonyl aniline with cyanamide at pH 2.0.90 °C: (a) moles HCl consumed, measured (green line), calculated (pink line); (b) sulfonyl guanidine, 2, measured (points) and calculated (solid line); (c) sulfonyl aniline, 1, measured (points) and calculated (solid lines). Calculated values derived from Scheme 4, with k_2, k_h, and pK_a(1H$^+$) as in Figure 1, and $k_u = 1.4 \times 10^{-5}$ s^{-1}.**

to aniline loss or guanidine formation, despite the 2-fold excess of cyanamide.

The uptake of acid required to maintain constant pH may be fitted to the same kinetic scheme, but with the additional inclusion of acid consumption due to the subsequent hydrolysis of urea to ammonia and CO_2. The results for pH 2 are shown in Figure 2, with the calculated line corresponding to k_2 and k_h from eqs 12 and 13, respectively, together with

$$k_u = 1.4 \times 10^{-5}\ \mathrm{s}^{-1} \tag{14}$$

This result is in quite good agreement with a previously reported literature value[5] of $k_u = 1.2 \times 10^{-5}$ s^{-1} at 90 °C and 0.05 M H_2SO_4. The hydrolysis of urea is independent of acid concentration, except at very high concentrations, with a suggested mechanism involving an intramolecular hydrogen transfer between the nitrogen atoms, and subsequent decomposition to give ammonia and cyanic acid[10] (which ionise to ammonium cyanate), the reverse of the well-known ammonium cyanate–urea conversion.

The hydrolysis of urea is relatively slow under the reaction conditions, but it is sufficient to cause consumption of more than 1 mol of HCl per mole of sulfonyl guanidine formed (Figure 2). This further complicates any potential processes involving a complete charge of acid at the beginning of the reaction.[5,8,10]

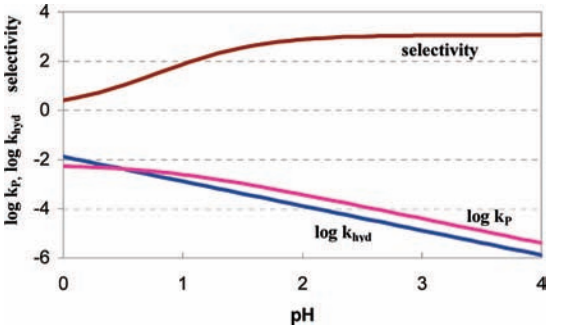

Figure 3. **pH-dependence of rate constants for product formation, k_P, cyanamide hydrolysis, k_{hyd}, and the selectivity towards product formation at $[1]_T$ = 1.0 M.**

Discussion

The measured rate constants, $k_2 = 4.00 \times 10^{-2}$ M^{-1} s^{-1} and $k_h = 1.31 \times 10^{-2}$ s^{-1}, may be used in conjunction with eqs 8, 10, and 11 to calculate overall rate constants for product formation, k_P, cyanamide hydrolysis, k_{hyd}, and reaction selectivity with respect to cyanamide consumption for a given level of sulfonyl aniline, **1**, at different pH values. The results are illustrated in Figure 3, for [**1**] = 1 M. At any given pH, the reaction selectivity will increase directly as the concentration of **1** increases, eq 11.

At high pH values, the selectivity is at a maximum, but the reaction rates are low. A reduction in pH leads initially to parallel increases in the rates of both the desired reaction and the competing cyanamide hydrolysis, due to the increasing levels of protonated cyanamide in solution, eqs 8 and 10. A further decrease in pH, to pH ~2 and below, results in an increased fraction of sulfonyl aniline, **1**, in its (unreactive) protonated form, **1**. Thus, although both rates increase with decreasing pH, there is a loss in selectivity, as the rate of product formation (Scheme 1) levels off to a plateau value, whereas the hydrolysis rate continues to increase directly with the increase in acidity. It is apparent that at practical concentrations, any process involving initial addition of the required amount of acid would generate pH < 0 and hence very low selectivity, resulting in the majority of the cyanamide being lost through hydrolysis. An examination of the observed rates and selectivity suggests that pH in the range 1.5–2.0 gives both acceptable selectivity (≥80% of the maximum) and reaction time.

The form of the pH-rate/pH-selectivity profiles is general for the addition of anilines to cyanamide. More basic anilines would require higher pH values for maximum selectivity, but the correspondingly higher reactivity of such anilines in nucleophilic addition should still result in viable reaction times.

Development of Aqueous Process

The control of pH within the desired range can be achieved either by carrying out the reactions under direct pH control (pH stat) or by addition of acid at a controlled rate, based on the known kinetics of the reaction. The latter was chosen as being more convenient for plant operation.

Initial experiments involving 3 equiv of cyanamide in 3.5 vol of water, at 85 °C, and the addition of 1.5 equiv of HCl

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(10) Shan, H. R.; Walker, D. G. *J. Am. Chem. Soc.* **1958**, *80*, 5337.

over 2.5 h gave 99% solution yield based on sulfonyl aniline and demonstrated the viability of the process. The measured pH varied from an initial 2.7 to a final value of 1.4. The final process, described below, used lower levels of cyanamide (2.2 mol equiv) based on hazard evaluation and produced 95% conversion at the end of reaction and an isolated yield of 85% at 99% w/w strength.

Experimental Section

Typical pH Stat Control Experiment for Reaction between 4-Methylsulfonylaniline (1) with Cyanamide in Water. The reaction was carried out in a Mettler-Toledo automated Multi-Max (4 × 50 mL reactor) system, equipped with a pH stat control system. The temperature and the pH of the reaction were recorded using WinRC Multi-Max software version 2.0. Although the equipment is capable of carrying four reactions in one go, only one vessel was used at any one time, due to the intense sampling of the reaction mixture for HPLC analysis. The glass pH electrode (3 M AgCl/KCl electrolytes) was calibrated with pH buffers 2.0 and 7.0 prior to use.

To a 50-mL glass reactor, equipped with glass pH probe, a thermocouple, and a water condenser, were added 4-methylsulfonylaniline (**1**) (6 g, 35 mmol, 1.0 mol equiv), water (18 mL, 3.0 rel vol) and aqueous cyanamide (47.4% w/w, 5.75 mL, 70 mmols, 2.0 mol equiv). The brown slurry was stirred at 25 °C for 10 min and then heated to 90 °C and held at 90 °C for 5 min, before the pH was adjusted to the desired pH, i.e., 1.5, 2.0, 2.5 and 3.0, with 5 M HCl. The reaction mixture was sampled for HPLC analysis every 15 min for a total of 4 h. The mixture was then cooled to 25 °C, and the solid was filtered, washed with water (2 × 3 mL), and dried in vacuo at 40 °C to give product (6.56 g, 75%), with loss to liquors (0.8 g, 9.0%).

Large-Scale Preparation of Sulfonylguanidine Hydrochloride Salt (2). To a hot (80 °C) solution of 4-(methylsulfonyl)aniline (650.0 g, 3.8 mol, 1.0 mol equiv) in water (2.275 L, 3.5 rel vol) was added an aqueous solution of cyanamide (50% w/w, 649 mL, 8.3 mol, 2.2 mol equiv) in one portion. The contents temperature was adjusted to 83 °C. Concentrated hydrochloric acid (37% w/w, 475 mL, 5.7 mol, 1.5 mol equiv) was then added over 3.5 h, keeping the reaction temperature at 83 °C. The mixture was cooled to 5 °C over 4 h to effect crystallisation. Concentrated hydrochloride acid (37% w/w, 317 mL, 3.80 mol, 1.0 mol equiv) was then added over 0.5 h, keeping the temperature at 5 °C. The mixture was held at 5 °C for 2 h and then filtered. The solid was washed with water (2 × 650 mL, 1 rel vol) and then dried in vacuo at 40 °C. The yield of sulfonylguanidine hydrochloride (**2**) was 802.9 g (98.7% w/w, 83.5%). ^{1}H NMR (DMSO-d_6, 500 MHz, 300 K) δ 10.73 (s, NH), 8.07−7.81 (m, 6H), 7.48 (d, $J = 8.6$ Hz, 2H), 3.22 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz, 300K) δ 155.8, 140.7, 137.1, 128.1 (2C), 123.7 (2C), 43.6. MS (ES) m/z 214 $(M + H)^+$.

HPLC Method. Column = Waters Atlantis C-18, 3μm, 3.9 × 150 mm; gradient as in table total run time = 12 min, post time = 2 min; flow = 1 mL/min; injection volume = 5 μL; wavelength = 254 nm; temperature = 40 °C. Sample preparation: take 10 μL of reaction mixture into 10 mL volumetric flask. Fill to volume with 70:30 water/MeOH. Sulphonyl guanidine, **2**: t_R 4.18. 4-Methylsulphonyl aniline, **1**: t_R 5.25.

time	% water	% MeOH	% 0.25 M NH_4OAc
0	90	0	10
8	0	90	10
9	0	90	10
11	90	0	10
12	90	0	10

Supporting Information Available

Sulfonyl aniline **1** and sulfonylguanidine **2** are known compounds. ^{1}H, ^{13}C, and LC/MS spectra for sulfonylguanidine **2** are available. This information is available free of charge via the Internet at http://pubs.acs.org.

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