POSTER 39

Reactive Crystallisation of Benzaldehyde Sodium Bisulfite

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Project Aim

The aim of this project is to use in-situ measurement techniques for real-time monitoring of reactive crystallization systems using bisulfite addition to benzaldehyde as a model system. The objectives are therefore as follows:

- To evaluate spectroscopic and particle characterization techniques for measuring the required process and product attributes.
- Investigate the impact of experimental parameters on the product attributes and determine kinetic information.
- Devise a workflow for the development of reactive crystallization systems and demonstrate its application in an industrial case study with GSK.

Background

Formation of the bisulfite adduct (product) occurs via nucleophilic addition of the bisulfite ion to the aldehyde or ketone carbonyl carbon as shown in figure 1 [1]. This reaction has multiple uses that make it particularly useful:

- Purification of aldehydes: the resulting bisulfite adduct can undergo further reaction to regenerate the aldehyde [2].
- Storage of aldehydes: aldehydes typically suffer from stability issues (i.e. degradation or oxidation) [3]. Reacting the aldehyde with bisulfite will produce a crystalline solid which has a better stability.
- Drug delivery: the bisulfite adduct is soluble in water, which means it can be delivered to patients by methods other than orally (i.e. intravenously) [1].

The bisulfite addition reaction is a complex equilibrium scheme that is dependent on the pH of the overall system. This is due to the multiple protonation and deprotonation reactions that can occur.

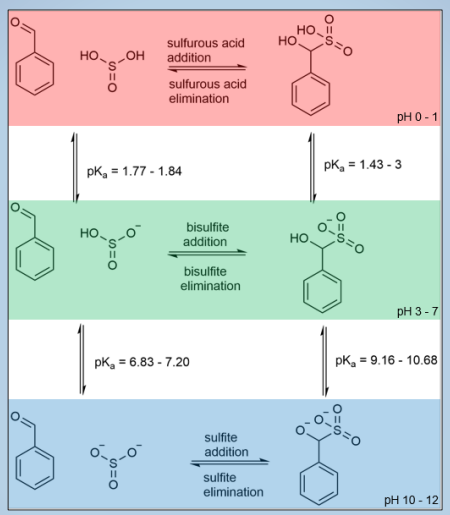

Figure 1: Bisulfite Equilibrium Scheme [4]

The equilibria of this reaction is well-characterized in the literature (see table 1), with papers as far back as the 1930s, however, the nucleation and crystal growth of these compounds have not been discussed. This research aims to understand the crystallisation kinetics and use it as a basis for gaining a greater understanding of reactive crystallisation systems in general.

Table 1: Equilibrium and Reaction Rate Constants of the pH-dependent Reaction Scheme from the Literature

Reaction	Equilibrium Constant (M^{-1})	Reaction Rate ($M^{-1}\ s^{-1}$)
Sulfurous Acid Addition	Not found	0.097 (21°C) [6]
Bisulfite Addition	6.4×10^3 (μ = 1.0 M, pH 3.55-5.27, 294 K, 5 v/v% EtOH in H_2O) [5] 1.4×10^4 (no pH given, 286 K, pure H_2O) [6] 4.7×10^3 (no pH given, 296 K, pure H_2O) [6] 1.9×10^3 (no pH given, 306 K, pure H_2O) [6] 1.7×10^4 (no pH given, 273 K, pure H_2O) [7] 6.57×10^2 (no pH given, 293 K) [7] 4.37×10^2 (no pH given, 303 K) [7]	0.43 (21°C) [4] 254 (13°C) [4] 0.71 (μ = 1.0 M, 25°C) [6]
Sulfite Addition	9.12×10^{-1} (μ = 1.0 M, pH 8-12.6, 294 K, 5 v/v% EtOH in H_2O) [5]	1.25×10^4 (21°C) [4] 2.15×10^4 (μ = 1.0 M, 25°C) [6]

Lab Work

Synthesis of Benzaldehyde sodium bisulfite

Benzaldehyde (0.09 mol, 9.6 mL) was mixed with 83 mL of ethanol, and sodium bisulfite powder (0.9 mol, 9.4 g) was dissolved in 35 mL of water. The benzaldehyde/ethanol mixture was placed in a beaker and a pH and temperature probe were placed in it. The sodium bisulfite powder was then added to the mixture resulting in the benzaldehyde sodium bisulfite "crashing" out. The pH and temperature changes were then recorded, the precipitate filtered, washed with a small amount of ethanol, dried in a vacuum oven, and then weighed again.

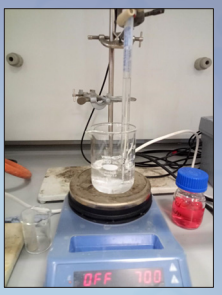

Figure 2: Experimental Set-up

Table 2: Results From Initial Experiments

Parameter	Value
Conversion	• First reaction: 92.35% • Second reaction: 96.08% • Third reaction: 92.29%
Temperature Change	• Starting point: 20.4 °C • End point: 33.9 °C
pH Changes	• Starting point: 5.34 • Reaction begins: >8 • Decreases back to 5.89 • Slowly increases to an end point of 6.09

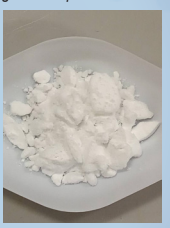

Figure 3: Benzaldehyde Sodium Bisulfite

Preliminary Solubility Data

The solubility of the product must be determined prior to determining solubility curves (see future work). A known mass of benzaldehyde sodium bisulfite was placed inside a beaker with a magnetic stirrer and set on top of a hotplate set to 1000 rpm. The solvent was added step-wise and left for 1 minute between each addition to allow for dissociation to occur. When the solution has fully clear, the mass of solvent was measured and recorded. The results of this are shown in table 3.

Table 3: Preliminary Solubility Data

Solvent Composition (Water:Ethanol w/w)	Benzaldehyde Sodium Bisulfite (g/kg)	Sodium Bisulfite (g/kg)
100 % Water	19.79 (22.1 °C)	436.00 (19 °C)
65/35	5.00 (25.4 °C)	135.24 (20.7 °C)
50/50	3.73 (23.7 °C)	34.24 (21.3 °C)
35/65	1.84 (23.1 °C)	9.37 (22.7 °C)

Future Work

- Validation of final product: using NMR to determine what is in the filtrate and the precipitate
- Amorphous or crystalline?: using PXRD to check the solid form of the sample.
- Unreacted sodium bisulfite: PXRD will be used to determine where unreacted sodium bisulfite ended up, i.e., in the filtrate or the precipitate.
- Solubility data: using the preliminary solubility data as a basis, solubility curves will be constructed using the Crystal-16 equipment via measuring the clear point temperature.
- Applying PAT to the system: after gaining a better understanding of the crystallisation kinetics, PAT will be used to monitor and control the product attributes.

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Affiliations: CMAC Hub and the Department of Pure and Applied Chemistry

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