Thiol Chlorination with N-Chlorosuccinimide: HCl-Catalyzed Release of Molecular Chlorine and the Dichotomous Effects of Water

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Research Article

Thiol Chlorination with *N*-Chlorosuccinimide: HCl-Catalyzed Release of Molecular Chlorine and the Dichotomous Effects of Water

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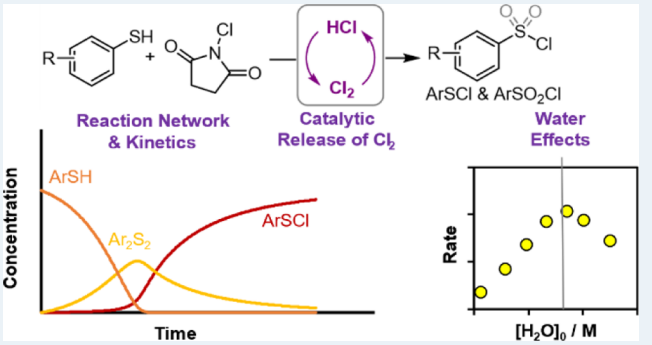
ABSTRACT: The kinetics of the conversion of thiophenols into sulfenyl chlorides using *N*-chlorosuccinimide (NCS) in dichloromethane have been investigated by *in situ* ^{1}H NMR and stopped-flow UV−vis spectroscopy. The study reveals that a slow direct chlorination of the thiophenol by NCS initiates a more rapid but indirect process involving *in situ* generation of a disulfide and then its cleavage by transient Cl_2. The latter is released from NCS by HCl and the switch in dominant pathway results in sigmoidal kinetics for the thiophenol consumption. The overall reaction rate can be attenuated by using an alkene to scavenge the sulfenyl chloride before it reacts with the thiophenol. The presence of water in the dichloromethane induces two distinct kinetic regimes, dependent on whether the water is below or above a critical concentration. The value of this critical concentration is dependent on the amount of HCl in the system. As the exogenous water is increased to the critical concentration, there is a proportionate acceleration of the HCl-mediated release of Cl_2 from the NCS. At water concentrations above this, there is a progressive reduction in the rate of Cl_2 release due to $\{H_2O + n\text{HCl}\}$ undergoing a change in speciation or physical phase. Alcohols, e.g., *i*-PrOH, efficiently catalyze the conversion of thiophenols into sulfenyl chlorides, with further oxidation retarded by trace amounts of disulfide, indicative of analogous HCl-catalyzed slow-release of Cl_2. High reactant concentrations can lead to sufficient exothermicity to trigger an abrupt and vigorous release of gaseous HCl. Potential methods to mitigate against developing these hazardous conditions are also discussed.



KEYWORDS: *chlorination, thiol, organosulfur, N-chlorosuccinimide, monitoring, UV−vis, NMR, safety*

1. INTRODUCTION

Sulfenyl chlorides, Scheme 1, are versatile precursors to numerous organosulfur compounds[1] and are usually prepared by the chlorination of a thiol or the corresponding disulfide.[2] Careful control of the stoichiometry is required when using gaseous Cl_2[3] or liquid SO_2Cl_2[4] to avoid generation of disulfides or over-chlorination side products. In the presence of nucleophilic solvents or hydroxyl-additives (e.g., H_2O, AcOH, MeOH), the chlorination leads to sulfinyl and/or sulfonyl chlorides[5] via organosulfur trichloride intermediates.[5f]

In 1951, Emde patented the use of *N*-chlorosuccinimide (NCS) as a convenient and safe reagent for thiol chlorination.[6] NCS is a stable and commercially available solid, much less corrosive and toxic than Cl_2, and easily added to reactions in known stoichiometry.[7] Moreover, the thiol chlorination co-product (i.e., succinimide, NHS) is readily removed[8] and relatively non-acidic, facilitating the isolation of pure sulfenyl chlorides containing acid-sensitive functional groups.[9] All of these features have led to NCS,[10] and related *N*-chloro species, being adopted as the reagents of choice for the conversion of thiols into sulfenyl chlorides, both as end-products[11] and as intermediates in "one-pot" processes.[12−14]

Despite the central role of thiol chlorination in organosulfur chemistry, numerous aspects of the mechanism remain speculative,[1−3,12,13] with three general scenarios (I, II, III, Scheme 1) proposed to date. Mechanism I involves a simple nucleophilic substitution at the chlorine atom of the reagent (Cl−Y) by the thiol. Mechanisms II and III involve a disulfide intermediate. This can be formed by direct oxidative thiol−thiol coupling (II) or by condensation of the remaining thiol with the nascent sulfenyl chloride (III). Both of the latter mechanisms are consistent with the reported detection of disulfides in incomplete thiol chlorination reactions or as a minor impurities in the product.

Herein, we describe a mechanistic study of the chlorination of thiophenols by NCS in dichloromethane. Using *in situ* NMR and stopped-flow UV−vis spectroscopy to analyze the kinetics,

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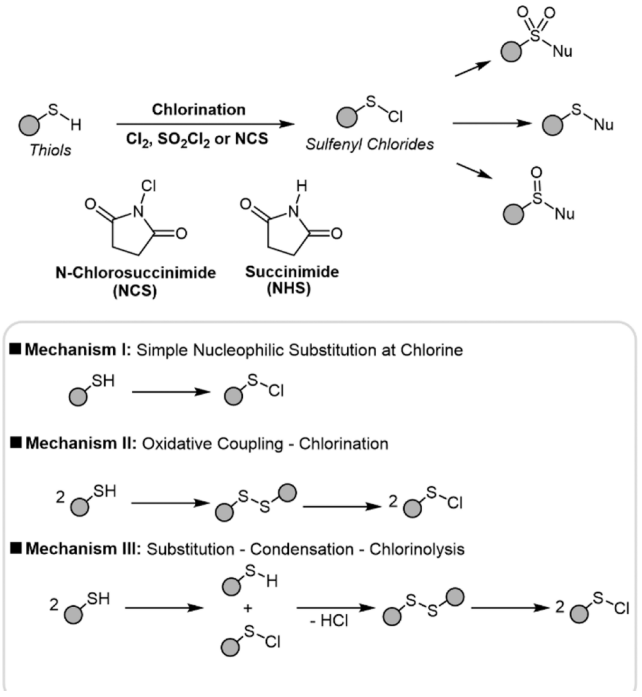
Scheme 1. Chlorination of Thiols and Possible Reaction Mechanisms



we have identified the overarching reaction network, including an acid-catalyzed release of Cl_2 from NCS. The parameters that control the rate of Cl_2 release, and how these then change the overall behavior of the process are also elucidated. To the best of our knowledge, this represents the first detailed kinetic study of the reaction of an organosulfur compound with NCS in organic (non-aqueous) media.[15]

2. RESULTS AND DISCUSSION

2.1. Preliminary Studies. The chlorination of 4-fluorothiophenol (**1**) under typical reaction conditions (i.e., reagent concentrations 0.030−0.3 M) proved ideal for *in situ* monitoring by ^{1}H and ^{19}F NMR spectroscopy. Reactions were conducted at 27 °C in CH_2Cl_2, using 1,3,5-trifluorobenzene as an internal standard, and analysis of the temporal concentration profiles at a series of initial thiol (**1**) concentrations proved informative, Figure 1. With thiol **1** as the limiting reagent, the corresponding disulfide **2** was found to accumulate then deplete prior to the sulfenyl chloride **3** being generated (Figure 1A). A series of para- and meta-substituted thiophenols were explored under analogous conditions, and while they showed similar kinetic profiles to **1**, there was no clear correlation between electronic effects and their reactivity, see the Supporting Information Section S2.4. These initial observations rule out a simple nucleophilic substitution mechanism (I, Scheme 1) between the thiol and the NCS but do not identify the provenance, or role, of disulfide **2**.

Reactions where the thiol (**1**) was in excess over the chlorinating agent were more revealing, especially at high initial concentrations. For example, reaction of **1** (198 mM) with NCS (97 mM) resulted in an accumulation then depletion of the sulfenyl chloride ($[\mathbf{3}]_{max} \approx 3$ mM) concurrent with formation of the disulfide **2** as the major product, Figure 1B.

2.2. Identification of HCl-Catalysis. Clear sigmoidal profiles for the consumption of NCS and **1** were observed under all conditions explored, see the Supporting Information Section S2. This behavior, see e.g., Figure 1A, is characteristic of the generation of a more reactive system as the thiol (**1**) and NCS are consumed.[16] No intermediate succinimide or organosulfur derivatives, other than NHS, disulfide **2**, and sulfenyl chloride **3** were detected. Aromatic electrophilic chlorinations are reported to be accelerated by sulfides and by HCl,[17] and we, thus, evaluated the effect of disulfide **2** and HCl on the chlorination of **1** by NCS. Reaction profiles for the consumption of **1** and NCS in the presence and absence of exogenous disulfide **2** were identical. Conversely, exogenous HCl reduced the induction period of the sigmoidal profile and increased the maximum rate. The higher the initial HCl concentration, the greater these effects became, see the Supporting Information Section S2.2.2. Analysis of the evolution of the net ^{1}H NMR signal arising from {HCl + nH$_2$O} Figure 1A,B; gray lines, indicated that there is a rise and then fall in the HCl concentration that mirrors that of the disulfide **2**. The kinetics of the reaction of the sulfenyl chloride **3** with thiol **1** were analyzed by stopped-flow UV−vis spectrophotometry, monitoring the consumption of **3** (λ = 390 nm) under pseudo first order conditions, and found to be rapid ($k_{SH} \approx 5.0$ M^{-1} s^{-1}) relative to the thiol chlorination process, **1** + NCS.

The observations outlined above suggested that the progressive accumulation of HCl, generated by rapid reaction of the thiol substrate (**1**) with the sulfenyl chloride (**3**), causes a progressive increase in the rate of consumption of **1**.[16] If correct, then efficient trapping of sulfenyl chloride **3** should attenuate the autoacceleration. Stopped-flow UV experiments identified cyclohexene **4** as a suitably efficient scavenger of the sulfenyl chloride **3** ($k_{ene}/k_{SH} \geq 20$). Chlorination of thiol **1** in the presence of alkene **4** proceeded with substantial reduction in the rate of consumption of **1** and co-generated the β-chlorothioether **5**, Figure 1C. The inhibition of the autoacceleration was more sustained at higher alkene concentrations. The impact of HCl was further manifested in the second stage of the overall reaction, i.e., the chlorination of the disulfide to generate the sulfenyl chloride (**2** → **3**). There was no reaction between NCS and independently synthesized disulfide **2** until addition of HCl,[18] upon which sulfenyl chloride **3** and NHS were cleanly generated, see the Supporting Information Section S3.1.

2.3. Mechanism of the HCl-Catalyzed Chlorination Pathway. The chlorinolysis of disulfide **2** is the final and key stage in the overall chlorination of thiol **1** and analysis of this step in isolation provided further insights into the roles of HCl as catalyst. Initial experiments demonstrated that disulfide **2** was unreactive to NCS, or to HCl, alone, but in combination led to production of sulfenyl chloride **3**, see the Supporting Information Section S3.1. Moreover, HCl and NCS cleanly generated NHS as the only ^{1}H NMR-detectable product, and addition of either thiol **1** or disulfide **2** to the pre-reacted combination of HCl and NCS immediately and quantitatively generated the sulfenyl chloride **3**. The material balance and reactivity are indicative of molecular chlorine as the "^{1}H NMR silent" co-product from HCl + NCS,[19] a conclusion further supported by the growth of a UV−vis absorption band at λ = 330 nm, characteristic of molecular chlorine,[20] Figure 1D, right. Monitoring the evolution of Cl_2 (λ = 330 nm) from HCl under pseudo-first order conditions allowed estimation of the bimolecular rate constant (k_{Cl2} = 0.027 M^{-1} s^{-1}; when [H$_2$O] ≈ 2 mM) for its slow-release from HCl and NCS in DCM, see the Supporting Information Section S5.3.[21a]

Further ^{1}H NMR-spectroscopic analysis of reactions of HCl with NCS indicated that the temporal evolution of HCl, NCS,

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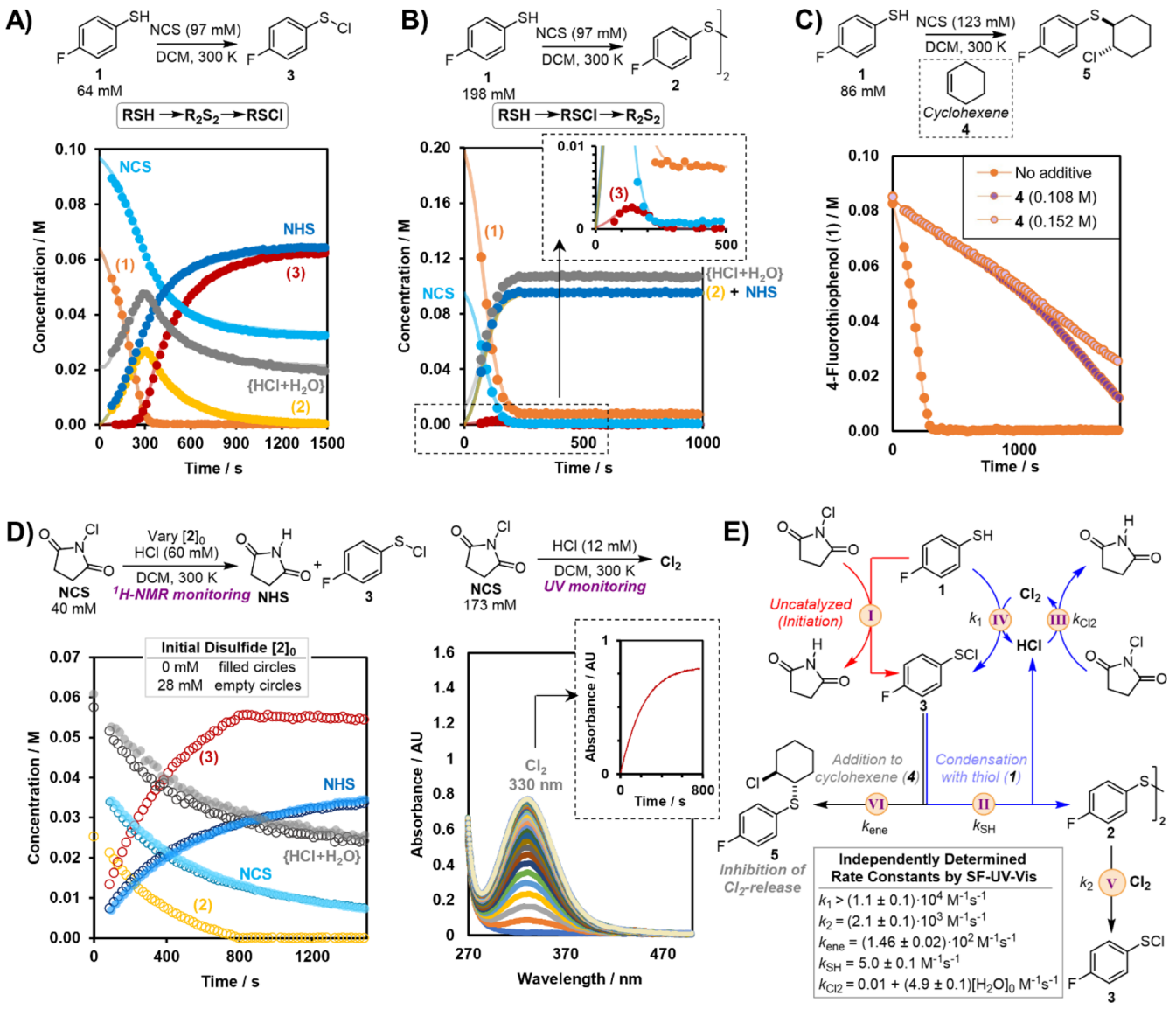
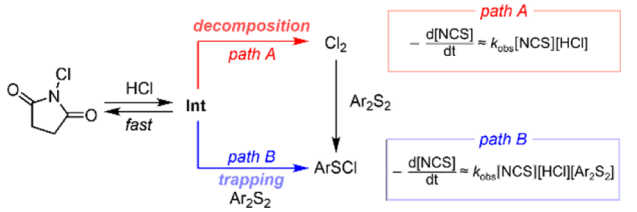


Figure 1. (A) NCS-mediated chlorination of 4-fluorothiophenol **1** (limiting reagent) and reaction profile analyzed by *in situ* ^{1}H NMR spectroscopy; (B) NCS-mediated chlorination of 4-fluorothiophenol **1** (excess) and reaction profile analyzed by *in situ* ^{1}H NMR spectroscopy—NB product **2** and NHS overlay; (C) effect of cyclohexene (**4**) on the rate of consumption of 4-fluorothiophenol **1**; (D) left: temporal concentration profiles indicating the independence of the rate of HCl-induced conversion of NCS to NHS on disulfide **2** concentration, as analyzed by *in situ* ^{1}H NMR spectroscopy. Right: UV monitoring of the growth of Cl_2 in the absence of disulfide **2** under pseudo first-order conditions; (E) minimal reaction network for the conversion of thiols into sulfenyl chlorides mediated by NCS, and bimolecular rate constants measured independently under pseudo-first order conditions at 27 °C by stopped-flow UV−vis spectrophotometry (for details see Supporting Information, Section S5).

and NHS were independent of the presence or absence of disulfide **2** even at high concentrations, Figure 1D, left. This strongly suggests that the chlorination of disulfide **2** by NCS involves free Cl_2 (Scheme 2, path A),[22] rather than a bifurcation via a reactive intermediate such as an NCS·HCl adduct (Scheme 2, path B).[23,24]

Moreover, addition of cyclohexene (**4**) into these reactions delivered *trans*-1,2-dichlorocyclohexane as the major product, without consumption of disulfide **2**. Mass balance analysis indicated that other products, including allylic chlorides, are also formed. The selectivity for *trans*-1,2-dichlorocyclohexane was constant throughout the reaction ($f_{Cl2} \approx 0.7$; see Supporting Information Section S3.2.3)[25] and consistent with the selectivity reported for reaction of **4** with Cl_2 in trichlorotrifluoroethane under comparable conditions (f_{Cl2}(lit.) = 0.75; $[Cyclohexene]_0 \approx 80-300$ mM; 25 °C).[26] The minimal overall reaction network

Scheme 2. Pathways Considered for the Chlorination of Disulfides with the NCS/HCl System



elucidated to account for the chlorination of thiols mediated by NCS comprises five steps (I–V) and is outlined in Figure 1E.[27] The NCS initiates the reaction by slow formation of sulfenyl chloride **3** (Figure 1E, step I). The sulfenyl chloride **3** then reacts with thiol **1**, step II, to generate HCl and disulfide **2**. The HCl-

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catalyzes the release of Cl_2, step III, which rapidly converts thiol **1** to sulfenyl chloride **3** and additional HCl, step IV, thus inducing the observed rate acceleration. Upon complete consumption of thiol **1**, the accumulated HCl reacts with NCS to slowly release Cl_2, which cleaves disulfide **2** to re-generate the sulfenyl chloride **3** as the final product, step V. Additives that can outcompete the thiol **1** in their reaction with sulfenyl chloride **3**, e.g., cyclohexene (**4**) where $k_{ene}/k_{SH} \geq 20$, step VI, result in inhibition of Cl_2-release and as a consequence the rate of consumption of the thiol.

2.4. Dichotomous Effects of Water. The presence of water in the dichloromethane solvent was found to induce two distinct effects on the rate of chlorination of thiol **1** by NCS.[28] The kinetics were explored in detail by ^{1}H NMR-spectroscopy under standardized conditions ($[\mathbf{1}]_0$ = 45 mM, $[NCS]_0$ = 65 mM) with varying quantities of water. Numerical method simulations, using the network depicted in Figure 1E, see the Supporting Information Section S7, indicated that at concentrations of up to about 35 mM, the water accelerates the rate of release of chlorine (k_{Cl2}) from the NCS (Figure 2A, left), with a first-order dependence on $[H_2O]_0$. The analysis yields $d[NHS]/dt = k_{Cl2}[HCl][NCS]$, where $k_{Cl2} \approx 5[H_2O]_0 + 0.02\ M^{-1}\ s^{-1}$. This is in reasonable agreement with the rates of Cl_2-release from HCl and NCS independently determined by UV−vis under both nominally anhydrous conditions[21a] and with exogenous water (see, Supporting Information Section S5.3).

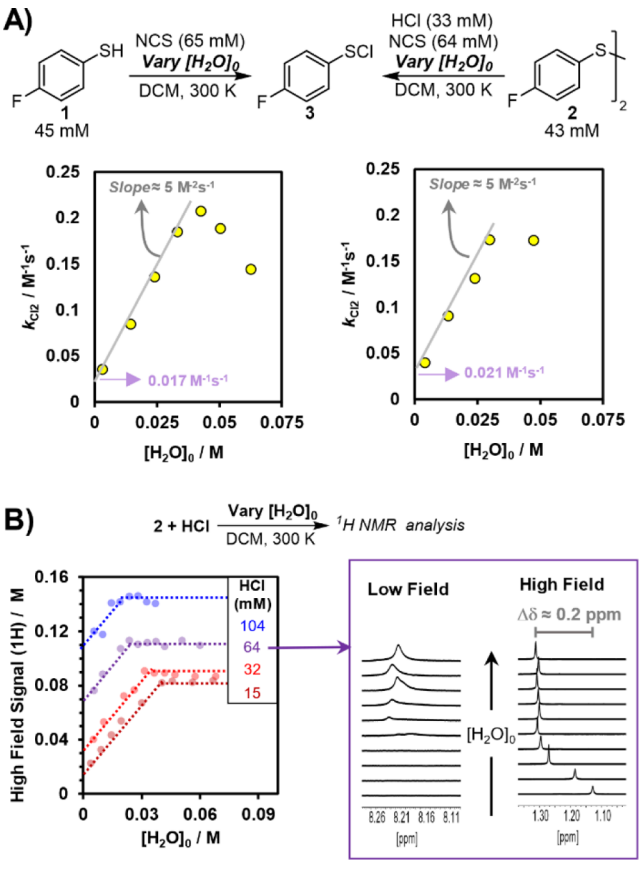

Figure 2. (A) Effect of exogenous water on the rate of Cl_2-release, k_{Cl2}, in the chlorination of thiophenol **1** (left) and its disulfide **2** (right) by NCS; (B) ^{1}H NMR analysis of the titration of *in situ* generated HCl solutions in DCM with water (*x*-axis; left) and the effects on the high-field ^{1}H NMR signal integral (*y*-axis, left) and chemical shift (right) of the time-averaged $\{H_2O + nHCl\}$ signals.

Analogous acceleration (k_{Cl2}) was observed for the chlorinolysis of disulfide **2** by NCS + HCl (Figure 2A, right). The first order dependence on water concentration and the characteristic changes in speciation and behavior of acidic mixtures at various water concentrations (Figure 2B), suggest catalysis via $[H_3O^+Cl^-]$.[21b] In both the chlorination of **1** and of **2**, the accelerating effect of water was lost at concentrations above about 35 mM, with further increases in water concentration leading to attenuated rates, Figure 2A. There were no changes evident in the chemical shift or line-shape of any of the ^{1}H NMR signals of **1**, **2**, **3**, NCS, or NHS between the two rate regimes of Cl_2-release. Indeed, the only signal that changes during reaction is the N−H of the NHS.

^{1}H NMR spectra recorded *in situ* during the chlorination of thiol **1** under the standard conditions contained a broad singlet arising from the time-averaged protons in the combination $\{H_2O + nHCl\}$. For reactions where the water concentration was ≤ 35 mM, the chemical shift of the singlet was $\delta_H \sim 1.5$ ppm at the start of the reaction, i.e., when $n = 0$. The shift decreased as the disulfide **2** formed ($\Delta\delta \approx -0.2$ ppm) and then increased as **2** was consumed to give the final sulfenyl chloride **3** (see Supporting Information Section S2.2.5). The integral of the singlet also changed, as HCl accumulated and then depleted, and this change mirrored the concentration profile of disulfide **2**, see Figure 1A. However, *in situ* ^{1}H NMR spectroscopic analysis of the chlorination reactions when the water concentration was ≥40 mM were distinctly different. As the reactions progressed and the HCl accumulated, a new species appeared at low field (δ_H = 7.2−8.2 ppm). After this point, the evolution of the integral of the $\{H_2O + nHCl\}$ singlet at $\delta_H \sim 1.5$ ppm no longer correlated with the concentration of disulfide **2**, see the Supporting Information Section S2.2.5.

The transition between the two distinct regimes in the rate of chlorine release occurred substantially below the limiting solubility of water in solutions of the internal standard in dichloromethane ($[H_2O]_{max} \approx 90-110$ mM). Significant insight was provided by ^{1}H NMR spectroscopic analysis of intensity of the $\{H_2O + nHCl\}$ singlet in reference samples containing four different initial HCl concentrations (15−105 mM), Figure 2B. The HCl was generated *in situ* from thiol **1** and sulfenyl chloride **3** (Figure 2B) and then small aliquots of water added, with ^{1}H NMR spectra recorded after each addition. The resulting plots exhibited two distinct regimes. In the first, there is a simple linear relationship between integral of the singlet at high field (δ_H = 1.0−1.5 ppm) and the added water corresponding to $[\{H_2O + nHCl\}] = [HCl]_0 + [H_2O]_{added}$. In the second regime, the integral and chemical shift of the high field singlet became independent of added water, and a set of a broad and overlapping peaks appeared at lower fields (δ_H = 7.8−8.2 ppm). The higher the initial concentration of HCl, the lower the total water concentration required to transition from one regime to the other. We tentatively interpret these phenomena as arising from changes in the speciation of $\{H_2O + nHCl\}$ and its partial microscopic separation from the bulk medium. Irrespective of the origin, the effect is detrimental to the rate of the chlorination. Thus, paradoxically, while both HCl and water can be effective catalysts for chlorination in dichloromethane solution, they prove detrimental to each other when combined above a critical concentration.

2.5. Role of HCl in Oxychlorination. It has been recently reported that alcohol additives induce NCS-mediated sulfide oxychlorination to afford sulfonyl halides, a process nominally proceeding via the corresponding sulfenyl chloride.[13a] The HCl-

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catalyzed pathway for thiol chlorinolysis, *vide supra*, provides an alternative perspective to the mechanism of the oxychlorination, however, to the best of our knowledge, the possibility that HCl plays a key role in this has not been previously discussed.

In situ ^{1}H NMR spectroscopic analysis of the kinetics of NCS-mediated oxychlorination of thiol **1** (Figure 3A) and sulfenyl

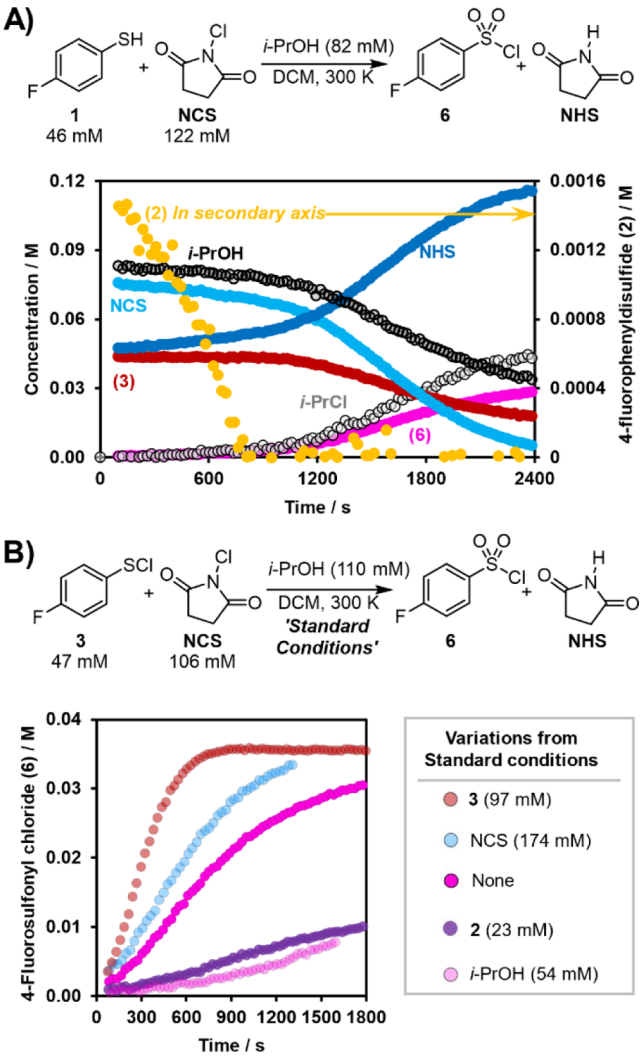


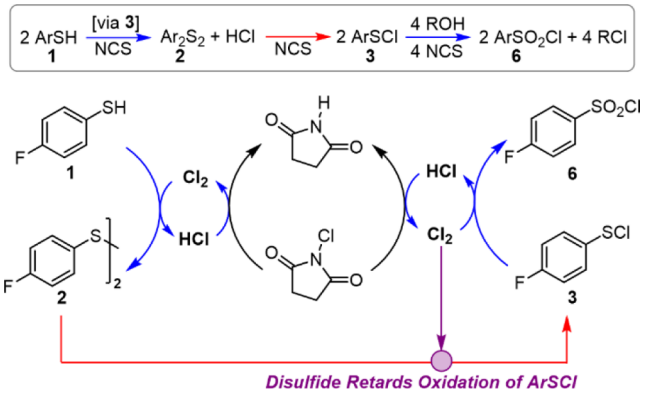
Figure 3. (A) Reaction profile for the NCS/*i*-PrOH-mediated oxychlorination of thiol **1**, analyzed by *in situ* ^{1}H NMR spectroscopy; (B) effect of reaction conditions and additives on the evolution of **6** in oxychlorination of **3**; analyzed by *in situ* ^{1}H NMR spectroscopy.

chloride **3** (Figure 3B) in DCM in the presence of *i*-PrOH proved insightful. Thiol **1** was converted into sulfenyl chloride **3** (≥94%) within ~90 s, Figure 3A, without any detectable loss of iso-propanol within this initial period. The rate of thiol chlorination is similar in magnitude to that observed in the low water concentration regime (Figure 2A), indicating that alcohols are also effective co-catalysts for Cl_2 release.[29] A significant induction period (~800 s) followed the initially fast accumulation of **3**, with the sulfenyl to sulfonyl oxidation (**3** → **6**) then taking place, with concomitant conversion of *i*-PrOH to *i*-PrCl.[30] The induction period was chronologically linked (Figure 3A) with the consumption of the last traces of the disulfide intermediate (**2**) from the initial thiol chlorination (**1** → **2** → **3**). Analysis of the kinetics of sulfenyl to sulfonyl oxidation (**3** → **6**) conducted independently, confirmed that the presence of disulfide **2** (23 mM) attenuates the rate (Figure 3B, bright pink *vs* purple datapoints).

Sulfenyl chloride **3** does not react with NCS or with *i*-PrOH independently, see the Supporting Information Section S4, and the overall oxidation rate (**3** → **6**; Figure 3B) depends, in a complex manner, on all three components:[**3**], [NCS], and [*i*-PrOH]. This dependency rules out a mechanism involving the slow generation of reactive chlorination reagent(s) from NCS and *i*-PrOH prior to substrate (**3**) commitment. The reactions also display sigmoidal profiles. Addition of exogenous HCl enhanced the rate of this process, whereas exogenous sulfonyl chloride (**6**) did not lead to any changes (see Supporting Information, Section S4.2.1). This is, thus, consistent with a slow NCS-mediated process evolving into a faster phase of HCl-catalyzed Cl_2-release.

Taking all the above observations into account, we suggest an alternative mechanism to those previously proposed for thiol oxychlorination by NCS[13a] and related species.[15c] In this mechanism, Scheme 3, there are two phases of HCl-catalyzed

Scheme 3. HCl-Catalyzed Thiophenol Oxychlorination with *N*-Chlorosuccinimide (NCS)[a,b]



[a]ROH = H_2O, *i*-PrOH. [b]Simplified sequence without the various initiation steps that lead to HCl-generation.

acceleration: **1** → **2** and **3** → **6**.[31] Disulfide (**2**) acts as an attenuator between the two phases, leading to two kinetically distinct reaction sequences, Figure 3A.

3. CONCLUSIONS

Using *in situ* ^{1}H NMR and UV−vis spectroscopic reaction monitoring in combination with numerical methods analysis of the kinetics, we have investigated the networks of reaction sequences that underpin the chlorination and oxychlorination of thiophenols by NCS in dichloromethane. The reactions have been investigated in the presence and in the absence of hydroxylic additives (H_2O and *i*-PrOH). A key overall finding is that several slow processes lead to the generation of HCl, and the HCl accelerates the release of Cl_2 from NCS. It is the Cl_2 that is the dominant chlorinating reagent throughout the reaction network, Scheme 3, effecting oxidation of thiols (**1**) and disulfides (**2**), and eventually oxidation of sulfenyl chlorides (**3**) to the corresponding sulfonyl chlorides (**6**) when water or alcohols are present. The processes are co-catalyzed by alcohols and, within physical limits of homogeneity, by water, Figure 2A.

There are two key outcomes from the investigation:

(i) NCS-mediated (oxy)chlorinations proceed primarily *via in situ* generated Cl_2, which undergoes rapid and

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exothermic reaction with the substrates and intermediates (**1**, **2**, **3**). The chlorine generation from NCS is catalyzed by HCl, and under some conditions, this can result in (oxy)chlorinations accelerating dangerously. This experimentally determined mechanistic evidence explains prior reports that ArSH/NCS chlorinations can "bump"[13a] or evolve with high exothermicity.[12e,14a,15b,19] For reactions involving high substrate concentrations, or conducted at scale, the slow addition of the substrate to *N*-chlorosuccinimide and/or use of lower temperatures may be a useful precaution to avoid "run-away" processes. In these cases, use of continuous-flow technologies may provide a safer alternative to batch reactors when the process is required to be run at scale.[15c] Moreover, a switch from a slow regime into accelerated release of Cl_2 could also be an important mechanism in other NCS-mediated processes that involve intermediacy or co-production of HCl.

(ii) The relative reactivities of the thiol (**1**), disulfide (**2**), and sulfenyl chloride (**3**), to the dominant chlorinating agent, i.e., Cl_2, to each other, and to other species such as cyclohexene (**4**) have been elucidated. The results inform the most time-effective procedures for preparing organosulfur species from thiols *via* their corresponding sulfenyl chlorides. Single-step multicomponent protocols are suitable for sulfenyl chloride scavengers that are either less reactive than the thiol ($k_{substrate} \leq k_{SH}$) or highly reactive but also produce an equimolar quantity of HCl.[13] Conversely, highly efficient sulfenyl chloride scavengers ($k_{substrate} > k_{SH}$) that do not co-generate HCl (e.g., alkenes) are best employed in two-step protocols where the scavenger is added after sulfenyl chloride generation is complete.[12]

Overall, the detailed insights into the mechanisms and kinetics of NCS-mediated (oxy)chlorination of thiols, disulfides, and sulfenyl chlorides in dichloromethane will inform the design of experimental conditions to optimize rates and selectivity and aid in safer application and scale-up of these processes.

4. SAFETY CONSIDERATIONS

Caution! Chlorination of thiols with *N*-chlorosuccinimide can lead to explosion when using reactive thiols and/or run under concentrated conditions in closed systems without temperature control. This is due to the exothermicity of the process and the decreased solubility of HCl in dichloromethane at raised temperatures. The use of low reagent concentrations, efficient cooling, and slow addition protocols are all recommended under batch conditions when possible. Alternatively, the use of continuous flow technologies can also be considered as a method to reduce the risk of developing hazardous conditions.

The mechanistic studies reported herein reveal that the catalytic action of the *in situ* released HCl accelerates the consumption of the starting thiophenol **1**. This is linked to the exothermic behavior exhibited under concentrated conditions (see Supporting Information, Section S8). Video recordings of reactions under these conditions (limiting reagent ≥0.2 M) showed that the higher the initial reagent concentrations, the faster the temperature rise. Reaction of **1** (0.3 M) with NCS (0.2 M) in CH_2Cl_2 (b.p. = 40 °C) in a loosely sealed round bottom flask resulted in the solution temperature increasing from 19 to 35 °C in 35 s, at which point there was an abrupt and vigorous evolution of gaseous HCl that resulted in the stopper being very forcefully ejected from the flask. These experiments were conducted to illustrate the potential for this process to become hazardous; they were risk assessed in advance, run under carefully controlled conditions, with full and appropriate personal protection equipment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c02380.

Experimental details, reaction profiles, kinetic analyses, experimental assessment of safety hazards, and characterization data (PDF)

Video recording of reaction of 4-fluorothiophenol (0.2 M) and NCS (0.2 M) (MOV)

Video recording of reactions of 4-fluorothiophenol (0.3 M) and NCS (0.3 M) (MOV)

Video recording of reactions of 4-fluorothiophenol (0.2 M) and NCS (0.4 M) (MOV)

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Notes

The authors declare no competing financial interest.

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(22) In the presence of chloride-anion in AcOH or in acidic aqueous conditions, the zero-th order dependence on substrate concentration (ethers, alcohols, arene) has been also used to justify a mechanism involving initial rate-limiting delivery of Cl_2 from NCS. See, (a) Farook, S. M.; Sivakamasundari, S.; Viswanathan, S. Kinetics of Chlorination of Certain Aromatic Compounds Using N-Chlorosuccinimide. *Indian J. Chem.* **1984**, *23A*, 239−240. (b) Srinivasan, N. S.; Venkatasubramanian, N. Oxidation of alcohols by N-chlorosuccinimide—a kinetic study. *Tetrahedron* **1974**, *30*, 419−425. Ethers in water (c) Priya, V.; Balasubramaniyan, M.; Mathiyalagan, N. Kinetic study on the reaction of N-chlorosuccinimide with benzyl phenyl ethers in aqueous acetic acid. *J. Chem. Pharm. Res.* **2011**, *3*, 522−528. and references therein

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(25) The constant reagent-independent selectivity would be consistent with the intermediacy of a cyclohexenyl-derived chloronium intermediate from which the products are obtained via chloride addition (1,2-dichlorocyclohexane) or proton elimination in the form of HCl (3-chlorocyclohexene). See ref 26.

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(27) The model is minimal and does not include a range of other processes that may catalyze the release of Cl_2 and hence change the reaction rate. Water, exogenous succinimide (NHS) and 4-fluorothiophenol (**1**) were all found to enhance the rate of formation of sulfenyl chloride **3** from either 4-fluorothiophenol (**1**) or 4-fluorophenyldisulfide (**2**). See Supporting Information, Section S7. An anonymous reviewer suggested the term ''intermediate delayed catalysis'' may better describe the overall production of sulfenyl chloride by reaction **1** → **3**, see also ref 16.

(28) Overoxidation products were not detected while monitoring of the conversion of 4-fluorothiophenol (**1**) was converted into 4-fluorsulfenyl chloride (**3**). We attribute this observation to the strong inhibitory role of 4-fluorophenyldisulfide (**2**) in the oxidation into its sulfonyl chloride (**6**), even when in trace amounts (see, Figure 3A).

(29) While water may contribute to acceleration, the water content alone (5−10 mM) does not account for the magnitude of the rate enhancement observed in these reactions for the conversion of thiol **1** into sulfenyl chloride **3**.

(30) Traces of water may be the source of the slight overproduction of sulfonyl chloride **6** relative to the amount of isopropanol consumed in these reactions. See Supporting Information, Section S4.1.

(31) Previous investigations have identified $ArSCl_3$ intermediates in the oxidation of arylsulfenyl chlorides with Cl_2 in acetic acid (see, ref 5f), and thus 4-fluorophenylsulfur trichloride may be involved in the conversion of **3** → **6** by the NCS/i-PrOH system.

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