Heteroatom Chemistry
Volume 18, Number 5, 2007

Reactions of Cysteine Sulfenyl Thiocyanate with Thiols to Give Unsymmetrical Disulfides

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Received 26 October 2006; revised 14 November 2006

ABSTRACT: *Cysteine sulfenyl thiocyanate (CSSCN) reacts with thiols at pH 0 to cleanly yield disulfides. 2-Mercaptoethanol (2-MESH), 3-mercaptopropionic acid (3-MPASH), penicillamine (PENSH), and glutathione (GSH) react with CSSCN to give the corresponding mixed disulfides: 2-MESSC, 3-MPASSC, PENSSC, and GSSC. These compounds are stable at pH 0 and have been characterized by ^{1}H and ^{13}C NMR spectroscopy.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:467–471, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20340

INTRODUCTION

One conventional approach to preparing unsymmetrical disulfides involves the reaction of a sulfenyl derivative with a thiol (Eq. (1)) [1].

$$RSX + R'SH \rightarrow RSSR' + HX \qquad (1)$$

Suitable electrophiles for preparing unsymmetrical disulfides via this approach include thiosulfinate esters (X = RSO), thiosulfonate esters ($X = RSO_2$), and sulfenyl chlorides (e.g., X = Cl); however, the foci of this report are sulfenyl thiocyanates (X = the pseudohalide SCN) [2–10]. Although methodologies exist to synthesize unsymmetrical disulfides, pure products can be difficult to isolate due to their tendency to undergo disproportionation to give thermodynamic mixtures [11] of symmetrical and unsymmetrical disulfides (Eq. (2)).

$$2RSSR' \rightleftharpoons RSSR + R'SSR' \qquad (2)$$

The synthesis of unsymmetrical disulfides is more challenging in protic solvents, where sulfenyl derivatives are generally subject to solvolysis (e.g., hydrolysis), and acid/base catalyzed disulfide disproportionation reactions can be facile [12,13]. Nonetheless, there is particular interest in preparing unsymmetrical disulfide derivatives of cysteine. Since cysteine itself is only soluble in water and the most polar protic organic solvents (e.g., methanol and acetic acid), one is obligated to either employ protic solvents or synthesize derivatives of cysteine that are soluble in aprotic organic solvents. The latter approach is complicated by the fact that the process of deprotecting the polar carboxylic and/or amine group of cysteine after preparation of the unsymmetrical disulfide can lead to the aforementioned disproportionation reactions. Accordingly, most of the syntheses that have involved cysteine made use of aqueous medium, or in some cases, mixed solvent systems.

One impetus for studying unsymmetrical disulfides of cysteine is that many such derivatives are known to be biologically active. For example, the mixed disulfide of L-cysteine and 2-mercaptoethanol plays a key role during the uptake of cysteine into

This paper was presented in part at the 22nd International Symposium on the Organic Chemistry of Sulfur (ISOCS-22), August 20–25, 2006, Omiya Sonic City, Saitama, Japan.

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Contract grant sponsor: Petroleum Research Fund.
Contract grant number: 42850-AC4.
Contract grant sponsor: American Heart Association.
Contract grant number: 0555677Z.
Contract grant sponsor: National Science Foundation.
Contract grant number: CHE-0503984.

mouse lymphoma cells that are cultured in the presence of L-cystine and 2-mercaptoethanol [14]. Intracellular reduction of the disulfide bond of the unsymmetrical disulfide provides the cysteine required for cell growth. Other biologically relevant derivatives include mixed disulfides of proteins. Indeed, glutathiolation of cysteine residues in proteins is believed to play an important role in the regulation of the functions and activities of many proteins and enzymes [15–19].

Using thiocyanogen, $(SCN)_2$, as an electrophilic thiocyanating agent [20], we have previously synthesized the sulfenyl thiocyanate derivatives of penicillamine (PENSCN) and of the tripeptide glutathione (GSSCN) [5]. We have observed that both compounds are stable indefinitely at pH 0 [5]. However, the sulfenyl thiocyanates are unstable above pH 0, whereupon hydrolysis yields a cascade of reactive sulfur species that are likely derived from sulfenic acid [5]. We report here the in situ synthesis of the parent compound, cysteine sulfenyl thiocyanate (CSSCN). We find that CSSCN reacts cleanly at pH 0 with 2-mercaptoethanol (2-MESH), 3-mercaptopropionic acid (3-MPASH), penicillamine (PENSH), and glutathione (GSH) to give the corresponding unsymmetrical disulfides: 2-MESSC, 3-MPASSC, PENSSC, and GSSC (Chart 1). Furthermore, the resulting unsymmetrical disulfides are stable with respect to disproportionation at pH 0. Thus, Eq. (3) suggests a general procedure for synthesizing unsymmetrical disulfides in aqueous solvent.

$$\begin{aligned} \mathrm{RSH} + (\mathrm{SCN})_2 &\xrightarrow{\mathrm{pH}=0} \mathrm{RSSCN} + \mathrm{H^+} + \mathrm{SCN^-} \\ \mathrm{RSSCN} + \mathrm{R'SH} &\xrightarrow{\mathrm{pH}=0} \mathrm{RSSR'} + \mathrm{H^+} + \mathrm{SCN^-} \end{aligned} \quad (3)$$

RESULTS

The sulfenyl thiocyanate derivative of cysteine was synthesized in situ using a procedure that was analogous to the one we previously employed to synthesize PENSCN and GSSCN: thiocyanogen was synthesized in an organic solvent and subsequently extracted into a 1 M HCl solution containing 1 molar equivalent of cysteine. The resulting CSSCN was characterized by ^{1}H and ^{13}C spectroscopy. In particular, the SCN functional group of CSSCN exhibits a characteristic ^{13}C chemical shift. The assignment (112.4 ppm), which was confirmed by preparing the S^{13}CN-enriched derivative, is comparable to the corresponding chemical shifts that have been previously reported for PENSCN (114.7) and GSSCN (114.9) [5]. It was necessary to employ approximately 10% excess $(SCN)_2$ to ensure complete conversion of CSH to CSSCN. The excess is probably required because once thiocyanogen is extracted into the aqueous phase, it undergoes competitive reactions that result in its decomposition [21,22]. Thiocyanogen can be stabilized in 1 M HCl by adding thiocyanate [5], but that was unnecessary in the present case because the rate of reaction of thiocyanogen with CSH is apparently competitive with respect to its rate of decomposition. Once CSSCN is prepared in situ, the subsequent addition of 1 molar equivalent of an additional thiol produces the corresponding disulfide in quantitative yield (as determined by ^{1}H NMR spectroscopy). In the cases where the second thiol is not CSH, the unsymmetrical disulfides were obtained exclusively for the four thiols that were tested (2-MESH, 3-MPASH, PENSH, and GSH). The unsymmetrical disulfides, which have all been

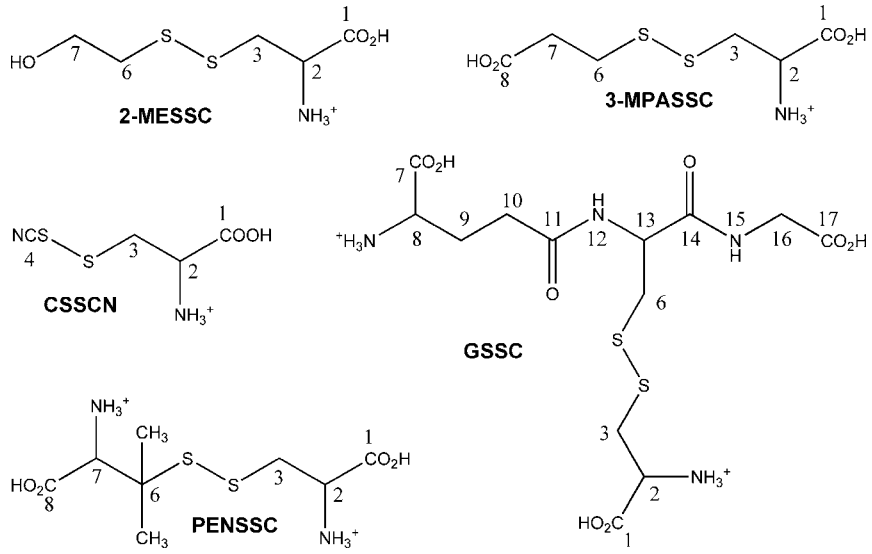

CHART 1

previously synthesized (vide infra), were characterized by ^{1}H and ^{13}C NMR spectroscopy.

DISCUSSION

Thiocyanogen has been previously employed by Hiskey et al. to prepare unsymmetrical disulfides of cysteine [2–4,6–10,23]. Hiskey's method consisted of a two-step procedure that involved in situ reaction of thiocyanogen with a cysteine derivative, often the ester, followed by the reaction of a second cysteine derivative. The intermediates were never characterized by Hiskey et al., but they were generally assumed to be sulfenyl thiocyanates. Different solvent systems were frequently employed by Hiskey for each step of the synthesis. In general, lower yields were observed when protic organic solvents were employed in the first step (e.g., AcOH), and no mixed disulfides were obtained if water or mixed aqueous solvent systems were employed in the first step [3]. In the interim, we have determined that sulfenyl thiocyanate derivatives of cysteine are subject to hydrolysis above pH 0, and that observation forms the basis of the modification of the Hiskey procedure that we report herein: water can be employed as a solvent in the first step, provided that the pH is adjusted to 0 before the addition of thiocyanogen.

As mentioned in the introduction, another challenge to preparing unsymmetrical disulfides is disproportionation. We note that the mixed disulfides we have prepared are stable in 1 M HCl for at least 4 days. This observation is somewhat surprising because acid-catalyzed disproportionation of disulfides has been reported previously [13]. Acid-catalysis has been explained by a general chain mechanism that involves nucleophilic attack by the disulfide on dithiosulfonium ions (Eq. (4)).

$$
\begin{aligned}
&\mathrm{RSSR' + H^+ \rightleftharpoons RSS(H)R'^{+} \rightleftharpoons RSSR'^{+}} \\
&\mathrm{RSSR' + RSS(H)R'^{+} \rightleftharpoons RSSSR'^{+} + RSH} \\
&\mathrm{RSSR' + RSS(H)R'^{+} \rightleftharpoons R'SSSR^{+} + R'SH} \qquad (4) \\
&\mathrm{RSSR' + R'SSSR^{+} \rightleftharpoons RSSSR'^{+} + RSSR} \\
&\mathrm{RSSR' + RSSSR'^{+} \rightleftharpoons RSSSR'^{+} + R'SSR'}
\end{aligned}
$$

Importantly, acid catalysis of disulfide disproportionation has not been found to be a particularly efficient process for the disulfides that have been studied to date. Significant rates for disproportionation are not generally observed for $[H^+]$ less than 5–10 M [13]. Thus, the rate of acid-catalyzed disproportionation at $[H^+] = 1$ M, the conditions we have employed, was anticipated to be very slow, and indeed this proved to be the case.

Although we have not observed significant disproportionation in 1 M aqueous acid, we note that disproportionation can be a facile process under more basic conditions. The base-catalyzed disproportionation mechanism is believed to proceed via partial hydrolysis of the disulfide bond to produce a catalytic amount of thiolate (Eq. (5)) [13].

$$
\begin{aligned}
&\mathrm{RSSR' + OH^- \rightleftharpoons RSOH + R'S^-} \\
&\mathrm{RSSR' + R'S^- \rightleftharpoons RS^- + R'SSR'\ \text{etc.}} \qquad (5)
\end{aligned}
$$

The mechanism of exchange of thiolates with disulfides has been extensively investigated by both experimental [24,25] and theoretical methods [26]. Given the facile disproportionation that can occur under more basic conditions, only acidic medium should be employed when working with unsymmetrical disulfides in aqueous solutions.

While the unsymmetrical disulfides 2-MESSC [27], 3-MPASSC [28], PENSSC [29], and GSSC [30] have been previously synthesized, the CSSCN route appears to be superior from the perspectives of chemical yields and the simplicity of the procedure. Furthermore, since thiocyanogen is very selective for thiols, we anticipate no serious limitations of the procedure we have outlined, provided the reacting thiol is water-soluble and stable in 1 M acid. Significantly, while thiols are catalysts for the disproportionation of disulfides under neutral and basic pH conditions via the aforementioned mechanism (Eq. (5)), thiols are in fact inhibitors of disproportionation under acidic conditions [13]. Thus, one need not be concerned with less than quantitative coupling of sulfenyl thiocyanates with thiols that might leave behind slight excess thiol, since the latter is not expected to promote disproportionation of the disulfide produced under the acidic conditions that we have employed. We anticipate that the general methodology that is summarized in Eq. (3) will be of particular utility when synthesizing polypeptides that cannot be rendered soluble in organic media. It may be particularly interesting to investigate the selectivity of the coupling when faced with multiple thiols during a polypeptide synthesis.

EXPERIMENTAL

Syntheses

Materials. L-cysteine (97%), D-penicillamine (97–102%), 2-mercaptoethanol, 3-mercaptopropionic acid (99+%), L-gluthathione (99%), and a 35% (w/w) solution of deuterium chloride in deuterium oxide (99% D) were used as received from Aldrich-Sigma (Milwaukee, Wisconsin). Deuterium oxide (99.9% D) and thiocyanate (98% ^{13}C) were used as received from Cambridge Isotope Laboratories, Inc., (Andover, Massachusetts). All other chemicals were American Chemical Society certified grade or better.

Preparation of Cysteinyl Thiocyanate. Solutions of thiocyanogen in CCl_4 were prepared by oxidation of lead(II) thiocyanate with bromine, as described in the literature [1]. Lead(II) thiocyanate was prepared as a white solid by reacting ice-cold solutions of $Pb(NO_3)_2$ and NaSCN (two-fold excess) for about 30 min. The product was dried under vacuum for 3 days. The concentration of $(SCN)_2$ in CCl_4 was determined spectrophotometrically, $\varepsilon_{296\,nm} = 140\ M^{-1}\ cm^{-1}$ [2]. The compound CSSCN was prepared by extracting 1.1 molar equivalents of $(SCN)_2$ into a 1.0 M DCl solution that contained L-cysteine. The yield of CSSCN was typically 90%, as determined by ^1H NMR (0.5 M DCl/0.5 M HCl, 399.96 MHz) δ: 4.63 (dd, 1H, $^3J_{(2\text{-}3)} = 4.7$ Hz, $^3J_{(2\text{-}3')} = 7.3$ Hz, **H**-2), 3.85 (dd, 1H, $^2J_{(3\text{-}3')} = 15.7$ Hz, $^3J_{(3\text{-}2)} = 4.7$ Hz, **H**-3), 3.72 (dd, 1H, $^2J_{(3'\text{-}3)} = 15.7$ Hz, $^3J_{(3'\text{-}2)} = 7.3$ Hz, **H**-3′); $^{13}C\{^1H\}$ NMR (0.5 M DCl/0.5 M HCl, 100.58 MHz) δ 169.3 (C1), 112.4 (SCN), 51.3 (C2), 38.1 (C3).

General Procedure for the Preparation of Symmetrical Disulfides. The disulfides of 2-mercaptoethanol, 3-mercaptopropionic acid, and D-penicillamine were prepared by extracting $(SCN)_2$ into 1.0 M DCl containing 2 equivalents of the individual thiols. The resulting symmetrical disulfides were identified by comparing their ^1H NMR spectra with authentic samples. The yields were quantitative by NMR.

General Procedure for the Preparation of Mixed Disulfides. The mixed disulfides of L-cysteine with 2-mercaptoethanol, 3-mercaptopropionic acid, D-penicillamine, and L-glutathione were prepared by reacting stoichiometric amounts of the thiols with CSSCN. Solutions of the thiols were prepared in 1.0 M HCl and mixed with equal volumes of CSSCN solutions to make 15–20 mM mixed disulfide. The yields of the corresponding unsymmetrical disulfides were quantitative (based on CSSCN) as determined by ^1H NMR.

S-(2-Hydroxyethylthio)-L-cysteine (2-MESSC). ^1H NMR (0.5 M DCl/0.5 M HCl, 399.96 MHz) δ: 4.53 (dd, 1H, $^3J_{(2\text{-}3)} = 4.3$ Hz, $^3J_{(2\text{-}3')} = 7.7$ Hz, **H**-2), 3.91 (t, 2H, $^3J_{(7\text{-}6)} = 5.9$ Hz, $^3J_{(7\text{-}6')} = 5.9$ Hz, **H**-7), 3.43 (dd, 1H, $^2J_{(3\text{-}3')} = 15.2$ Hz, $^3J_{(3\text{-}2)} = 4.3$ Hz, **H**-3), 3.28 (dd, 1H, $^2J_{(3'\text{-}3)} = 15.2$ Hz, $^3J_{(3'\text{-}2)} = 7.7$ Hz, **H**-3′), 2.97 (t, 1H, $^3J_{(6\text{-}7)} = 5.9$ Hz, **H**-6); 2.96 (t, 1H, $^3J_{(6'\text{-}7)} = 5.9$ Hz, **H**-6′); $^{13}C\{^1H\}$ NMR (0.5 M DCl/0.5 M HCl, 100.58 MHz) δ 170.7 (C1), 59.1 (C7), 51.9 (C2), 39.4 (C6), 36.9 (C3).

S-(β-Carboxyethylthio)-L-cysteine (3-MPASSC). ^1H NMR (0.5 M DCl/0.5 M HCl, 399.96 MHz) δ: 4.51 (dd, 1H, $^3J_{(2\text{-}3)} = 4.5$ Hz, $^3J_{(2\text{-}3')} = 7.6$ Hz, **H**-2), 3.42 (dd, 1H, $^2J_{(3\text{-}3')} = 15.1$ Hz, $^3J_{(3\text{-}2)} = 4.5$ Hz, **H**-3), 3.29 (dd, 1H, $^2J_{(3'\text{-}3)} = 15.1$ Hz, $^3J_{(3'\text{-}2)} = 7.6$ Hz, **H**-3′), 3.04 (t, 2H, $^3J_{(6\text{-}7)} = 6.5$ Hz, **H**-6), 2.88 (t, 2H, $^3J_{(7\text{-}6)} = 6.5$ Hz, **H**-7); $^{13}C\{^1H\}$ NMR (0.5 M DCl/0.5 M HCl, 100.58 MHz) δ 176.1 (C8), 170.2 (C1), 51.4 (C2), 36.3 (C3), 33.1 (C7), 31.6 (C6).

L-Cysteine-D-penicillamine Disulfide (PENSSC). ^1H NMR (0.5 M DCl/0.5 M HCl, 399.96 MHz) δ: 4.50 (dd, 1H, $^3J_{(2\text{-}3)} = 4.9$ Hz, $^3J_{(2\text{-}3')} = 6.2$ Hz, **H**-2), 4.25 (s, 1H, **H**-7), 3.47 (d, 1H, $^3J_{(3\text{-}2)} = 6.2$ Hz, **H**-3), 3.48 (d, 1H, $^3J_{(3'\text{-}2)} = 4.9$ Hz, **H**-3′), 1.63 (s, 3H, **H**-6a), 1.53 (s, 3H, **H**-6b); $^{13}C\{^1H\}$ NMR (0.5 M DCl/0.5 M HCl, 100.58 MHz) δ 170.4 (C1), 169.7 (C8), 59.7 (C7), 52.2 (C2), 51.2 (C6), 39.1 (C3), 25.9 (C6a), 22.6 (C6b).

L-Cysteine-glutathione Disulfide (GSSC). ^1H NMR (0.5 M DCl/0.5 M HCl, 399.96 MHz) δ: 8.50 (d, $^3J_{(12\text{-}13)} = 8.0$ Hz, NH_{12}), 8.43 (br. t, $^3J_{(15\text{-}16)} = 6$ Hz, NH_{15}), 4.80 (ddd, 1H, $^3J_{(13\text{-}12)} = 8.0$ Hz, $^3J_{(13\text{-}6')} = 9.0$ Hz, $^3J_{(13\text{-}6)} = 4.5$ Hz, **H**-13), 4.52 (dd, 1H, $^3J_{(2\text{-}3)} = 4.2$ Hz, $^3J_{(2\text{-}3')} = 7.7$ Hz, **H**-2), 4.15 (t, 1H, $^3J_{(8\text{-}9)} = 6.5$ Hz, **H**-8), 4.05 (m, 2H, **H**-16), $^3J_{(16\text{-}15)} = 6$ Hz, 3.46 (dd, 1H, $^2J_{(3\text{-}3')} = 15.2$ Hz, $^3J_{(3\text{-}2)} = 4.2$ Hz, **H**-3), 3.32 (dd, 1H, $^2J_{(6\text{-}6')} = 14.2$ Hz, $^3J_{(6\text{-}13)} = 4.5$ Hz, **H**-6), 3.27 (dd, 1H, $^2J_{(3'\text{-}3)} = 15.2$ Hz, $^3J_{(3'\text{-}2)} = 7.7$ Hz, **H**-3′), 3.07 (dd, 1H, $^2J_{(6'\text{-}6)} = 14.2$ Hz, $^3J_{(6'\text{-}13)} = 9.0$ Hz, **H**-6′), 2.67 (m, 2H, **H**-10), 2.28 (m, 2H, **H**-9); $^{13}C\{^1H\}$ NMR (0.5 M DCl/0.5 M HCl, 100.58 MHz) δ 174.6 (C11), 173.0 (C17), 172.6 (C14), 171.5 (C7), 170.5 (C1), 52.5 (C13), 52.3 (C8), 51.8 (C2), 41.3 (C16), 38.1 (C6), 36.7 (C3), 31.1 (C10), 25.4 (C9).

NMR Studies

NMR experiments were carried out on a Varian Inova 400 MHz Spectrometer with VNMRJ2.1B software. 3-(Trimethylsilyl)-1-propane sulfonic acid, sodium salt (DSS, $\delta = 0.015$ ppm), and 1,4-dioxane ($\delta = 66.6$ ppm) were used as references for ^1H and ^{13}C NMR measurements, respectively. Assignments

were made using a combination of 1D (^{1}H, ^{13}C) and 2D methods (gCOSY, HSQC, and gHMBC). Pulse sequences were used as supplied by Varian. ^{1}H experiments employed presaturation to suppress the water signal. 1D ^{13}C experiments typically used a 5–10 s delay with a 45° pulse angle and were collected in 700–9000 transients with the exception of CSSCN. To aid in the observation of the carbon chemical shift in the thiocynate group of CSSCN, the T1 of ^{13}C-enriched thiocyanate was determined by inversion-recovery experiments to be 16.6(2) s. In addition, the thiocyanate group of CSSCN was ^{13}C-enriched and the ^{13}C spectrum was collected with a 30° pulse width, a 30-s delay and 2200 transients. In all cases, gCOSY experiments were collected with 1 transient and 128 increments. HSQC experiments were collected with 88 transients and 128 increments. gHMBC experiments were collected with 32–200 transients and 128 increments.

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