Table III. Rate Constants for Symmetrical Thiol/Disulfide Exchange

thiol disulfide pair	pD	k, L/mol s
glutathione/oxidized glutathione	8.46	9.1[a]
	8.93	21[a]
	9.43	45[a]
	10.41	60[a]
	11.40	60[a]
cysteine/cystine	10.52	12[b]
	10.60	9.1[c]
	11.40	5.0[c]
homocysteine/homocystine	11.2	27[d]
	11.7	17[e]
	12.4	20[e]
2-mercaptoethanol/2-hydroxyethyl disulfide	9.45	4.9[f]
	10.40	27[f]
	11.40	25[f]
mercaptoacetic acid/2,2'-dithiodiacetic acid	10.28	2.6[g]
	11.06	2.5[g]
	12.04	2.6[g]
3-mercaptopropionic acid/3,3'-dithiodipropionic acid	10.60	4.2[h]
	11.45	8.9[i]
cysteamine/cystamine[j]	12.58	22[j]
	13.63	24

[a] 33 °C; 0.20 M GSH, 0.10 M GSSG; measured by doing the inversion-transfer experiment using the Cys-C_α carbon resonances of GSH and GSSG. [b] 29 °C; 0.300 M CSH, 0.150 M CSSC; C_α carbon resonances. [c] 25 °C; 0.200 M CSH, 0.100 M CSSC; $C_\alpha H$ proton resonances. [d] 38 °C; 0.362 M HCSH, 0.149 M HCSSCH; C_α carbon resonances. [e] 38 °C; 0.568 M HCSH, 0.235 M HCSSCH; C_α carbon resonances. [f] 33 °C; 0.196 M MSH, 0.138 M MSSM; β-CH_2 carbon resonances. [g] 25 °C; 0.191 M MASH, 0.148 M MASSAM; CH_2 proton resonances. [h] 30 °C; 0.189 M MPSH, 0.128 M MPSSPM; α-CH_2 carbon resonances. [i] 35 °C; 0.189 M MPSH, 0.128 M MPSSPM; α-CH_2 carbon resonances. [j] 27 °C; from ref 16.

For example, the results in Table III indicate that the rate constants for RSH/RSSR interchange are lower when R has a negative charge (e.g. CSH/CSSC, MASH/MASSAM, and MPSH/MPSSPM exchange) than when R is neutral (MSH/MSSM and CySH/CySSCy exchange) and that the rate constants increase when the number of atoms between carboxylate groups of R and the sulfur increase (e.g. HCSH/HCSSCH exchange vs CSH/CSSC exchange and MPSH/MPSSPM exchange vs MASH/MASSAM exchange). It has been found in previous studies that the rate constant for reaction of RS^- at the RS sulfur of $RSSC_6H_4NO_2$ increases as the charge on R changes from negative to zero, and it increases as the number of atoms between the negative charge on R and the sulfur increase.[13c]

In view of the effect of negative charge on the rate of thiol/disulfide interchange, the rate constants for GSH/GSSG exchange are surprisingly large (at pD 11.4, GSH has a charge of -3 and GSSG a charge of -4). However, it has been found previously that the effect of charged groups on the kinetics of thiol/disulfide interchange reactions involving cysteine residues in peptides decreases as the number of atoms separating the cysteine sulfur from positive or negative charges on adjacent residues increases.[14] In GSH and GSSG, the negative carboxylate oxygens of the glycine and glutamyl residues are seven and nine bonds removed from the sulfur atom as compared to being three, four, and five bonds removed from the sulfur in MASH, CSH, and HCSH, respectively.

The pD dependence of the observed rate constants for GSH/GSSG exchange is also consistent with an apparent absence of effects due to the charge on the glutamyl residue. Since the thiolate anion is the reactive thiol species, $k_{obs} = \alpha k$ where α is the fraction of GSH in the thiolate form and k is the rate constant for reaction of the thiolate anion of GSH with GSSG. If the rate of GSH/GSSG exchange were influenced by the protonation state of the amino group of the glutamyl residues of GSH and GSSG, and thus the charges on the glutamyl residues, the rate constant k would change over the pD region 8.46-11.40. Over this pD range, the net charges on GSH and GSSG change from -2 and -2, respectively, to -3 and -4. Substitution of the relationship $\alpha = K_{SH}/(K_{SH} + [D^+])$, where K_{SH} is the acid dissociation constant of the thiol group of GSH, into the above equation, and rearrangement gives eq 6. Using the data for GSH/GSSG in Table III, a value

$$[D^+]k_{obs} = -K_{SH}k_{obs} + kK_{SH} \quad (6)$$

of 9.24 ± 0.06 is obtained for pK_{SH} from a plot of $[D^+]k_{obs}$ vs k_{obs}. This value is in good agreement with literature values for pK_{SH} for GSH in H_2O,[26-30] which indicates that the rate constant is constant over the pD range 8.46-11.40 and does not depend on the protonation state of the glutamyl groups.

The results of this study indicate that the inversion-transfer experiment is a convenient method for measuring the rates of symmetrical thiol/disulfide interchange reactions of biological thiols. With two-dimensional exchange spectroscopy, it should be possible to also measure the rates of unsymmetrical thiol/disulfide interchange reactions for a wide range of systems under equilibrium conditions.

Registry No. GSH, 70-18-8; GSSG, 27025-41-8; CSH, 52-90-4; CSSC, 56-89-3; HCSH, 6027-13-0; HCSSCH, 462-10-2; MSH, 60-24-2; MSSM, 1892-29-1; MASH, 68-11-1; MASSAM, 505-73-7; MPSH, 107-96-0; MPSSPM, 1119-62-6; CySH, 60-23-1; CySSCy, 51-85-4.

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Sonication-Induced Reductive Decarboxylation of Thiohydroxamic Esters

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Introduction

There have been several recent reports of reductive decarboxylation of unactivated carboxylic acid derivatives by various radical methods.[1,2] One of these methods is the reductive decarboxylation of thiohydroxamic esters (mixed anhydrides).[3] This attractive method involves the

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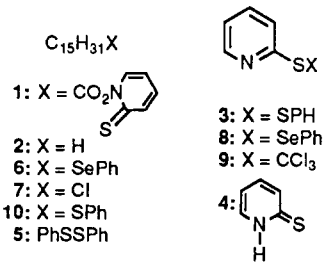
Table I. Results of Various Radical Traps

entry	trap	equiv of trap in CCl_4	products (%)
1	PhSH	3	**2** (85), **4** (87), **5** (70)
2	PhSeSePh	1	**6** (77), **7** (10)
3	PhSeSePh	2	**6** (80), **7** (0), **8** (68–88), **9** (8–14)
4	PhSSPh	2	**7** (91), **10** (2), **3** (3), **9** (70)
5	PhSSPh	5	**7** (80), **10** (8), **3** (8), **9** (73)



decomposition of the thiohydroxamic ester into radical fragments by light or heat in the presence of a hydrogen donor such as a thiol or tributyltin hydride.

We have recently developed a sonication-induced halogenative decarboxylation of thiohydroxamic esters.[4,5] This procedure relied on the radical decomposition of carbon tetrachloride (CCl_4) into $^{\bullet}CCl_3$ as the initiating species during sonication. The ensuing radical decomposition of the thiohydroxamic ester produced an alkyl radical. It is this alkyl radical that, potentially, could be captured by a radical trap added to the solution. The radical trap would have to react faster with the alkyl radical than the CCl_4 solvent. In principle, this could generate a variety of functional groups and, specifically, with a hydrogen donor become a method for reductive decarboxylation. Along these lines, we have done the following study.

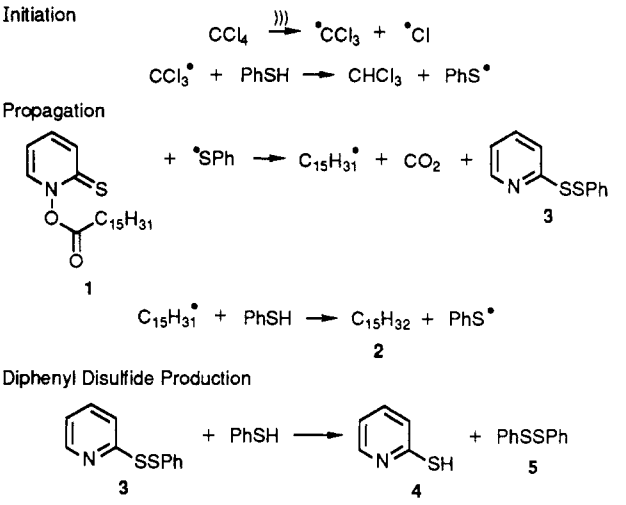
Results and Discussion

Thiohydroxamic ester **1** was used as a representative thiohydroxamic ester throughout this study. Ester **1** was easily prepared from palmitic acid via the acid chloride and the sodium salt of the corresponding thiohydroxamic acid (98% from palmitic acid).[4]

Thiophenol was the first radical trap added to a CCl_4 solution of ester **1**, because carbon radicals are known to abstract hydrogen from thiophenol extremely fast.[6] In a typical experiment, a solution of thiohydroxamic ester **1** and 3 equiv of thiophenol in CCl_4 was sonicated at room temperature. After chromatography, pentadecane (**2**), pyridyl-2-thiol (**4**), and diphenyl disulfide (**5**) were isolated in good yield (Table I, entry 1).

The mechanism of this reductive decarboxylation can be thought of as follows (Scheme I). The initiation proceeded by cavitation of the CCl_4 which upon collapse of the microbubbles produced $^{\bullet}CCl_3$. The $^{\bullet}CCl_3$, so produced, abstracted a hydrogen atom from the thiophenol to produce PhS$^{\bullet}$ which completed the initiation. The fate of the Cl$^{\bullet}$ was, presumeably, through combination to give Cl_2, which was degassed from the solution and is a known

Scheme I. Mechanism of Thiophenol Reductive Decarboxylation



sonochemical outcome of CCl_4 sonication.[4,7] The propagation resulted from the PhS$^{\bullet}$ acting as a chain carrier, which attacked thiohydroxamic ester **1** to produce $C_{15}H_{31}^{\bullet}$, CO_2 and **3**. The carbon radical so produced ($C_{15}H_{31}^{\bullet}$) reacted with the thiophenol to complete the reduction and generate another chain carrier. The mixed sulfide **3** produced was reduced by excess thiophenol present to give **4** and **5**. This type of reduction to a symmetrical disulfide is a well-known reaction in other very similar systems[3d,6a] and was confirmed by reducing pure **3** with thiophenol in CCl_4 to **4** and **5**.

Diphenyl diselenide was tried as a second radical trap, because it also reacts rapidly with carbon radicals.[8] With 1.0 equiv of diphenyl diselenide (entry 2), **6** was the major compound obtained with a small amount of chloride **7**. To eliminate the formation of **7**, 2.0 equiv of diphenyl diselenide (entry 3) was used, and only **6** was produced. The mechanism was apparently more complex than for thiophenol reduction, but the main chain carrier was probably PhSe$^{\bullet}$ as **8** was isolated in various amounts along with a smaller amount of **9**.

Diphenyl disulfide **5** was tried as a third radical trap. The rate of a carbon radical attack on diphenyl disulfide[9] is getting near the rate of carbon radical attack on CCl_4, so competition would be anticipated depending on their relative amounts present. With 2.0 equiv of **5** (entry 4), mainly **7** was isolated with a trace of **10**. With 5 equiv of **5** (entry 5), a mixture of **7** and **10** were isolated. Again, the mechanism was more complex than for the thiophenol reduction, but the main chain carrier was apparently $^{\bullet}CCl_3$ as much more **9** was isolated than **3** in both runs.

In conclusion, the sonication generation of $^{\bullet}CCl_3$, which, in turn, was used to homolytically fragment thiohydroxamine ester **1**, worked well to provide various functionalities based on the radical trap present.

Experimental Section

General. Carbon tetrachloride and thiophenol were distilled prior to use. All other reagents were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra

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were determined with the following spectrometers: UCB-200 and UCB-250 (super-conducting, FT instruments operating at 200 and 250 MHz). Chemical shifts are expressed in ppm downfield from tetramethylsilane using tetramethylsilane as an internal standard for ^{1}H NMR and chloroform (77.0) for ^{13}C NMR. ^{1}H NMR data are tabulated in the order of: multiplicity (s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet), number of protons, coupling constants in hertz. The ultrasonic waves were produced by a 250-W high-intensity ultrasonic processor, Vibra Cell from Sonics & Materials Inc. During our reactions the power meter showed an average power of 23% corresponding to a power of about 45 W cm^{-2}. Ultrasonic irradiation was carried out with the tip of the horn immersed directly in the solution.

General Procedure for the Decomposition of Esters by Sonication. The ester was dissolved in the solvent system listed and irradiated with ultrasonic waves under an argon atmosphere until thin-layer chromatography indicated complete consumption of starting ester.[10] A 20 °C water bath was kept around the reaction vessel during sonication, and this maintained the internal reaction temperature at 20 °C up to a maximum of 35 °C. Aluminum foil was used to surround the reaction vessel to completely exclude light from the reaction mixture. There was no need to stir the reaction mixture during the sonication process. The solvent was then evaporated under reduced pressure, and the residue was purified by chromatography on silica gel using a solvent gradient, generally pentane, followed by ethyl acetate–pentane mixtures. The compounds obtained by this method are listed below.

Pentadecane (2). Sonication of a solution of ester 1 (0.105 g, 0.287 mmol), carbon tetrachloride (10 mL), and thiophenol (0.088 mL, 0.857 mmol, 3 equiv) for 20 min gave, after chromatography (pentane), fractions A and B.

Fraction A contained **2** as a clear liquid (0.051 g, 85%): identical with an authentic sample.

Fraction B contained **5** as yellow-white crystals (0.088 g, 70%): identical with an authentic sample.

The column was further eluted (ethyl acetate) to give **4** as a yellowish solid (0.028 g, 87%): identical with an authentic sample.

Pentadecylselenobenzene (6) and 1-Chloropentadecane (7). Sonication of a solution of ester 1 (0.26 mmol, 1.0 equiv), carbon tetrachloride (10 mL), and diphenyl diselenide (0.26 mmol, 1.0 equiv or 0.52 mmol, 2.0 equiv) for 30 min gave, after chromatography (pentane), **6** (77% or 80%, see table) [^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3, J = 7.0 Hz), 1.2–1.4 (m, 24), 1.72 (tt, 2, J = 7.0, 7.0 Hz), 2.95 (t, 2, J = 7.0 Hz), 7.26 (m, 3), 7.53 (m, 2); identical with the published spectrum[8a]] and **7** (10% or 0%, see table), identical with an authentic sample.[4]

The column was further eluted (pentane 90%, ethyl acetate 10%) to give **8** (68–88%, see table): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02–7.08 (m, 1), 7.26–7.29 (m, 3), 7.57–7.69 (m, 4), 8.45–8.47 (m, 1); ^{13}C NMR (200 MHz, $CDCl_3$) δ 149.40, 137.11, 131.61, 129.82, 129.24, 127.73, 121.27, 120.62; decomposed slowly during chromatography.

The column was further eluted (pentane 90%, ethyl acetate 10%) to give **9** (8–14%, see table): identical with an authentic sample.[4]

Pentadecylthiobenzene (10) and 1-Chloropentadecane (7). Sonication of a solution of ester 1 (0.107 g, 0.29 mmol, 1.0 equiv), carbon tetrachloride (10 mL), and diphenyl disulfide (0.58 mmol, 2.0 equiv or 1.45 mmol, 5.0 equiv) for 30 min gave, after chromatography (pentane), **7** (91% or 80%, see table) mixed with a small amount of **10** (2% or 8%, see table): mp 49–50 °C (lit.[8a] mp 51 °C).

The column was further eluted (pentane 90%, ethyl acetate 10%) to give **3** (3% or 8%, see table): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.06–7.13 (m, 1), 7.22–7.35 (m, 3), 7.49–7.68 (m, 4), 8.46–8.48 (m, 1); ^{13}C NMR (200 MHz, $CDCl_3$) δ 149.56, 149.45, 137.26, 137.21, 129.09, 127.23, 120.84, 119.48. Anal. Calcd C, 60.24; H, 4.14; N, 6.39. Found: C, 60.26; H, 4.24, N, 6.21.

The column was further eluted (pentane 90%, ethyl acetate 10%) to give **9** (70% or 73%, see table).

Reduction of 3 with Thiophenol. In 2 mL of CCl_4 was dissolved **3** (32 mg, 0.15 mmol) followed by thiophenol (16 mg, 0.15 mmol). The solution turned yellow, and ^{1}H NMR (200 MHz, $CDCl_3$) of the concentrated solution indicated the presence of only **4** and **5**.

(10) No reactions occurs if the reaction solution was allowed to stand without irradiation at room temperature.

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A Light-Initiated Process for Rapid Debenzylation of Carbohydrates

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During the synthesis of several disaccharides to be used in the preparation of analogues of the anticancer agent mithramycin (1), difficulties (slow and sometimes incomplete reaction) were encountered with catalytic hydrogenolysis, the traditional method for removal of benzyl protecting groups. Although these difficulties, which have been known for some time to accompany occasionally the hydrogenolysis of benzyl ethers,[1,2] were not insurmountable, they created sufficient inconvenience to stimulate interest in other debenzylation reactions. A number of alternatives to catalytic hydrogenolysis have been reported. These include reaction with molecular bromine,[3] sodium in liquid ammonia,[1] boron trifluoride etherate,[4] iodotrimethylsilane (followed by hydrolysis),[5] ferric chloride,[6] ruthenium tetraoxide,[7] and ozone.[8] Other known methods involve electrochemical oxidation,[9] catalytic transfer hydrogenation,[2,10,11] and homogeneous electron transfer.[12]

The ease with which β-linked disaccharides constructed from 2,6-dideoxy sugars undergo acid-catalyzed reaction discouraged use of some of the reported debenzylation reactions while other methods were eliminated from consideration by the facility with which acyl groups are removed under basic conditions. Even with these restrictions, several of the known debenzylation methods remained viable possibilities; in addition, another reaction, developed several years ago for the conversion of benzylidene acetals into benzoate esters,[13] also seemed promising. In this reaction the acetals were partially deprotected by photolysis in the presence of *N*-bromosuccinimide, barium carbonate, and water (eq 1). These same conditions appeared to satisfy the requirements placed on the desired debenzylation reaction and seemed likely to provide an effective method for removal of benzyl groups.

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