Thiol Catalysis of Geometric Isomerization of Benzaldehyde Semicarbazone by Nucleophilic Addition[1]

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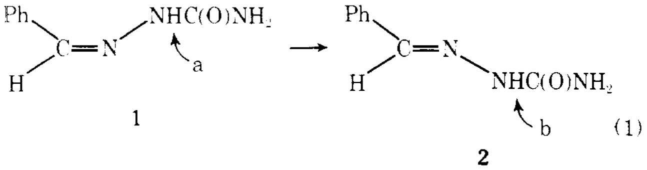
The isomerization of (*Z*)- to (*E*)-benzaldehyde semicarbazone is catalyzed by aliphatic and aromatic thiols. The proposed reaction mechanism involves rate-determining formation of a tetrahedral addition intermediate which undergoes fast bond rotation, nitrogen inversion, and/or proton exchange, followed by loss of thiol to generate the isomeric semicarbazone. The reaction, which provides a convenient method for measuring rates of nucleophilic addition of thiols to a carbon–nitrogen double bond in a system where equilibrium formation of the tetrahedral addition intermediate is highly unfavorable, has been used to investigate the detailed mechanism of this addition reaction in water at 25 °C. Addition of strongly basic thiols to the semicarbazone follows the rate law $k_{\text{thiol}} = k_{\text{RS}^-}[\text{RS}^-] + k_{\text{RSH}}[\text{RSH}]$; for weakly basic thiols k_{RSH} is large and k_{RS^-} cannot be detected. Rate constants, k_{RS^-}, show little or no dependence on the pK_a of the thiol ($\beta_{\text{nuc}} \leq 0.13$) for thiols of p$K_a$ 7.9–10.3. Rate constants, k_{RSH}, for thiols of p$K_a \geq 5.5$ follow a Brønsted-type relationship with a slope of log k_{RSH} vs. pK_a of −1.1, consistent with a mechanism involving rate-determining addition of the thiol anion to the protonated semicarbazone with β_{nuc} approximately 0. For less basic thiols (pK_a 2.7–5.5) the slope of log k_{RSH} vs. pK_a is ca. −0.65, corresponding to β_{nuc} for the anion of 0.35. For strongly basic thiols the β_{nuc} of 0 and calculated rate constants for anion attack on the protonated semicarbazone are consistent with a rate-determining diffusion-controlled reaction of RS$^-$ with the protonated semicarbazone, a "one-encounter" mechanism with rate-determining reorganization of the complex formed upon protonation of the semicarbazone by the thiol, or rate-determining semicarbazone protonation by H_3O^+ in the presence of "spectator" thiol anion. The value of β_{nuc} ~0.35 for weakly basic thiols may reflect a change in rate-determining step or curvature in the Brønsted-type plot that results from a change in transition-state structure corresponding to significant carbon–sulfur bond formation for the poorer nucleophiles.

Catalysis of geometric isomerization of the C═N double bond can, under some circumstances, provide a lower energy pathway for this process than uncatalyzed mechanisms[2] involving bond rotation or inversion at nitrogen. Possible catalytic mechanisms for geometric isomerization of imines and related compounds include (a) protonation at nitrogen,[3] which decreases the double-bond character of the C–N bond and facilitates bond rotation, (b) base-catalyzed enamine formation[4] (for compounds possessing an α-hydrogen), and (c) nucleophilic addition[5] followed by inversion or proton exchange at nitrogen and subsequent elimination of the nucleophile. In this paper we describe a facile thiol-catalyzed *Z–E* isomerization of benzaldehyde semicarbazone (eq 1) that is most reasonably explained by a polar addition–elimination mechanism.



1 → 2 (1)

This isomerization provides a convenient method for measuring the rate of nucleophilic addition to a C═N double bond in a system where the tetrahedral addition compound is not present in measurable concentrations at equilibrium.

Experimental Section

Materials. Reagent grade inorganic salts and acetic acid were used without further purification. Organic reagents were recrystallized or distilled before use. Glass-distilled water was used in all experiments.

The *E* isomer of benzaldehyde semicarbazone (**2**), mp 221–223 °C, was prepared in 80% yield from 0.08 mol of benzaldehyde and 0.072 mol of semicarbazide hydrochloride in 80 mL of ethanol containing 12 g of sodium acetate and recrystallized from ethanol–water. The NMR spectrum of this product in dimethyl sulfoxide exhibited the characteristic peak for the ureido proton, b (eq 1), of the *E* isomer only at 10.4 ppm relative to Me_4Si (lit.[6] 10.33 ppm). This isomer (0.012 mol) was converted to a mixture of the *E* and *Z* isomers by a modification of the method of Stenberg et al.[6] (*E*)-Benzaldehyde semicarbazone (2 g, 0.012 mol) in 100 mL of anhydrous tetrahydrofuran was photolyzed in a quartz reaction vessel with a water-cooled condenser under nitrogen for 24 h using a Rayonet RPR-208 photochemical reactor with RUL-3000A lamps. Thin-layer chromatography of the reaction mixture on silica using 1:1 benzene–tetrahydrofuran showed two spots of approximately equal size whose ratio did not change appreciably with longer reaction times. The product mixture isolated after solvent evaporation showed a new NMR signal at 9.27 ppm corresponding to the ureido proton, a, of the *Z* isomer;[6] the ratio of *E/Z* isomers from integration of the peaks at 9.27 and 10.4 ppm was approximately 1.3:1. Medium-pressure preparative chromatography of the isomer mixture on a column of silica using 1:1 benzene–tetrahydrofuran as the eluent gave good separation of the isomers, but attempts to crystallize pure **1** resulted in its spontaneous isomerization. A mixture enriched in **1** could be obtained by continuous extraction of the isomer mixture with hexane in a Soxhlet extractor. For kinetic experiments the mixture containing ~40% **1**, as obtained from photolysis, was used without further purification.

Kinetics. Rates of isomerization of benzaldehyde semicarbazone in water at 25 °C and ionic strength 1.0 (KCl) were followed spectrophotometrically in stoppered cuvettes at 300 nm. A Bausch and Lomb Spectronic 710 spectrophotometer equipped with a thermostatted cell compartment, recorder, and Caltronics Linear Auto-Expander calibrated to produce a full scale recorder response per 0.10 absorbance change was used. Reactions were ordinarily initiated by adding 30 μL of 2.5×10^{-3} M semicarbazone isomer mixture to 3.0 mL of a buffered solution of the appropriate thiol, to give a final semicarbazone concentration of 2.5×10^{-5} M. Under these conditions the observed absorbance change during the reaction is approximately 0.075 absorbance unit. Because of the insolubility in water of benzenethiol and 3,4-dichlorobenzenethiol, the reactions catalyzed by these thiols were initiated by adding 30 μL of an appropriate dilution of the thiol in ethanol to a reaction mixture already containing the semicarbazone. Thiol stock solutions were prepared, freshly each day, by weight (or by volume for compounds of known density) from redistilled thiols which had been stored cold under argon or nitrogen. Stock thiol solutions were kept under argon or nitrogen. Particular care was required to prevent oxidation of ethanedithiol and benzenethiol, and kinetics of reactions involving these thiols were followed under an argon atmosphere in stoppered cuvettes. For reactions of ethanethiol, *p*-nitrobenzenethiol, and methyl thioglycolate at pH 10.4, cell spacers were used to give a path length of 0.2 cm, and reaction mixtures contained 1.56×10^{-4} M semicarbazone. For experiments in which appreciable amounts of ethanethiol were present as the volatile neutral form, the ethanethiol concentration in each cuvette was determined after completion of reaction by removal of an aliquot, dilution, and assay with Ellman's reagent.[7]

For strongly basic thiols either dilute potassium hydroxide or a mixture of the thiol and its conjugate base was ordinarily used to

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maintain pH. The following external buffers were used with the less basic thiols. Potassium dihydrogen phosphate–potassium hydrogen phosphate buffers (0.01 M total buffer concentration): with pentafluorobenzenethiol, 26% dianion (pH 6.19) and 63% dianion (pH 6.71); with thioacetic acid, 78% dianion (pH 7.05); with *p*-nitrobenzenethiol, 53% dianion (pH 6.56); with benzenethiol, 50% dianion (pH 6.50) and 78% dianion (pH 7.07). Acetic acid–potassium acetate buffers (0.01 M total buffer): with thioacetic acid, 88% anion (pH 5.57); with 3,4-dichlorobenzenethiol, 26% anion (pH 4.17). Potassium carbonate–bicarbonate buffers (0.1 M total buffer) were used with methyl thioglycolate: 17% dianion (pH 9.08) and 67% dianion (pH 10.4). Phosphate buffer (36% dianion) up to 0.2 M total concentration was shown to have less than a 3% effect on the rate of the reaction of *p*-nitrobenzenethiol at pH 6.4; hence, no corrections were made for buffer catalysis in any of these experiments.

Analysis of Data. Second-order rate constants, k_{thiol}, for thiol catalysis of isomerization were determined from plots of the observed pseudo-first-order rate constant against total thiol concentration. For thiols whose acidic and basic forms are both catalytic, rate constants k_{RSH} and k_{RS^-} for catalysis by the neutral and anionic species, respectively, were determined from the intercepts at 1.0 and 0 of plots of k_{thiol} against mole fraction of protonated thiol. Rate constants for catalysis by the three ionic species of ethanedithiol were determined from observed rate constants and the independently determined ionization constants, K_1 and K_2, for dissociation of ethanedithiol and ethanedithiol monoanion, respectively, as follows. The rate constant $k_{\text{RS}_2{}^{2-}}$ for catalysis by the dianion was measured at pH 13 where essentially all the thiol is present as the dianion. Rate constants $k_{\text{RS}_2\text{H}_2}$ and $k_{\text{RS}_2\text{H}^-}$ were determined from a plot of $(k_{\text{thiol}} - k_{\text{RS}_2{}^{2-}}\alpha)(K_1[\text{H}^+] + K_1K_2 + [\text{H}^+]^2)/[\text{H}^+]$ against $[\text{H}^+]$, where α is the mole fraction of thiol present as the dianion and is given by $K_1K_2/(K_1[\text{H}^+] + K_1K_2 + [\text{H}^+]^2)$. The slope of such a plot is $k_{\text{RS}_2\text{H}_2}$, and the y intercept is $K_1k_{\text{RS}_2\text{H}^-}$.

For very weakly basic thiols, for which no k_{RS^-} term was detected, k_{RSH} was ordinarily calculated by dividing k_{thiol} by the mole fraction of thiol present as the conjugate acid, calculated from the pK_a and the measured pH.

Dissociation Constants for Ethanedithiol. The pK_a values for ethanedithiol were determined by potentiometric titration of 0.02 M thiol with potassium hydroxide at 25 °C and ionic strength 1.0 (KCl) under argon. Since the two ionization constants are not well separated, the pK_a values were calculated from the observed titration curve (after correction for solvent titration) using the Noyes method.[8]

Results

In the presence of thiols the thermodynamically unstable *Z* isomer **1** of benzaldehyde semicarbazone undergoes rapid conversion to the *E* isomer **2** (eq 1). This isomerization can be demonstrated directly by the changes in the NMR spectrum of a sample containing a mixture of **1** and **2** upon addition of pentafluorobenzenethiol. After ~1 h in deuterated dimethylformamide containing a trace of water and ~0.01 M pentafluorobenzenethiol, the peak at 9.06 ppm, corresponding to proton a of **1**, and a complex signal around 7.5 ppm disappear completely. The spectrum of the product is identical with that of pure **2**, and no new peaks are observed. The isomerization is also demonstrable by thin-layer chromatography on silica (1:1 benzene–tetrahydrofuran solvent) of samples of a mixture of isomers **1** and **2** in ethanol–water in the presence of 0.1 M mercaptoethanol. The faster moving spot, which corresponds to the *Z* isomer, disappears as a function of time over a period of ~1 h until eventually the slower moving *E* isomer is the only chromatographically detectable species present.

Since isomers **1** and **2** of benzaldehyde semicarbazone possess different ultraviolet absorption spectra, the conversion of **1** to **2** is accompanied by a small increase in absorbance (λ_{max} 280 nm) corresponding to the absorption maximum of **2**. The kinetics of the isomerization reaction were followed spectrophotometrically; to avoid interference by thiol absorption, the absorbance change was normally monitored at 300 nm. The reaction is cleanly pseudo first order for 3–4 half-lives, even when the initial thiol concentration is only 1–2 times the total concentration of semicarbazone, consistent with a catalytic mechanism in which the thiol is not consumed during the reaction. Measured pseudo-first-order rate constants depend linearly on the concentration of thiol, and little or no reaction occurs in the absence of thiol, as shown by small or 0 intercepts of plots (Figure 1) of observed rate constant against total thiol concentration at constant pH.

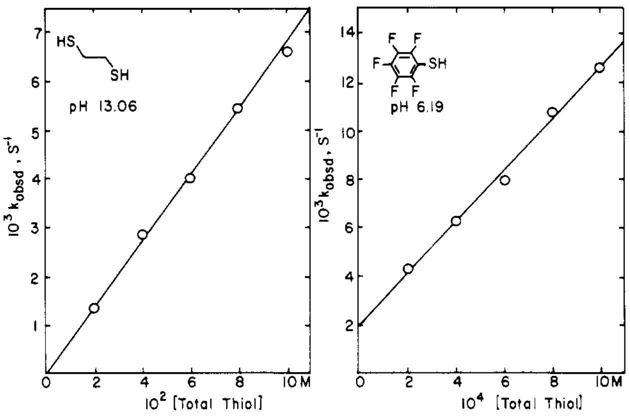


Figure 1. Dependence of the observed rate constants for benzaldehyde semicarbazone isomerization at 25 °C and ionic strength 1.0 on the concentration of thiols. The experiment at pH 13.06 was carried out in 0.1 M potassium hydroxide and that at pH 6.19 in 0.01 M potassium phosphate buffer, 26% dianion.

In two instances where possible general acid–base catalysis of the reaction of thiols by buffers was investigated, no evidence for it was found. (1) The rate of isomerization in the presence of 0.02 M mercaptoethanol (76% anion) is unaffected, within experimental error, by concentrations of 3-quinuclidinol buffer (50% base) from 0.05 to 0.20 M. For a hypothetical catalytic mechanism involving thiol anion and quinuclidinol cation (QH$^+$) according to the rate law k_{thiol}[total thiol] = k_0[total thiol] + $k_{\text{cat}}[\text{QH}^+][\text{RS}^-]$, an upper limit for k_{cat} of 9×10^{-2} M^{-2} s^{-1} is estimated, based on the assumption that a 20% increase in k_{obsd} at 0.2 M buffer concentration would have constituted evidence for catalysis. (2) In the presence of a weakly basic thiol, 5×10^{-4} M *p*-nitrobenzenethiol, no catalysis (<3% increase in k_{obsd} at the highest buffer concentration) is found in the presence of 0.01–0.20 M potassium hydrogen phosphate–potassium dihydrogen phosphate buffers, 36% dianion.

The isomerization catalyzed by 0.01 M (total) methyl thioglycolate at pH 8.45 exhibits no change in rate in the presence of 5×10^{-4} M hydroquinone, which was expected to act as a radical scavenger. In light of this observation and the fact that the kinetics are well behaved and reproducible, even when oxygen is not rigorously excluded from the reaction mixtures, we believe that a mechanism involving free radicals is unlikely.

Catalysis of semicarbazone isomerization by strongly basic thiols involves kinetic terms proportional to both the protonated and the anionic forms of the thiol (eq 2). For weakly basic thiols, k_{RSH} is large and k_{RS^-} cannot be detected, even at pH values several units above the pK_a, because of the magnitude of k_{RSH}. Rate constants k_{RSH} and k_{RS^-} for a series of thiols are summarized in Table I.

$$k_{\text{thiol}}[\text{total thiol}] = k_{\text{RS}^-}[\text{RS}^-] + k_{\text{RSH}}[\text{RSH}] \qquad (2)$$

Discussion

In the course of studies initially intended to measure rates of nucleophilic attack on (*E*)- and (*Z*)-benzaldehyde semicarbazones, we observed an extremely facile interconversion of these isomers catalyzed by thiols. In aqueous solutions between pH ca. 4 and 13 little or no isomerization occurs in the absence of thiols during the time periods (ranging from several minutes to 2–3 h) required for these experiments, as indicated by the small or zero ordinate intercepts of plots of

Table I. Rate Constants for Catalysis of *Z* to *E* Isomerization of Benzaldehyde Semicarbazone by Thiols (RSH)[a]

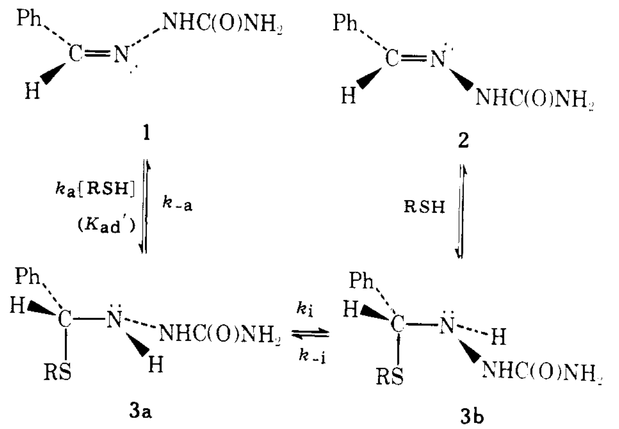
RSH	registry no.	pK_a	pH	concn range (total thiol), M	k_{thiol}, $M^{-1} s^{-1}$	k_{RSH}, $M^{-1} s^{-1}$	k_{RS^-}, $M^{-1} s^{-1}$
1. F_5C_6SH	771-62-0	2.68[b]	6.19	2×10^{-4}–10^{-3}	10.4		
			6.71	1–5×10^{-4}	3.66	3.64×10^4	
2. $CH_3C(O)SH$	507-09-5	3.20[b]	5.57	10^{-4}–2×10^{-3}	7.97		
			7.05	2–5×10^{-3}	0.26	1.81×10^3	
3. p-$O_2NC_6H_4SH$	1849-36-1	4.50[b]	6.56	2.5×10^{-4}–2×10^{-3}	8.65	1.01×10^3	
4. 3,4-$Cl_2C_6H_3SH$	5858-17-3	5.48[c]	4.17	2.5×10^{-5}–4×10^{-4}	4.70	500	
5. C_6H_5SH	108-98-5	6.43[b]	6.50	5×10^{-5}–4×10^{-4}	20.7		
			7.07	5×10^{-5}–4×10^{-4}	7.18	41	
6. $CH_3OC(O)CH_2SH$	2365-48-2	7.91[b]	7.90	0.02–0.10	0.36		
			8.37	0.02–0.10	0.20		
			9.08	0.02–0.10	0.06		
			10.4	0.02–0.10	0.03	0.73	0.026 ± 0.004
7. $HOCH_2CH_2SH$	60-24-2	9.61[b]	9.2	0.05–0.40	0.020		
			9.49	0.05–0.50	0.022[d]		
			10.00	0.05–0.40	0.021[d]		
			12.90	0.05–0.20	0.021	0.018	0.021
8. C_2H_5SH	75-08-1	10.35[b]	10.0[e]	0.03–0.075	0.016		
			e, f	0.04–0.11	0.033		
			12.8	0.011–0.098	0.041	$\leq 5 \times 10^{-3}$	0.045 ± 0.004
9. $HSCH_2CH_2SH$	540-63-6	9.16[g]	9.33	0.02–0.08	0.050		
			9.93	0.02–0.20	0.053		
			10.62	0.02–0.10	0.063	0.032	0.056
10. $^-SCH_2CH_2SH$	68170-95-6	10.63[g]	13.06	0.02–0.10	0.067		0.067

[a] At 25 °C, ionic strength 1.0 (KCl). [b] W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93,** 4433 (1971). [c] Reference 17. [d] A slight upward curvature was observed in some plots of k_{obsd} vs. total thiol concentration, possibly due to a very small second-order term in thiol. These values of k_{thiol} were determined from the ordinate intercepts of plots of k_{obsd}/[total thiol] against [total thiol]. [e] Concentrations of RSH and RS^- determined from Ellman's reagent assay of total thiol (see text) and stoichiometric amount of potassium hydroxide in reaction mixtures. [f] pH not measured; RS^-/RSH, 7:3. [g] This work.

k_{obsd} against thiol concentration (Figure 1); concentrations of thiols in some cases as low as 10^{-5}–10^{-4} M cause extremely rapid conversion of the *Z* to the *E* isomer. Hydrolysis of the semicarbazone presumably does not compete with this reaction since observed rates of the reaction with thiols are several orders of magnitude greater than the expected rates for hydrolysis. For example, the pseudo-first-order rate constant (k_r) for hydrolysis of benzaldehyde semicarbazone at pH 4.17 (the lowest pH value used, where hydrolysis should be fastest) is estimated to be $\sim 2 \times 10^{-6}$ s^{-1} from a calculated forward rate constant[9] (k_f) of 0.44 M^{-1} s^{-1} and the relationship $k_r = k_f/K_{ov}$ (using a value of K_{ov}, the equilibrium constant for semicarbazone formation, of 2.2×10^5 M^{-1} based on the observed value of 5.1×10^5 M^{-1} for this equilibrium constant[10] for p-chlorobenzaldehyde and $\rho^{11} = 1.64$). This is approximately four orders of magnitude slower than the observed pseudo-first-order rate constant of 2×10^{-2} s^{-1} for isomerization in the presence of 2.5×10^{-5} M 3,4-dichlorobenzenethiol at this pH. Thiol-catalyzed isomerization also occurs in dimethylformamide containing only traces of water; the NMR spectrum of the reaction mixture shows that no products other than the *E* isomer are formed.

We believe that the most reasonable mechanism for the reaction is an addition–elimination mechanism (Scheme I) in which *N,S*-acetal **3a,** formed as a steady-state intermediate, undergoes bond rotation and nitrogen inversion or hydrogen exchange followed by elimination of thiol to regenerate thiol and the isomerized product. According to this mechanism the thiol is not consumed in the reaction, nor is it bound in significant amounts in any intermediates (since **3a** and **3b** do not build up); this mechanism is consistent with the observation that the observed reaction follows first-order kinetics even when the total concentration of thiol is no greater than the total concentration of semicarbazone in the reaction mixture. Addition reactions of thiols to carbon–nitrogen double bonds are well known,[12,13] and the behavior of these reactions in polar solvents is consistent with an ionic mechanism.[13,14] We also have found no evidence for involvement of free radicals in the present isomerization reaction.

Scheme I



The mechanism of Scheme I and the high reactivity of sulfur nucleophiles provide a rationale for the remarkable catalytic efficiency of thiols in this reaction. The rate of reaction of 0.1 M hydroxide ion with the semicarbazone is insignificant compared to that of the anions of mercaptoethanol, ethanethiol, or ethanedithiol (Figure 1). If the isomerization catalyzed by thiolate anions involves rate-determining thiolate attack on the semicarbazone (see below), the rate constant, k_{RS^-}, for attack by ethanethiol anion is $\sim 10^4$ times greater than the corresponding rate constant, k_{OH^-}, for hydroxide ion attack. The attack of hydroxide ion on benzaldehyde semicarbazone is the rate-determining step for semicarbazone hydrolysis at high pH, and k_{OH^-} for this process (for the *E* isomer) is estimated to be $\sim 2 \times 10^{-6}$ M^{-1} s^{-1} from published values[10] for rate and equilibrium constants for formation of the semicarbazone (presumably the *E* isomer) from p-chlo-

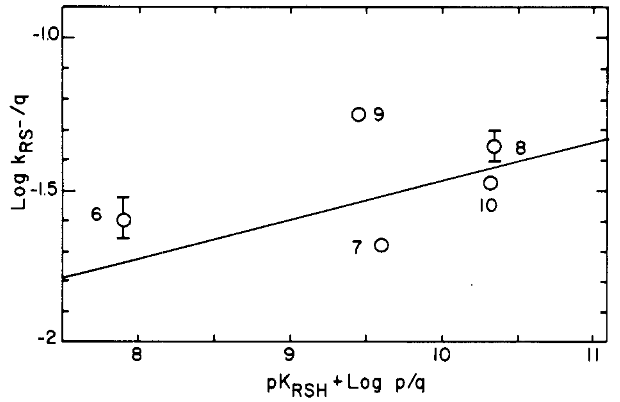


Figure 2. Dependence of rate constants k_{RS^-} for thiol anion attack on benzaldehyde semicarbazone on the pK_a of the thiol. The thiols are identified in Table I. Statistical corrections were applied to the pK_a values of ethanedithiol and to k_{RS^-} for ethanedithiol dianion according to the method of R. P. Bell and P. G. Evans [*Proc. R. Soc. London, Ser. A*, **291**, 297 (1966)]. The line is drawn with a slope of 0.13.

robenzaldehyde and a ρ value[15] of −0.3. Assuming that there is not a *large* difference between k_{OH^-} for the *E* and *Z* isomers, the calculated ratio of k_{RS^-}/k_{OH^-} of ~10^4 for ethanethiolate and hydroxide ions is roughly comparable to the ratio of 10^5 for attack of propanethiolate and methoxide ions on aromatic Schiff bases in methanol estimated by Ogata and Kawasaki[13] and much larger than analogous rate ratios for attack of basic sulfur and oxygen nucleophiles on *p*-nitrophenyl and *p*-nitrothiophenyl acetates.[17]

The isomerization reaction reported here is of particular interest because it provides a simple method for measuring rates of nucleophilic attack on a carbon–nitrogen double bond in a system where equilibrium adduct formation is highly unfavorable, and the nucleophilic reaction would be undetectable in the absence of isomerization. Two lines of reasoning support our belief that nucleophilic attack, rather than the interconversion of intermediates **3a** and **3b**, is rate determining for these reactions. (1) Correlations of k_{RSH} and k_{RS^-} with the basicity of the thiols are consistent with transition states in which there is a large negative charge on sulfur. (2) The magnitude of the rate constant, k_{RSH}, for mercaptoethanol is too small to be consistent with fast preequilibrium formation of **3a** which is converted to **3b** in a rate-determining step. (1) The rate constants, k_{RS^-}, for reaction of thiol anions show little dependence on the pK_a of the thiols (Figure 2), and the rate constants, k_{RSH}, for undissociated thiols are strongly dependent of the pK_a of the thiols (Figure 3), consistent with transition states for both processes in which significant negative charge resides on sulfur. Any steps in the conversion of **3a** to **3b** would involve transition states with complete carbon–sulfur bond formation and little or no negative charge buildup on sulfur. A steric effect of benzene substitution on the thiol might be expected to be important for rate-determining conversion of **3a** to **3b**, but no evidence for any such effect is apparent from the structure–reactivity correlation of Figure 3, in which two aromatic thiols do not deviate significantly from the plot of log k_{RSH} vs. pK_a for aliphatic thiols. (2) For the reaction that is kinetically dependent on the concentration of neutral thiol (k_{RSH}), the initial intermediate that is formed is presumably the neutral *N,S*-acetal **3a**. The equilibrium constant, K_{ad}, for the formation of **3b** (and **a**) from (*E*)-benzaldehyde semicarbazone and mercaptoethanol is estimated to be ~1.3×10^{-2} M^{-1} if the corresponding equilibrium constant for water addition[18] is 1.9×10^{-6} M^{-1} and $\Delta\gamma$[19] for water and mercaptoethanol is 3.85; the equilibrium constants for propanethiol and methanol addition to aromatic Schiff bases are consistent with a correlation of log K_{ad} with γ.[13] The equilibrium constant, K_{ad}', for addition to the less stable *Z* isomer presumably would be no *smaller* than this value of K_{ad}. If rotation or inversion of **3a** with a rate constant k_i were rate determining, the observed rate constant k_{RSH} would be given by $k_{RSH} = K_{ad}'k_i$ and k_i would be k_{RSH}/K_{ad}', or ≤ ~1.5 s^{-1} at 25 °C, which is many orders of magnitude smaller than expected rate constants for similar processes. For example, rate constants for inversion at nitrogen of acyclic substituted hydrazines[20] are ~10^2 s^{-1} at −100 °C or below, and assuming an activation energy[21] of 16 kcal/mol gives rate constants at room temperature that may be as much as eight orders of magnitude larger. Hence, the magnitude of the observed rate constant requires that some step that is slower than k_i must be rate determining for this reaction.

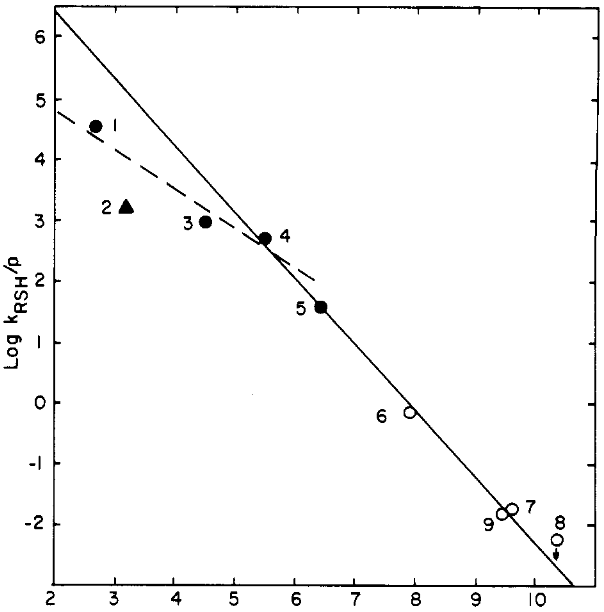
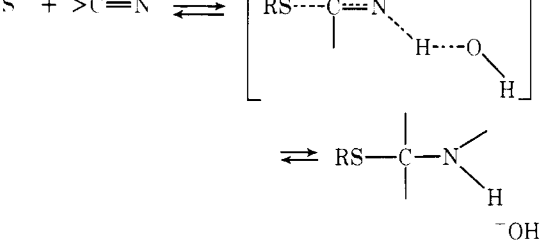


Figure 3. Dependence of rate constants k_{RSH} (eq 2) for thiol addition to benzaldehyde semicarbazone on the pK_a of the thiol for aliphatic (○) and aromatic (●) thiols and thioacetic acid (▲). The thiols are identified in Table I. Statistical corrections [R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A*, **291**, 297 (1966)] were applied to the pK_a and k_{RSH} for ethanedithiol (9 in Table I). The solid line has a slope of −1.1, and the broken line has a slope of −0.65.

The attack of basic thiol anions on benzaldehyde semicarbazone, k_{RS^-} (eq 3), corresponds in the reverse direction to

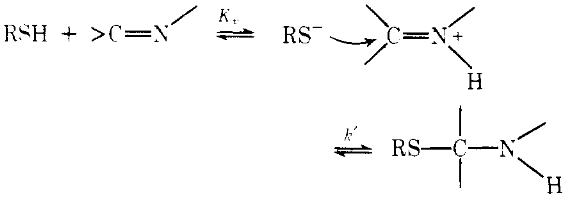


(3)

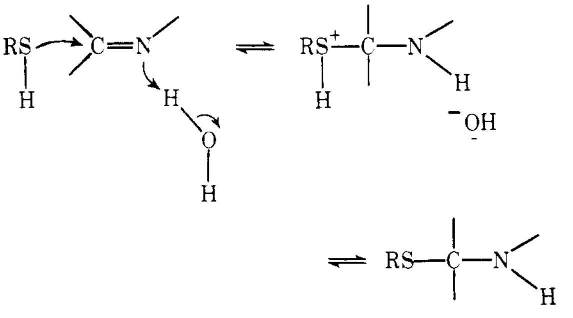
specific base catalysis, or general base catalysis by hydroxide ion, of thiolate expulsion from the *N,S*-acetal and probably occurs by a mechanism that is analogous to the attack and loss of hydroxide and alkoxide anions. General acid catalysis of mercaptoethanol anion attack on the semicarbazone by 3-quinuclidinol cation, corresponding to general base catalysis of thiol anion expulsion, was not experimentally detected. An upper limit for α is 0.4, based on an upper limit of $k_{cat} \leq 9 \times 10^{-2}$ M^{-2} s^{-1} for quinuclidinol cation and $k_{cat} = 3.8 \times 10^{-4}$ M^{-2} s^{-1} for water. Consistent with this observation, the value of α for general acid catalysis of thiolate attack is expected to be no larger than the value of approximately 0.3 for hydroxide ion attack on similar compounds[10] and is probably even smaller; analysis of three-dimensional reaction coordinate-free-energy diagrams[22] for nucleophilic addition of RX^- to the carbon–nitrogen double bond suggests that stabilization of the C–X bond when X equals sulfur should favor a transition state with less proton transfer to nitrogen and a *smaller* α value than the analogous system with X equal to oxygen.

The rate constants, k_{RS^-}, for uncatalyzed attack of thiol anions (Figure 2) exhibit little if any systematic dependence on the basicity of the thiol, consistent with a transition state in which little loss of negative charge on the thiol anion has occurred. This is similar to the situation that pertains (in the reverse direction) with oxygen nucleophiles, for which β_{lg} is approximately -1.0 for tosylhydrazone formation from the alcohol adducts of *p*-chlorobenzaldehyde tosylhydrazone.[16] If the attack of oxygen nucleophiles proceeds with little bond formation in the transition state and a small value of β_{nuc}, this trend should be even more pronounced with sulfur nucleophiles because of the ability of the polarizable sulfur atom to stabilize an "early" transition state. Back-bonding from the incipient nitrogen anion to a sulfur d orbital may also contribute negative charge to the sulfur, compensating for any electron density lost by partial bond formation to carbon. The small value of β_{nuc} for thiols in this reaction is also similar to values of β_{nuc} that are observed for thiol anion attack on carbonyl[23] and acyl[17] compounds.

Addition of thiols to benzaldehyde semicarbazone also occurs via a process, k_{RSH}, that is kinetically dependent on the un-ionized thiol. This process is detectable for thiols of $pK_a \leq 9.6$ and represents the most important mechanism for addition of weakly basic thiols. Values of k_{RSH} are strongly dependent on the pK_a of the thiol (Figure 3) with a slope of -1.1 for a Brønsted-type plot of log k_{RSH} vs. pK_a of basic thiols. This slope corresponds to substantial negative charge buildup on sulfur and is most consistent with a mechanism (eq 4) involving attack of the thiol anion on the protonated semicarbazone, with a β_{nuc} of approximately 0, rather than the kinetically equivalent addition (eq 5) of neutral thiol to unprotonated semicarbazone. The mechanism of eq 4 is the same as that observed for attack and loss of water in the uncatalyzed hydrolysis of imines, hydrazones, and related compounds.[10,24]

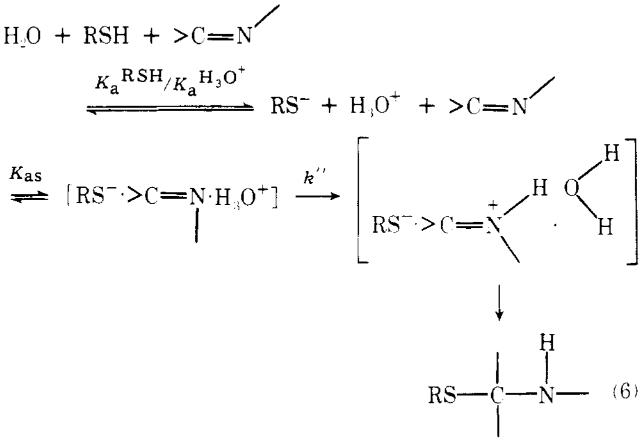


(4)



(5)

The β_{nuc} of approximately 0 for attack of strongly basic thiol anions on the protonated semicarbazone means that there is an effective charge of about -1 on sulfur in the transition state and essentially no bond formation between carbon and sulfur. This is consistent with either (1) a rate-determining transport process involving thiol anion and protonated semicarbazone or (2) a preassociation mechanism with rate-determining proton transfer from the hydronium ion to the semicarbazone, in the presence of "spectator" thiol anion. (1) For the mechanism of eq 4, $k' = k_{RSH}/K_e$, where $K_e = K_a^{RSH}/K_a^{C=N}$. The pK_a for benzaldehyde semicarbazone must be less than -1.05,[11] and a reasonable approximation for $pK_a^{C=N}$ of -3.50 is obtained from the pK_a of -1.20 for benzaldoxime[24a] and a ΔpK of 2.3 for hydroxylamine (pK_a 6.15)[25] and semicarbazide (pK_a 3.86).[26] By analogy with the *E* and *Z* isomers of a phenyl imido ester,[4] the pK_a values for the *Z* isomers of the oxime and semicarbazone, in which the proton may be less destabilized by interaction with the nearby phenyl ring, may be 1.5 units higher than the pK_a's of the *E* isomers. Since it is unknown which isomer of the oxime was predominant under the conditions of the pK_a determination, there is hence an uncertainty in the estimated pK_a of the conjugate acid of 1, but it is reasonable to assume that this pK_a is no greater than -2. Using a pK_a of -2.0, K_e for protonation by mercaptoethanol is $\sim 2.5 \times 10^{-12}$ and the calculated value for k' is greater than 10^9 M^{-1} s^{-1}. This value of k' lies within the range expected for a diffusion-controlled reaction.[27] A "one-encounter" mechanism in which the semicarbazone is protonated by the thiol followed by a rate-determining reorganization of the complex with a rate constant that is faster than diffusional separation and recombination of thiol anion and protonated semicarbazone is also possible. Such a mechanism might be favored by the charge neutralization that stabilizes the complex of thiol anion and protonated semicarbazone. The rate constant of 0.056 M^{-1} s^{-1} for reaction of ethanedithiol monoanion is slightly larger than the rate constants k_{RS^-} for any of the other thiol anions (except ethanedithiol dianion, which presumably exhibits greater reactivity for statistical reasons) and is more than an order of magnitude larger than the expected value of k_{RSH} for a thiol of pK_a 10.63. This enhanced reactivity, although small, may reflect a one-encounter mechanism in which one sulfhydryl group transfers a proton to the nitrogen, followed by nucleophilic attack of the *other* sulfhydryl group within the encounter complex. (2) An alternative mechanism for the k_{RSH} reaction involves a preassociation or hydrogen bonding mechanism for catalysis by the hydronium ion in which the rate-determining step is proton transfer (k'') from the hydronium ion to the semicarbazone in the presence of thiol anion which does not participate in the reaction (eq 6).



(6)

For this mechanism $k_{RSH}/[H_2O] = k''K_{as}K_a^{RSH}/K_a^{H_3O^+}$. An approximate value for k_{RSH} can be calculated for mercaptoethanol as follows; if it is assumed[28] that K_{as} for encounter complex formation is $\sim 10^{-2}$ M^{-2}, and semicarbazone protonation within the complex follows a Brønsted relationship, $\log k'' = 10 + 0.5\Delta pK_a$, the use of pK_a values of -2 ± 1 for the semicarbazone and -1.7 for hydronium ion gives $\log k'' = 9.9 \pm 0.5$ and $\log k_{RSH} = -1.7 \pm 0.5$, consistent with the observed value of $\log k_{RSH} = -1.75$.

Values of k_{RSH} for weakly basic aromatic thiols show a small but significant deviation from the Brønsted relationship for strongly basic thiols. The slope for weakly basic thiols (excluding thioacetic acid[29]) is 0.65, corresponding to a β_{nuc} of $\sim$0.35 for anion attack on the protonated semicarbazone. It has been shown that aliphatic and aromatic thiol anions exhibit no systematic differences in nucleophilic behavior toward thiol or oxygen esters.[17] Hence, the deviation of the most weakly basic thiol anions probably reflects a change in rate-determining step or transition-state structure for these compounds.[30] We speculate that this may result from a shift in transition-state structure for the $\mathrm{RS^-}$- - -$\mathrm{C{=}N^+(H)}$- system toward a more product-like transition state with a significant amount of carbon–sulfur bond formation for the more weakly basic thiols. Consistent with this idea is the observation that attack of aliphatic thiol and benzenethiol anions on a less electrophilic iminium species, the benzylidenedimethyliminium ion,[14] exhibits an even larger β_{nuc} of 0.43. These variations in β_{nuc} may possibly be a fairly straightforward manifestation of a "Hammond effect" for a system in which only one bond is being formed along the reaction coordinate.

Registry No.—**1**, 17539-52-5; **2**, 17539-53-6.

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Study of the Thermal Decomposition of Dinitrophenyl *N,N*-Dialkyldithiocarbamates and Related Compounds[1] [+]

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The thermal cyclization of substituted dinitrophenyl *N,N*-dimethyldithiocarbamates is shown to be a general method for the synthesis of a variety of nitro-1,3-benzodithiol-2-ones. The mechanism of this reaction is discussed.

In an earlier communication[2] we described the reaction of 3,5-dinitro-4-chlorobenzotrifluoride (**1a**) and other dinitrochlorobenzenes **1b–f** with the sodium salt of *N,N*-dimethyldithiocarbamic acid (**2**). The intermediate dithiocarbamates could not be isolated in all cases. For example, dithiocarbamates **3a–d** cyclized at 15–20 °C to produce 1,3-benzodithiol-2-ones **4a–d**, and in some cases the formation of disulfides **5a** and **5d** was also observed. D'Amico and coworkers[3] have also studied the reaction of **1a** with **2** and reported the formation of **5a**. Their structural assignment for **5a** is based on an X-ray crystal diffraction study. We regret that in our earlier note[2] the structures assigned to **5a, 5d,** and **9a** were in error, although the identity of **5a** with the disulfide isolated by D'Amico and co-workers had been confirmed.

The 2,4-dinitrophenyl *N,N*-dimethyldithiocarbamates **7a** and **7b** show greater thermal stability than the isomeric dithiocarbamates **3a** and **3e.** In particular **7b** required comparatively drastic conditions for cyclization and yielded 5-nitro-1,3-benzodithiol-2-one (**8b**) in 5% yield (Scheme I). Product **8b** was shown to be identical with that obtained by Hurtley and Smiles[4] on nitration of 1,3-benzodithiol-2-one; the isomeric 4-nitro-1,3-benzodithiol-2-one (**4e**) was found by TLC to be absent. We were able to isolate the dithiocarbamate **7c**, but it was observed to evolve nitrogen oxides slowly at room temperature as a solid, indicating ready cyclization. The excellent conversions of **7c** and analogous dithiocar-

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[+] Dedicated to Professor Georg Wittig.

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