Reactions of Charged Substrates. 1. The Effect of Product Isomerization on Kinetics in the Reaction of Thiocyanate with (4-Methoxybenzyl)dimethylsulfonium Chloride

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For over 100 years it has been known that thiocyanates undergo a thermal rearrangement to isothiocyanates.[1] It was not until the 1960s and early 1970s, however, that the mechanisms of this rearrangement were understood. While allyl substrates rearrange by several pathways,[2] including internal cyclization and dissociation to an ion pair, rearrangements of benzyl substrates are limited to "sluggish" dissociative[3] or kinetically bimolecular[4] pathways; an equilibrium mixture is established in the dissociative pathway.

During our investigation[5] of the nucleophilic substitution reactions of (4-methoxybenzyl)dimethylsulfonium chloride 1 ($RSMe_2^+$, R = 4-$MeOC_6H_4CH_2$), we found that clean pseudo-first-order kinetics could be obtained for pyridine, azide, and sulfite in D_2O by measuring the loss of the signal for SMe_2^+ in the NMR. Rate plots for thiocyanate, however, were linear only for the first half-life, after which the reaction slowed significantly and the lines curved (Figure 1). Use of either an infinity point or the Guggenheim method to analyze the data reduced but did not eliminate the curvature.

In addition to an S_N1 component, the reactions of the other nucleophiles with 1 depends on the concentration of nucleophile, with different mechanisms that depend on conditions.[5] Based on first half-life rates, the reaction of 1 depends on [NaSCN], although in a plot of k_{obsd} vs [NaSCN] data are badly scattered compared with the same plots for the other nucleophiles (Figure 2).

One source of the curvature in the rate plots was immediately apparent. We found that the signal for the benzyl methylenes decreased at a faster rate than the corresponding signal for the aromatic protons. The secondary α-deuterium isotope effects k_H/k_D are ca. 1 for S_N2 reactions of neutral benzyl systems, while they are in the range 1.2-1.3 for the S_N1 reactions.[6] Thus, exchange of the benzyl protons for deuterons in 1 would lower k_{obsd} because of the effect on the S_N1 reaction. (Attempts to measure the rates in H_2O using solvent saturation techniques were unsuccessful.) This alone cannot account for the extent of curvature in Figure 1, however. For most reactions of 1 in the presence of most nucleophiles, the signal for SMe_2^+ disappeared completely,[5] but with thiocyanate a residual signal always remained (ca. 90-95% reaction depending on conditions) even after 1 h at 80 °C. This result was baffling.

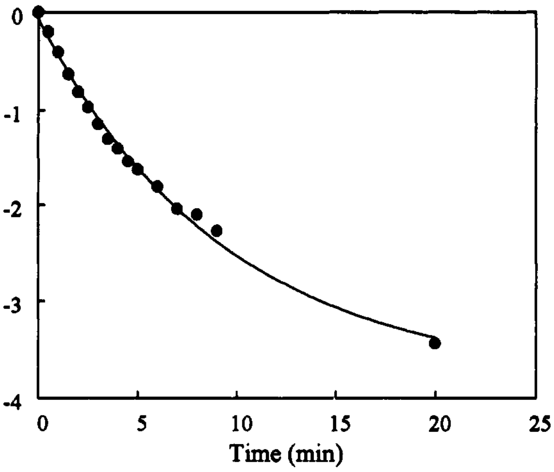

Figure 1. Plot of $\ln(C_t/C_o)$ vs time for the reaction of 1 with 2 M NaSCN in D_2O at 80 °C. The curvature is typical for this reaction with 0.5-5 M NaSCN with or without exogenous salt added to control ionic strength.[5]

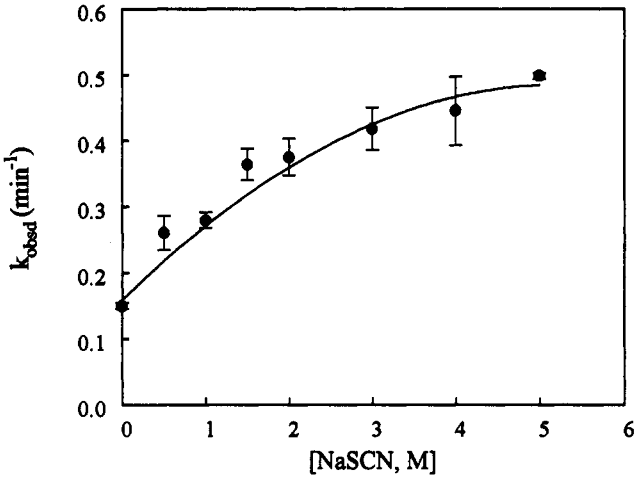

Figure 2. Plot of k_{obsd} vs [NaSCN] for 1 in D_2O at 80 °C with no exogenous salt added to control ionic strength. Values of k_{obsd} are based on first-half-life rate constants and are the averages of 3-5 determinations; bars are SE.

Also baffling was the following finding. The signals for the benzyl protons of the products RSCN and RNCS could be seen during the course of the reaction, with [RSCN] > [RNCS] at 5-10 min (or 2-4 half-lives depending on the [NaSCN]). The amount of ROH produced by solvent-trapping of R^+ remained constant. When the selectivities were determined from $CDCl_3$ extracts of reactions run in various concentrations of NaSCN (in H_2O to avoid exchange) for >10 half-lives, however, [RNCS] ≫ [RSCN].

These issues were resolved by measuring the kinetics of the conversion of RSCN to RNCS by taking chloroform extracts of the aqueous reaction mixtures; for these studies, H_2O was used to avoid exchange of the benzyl methylene protons. Changes in the intensities of the benzyl methylene peaks[7] for the two thiocyanate-derived products were measured in 5-min intervals until equilibrium had been

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[1] Spurlock, L. A.; Porter, R. K.; Cox, W. G. *J. Org. Chem.* **1972**, *37*, 1162-1168, provide a list of leading references.

[2] Iliceto, A.; Fava, A.; Mazzucato, U. *Tetrahedron Lett.* **1960**, *11*, 27-35. Smith, P. A. S.; Emerson, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 3076-3082.

[3] Spurlock, L. A.; Fayter, R. G. *J. Org. Chem.* **1969**, *34*, 4035-4039.

[4] Fava, A.; Iliceto, A.; Bresadola, S. *J. Am. Chem. Soc.* **1965**, *34*, 4791-4794.

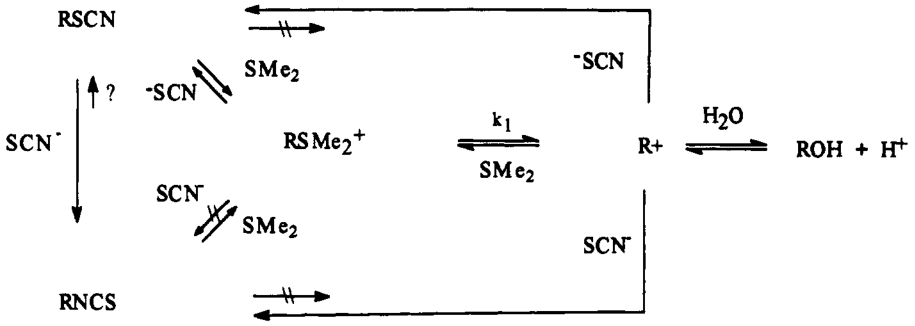
[5] Buckley, N.; Oppenheimer, N. J. Manuscipt in preparation.

[6] Shiner, V. J. In *Isotope Effects in Chemical Reactions*; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand Reinhold: New York, 1970; pp 91-159.

[7] Peak assignments from Parks, T. E.; Spurlock, L. A. *J. Org. Chem.* **1973**, *38*, 3922-3924, corrected to $CDCl_3$ from CCl_4.

0022-3263/94/1959-0247$04.50/0

Scheme 1



R = 4-MeOC$_6$H$_4$CH$_2$-

reached. There was a smooth conversion of RSCN to RNCS that leveled off at 13:87. Pseudo-first-order rate constants calculated from these data, with the inclusion of the equilibrium infinity value in the calculations, showed that under either set of conditions, doubling the [NaSCN] led to a doubling of the rate of conversion (Table 1). Plots of k_{obsd} vs [NaSCN] (not shown) pass through the origin, which rules out a unimolecular process and therefore rules out isomerization by ionization. The 2.4-fold difference between the second-order rate constants for $\mu = 5$ and the no-salt conditions is consistent with a small effect of ionic strength on second-order reactions of a neutral substrate with an anionic nucleophile.[8]

Fava *et al.*[4] showed that conversion of benzyl thiocyanate to benzyl isothiocyanate in the presence of NaSCN in methyl ethyl ketone at 110 °C was first-order in nucleophile, and that thermal isomerization through the ionization pathway was not important. Spurlock's finding that this conversion in the absence of nucleophile is slow at >100 °C is also consistent with our data.[3] In contrast, Songstad and co-workers[9] have reported that 4-NO$_2$, -H, and -Me benzyl substrates, which should undergo a second-order reaction much better than the 4-MeO substrate, yielded only the respective thiocyanates in acetonitrile at 25 °C. In this instance, it seems probable that the temperature used was too low to allow the bimolecular reaction with SCN$^-$ to occur at a measurable rate.

Fava's results[4] do not explain why an apparent equilibrium for all compounds except ROH is reached in our case. (Fava *et al.* did not report the extent of reaction for their system.) We found that kinetically bimolecular reactions occur only with nucleophiles of intermediate hardness.[5] The sulfur of the ambident SCN$^-$ is 1000-fold more reactive toward benzyl halides than the nitrogen,[10] and, because it is the softer of the two nucleophilic sites, would be expected to react preferentially with 1 as well. Because k_{obsd} for bimolecular reactions of 1 and RSCN with NaSCN are of the same magnitude, we suspect that the majority of RNCS must be formed either from RSCN or by trapping of the carbenium ion generated from the unimolecular reaction. In support of this position, we found[5] that the reaction of 1 with sodium cyanate is zero-order in nucleophile; thus neither the hard oxygen nor the softer nitrogen can undergo a second-order reaction with 1. The products with cyanate include ROCN, RNCO, and the respective hydrolysis products. No attempt was made to quantitate the components of this complex mixture.

Table 1. Pseudo-First-Order and Second-Order Rate Constants for the Conversion of RSCN to RNCS at 80 °C in H$_2$O in the Presence of NaSCN

	k_{obsd} (min^{-1})	
[NaSCN, M]	no salt	$\mu = 5$
0.5	0.041	0.020
1.0	0.096	0.040
k_2 (l/mol min)	0.096	0.040

The predominance of RNCS shows that both the hardness of the nucleophile, the charge on the substrate, and the hardness or softness of the leaving group must be considered. In this regard, we suggest that displacement of SCN$^-$ by SMe$_2$ occurs under the reaction conditions and leads to an equilibrium mixture of the starting material (5–10% of the total) and the two thiocyanate-derived products (Scheme 1).

In the hydrolysis reaction of 1, in equilibrium is established among ROH, H$^+$, SMe$_2$, and RSMe$_2^+$, but the reaction is pulled to completion in the presence of nucleophiles that can form stable products, either by direct reaction with RSMe$_2^+$ or by trapping of the carbenium ion.[5] Therefore it is highly doubtful that the residual RSMe$_2^+$ found in the presence of thiocyanate is the result of this equilibrium. Unfortunately, because of the insolubility of SMe$_2$ in water, it is not possible to measure directly or accurately either the rate constants for or the extent of substitution.[11] Fava *et al.*[4] showed that the exchange of ^{35}SCN for ^{32}SCN in benzyl thiocyanate is much faster than isomerization. The similarity of the Swain–Scott n_{MeI} and n_{Pt} values for SCN$^-$ and SMe$_2$ suggests that the exchange of SMe$_2$ for SCN$^-$ can occur, a process that is consistent with soft–soft symbiosis.[12] The 95:5 ratio of total thiocyanate-derived product to sulfonium is also consistent with the relative concentrations of the two nucleophiles in the reaction mixtures. Nonetheless, even though the mechanism by which 1 is apparently regenerated in the reaction mixture is a reasonable one, it must remain a conjecture.

Thus the lack of clean pseudo-first-order kinetics is the result of a combination of complex kinetically and thermodynamically controlled processes. If we had mea-

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(8) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell: Ithaca, NY, 1953; pp 306–408.

(9) Maartmann-Moe, K.; Sanderud, K. A.; Songstad, J. *Acta Chem. Scand.* **1982**, *36B*, 211–223.

(10) Schiavon, G. *Ric. Sci.* **1962**, *32*, 69–75.

(11) In our work on the hydrolysis of 1 (ref 5), we encountered the same difficulty and used other methods in attempts to show either common leaving group suppression or product–substrate equilibria; these methods are not applicable in this system.

(12) Pearson, R. G. In *Advances in Free Energy Relationships*; Chapman, N.B., Shorter, J., Eds.; Plenum Press: New York, 1972; pp 281-319.

sured the selectivities strictly by the book at long reaction times, we would have been misled concerning the relative nucleophilicities of the sulfur and nitrogen ends of the ambident SCN^-. Indeed, if selectivities are necessary to differentiate among mechanisms, as is the case for 1, the inability to define with precision the preference of the substrate for the hard or soft end of the nucleophile would have led to a false or overly complicated interpretation of data in a system that is sufficiently complex without the need of added ambiguity.[5]

Experimental Section

General. All solvents and precursors were obtained from Aldrich and used without further purification. ^1H NMR spectra were recorded on a General Electric QE 300 FT-NMR with a variable temperature probe rated at ±0.1 °C.

Kinetics. Reaction of 1 with NaSCN in D_2O. All rate constants were determined at 80 °C in the NMR. NMR tubes containing solutions of NaSCN in D_2O (0.5 to 5.0 M) were heated in the probe of the machine. The tube was removed and substrate sufficient to give 5–10 mM solutions was dissolved in hot thiocyanate solution; the tube containing the reaction mixture was returned to the probe and shimmed to constant values (ca. 1 min.). Data were collected at various intervals with one-pulse 45° sequences with 2-s delays (to allow complete relaxation). The disappearance of 1 was followed by integrating the singlet for the SMe_2^+ (δ 2.8 ppm relative to HOD at δ 4.30 ppm). Values of k_{obsd} were obtained by linear regression from slopes of plots of $\ln(C_t/C_o)$ vs t; these plots were linear only over ca. 1 measured half-life ($r > 0.990$), after which severe curvature occurred (see Figure 1). Curvature is not removed by including an infinity value or by using the Guggenheim method to analyze the data.

Conversion of RSCN toRNCS under the Reaction Conditions. Aliquots of stock solutions (ca. 10 mM) of 1 in 0.5 and 1.0 M solutions of NaSCN alone or at $\mu = 5$ (NaCl) in H_2O were heated at 80 °C in a heat block and extracted with $CDCl_3$ at 5-min intervals for up to 1 h. (No residual product could be detected by NMR in D_2O samples treated this way.) Extracts were passed through a short column of anhydrous sodium sulfate into a dry NMR tube. The isomerization could be monitored in ^1H spectra by observing the change in the intensities of the signals for the methylenes of RNCS ($\delta = 4.64$ ppm) and RSCN ($\delta = 4.15$ ppm).[7] Values of k_{obsd} were obtained by linear regression from slopes of plots of $\ln[(C_t - C_\infty)/(C_o - C_\infty)]$ vs t, where the infinity value was the peak intensity at equilibrium ($r > 0.990$ for three plots, $r = 0.976$ for one plot). With or without control of ionic strength, doubling the concentration of nucleophile produced a doubling in k_{obsd} (Table 1).

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