with decomposition; IR (Nujol) 3290, 3090, 1760, 1640, 1555 cm^{-1}; ^1H NMR for major diastereomer (200 MHz, DMSO-d_6) δ 8.71 (d, J = 8 Hz, 1 H), 8.57 (d, J = 8 Hz, 1 H), 8.42 (unresolved d and t, 2 H), 5.36 (d, J = 8 Hz, 1 H), 5.03 (d, J = 8 Hz, 1 H), 4.45 (m, 1 H), 4.11 and 4.07 (two overlapping q, J = 7 Hz, 4 H), 3.11 (m, 2 H), 2.01 (m, 1 H), 1.89 (s, 3 H), 1.16 (t, J = 7 Hz, 6 H), 1.03 (t, J = 7 Hz, 3 H), 0.88 (m, 6 H). Anal. Calcd: C, 51.34; H, 7.26; N, 12.60. Found: C, 51.43; H, 7.31; N, 12.52.

N^{α}-Acetyl-D,L-Ama-L-valyl-D,L-Ama N-Ethylamide. N^{α}-Acetyl-α-carbethoxyglycyl-L-valyl-α-carbethoxyyglycine N-ethylamide (0.166 g, 3.74×10^{-4} mol) was added to 20 mL of 50% aqueous ethanol. Potassium hydroxide (0.47 mL, 2 N KOH, 2.5 equiv) was added, and the reaction mixture was stirred at ambient temperature until all of the starting material had dissolved, approximately 3 h. The solvent was rotory evaporated, and the residue was triturated with 30 mL of absolute ethanol. The solid material was collected by filtration and washed with additional ethanol. The product was dissolved in 10 mL of distilled deionized water and placed on a 2-mL column of Bio-Rad analytical grade cation exchange resin (AG 50W-X8, H^+ form), which had been repeatedly washed with water. The product was eluted at a flow rate of 1 mL/min, and additional water was added as needed. Fractions were collected in 1-mL increments, placed on ice, and analyzed by HPLC. HPLC analysis shows the presence of four diastereomers, which were individually collected. Reinjection of the separate fractions showed the presence of all four diastereomers, indicating that racemization of the Ama residues had occurred. The pure product eluted in fractions 3-9 from the ion exchange column. The fractions were combined, and the solvent was rotary evaporated. The product was further dried in a vacuum desiccator to give 0.0558 g (38% yield) of product. The product had the following properties: mp decarboxylation at 132 °C, further heating gave mp 206-208 °C with decomposition; IR (Nujol) 3670-2500, 3280, 1750, 1635 (s, broad), 1540 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 4.31 (m, 1 H), 3.21 (q, J = 7 Hz, 2 H), 2.10 (m, 1 H), 2.08 (s, 3 H), 1.10 (t, J = 7 Hz, 3 H), 0.93 (m, 6 H); FAB mass spectrum (negative ion, 3:1 dithiothreitol-dithioerythritol matrix) m/z (relative intensity) 387 (32), 343 (20), 299 (100). Anal. Calcd for $C_{15}H_{24}N_4O_8 \cdot 0.5H_2O$: C, 45.34; H, 6.34; N, 14.10. Found: C, 45.35; H, 6.38; N, 14.08.

Base Hydrolysis and Amino Acid Analysis.[24] Samples (5-15 mg) were added to 2-4 mL of sterile filtered 2 N KOH in Teflon-lined hydrolysis tubes, and the solutions were degassed with nitrogen for 30 min. Tubes were sealed under nitrogen and placed in an oil bath at 108-110 °C for 24 h. After cooling, samples were transferred to 20-mL beakers. Hydrolysis tubes were rinsed with an additional 2-4 mL of water, and rinsings were combined with the samples. The samples were cooled to 0 °C and acidified with concentrated and then dilute perchloric acid to pH 6.0 while keeping the samples on ice. The samples and precipitate were transferred to centrifuge tubes and centrifuged at 10000 rpm and 4 °C for 20 min. The supernatants were removed and evaporated by high vacuum rotory evaporation. The potassium perchlorate pellets were triturated with an additional 4-5 mL of water, cooled, and centrifuged again. The supernatants were added to the sample and evaporated. The samples were dissolved in an appropriate volume of distilled, deionized water and refrigerated to allow the precipitation of additional potassium perchlorate. The supernatants were filtered through 0.2-μm filters and then diluted with an appropriate volume of 0.4 N borate buffer (pH 10.2) and again filtered prior to HPLC analysis. Aliquots of samples in the borate buffer (typically 20-60 μL) were combined with o-phthalaldehyde derivatizing solution using volumes that gave at least a 5-fold excess of o-phthalaldehyde. Samples were mixed for exactly 60 s, diluted with a measured volume of eluent A, and mixed for 30 s. Aliquots of 20 μL were analyzed by HPLC using a 1090 Hewlett-Packard HPLC system equipped with a diode-array detector monitoring at 338 nm. The column was an Alltech Adsorbosphere OPA-HR 5μm 150 × 4.6 mm cartridge. Eluent A was 98%, 0.05 M NaOAc adjusted with 1 N HCl to pH 5.8, 1% THF, 1% MeOH; eluent B was 99% MeOH, 1% THF. The gradient was 0-5 min, isocratic A; 5-8 min, linear gradient to 10% B; 8-12 min, linear gradient to 20% B; and 12-20 min, isocratic 80% A and 20% B. Retention time for Ama derivative was 3.5 ± 0.1 min and for Gly derivative, 15.4 ± 0.1 min. Calibration curves were determined with use of authentic samples of Ama (monopotassium salt) and glycine.

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Dual Mechanisms of Bimolecular Nucleophilic Substitution of a Heterobenzylic Bromide Related to Thiamin†

John A. Zoltewicz*

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Georg Uray

Institut für Organische Chemie, Karl-Franzens-Universität, A-8010 Graz, Austria

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4-Amino-5-(bromomethyl)-1,2-dimethylpyrimidinium ion at 25 °C in 0.9 M KCl made to an ionic strength of 1 M with buffers reacts with hydroxide ion with a rate constant of 725 M^{-1} s^{-1}. Evidence for an intermediate is found in the large common ion rate retarding effect of added bromide ion. An addition-elimination mechanism ($S_N(AE)$) involving the addition of hydroxide ion to give a pseudobase intermediate followed by loss of bromide ion is advanced. Chloride ion reacts by an S_N2 mechanism (5.9×10^{-5} M^{-1} s^{-1}). When 2-thiopyridone acts as a nucleophile by the S_N2 mechanism, its sulfur atom is heterobenzylated with a rate constant of 0.28 M^{-1} s^{-1} (31 °C). Two different bimolecular mechanisms of nucleophilic substitution are thereby observed.

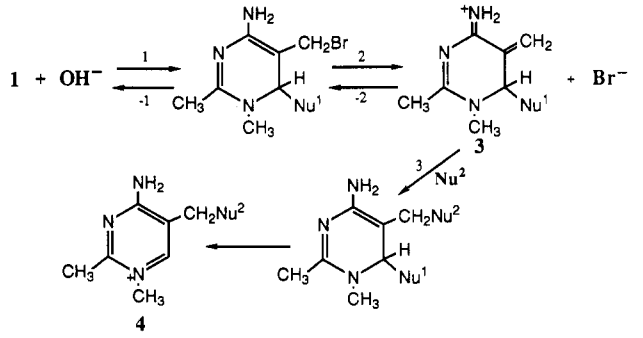
Pyrimidinylmethyl bromide **1**, a "heterobenzylic" bromide, undergoes nucleophilic substitution by a novel combination of bimolecular routes. Cation **1** is an N-methylated analogue of thiamin in which the bromine atom is attached to the methylene side chain in place of the thiazole ring.

In a marked contrast, **1** reacts some 10^6 times faster with

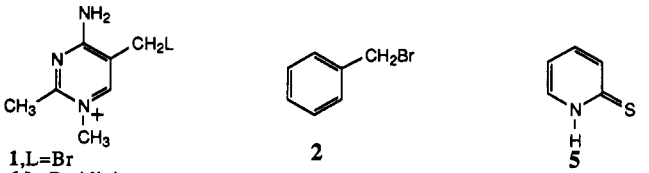
† Dedicated to Professor Edward C. Taylor, Jr., on the occasion of his 65th birthday.

0022-3263/89/1954-1370$01.50/0

Scheme I



hydroxide ion than benzyl bromide (**2**)[1] at 25 °C. But with neutral water **1** is at least 100 times less reactive than **2**.[2]



1,L=Br
6,L=Pyridinio
7,L=p-Cyanophenoxy
8,L=2-Pyridylthio

The hydrolysis mechanisms involving hydroxide ion are completely different for **1** and **2**. A multistep mechanism having as a key feature the addition of hydroxide ion to the electrophilic, cationic pyrimidine ring of **1** prior to the elimination of bromide ion provides intermediate **3** (Nu^1 = OH) that leads to substitution products **4** (Nu^2 = OH), Scheme I, an $S_N(AE)$ pathway. However, **2** reacts with hydroxide ion and water by the common S_N2 route. The vast difference in rates at high pH is easily understood in terms of the different mechanisms and reactivities.

Bromide **1** undergoes nucleophilic substitution with chloride ion and with 2-thiopyridone (**5**) in aqueous solution by an S_N2 mechanism. Curiously, then, **1** can react by completely different bimolecular mechanisms, depending on the identity of the nucleophile, a novel observation.

Results

Hydrolysis. The hydrolysis of **1** was easily followed spectrophotometrically in aqueous buffers at 25 °C over the pH interval 4.69–8.81. The ionic strength was maintained at 1 M, generally with 0.9 M KCl, buffer comprising the remaining salts. An essentially pH-independent rate plateau extends from the lowest value to about pH 7, and then the rate increases rapidly at higher pH values, showing first an *apparent* water reaction and then a kinetic dependence on hydroxide ion, Figure 1.

The term for the apparent reaction with water is mainly a term for chloride ion electrolyte acting as a nucleophile.[5] When the usual potassium chloride electrolyte was replaced by sodium perchlorate at pH 8.62 where lyate ion hydrolysis is the major process, almost no rate change was found. The new mixture is only 15% less reactive. But

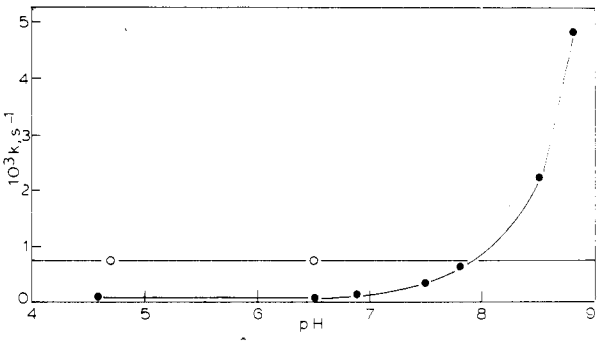


Figure 1. Pseudo-first-order rate constants as a function of pH for **1** (curved line) and **2** at 25.0 °C in 0.9 M KCl maintained at a total ionic strength of 1 M by the addition of buffers. Points for **2** in 0.010 and 0.10 M NaOH are not shown.

at pH 6.28 in a phosphate buffer where the pH-independent reaction predominates, replacement of chloride by perchlorate ion gives rise to a 2.4-fold reduction in the rate constant (8.13×10^{-5} vs 3.32×10^{-5} s^{-1}). Again, in a dilute acetate buffer (pH 4.69, 5×10^{-3} M acetate ion) this same salt substitution produces an even larger rate retardation. The observed rate constant of approximately 1.6×10^{-6} s^{-1} (half-life about 5 days) is some 34 times smaller than that found when chloride ion is present (5.43×10^{-5} s^{-1}). Because the former reaction was so slow, no attempt was made to prove that the reactive nucleophile indeed is water in what we call the "water" reaction. Chloride ion successfully competes with water, but it does not compete with high concentrations of hydroxide ion, and so smaller changes in rate are observed at higher pH values when the unreactive perchlorate ion is replaced by chloride ion.

The reason for the faster reaction when chloride ion replaced perchlorate ion became even more evident by a product analysis where another, more concentrated reaction mixture was analyzed by NMR. When a suspension of **1** and 5.4 M KCl was stirred at room temperature at a starting pH of 6 in buffer-free water for a day and the supernatant was examined by NMR, two products were observed along with starting material. In addition to the expected hydrolysis product **4** (Nu^2 = OH) containing the hydroxy group, there was present a second substance differing in chemical shift from **1** mainly in the position of the CH_2 signal: 4.52 (Br) vs 4.75 ppm. This other product most likely is the chloro analogue of **1**. The three substances were present in a ratio 1:hydroxy:chloride that equals 1.6:1:2.4. The reason for the faster reaction of **1** when chloride ion is present instead of perchlorate ion at lower pH is that chloride ion acts as a nucleophile in competition with water, thereby converting the starting bromide to the hetaryl chloride.

Similar product studies using phosphate buffer and NMR analysis show that the buffer may be incorporated into product. The signal for CH_2 is spin coupled to phosphorus as required for a $CH_2OPO_3^{2-}$ group.

An approximate rate constant may be estimated for chloride, assuming that the observed rate constant at pH 4.69 based upon perchlorate ion electrolyte may serve as a refererence for the "water"-catalyzed reaction. Comparison with the data for a solution of the same pH containing chloride ion (5.43×10^{-5} s^{-1}) gives the corrected first-order constant (5.27×10^{-5} s^{-1}) and a second-order constant of 5.9×10^{-5} M^{-1} sec^{-1}.

The data in Figure 1 now may be described in terms of three rate constants, one for chloride ion, k_{Cl}, one for water, k_{H_2O}, and one for hydroxide ion, k_{OH}, where the latter has the value 725 M^{-1} s^{-1}, which is obtained from the high pH

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Table I. Common Ion Rate Retardation of 1 at 31 ± 1 °C in Phosphate-Bromide-Perchlorate Ion Solutions at pH 6.26[a]

$[NaClO_4]$, M	[NaBr], M	$10^5 k_{obsd}$, s^{-1}
0.90	0	5.84
0.85	0.05	2.61
0.75	0.15	1.46
0.40	0.50	1.00

[a] Ionic strength is 1 M.

part of the curve in Figure 1. The line in Figure 1 shows the curve calculated by using eq 1.

$$k_{obsd} = k_{H_2O} + k_{Cl}[Cl^-] + k_{OH}[OH^-] \quad (1)$$

Potassium bromide at pH 8.62 provided a different kinetic outcome from that with chloride ion: a marked rate reduction that is most revealing mechanistically. Replacement of 0.88 M perchlorate ion by the same concentration of bromide ion gave rise to an observed rate constant 8.6 times smaller (3.34×10^{-3} vs 3.90×10^{-4} s^{-1}). Common ion retardation seems to be the likely explanation.

A more extensive study of the influence of bromide ion was carried out in the plateau region in a phosphate buffer at pH 6.26 and 31 °C. A series of solutions containing varying amounts of perchlorate and bromide ions was made to a constant ionic strength of 1 M. In accordance with a gradual increase in the concentration of bromide ion from 0 to 0.50 M, Table I, the observed rate constant decreases sharply, dropping eventually by a factor of 5.8.

Similar but limited experiments were carried out with **2** in order to establish its characteristics under our reaction conditions, Figure 1. As observed by others,[1-4] the rate of hydrolysis is independent of basicity over a wide pH range. Hydroxide ion is too weak a nucleophile to compete with water and chloride ion when present in low concentrations. Starting at pH 4.69 and ending with 0.1 M NaOH there is no significant change in the observed rate constant. The first-order constant of 7.63×10^{-4} s^{-1} makes **2** 10 times less reactive than **1** under the same conditions of high chloride ion concentration at pH 9 and 14 times more reactive at low pH, Figure 1. When the chloride ion is replaced by 0.9 M perchlorate ion to maintain the ionic strength at 1.0 M the rate constant for **2** decreases by a large factor of 4.2. Our constant (1.8×10^{-4} s^{-1}) obtained with the perchlorate medium is similar to the reported values of 2.75×10^{-4} s^{-1} (30 °C)[2] and 1.56×10^{-4} s^{-1} [4] observed for salt-free water.

A second-order constant of 6.5×10^{-4} M^{-1} s^{-1} may be computed for chloride ion reacting with **2**.[5] The perchlorate derived value was used to correct the chloride data to reflect reaction with water.

As expected, there is no common ion effect for **2**. Replacing the perchlorate ion by an equivalent amount of bromide ion brings about little change. The bromide sample is 9% less reactive.

Sulfur Nucleophile. Experiments were designed to establish whether an intermediate forms from **1** during the course of the reaction in the rate plateau region. In our earlier studies *p*-nitrobenzenethiolate ion served to trap intermediate **3** (Nu^1 = OH) formed from substrates **6** and **7**;[6] these differ from **1** in the identity of the leaving group, pyridine and *p*-cyanophenoxide ion, respectively. However, both are less reactive toward hydroxide ion than **1**, 340 and 3000 times, respectively. In the present case 2-thiopyridone **5**, a neutral, ambident nucleophile (pK_a[7] = 10) seemed to be a good choice. It has an absorption peak at 340 nm that disappears when it reacts at its sulfur but not at its nitrogen atom. When **5** was present in excess, pseudo-first-order rates were obtained easily by following the disappearance of the thiopyridone at long wavelengths where **1** does not absorb. Rates were examined at low pH where the conversion of **1** proceeds predominantly by a pH-independent process so that the anionic, more reactive form of **5** would not be present. The observed decrease in the intensity of the long wavelength absorbance confirms that the reaction takes place at the more nucleophilic sulfur atom, consistent with the conclusion that **8** is a product. We prepared **8** independently from *N*-methylthiaminium ion[8] and **5**.

Table II. Conditions and Results for the Reaction of 1 and 2 with 2-Thiopyridone in Various Salts at 1 M Ionic Strength

pH	10^4[thione], M	$10^4 k_{obsd}$, s^{-1}	k_2, M^{-1} s^{-1}
		Compound **1** at 25 °C	
6.52[a]	4.40	2.06	0.276
6.49[a]	1.90	1.41	0.297
4.69[a]	1.70	1.04	0.273
6.49[b]	10.20	2.86	0.248
6.28[b]	4.75	1.65	0.278
5.62[c]	8.14	3.33	0.330
			av 0.284 ± 0.020
		Compound **2** at 31 °C	
6.49[b]	13.10	54.3	3.98
6.49[b]	6.21	28.1	4.24
6.49[b]	2.68	12.8	4.10
6.02[b]	7.92	35.7	4.28
6.02[b]	2.68	12.8	4.10
			av 4.14 ± 0.10
6.02	12.7	49.3	3.74[d]

[a] 0.88 M KCl. [b] 0.88 M $NaClO_4$. [c] 0.90 M KBr. [d] 25 °C.

The data in Table II show that **5** accelerates the rate of disappearance of **1** in a pH-independent process and therefore is involved in a second-order reaction. Trapping of **3** in a fast step is not observed. The substitution of either perchlorate or bromide ion electrolyte for chloride ion has no significant influence on the value of the second-order rate constant, Table II. There is no evidence of a common ion effect. After correcting the observed first-order constant for competing hydrolysis a second-order term of 0.28 M^{-1} s^{-1} is computed for **5** reacting with **1** at 25 °C.

For comparison **5** was allowed to react with **2** using perchlorate ion as the supporting electrolyte. The second-order rate constant has the value of 4.1 M^{-1} s^{-1} at 31 °C and 3.74 M^{-1} s^{-1} at 25 °C, making **2** 13 times more reactive than **1** toward the same nucleophile, Table II.

Discussion

The mechanistic possibilities for the bimolecular reaction of **1** with the various nucleophiles encountered in this study include S_N2, E1cb, and $S_N(AE)$. Since the latter two are not possible for **2**, comparisons between **1** and **2** will be worthwhile.

Scheme I describes the $S_N(AE)$ route for **1** and eq 2 expresses the general pseudo-first-order rate constant for this scheme, making the assumption that the final, rearomatization step is fast.

$$k_{obsd} = \frac{k_1[Nu^1]k_2k_3[Nu^2]}{k_{-1}k_{-2}[Br^-] + k_{-1}k_3[Nu^2] + k_2k_3[Nu^2]} \quad (2)$$

Among the several possible limiting cases for eq 2, two are especially relevant. According to eq 3 there is no

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common or external ion effect, i.e., $k_{-2}[Br^-] < k_3[Nu^2]$ and capture of intermediate **3** by buffer and solvent-derived nucleophiles is faster than that of bromide ion. Addition of the first nucleophile (Nu^1) or loss of the bromide ion leaving group (k_2) may be rate limiting.

$$k_{obsd} = \frac{k_1[Nu^1]k_2}{k_{-1} + k_2} \quad (3)$$

Equation 4 applies when there is a common ion effect, $k_{-2}[Br^-] > k_3[Nu^2]$, where in the presence of added bromide ion intermediate **3** is readily captured and returned back to starting material. The value of the observed rate constant is depressed by added bromide ion and increased by raising the concentration of Nu^2.

$$k_{obsd} = \frac{k_1[Nu^1]k_2k_3[Nu^2]}{k_{-1}k_{-2}[Br^-]} \quad (4)$$

Hydroxide Ion. Comparison of the second-order rate constants for the hydrolysis of **1** and **2**[1] by hydroxide ion shows that **1** reacts an astonishingly 10^6 times faster than **2**. These observations and the common ion retardation found for **1** but not for **2** require different mechanisms for the two substrates. The common ion effect demands the presence of an intermediate, one lacking the bromine atom and hence rules out an S_N2 mechanism for **1**.

The large value of the second-order rate constant for lyate ion is consistent with pseudobase formation as encountered in the $S_N(AE)$ mechanism and further indicates that an S_N2 mechanism is not followed. Hydroxide ion is a notoriously poor nucleophile toward benzylic carbon.[9] By contrast, addition of hydroxide ion to the electrophilic carbon atom of charged heteroaromatic rings to give pseudobases can be very fast.[10-12]

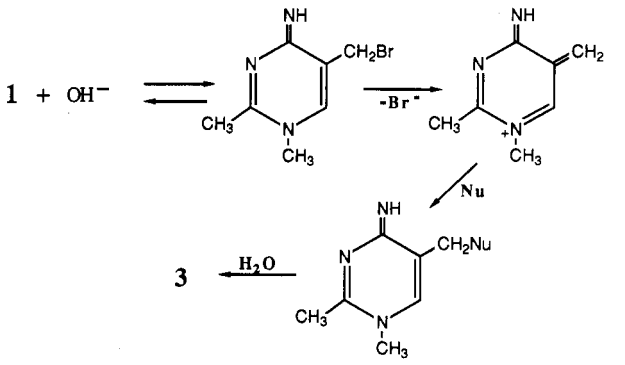
We suggest that **1** reacts by the $S_N(AE)$ route as outlined in Scheme I where Nu^1 is hydroxide ion. When the concentration of bromide ion is low and there is no retardation, either addition of hydroxide ion or loss of bromide ion may be rate limiting, eq 3. But with common ion retardation, capture of **3** by various nucleophiles becomes rate limiting, eq 4.

In view of statements that the lifetime of the 1-phenylethyl cation is only about 10^{-11} s in water–trifluoroethanol[13] and that benzyl tosylate reacts with water by an S_N2 mechanism,[14] **2** probably reacts with water and also hydroxide ion by this same S_N2 process.

E1cb. An E1cb process also is consistent with our data for hydroxide ion. According to this, lyate ion first deprotonates the amino group of **1**, converting it into its conjugate base that in the rate-limiting step then expels bromide ion to give an intermediate. This intermediate reacts with the various nucleophiles present to give substitution products, Scheme II. This pathway is consistent with common ion retardation by bromide ion. Others have proposed such a mechanism for substrates expelling a leaving group from a methylene side chain following deprotonation at nitrogen.[15,16]

Although we cannot rigorously exclude the E1cb mechanism, we do not favor it. Our earlier investigations using

Scheme II



sulfite ion as the nucleophile with **1**[17] and our results for the hydrolysis of analogues of **1**[18] speak against this mechanism. A multistep $S_N(AE)$ route must be followed when sulfite ion is the nucleophile toward **1**. The observed pH dependence is associated with the conversion of bisulfite ion to the more reactive sulfite ion; amino group deprotonation is not relevant. These observations show that a multistep mechanism of substitution is possible for **1** and its analogues under similar conditions of acidity.

Halide Ion Nucleophiles. Halide ions could react with **1** in several different ways. Unlikely is the possibility that chloride ion causes a rate acceleration by serving as Nu^1 in Scheme I, eq 3. If chloride were to act in this way, so too should bromide ion. But added bromide ion retards, not accelerates. Therefore, neither halide ion adds to an annular carbon atom of **1** to induce the multistep mechanism.

Although chloride ion could influence rates according to Scheme I when it reacts with **3** serving as Nu^2, this cannot happen under conditions where there is no added bromide ion. In order for this capture step to be kinetically important, the preceding step must be reversible and kinetically significant, i.e., bromide ion must also capture **3**. This is unlikely under conditions where bromide ion only comes from the starting substrate, and the concentrations of other nucleophiles, including chloride ion, remain high. The bromide ion concentration is only on the order of 5×10^{-4} M. Chloride ion could capture **3** in a fast step (k_3) without the preceding step being kinetically important but this would not influence the rate, eq 3.

The accelerating effect of chloride ion was also observed for **2** where the $S_N(AE)$ mechanism is impossible and an S_N2 mechanism is expected. This suggests that both substrates react with chloride ion by a similar mechanism, and this must be S_N2. Compound **1** is 11 times less reactive (5.9×10^{-5} vs 6.5×10^{-4} $M^{-1}s^{-1}$) than **2** toward this nucleophile.

The nature of the participation by bromide ion is easier to discern because it cannot accelerate substitution by an S_N2 route; this reaction is degenerate, starting material and product are the same. The main kinetically important role for bromide ion must be as a trapping agent for **3**.

In short, both chloride and bromide ions may react with **3**. Chloride ion also reacts by an S_N2 mechanism.

Thiopyridone Nucleophile. The pH-independent bimolecular reaction between bromide **1** and **5** to give **8** is not likely to proceed by the $S_N(AE)$ route in Scheme I. Some nucleophile such as water must first react with **1** to give intermediate **3** that then is trapped by **5** acting as Nu^2. But in order for the trapping step to be manifested ki-

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netically, the step for the loss of bromide ion to generate 3 must be *reversible*. Adding bromide ion should lead to common ion retardation. None was found, and so this mechanism can be ruled out.

A variation of the $S_N(AE)$ mechanism cannot be eliminated as a possibility for the reaction of **5** with **1**, one in which **5** acts as Nu^1 to initiate the multistep sequence. This, of course, does not require common ion retardation provided that the following steps are fast and **5** traps intermediate **3**.

We favor an S_N2 process in which the sulfur atom of **5** attacks the benzylic-like side chain instead of the annular carbon atom. Such an S_N2 process must pertain to **2** and **5**. Compound **1** is only 13 times less reactive than **2** toward **5** and about 11 times less reactive toward chloride ion than **2**, reasonable ratios considering that substituent effects have only a modest influence on reactivity in S_N2 reactions.[19,20]

Thioamide **5** is a powerful, neutral nucleophile having a reactivity not unlike those of thiourea and pyridine,[21-24] for example. It might serve to supplement the use of thiourea in mechanism studies because it has the distinct advantage of containing an intense chromophore while the thiourea does not, thereby allowing kinetic studies to be readily carried out spectrophotometrically.

Conclusions

The relative second-order rate constant ratio of OH^-:**5**:Cl^-:H_2O is $1:(4 \times 10^{-4}):(8 \times 10^{-8}):(4 \times 10^{-11})$ for **1** and for **2** it is $(2 \times 10^{-4}):1:(2 \times 10^{-4}):(8 \times 10^{-7})$. A very different order is found for the two.

The rate plateau shown in Figure 1 for **1** is not primarily due to reaction with water. Rather, it is associated with an S_N2 reaction with chloride ion electrolyte. A true rate plateau representing reaction with water would have a much smaller value.

The nature of the nucleophile determines the course of substitution reactions with **1**. Bromide **1** therefore presents an interesting challenge, one that is quite different from that found with the usual benzylic substrates such as **2** where bimolecular S_N2 routes are observed. In the present case there is a choice between the two very different bimolecular pathways. The factors that determine which bimolecular mechanism will be followed by the heterobenzylic halide remain to be uncovered.

Experimental Section

Kinetics. Acetate, phosphate, phosphate–borate, and carbonate ion buffers usually contained KCl to make an ionic strength of 1 M. In some experiments the chloride ion was replaced by bromide or perchlorate ion. The chloride ion concentration often was about 0.9 M. Concentration changes in **1** were followed at 290 nm (3460 M^{-1} cm^{-1}). A slight downward absorbance drift near "infinity" reaction times in some of the runs was corrected by back extrapolation of the linear region and by measuring absorbance changes relative to this line. These corrections produced a rate constant larger by as much as 25%. Data were fitted to a least-squares semilog equation by a microcomputer over at least 4 half-lives. The computer program was able to iterate the infinity value to optimize the fit, which usually had a correlation coefficient of 0.999. Many such plots were linear over 7–8 half-lives. The ion product of water was taken to be 14.00;[25] no correction was made for the influence of salt.

A serial dilution experiment employing KCl and monohydrogen phosphate base at 0.10 M (pH 7.49) and 0.020 M (pH 7.46) to check for buffer catalysis gave essentially identical rate constants, indicating the lack of significant buffer catalysis. In the acetate buffer the free base concentration was 0.005 M. At the end of the reaction the only major absorbance was at 249 nm.

When 2-thiopyridone was present the wavelengths were either 340, 370, 380, or 390 nm, regions in which the organic bromide has no absorbance. The longer wavelengths were used with more concentrated solutions. In the absence of substrate the thione demonstrated a slow, linear drift in absorbance when chloride ion was the supporting electrolyte. After substitution the rate of drift seemed to be the same as that before substrate was added. Therefore, the kinetic runs were allowed to proceed for long times to establish the rate of drift, its constant slope being expressed as chart units/minute. Drift corrections were made as a function of time by multiplying the drift factor by time and then adding the resultant value to the observed absorbance. The net effect of this correction was to decrease the size of the absorbance change and to increase the apparent rate constant by as much as 20% and increase the value of the correlation coefficient. Reactions were followed for at least 4 half-lives; correlation coefficients were >0.99. The concentration of unionized thiopyridone was calculated either from its initial absorbance at 340 nm by using a reported absorptivity of 8700 M^{-1} cm^{-1} [26] or at 370 (3700), 380 (1670), or 390 (644).

Benzyl bromide was solvolyzed in acetate, borate, and dilute hydroxide ion solutions (0.010 and 0.10 M) made to 1 M ionic strength usually with KCl at 25.0 °C. Some runs contained NaBr or $NaClO_4$ in place of KCl. The wavelength was 250 nm. Plots were linear over 6–8 half-lives.

Product Studies. A suspension of 1 g of bromide **1**[27] was stirred at room temperature for 1 day with 5 mL of water and 2 g of KCl after adjusting the pH to 7 with $NaHCO_3$. Solid material then was removed from the strongly acidic solution. The NMR (200 MHz) of the dried solids dissolved in D_2O revealed the presence of three components: the starting bromide, the expected hydroxy hydrolysis product **4** (Nu^2 = OH), and the corresponding hetaryl chloride **4** (Nu^2 = Cl). The position of the CH_2 signal at low field allows assignment of the chloride structure. Chemical shifts in ppm area as follows: CH 8.32 (Br), 8.30 (Cl), 8.12 (OH); CH_2 4.52 (Br), 4.65, (Cl), and 4.60 (OH). The NCH_3 (3.87) and CCH_3 (2.68) signal positions are constant.

Bromide **1**[27] was dissolved in 0.5 mL of D_2O, and the NMR spectrum was taken immediately. After 15 min a second spectrum showed no change. Addition of 0.5 equiv of 2 N NaOH revealed the prompt formation of 50% of the hydroxy hydrolysis product **4** (Nu^2 = OH), identified by the addition of authentic compound. The solution was somewhat yellow and after 1 day at room temperature some unreacted starting material remained. Addition of the second half of the NaOH cleanly generated the spectrum of the hydrolysis product alone. A similar experiment carried out with Na_2HPO_4 clearly showed the presence of the hydroxy product (25%) along with a new material formed by reaction of **1** with the phosphate buffer. This assignment follows from the doublet structure (J = 6 Hz) of the CH_2 signal (4.75 ppm) representing coupling to phosphorus, clearly the buffer can be incorporated into product.

2-(Benzylthio)pyridine has been prepared from **5** and benzyl chloride.[26]

Stability of Sulfide 8. Authentic 4-amino-1,2-dimethyl-5-[(2-pyridinylthio)methyl]pyrimidinium perchlorate, mp 195.5–196.5 °C, was stable toward hydrolysis. It was prepared from *N*-methylthiaminium diperchlorate[28] and 2-thiopyridone by the same method as that for the corresponding 4-thio derivative. At pH 6.50 in a phosphate buffer no absorbance change was noticed at 340 nm over 91 h (25 °C), a period corresponding to

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38 half-lives for hetaryl bromide under the same conditions. Any liberated 2-thiopyridone would have been detected at this wavelength of maximum absorbance. This sulfide has a maximum absorbance at 243 nm with a shoulder at 275 nm and no significant absorbance at 340 nm.

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One-Pot Preparation of Crowded Olefins from Hindered Ketones with Alkyllithiums and Thionyl Chloride[1]

George A. Olah,* An-hsiang Wu, and Omar Farooq

The Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661

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A series of crowded olefins were prepared in high yield by the one-pot reaction of in situ generated lithium alkoxides, formed from hindered ketones and alkyllithiums, with thionyl chloride. The prepared olefins are generally inaccessible by either the Wittig reaction or using Grignard reagents because of predominant electron-transfer reduction of the hindered ketones.

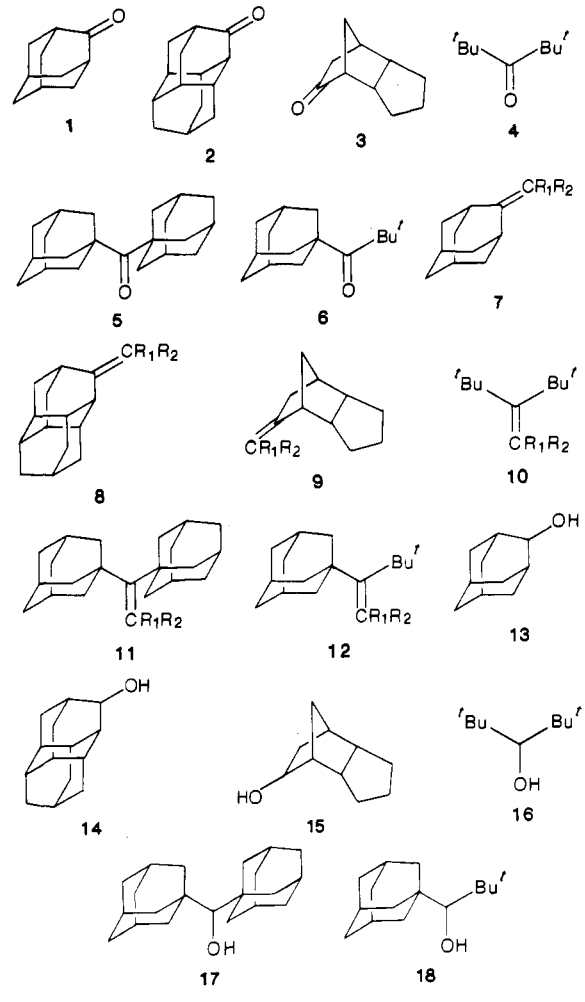
Introduction

Preparation of olefins can be accomplished in addition to dehydrogenation, dehydration, and dehydrohalogenation by a great variety of methods[2] from various functional groups such as carboxylic acids, vicinal dicarboxylic acids, alkyl halides and vicinal dihalides, halohydrins, β-hydroxy sulfonamides, amines, etc. The most widely used olefin synthesis from carbonyl compounds is the Wittig reaction.[3] A host of substituted olefins are also prepared, among other methods, by Perkin,[4] Stobbe,[5] and Darzenes'[6] reactions from carbonyl compounds.

When the Wittig reaction between alkylidenephosphorane and an enolizable ketone is sterically hindered, the enolate of the ketone is formed, together with phosphonium salt and the products of self-condensation of ketone.[7] With a nonenolizable ketone (or one that enolizes with great difficulty), no reaction under usual Wittig conditions between alkylidenephosphoranes and ketones is observed.[8] Our previous studies of preparing hindered olefins from nonenolizable ketones 2-adamantanones (**1**)[9,10] and 3-diamantanones (**2**)[10] with hindered alkylidenephosphoranes were unsuccessful, and instead we observed electron-transfer reduction.

For dehydration of alcohols to olefins among other dehydrating agents, thionyl chloride in combination with excess pyridine has been widely used.[11] Thionyl chloride, otherwise, is a chlorinating agent[12] for alcohols, reacting through intermediate chlorosulfite derivatives[13] in an S_Ni type reaction.[14] In the absence of pyridine, use of thionyl chloride as dehydrating agent for alcohols to olefins has

Scheme I[a]



[a] **a**, $R_1 = R_2 = H$; **b**, $R_1 = R_2 = CH_3$; **c**, $R_1 = CH_3$, $R_2 = CH_2CH_3$.

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