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Reaction of Halide Ion with 2-(Phenylthio)ethyl Halides in Acetone

Samuel P. McManus,* Rashid M. Karaman, Reza Sedaghat-Herati, and J. Milton Harris

Department of Chemistry, University of Alabama in Huntsville, Huntsville, Alabama 35899

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2-(Phenylthio)ethyl chloride specifically deuterated α to the sulfur atom (i.e. **2-Cl**) was employed to study the mechanism of displacement of chloride ion by iodide ion in dry acetone solution. Experimental evidence including rate studies has been accumulated that allows the conclusion to be drawn that iodide ion displaces chloride ion from **2-Cl** by a classical S_N2 mechanism to give **2-I**. Under the reaction conditions, however, **2-I** is reactive toward anchimerically-assisted ionization which leads to product with the deuterium label scrambled. Reaction of **2-Cl** with bromide ion follows a similar course. Our displacement reactions of halide ions by halide ions showed the expected nucleophilicity order of $Cl^- > Br^- > I^-$ and the normal leaving group order of $I^- > Br^- > Cl^-$. An interesting counterion effect was noted with iodides displacing chloride ion. While potassium iodide in acetone converted **2-Cl** to the mixture of iodides **2-I** and **3-I**, tetrabutylammonium iodide caused conversion but the products reverted completely back to the label-scrambled chlorides. The difference in these results is probably because of differences in the thermodynamics of the two systems.

During a kinetic study of the reaction of several alkyl chlorides with potassium iodide in acetone, Bordwell and Brannen measured second-order kinetics for the reaction of 2-(phenylthio)ethyl chloride (**1-Cl**) with potassium iodide in acetone and concluded that the reaction was a simple S_N2-type displacement reaction.[1] As part of our studies of β-(alkylthio)- and β-(arylthio)ethyl chlorides, as models for the reactivity of "mustard gas" (2,2′-bis(chloroethyl) sulfide), we uncovered evidence about the reactivity of **1-Cl** and its analog the brosylate **1-OBs** that led us to question[2] Bordwell and Brannen's conclusions about the displacement mechanism for **1-Cl**.

We repeated the Bordwell and Brannen study of **1-Cl** and confirmed that the reaction of **1-Cl** with KI is a bimolecular process. However, various other evidence on the reactivity of **1-Cl**, obtained since noting our concern, caused us to view this reaction as a more complex process. For example, we had found that several good nucleophiles, e.g. thiourea and iodide, undergo reaction with the naphthalenesulfonate ester **1-ONps** in acetonitrile or dimethyl sulfoxide (DMSO) without being kinetically involved; the disappearance of **1-ONps** is first-order in substrate. Also, at the time of our report, we had carried out several attempts to prepare a labled β-(alkylthio)- or β-(arylthio)ethyl chloride, e.g. **2-Cl** or **3-Cl**, without success; in each attempt we obtained a 50:50 mixture of **2-Cl** and **3-Cl**. We were able, however, to prepare the labeled brosylate **3-OBs**.[2] After finding that we could successfully carry out S_N2 displacements on **3-OBs** with arenethiolate ions in DMSO,[2] we tried to synthesize **3-Cl** by reaction of tetrabutylammonium chloride with **3-OBs** in DMSO-d_6. The solution's ^1H NMR spectrum revealed that the product was a 50:50 mixture of **2-Cl** and **3-Cl**. We then decided to see if KI in acetone produced brosylate displacement by a simple S_N2 mechanism. With **3-OBs** in acetone, potassium iodide reacted to give a 50:50 mixture of **2-I** and **3-I**. Kinetics were not carried out with the brosylate and iodide in acetone, but we rationalized that the S_N2 mechanism was improbable.[2]

$PhSCH_2CH_2X$ **1-X** (X=Cl,Br, etc.)

$PhSCD_2CH_2X$ **2-X**

$PhSCH_2CD_2X$ **3-X**

With our recent successful synthesis of a specifically labeled β-(arylthio)ethyl chloride derivative, i.e. **2-Cl**,[3] we can now address our concerns about the mechanism of displacement of chloride from **1-Cl** by KI in acetone. Therefore, in this report we describe the results of new experiments with **2-Cl** which finally resolve the issues we previously raised.

Results and Discussion

The reaction of a 0.0303 M solution of **2-Cl** and potassium iodide (0.0314 M) in $(CD_3)_2CO$ was studied at 110 °C by proton NMR. The reactant methylene resonance at δ 3.69 ppm decreased as two product peaks of roughly equal peak area appeared as singlets at 3.35 and 3.40 ppm. By comparison with a known sample of the iodide **1-I**, these peaks are identified as the methylene singlets from the two deuterated iodides **3-I** and **2-I**, respectively. Thus the displacement reaction occurs to give scrambled product but the NMR spectrum reveals that the chloride reactant (**2-Cl**) does not scramble during the process. Although we previously had conducted rate studies with **1-Cl** and KI in acetone which confirmed Bordwell and Brannen's finding that the displacement reaction follows second-order kinetics, we now investigated the kinetics of the labeled derivative **2-Cl** in the same reaction by following the rate of disappearance of the **2-Cl** methylene peak using ^1H NMR spectroscopy. Excellent second-order kinetics resulted when we assumed that the iodide ion disappeared at the same rate as **2-Cl** disappears, $k_2 = 3.99 \times 10^{-3}$ L mol^{-1} s^{-1} (R = 0.995).

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1995.

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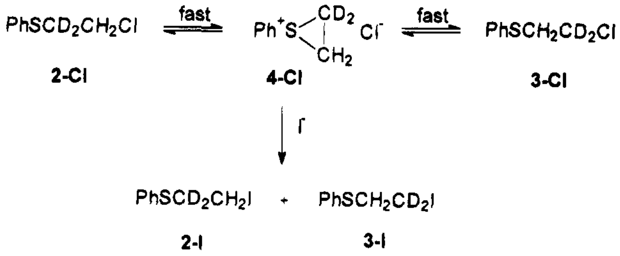
(2) Sedaghat-Herati, M. R.; McManus, S. P.; Harris, J. M. *J. Org. Chem.* **1988**, *53*, 2539.

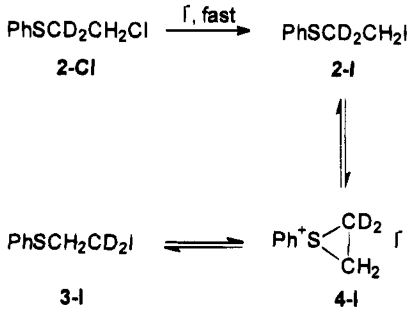
(3) McManus, S. P.; Karaman, R. M.; Sedaghat-Herati, R.; Hovanes, B. A.; Ding, X.-T.; Harris, J. M. *J. Org. Chem.* **1993**, *58*, 6466.

0022-3263/95/1960-4764$09.00/0

Scheme 1



Scheme 2



The appearance of label-scrambled 2-(phenylthio)ethyl iodide as the sole product is inconsistent with the sole operation of a simple S_N2 mechanism for the above displacement. Explanations which are consistent with the observations include the following: (1) iodide product results from initial ionization of **2-Cl** leading to a cyclic sulfonium ion **(4-Cl)** which gives product by iodide attack (Scheme 1), and (2) iodide product is formed by direct displacement (S_N2) but **2-I** rapidly scrambles via formation of a cyclic sulfonium ion (**4-I**, Scheme 2). We now discuss evidence that leads us to a preferred mechanistic understanding.

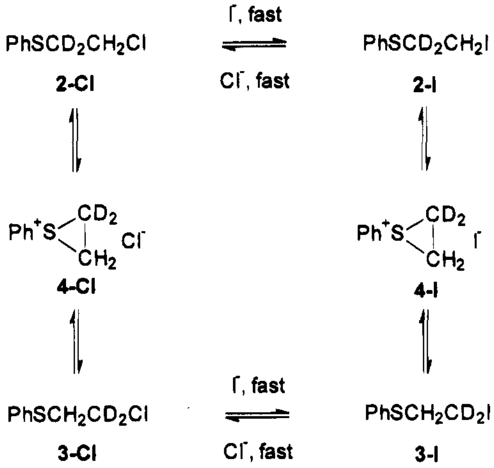
To help determine if a unimolecular loss of chloride ion from **2-Cl** occurs which involves anchimeric assistance by the sulfur atom, e.g. step 1 in Scheme 1, we measured the rate of reaction of n-butyl chloride under the conditions used to convert **2-Cl** to the iodide product. The second-order rate constant, k_2, determined at 110 °C using a $(CD_3)_2CO$ solution 0.033 M in n-butyl chloride and 0.0337 M in KI and based on the decrease in the CH_2Cl proton peak with time (and the assumption that the iodide concentration changes at the same rate) is 4.22×10^{-3} L mol^{-1} s^{-1} ($R = 0.993$). Thus n-butyl chloride reacts only slightly faster than **2-Cl** under these conditions, $k_{BuCl}/k_{2\text{-}Cl} = 1.06$, leading us to suggest that both reactions are occurring by the same mechanism. If instead **2-Cl** were reacting by initial formation of the cyclic sulfonium ion **4-Cl**, literature precedents suggest that the reaction of **2-Cl** with KI would occur *faster*, not slower, than that of *n*-butyl chloride with KI.[4]

To provide a measure of the facility for ionization at 110 °C in deuteroacetone of **2-Cl** to the cyclic sulfonium ion **4-Cl** followed by label scrambling to a give a 50:50 mixture of **2-Cl** and **3-Cl**, we determined first-order rate constants for decrease of the methylene peak in **2-Cl** and for the increase in the methylene peak in **3-Cl**. The scrambling rate was found to be very slow, e.g. the half-life of **2-Cl** ≅ 20 h, which led to poor NMR kinetics. Nevertheless, recording several points for two independent runs over more than a half-life gave an average rate, k_1, of $9.4 \pm 0.4 \times 10^{-6}$ s^{-1}, Table 1, which is far too slow to allow us to suggest that Scheme 1 is applicable. However, salt effects cannot be ignored. To determine if a salt effect may be accelerating the rate of label-scrambling, we heated 0.0337 M **2-Cl** to 110 °C in deuteroacetone containing 0.0337 M tetrabutylammonium tetrafluoroborate. In this case the ^{1}H NMR spectrum of the solution showed that only scrambling of the deuterium label in **2-Cl** occurred, $k_1 = 1.9 \times 10^{-5}$ s^{-1}, Table 1. Therefore, the salt effect is noticeable but it does not speed the ionization of **2-Cl** sufficiently to account for the rate observed for **2-Cl** with KI. Specifically, the half-life for deuterium scrambling in **2-Cl** is approximately 10 h while the half-life for **2-Cl** conversion to **2-I** and **3-I** is about 1.6 h.

Table 1. Pseudo First-Order Label Scrambling Rates for 2-Cl at 110 °C in Acetone with Various Added Salts

added salt	10^5k, s^{-1}
none	0.94
$(n\text{-Bu})_4BF_4$	1.9
$(n\text{-Bu})_4I$	8.62
$(n\text{-Bu})_4Br$	6.5
$(n\text{-Bu})_4Cl$	0.86

Scheme 3



We next considered a suggestion[5] that the potassium ion might electrophilically catalyze the scrambling. To provide evidence for this, we reacted 0.0337 M tetrabutylammonium iodide with 0.0337 M **2-Cl** in $(CD_3)_2CO$ at 110 °C and measured the rate of decrease of the methylene peak for **2-Cl** using ^{1}H NMR spectroscopy. The first-order rate calculated for this process is 8.62×10^{-5} s^{-1}, Table 1. Surprisingly, no apparent incorporation of iodide occurred, but label-scrambled chloride formed and persisted. Since this measured rate is significantly higher than the scrambling rate in the presence of tetrabutylammonium tetrafluoroborate, a reaction scenario was suggested which involves iodide displacement of chloride from **2-Cl** to give **2-I**, which immediately ionizes to the cyclic sulfonium ion **4-I** which then undergoes chloride ion attack leading to scrambled product (**2-Cl** and **3-Cl**, Scheme 3). Indeed this possibility is attractive since it is well known that chloride ion is a stronger nucleophile than iodide ion in acetone as solvent[6] while the iodide ion is the better leaving group. In fact, with the tetrabutylammonium counterion, chlo-

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[4] Capon, B.; McManus, S. P. Neighboring Group Participation; Plenum Publishing Corp.: New York, 1976; pp 52–53.

[5] We acknowledge Dr. Fred Menger for this suggestion, cf. personal conversation with S. P. McManus, November, 1991.

[6] Winstein, S.; Savedoff, L. G.; Smith, S. G.; Stevens, I. D. R.; Gall, J. S. *Tetrahedron Lett.* **1960**, *No. 9*, 24.

ride ion is known to be significantly better as a nucleophile than iodide ion,[6] an observation which apparently relates to both the lack of solvation for the small chloride ion and the lack of association with the counterion.[6,7] Thus formation of **2-I** and **3-I** using potassium iodide, but not when using tetrabutylammonium iodide, is probably the result of a thermodynamic effect.

We further explored the interesting reactivity–stability relationships introduced above by studying the reaction of tetrabutylammonium bromide with **2-Cl** in $(CD_3)_2CO$ at 110 °C. No bromide product resulted but **2-Cl** scrambling occurred with $k_1 = 6.5 \times 10^{-5}$ s^{-1}, Table 1. When comparing the three tetrabutylammonium salts, i.e. the chloride, bromide and iodide, we observed different scrambling rates for **2-Cl**; we suggest that this is due to nucleophilicity effects. A consideration of all these facts prompts us to offer the following rationale: once the initial displacement product is formed, the respective iodide (**2-I**) or bromide (**2-Br**) undergoes rapid scrambling via the cyclic sulfonium ion (**4-I** or **4-Br**). With either the bromide or iodide product the chloride ion rapidly displaces either iodide ion (from **2-I** and **3-I**) or bromide ion (from **2-Br** and **3-Br**) to give the scrambled chlorides (**2-Cl** and **3-Cl**) which are the observed products.

To shed light on the mechanism suggested above, we carried out some experiments with **1-Br**. First, we reacted **1-Br** (0.0337 M) with an equimolar amount of potassium iodide in deuteroacetone at 110 °C. The reaction was fairly rapid as determined by the disappearance of the CH_2Br peak (3.56 ppm) in **1-Br**. The SCH_2 peak (3.37 ppm) in **1-Br** also decreased significantly as the peaks for **1-I** (3.35 ppm for SCH_2 and 3.40 ppm for CH_2I) grew around it. The formation of a white residue, probably KBr, was observed. Next tetrabutylammonium chloride was reacted with **1-Br** in deuteroacetone at 110 °C. The reaction to apparently form **1-Cl** was very rapid. Repeating the reaction at 25 °C allowed the observation of the decrease of the two methylene triplets for **1-Br** (at 3.37 and 3.56 ppm) and the increase of the two methylene triplets (at 3.30 and 3.69 ppm) due to **1-Cl**. The most discernible peak in the two ammonium salts, the CH_2N methylene resonance, is of no analytical value since the CH_2N peak for the bromide appears at 3.50 ppm while that for the chloride appears at 3.51 ppm. Although integration of the methylene triplets to produce good kinetic data was not totally successful, we were able to estimate the half-life of **1-Br** to be 1 h. These experiments confirm that chloride ion can rapidly displace bromide from **1-Br** at 120 °C and thus validates the suggestion above that chloride scrambling in **2-Cl** may occur through transformation to **2-Br** or **2-I**. Of course, chloride scrambling is only faster by this route if **2-Br** and **2-I** rapidly scramble (e.g. Scheme 3, clockwise pathway). A wealth of data on ring closure reactions with cyclic sulfonium ion formation suggests that bromides react significantly faster than chlorides.[4] This is consistent with other studies of leaving group tendencies which show the order $I^- > Br^- > Cl^-$ in all solvents.[8]

A final experiment was conducted to confirm that chloride scrambling is enhanced by addition of tetrabutylammonium bromide or iodide. To show this we carried out a scrambling reaction with **2-Cl** (0.0337 M) in the presence of an equimolar amount of tetrabutylammonium chloride in deuteroacetone at 110 °C. Scrambling occurred very slowly leading to poor NMR kinetics. However, the rate, calculated after recording and integrating eighteen spectra over 36 h, is similar to that for the scrambling of **2-Cl** containing no salt, $k_1 = 8.6 \times 10^{-6}$ s^{-1}, Table 1. Since chloride ion must be rapidly reacting with **2-Cl** to produce **2-Cl** (an invisible process by NMR) this experiment clearly demands the conclusion that the scrambling of **2-Cl** in the presence of tetrabutylammonium iodide is explained by Scheme 2. The scrambling of **2-Cl** in the presence of tetrabutylammonium bromide can be explained by a similar scheme.

Now that we seem to have no evidence to support Scheme 1 but have strong evidence for Scheme 3, we sought confirmatory evidence that **2-Cl** is initially converted solely to **2-I**, which then scrambles. Reaction of **2-Cl** (0.02 M) with excess potassium iodide (0.03 M) in deuteroacetone at 110 °C was carried out and spectra were recorded to allow us to calculate the rate of disappearance of **2-Cl** and the rate of appearance of **2-I** and **3-I** during the first half-life of reaction. The respective rates are $k_1 = 1.15 \times 10^{-4}$, 1.75×10^{-4}, and 1.33×10^{-4} s^{-1}. Unless the computational error is greater that ca. 20%, **2-I** is forming at a slightly faster rate than **3-I** which is consistent with Scheme 2.

In summary, we have confirmed Bordwell and Brannen's conclusion that **1-Cl** reacts with potassium iodide in acetone by a S_N2-type mechanism. Our results allow us to infer that **1-Br** and **1-I** are very much more reactive toward ionization than **1-Cl**, hence we were unable to prepare **2-I** and **2-Br** from **2-Cl** without label scrambling. We also confirm the high nucleophilicity of the chloride ion in aprotic solvents. Our results reveal the significant finding that tetrabutylammonium chloride in acetone can be used to completely convert alkyl bromides and alkyl iodides into alkyl chlorides. In this respect, because of differences in association of the ions and the stability of the associated versus unassociated halides, tetrabutylammonium chloride reveals a significant advantage over potassium chloride as a nucleophile.

Experimental Section

The highest quality reagents were purchased either from Aldrich, Fisher, or Parish. Dry acetone was stored over activated 3 Å molecular sieves, and all transfers were carefully conducted to minimize moisture incorporation. All glassware was baked in an oven and carefully dried to prevent incorporation of moisture. The tetrabutylammonium salts were dried by azeotropic distillation of benzene. The salts were then stored in the benzene solution and removed just before use. The residual benzene was removed *in vacuo*, the salts were immediately weighed and covered with dry acetone, and the vessel was resealed and stored in a desiccator until the experiment was initiated. All NMR tubes containing samples for kinetic runs were sealed. A IBM- Bruker AFT-200 (200 MHz) NMR spectrometer was used for the proton NMR spectra. Samples were heated to 110 °C in a thermostated oil bath and removed at timed intervals and quenched to room temperature for NMR spectral determinations. This procedure allowed determination of duplicate first- and second-order rate constants that agreed within about 5–15%.

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