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The kinetic acidity of halomethyltrimethylammonium salts†

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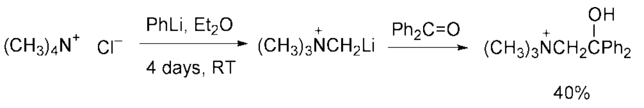
The kinetic acidities of members of a series of halomethyltrimethylammonium salts ($Me_3N^+CH_2X$, BF_4^-) have been measured under conditions of $^-OD/D_2O$ at 50 °C, with the rate constants being found to increase X = Cl < Br < I. The observed trend is rationalized on the basis of the polarizabilities and electron repulsion factors of the respective halogen substituents. The observed rate constants indicate a lowering of the $\Delta G^\ddagger$ for deuterium/hydrogen exchange of 12–13 kcal mol^{-1} due to the presence of the α-halo substituents. The kinetic acidity of chloromethyldimethylsulfonium BF_4^- was ~10^6 that of the analogous chloromethylammonium salt.

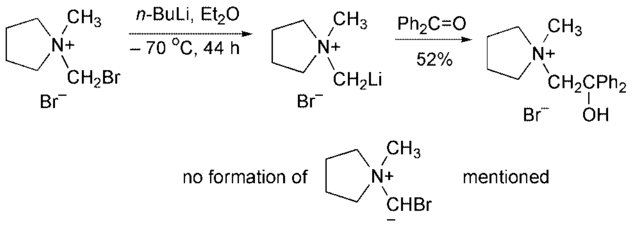
More than fifty years ago, Wittig initiated a series of studies in which he examined the nature and reactivity of ammonium ylides.[1] In the course of these studies, he developed two methods for preparing these ylides, the first involving deprotonation of tetramethylammonium chloride using phenyllithium[1] or phenyllithium–phenylsodium (1:5) in ether (Scheme 1),[2]



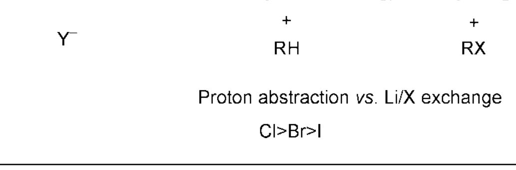
$$(CH_3)_4N^+\ Cl^- \xrightarrow[\text{4 days, RT}]{\text{PhLi, Et}_2\text{O}} (CH_3)_3\overset{+}{N}CH_2Li \xrightarrow{Ph_2C=O} (CH_3)_3\overset{+}{N}CH_2\overset{OH}{C}Ph_2 \quad 40\%$$

Scheme 1

whereas the second involved lithium–halogen exchange of either a chloro- or a bromomethyltrialkylammonium precursor (Scheme 2).[3] There was no mention in the studies involving halomethylammonium species, of deprotonation to form α-halo carbanions being competitive with the halogen–metal exchange process. This was in contrast to the situation with halomethylphosphonium compounds, which exhibited varying degrees of competitive deprotonation upon treatment with PhLi (reaction (1), Cl > Br > I, which probably is more of a reflection of the relative halogen–metal exchange rates rather than the relative acidities of the three halomethylphosphonium salts).[4–7]

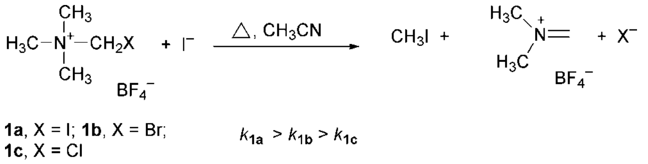


Scheme 2

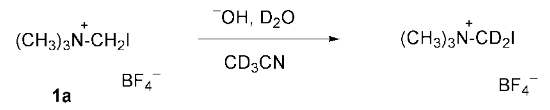


$$Ph_3\overset{+}{P}CH_2X\ Y^- \xrightarrow{RLi} Ph_3\overset{+\,-}{P}CHX + RH \quad \text{or} \quad Ph_3\overset{+\,-}{P}CH_2 + RX \qquad (1)$$

In the course of our own mechanistic study of the substitution/fragmentation reactions of halomethyltrialkylammonium salts, **1a**–**c** (Scheme 3),[8,9] we had the occasion to examine the reaction of iodomethyltrimethylammonium tetrafluoroborate, **1a**, with hydroxide ion, which, unlike I^-, is a base as well as a nucleophile. Carrying out the reaction in D_2O, in order to follow the reaction by ^1H NMR, it was observed that the hydrogens of the iodomethyl group exchanged with deuterium very rapidly and before any other reaction could occur [reaction (2)]. This serendipitous observation opened the door to the study that is reported here, namely a probe of the effect of α-halo substituents on the stability of ammonium ylides.



Scheme 3 Bimolecular substitution/fragmentation reactions of halomethylammonium salts.



$$\underset{\mathbf{1a}}{(CH_3)_3\overset{+}{N}\text{-}CH_2I\ BF_4^-} \xrightarrow[CD_3CN]{^-OH,\ D_2O} (CH_3)_3\overset{+}{N}\text{-}CD_2I\ BF_4^- \qquad (2)$$

There have actually been few quantitative, comparative studies of α-halo carbanion stabilities,[10,11] and the structure–activity relationships regarding the nature of the influence of halo and other hetero substituents on carbanion stability have been the subject of some controversy.[12–18] Structure–activity investigations on the stability of various types of ylide carbanions (*i.e.*, P, N, As, S) have also been reported.[19–21] Our halomethyltrimethylammonium system, **1**, provided an opportunity to examine how these two stabilizing influences might act *together*.

The kinetic acidities of the series of halomethyltrimethylammonium tetrafluoroborates, **1a**, **b** and **c** were examined under the conditions shown in Scheme 4, with the process of deuterium exchange assumed to be that shown above, wherein the ammonium ylides, **2a**–**c**, are the intermediates.

Results and discussion

The deuterium exchange rate was measured by monitoring the disappearance of the CH_2I peak at 4.93 ppm in the ^1H NMR

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† The kinetic acidities of halomethyltrimethylammonium salts are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b001689f/

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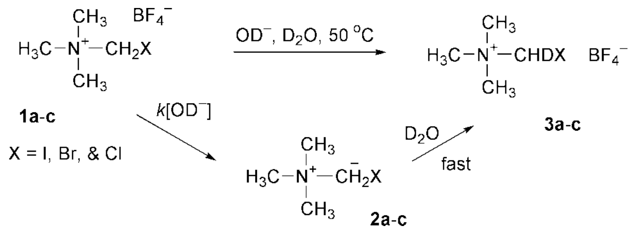
Table 1 Rate constants for exchange of halomethylammonium salts[a]

Ammonium salt X = BF_4^-	Conversion (%)	Rate constant $10^4\ k/M^{-1}\ s^{-1}$
$Me_3N^+CH_2I\ X^-$, **1a**	30	11.8 ± 0.1
$Me_3N^+CH_2Br\ X^-$, **1b**	32	9.28 ± 0.10
$Me_3N^+CH_2Cl\ X^-$, **1c**	21[b]	2.19 ± 0.03
$Me_3N^+CH_2C_6H_4CN\ X^-$, **4**	18[c]	10.9 ± 0.8

[a] All exchange rates were measured in D_2O at 50 °C, [**1**] = 0.67 M; $[OD^-]$ = 0.68 M. [b] Reaction was too slow to reach 30% conversion within timeframe of study. [c] When conversion was more than 18%, the plot was no longer linear.



Scheme 4 Kinetic deuterium exchange experiment.

spectrum (300 MHz) of **1a** (X = I). No other changes occur in the ^1H spectrum during the time frame of the experiment. Concomitant with the decrease in the CH_2I signal was the growth of a new, broader signal slightly upfield, due to the CHDI group. Since baseline separation could not be achieved, the rate of exchange was determined by integration of the sum of both peaks (A_t) as a function of time and relative to the integration of the CH_2I peak at time zero (A_o). The plot of $\ln[2A_t - A_o]$ *versus* time was found to be linear [eqn. (3)] until 30% exchange

$$\ln[2A_t - A_o] = -k_{obs}t \qquad (3)$$

had occurred,[22] after which dideuteration started to become kinetically significant. The negative slope of the plot is k_{obs}, which is the pseudo-first-order rate constant. ($k_{obs} = k[OD^-]$, where $[OD^-]$ is constant.) Thus the second order rate constant, k, could be obtained from knowledge of the $[OD^-]$.

In this manner, the second order rate constants for deuterium exchange of the three halomethyltrimethylammonium salts were obtained. They are summarized in Table 1, along with the analogously obtained rate constant for exchange of *p*-cyanobenzyltrimethylammonium tetrafluoroborate, **4**, which was obtained for comparison purposes.

From Table 1, it can be seen that the acidities of the halomethylammonium salts increase in the order Cl < Br < I. Consistent with current thinking on the subject,[12–15,17,18] this trend appears to have little, if anything, to do with $(p\rightarrow d)_\pi$ conjugation, but rather derives from some combination of polarizability and electron repulsion factors. The larger atoms are more polarizable, that is substituents attached to a carbanionic center can stabilize the species by dispersing charge over the molecule. Thus, Cl, Br, and I should "buffer" the negative charge with increasing effectiveness. Electron repulsion factors enter in because of the destabilizing (carbanion lone pair, halo atom lone pairs) interaction. It has been demonstrated computationally that a carbanion next to a sulfur atom prefers that *gauche* conformation wherein the carbanionic lone pair avoids an antiperiplanar (app) interaction with the sulfur lone pairs.[14,15] Since halogens have *three* lone pairs, such repulsive app interactions cannot be avoided for α-halocarbanions. However, as one progresses from F to Cl to Br to I, the C–X bond lengthens progressively, and the orbitals bearing the lone pairs become increasingly diffuse—hence the resultant destabilization due to such app interactions will diminish going from F to I.

Table 2 Rate constants for deuterium/hydrogen exchange of **1c**

T/°C	50	65	80
$10^4k/M^{-1}\ s^{-1}$	2.19 ± 0.03	15.6 ± 1.2	70.0 ± 5.4

log A = 13.7 ± 1.0, E_a = 25.6 ± 0.1 kcal mol^{-1} ($\Delta H^\ddagger$ = 25.0 kcal mol^{-1}, $\Delta S^\ddagger$ = +2.2 cal deg^{-1} mol^{-1}, $\Delta G^\ddagger$ = 24.3 kcal mol^{-1} at 298 K).

It is interesting that the inductive effects of the halogens (due to their respective electronegativities operating through the σ network), which would predict an exact *opposite* acidity trend, are apparently overwhelmed by the polarizability and electron repulsion factors. This appears to be a characteristic of α-hetero-substituted carbanions, as opposed to β- or γ-hetero-substituted anions, such as $XCH_2CH_2O^-$, where inductive effects dominate.

Our observed trend in kinetic acidities of **1a**–**c** is consistent with Hine's 1957 study of the relative kinetic acidities of the haloforms where he concluded that differences in polarizability were the probable reason for the observed order of reactivity: $CDFCl_2 < CDCl_3 < CDBr_3 \sim CDI_3$.[10]

Nibbering's 1985 study of gas phase acidities led him to conclude that the halomethanes exhibited increased acidity in the order: $CH_3F < CH_3Cl < CH_3Br < CH_3I$,[11] the same order as the atomic polarizabilities of the halogen atoms: F (0.557 Å^3), Cl (2.18 Å^3), Br (3.05 Å^3), and I (5.35 Å^3).[23]

Recognizing that sulfonium ylides are significantly more stabilized than ammonium ylides,[19–21] and since we had a sample of $(CH_3)_2S^+CH_2Cl\ BF_4^-$, **5**, in hand,[24] we sought to compare the kinetic acidity of the chloromethylammonium salt **1c**, with that of the chloromethylsulfonium salt, **5**.

Although the deuterium/hydrogen exchange of the CH_2Cl protons was observed to be extremely fast, unfortunately the sulfonium salt **5** also underwent a competitive destructive reaction with hydroxide ion (perhaps *via* an S_N2 process on methyl) that prevented an accurate measurement of the exchange rate to be made. Our best, *lower* estimate (because the $[^-OH]$ will always be overestimated) of the exchange rate constant is 6 $M^{-1}\ s^{-1}$ at 20 °C, based on a kinetic run using 0.12 M **5** and 0.0012 M NaOD.

With the Arrhenius parameters for the exchange process of chloromethylammonium salt, **1c**, having been determined by obtaining rate constants for exchange at three temperatures, as shown in Table 2, it was possible to calculate the rate for exchange of **1c** at 20 °C ($3.8 \times 10^{-6}\ M^{-1}\ s^{-1}$) and do a rough comparison of the rate constants for **5** *versus* **1c**. Thus, α-chlorosulfonium salt, **5**, appears to undergo exchange ~ 1 × 10^6 faster than α-chloroammonium salt, **1c**.

For a series of similar compounds, the *kinetic* acidities of compounds in the series generally can be correlated with their respective *equilibrium* acidities. Unfortunately, the α-haloammonium ylides, **2a**–**c**, do not appear to have sufficient kinetic stabilities to allow pK_a measurements, nor is there a good model of known pK_a with which to make a reliable correlation. Nevertheless, in an attempt to obtain *some* measure of the pK_as of **1a**–**c**, the kinetic acidity of one ammonium ylide whose pK_a was known was determined under our conditions, that of *p*-cyanobenzyltrimethylammonium tetrafluoroborate, **4**. The pK_a of **4** has been measured to be 27.1 in DMSO by the overlapping indicator method.[20] Because the stabilization of the resulting ylide from **4** derives to an extent from π-delocalization of the negative charge, it is obviously not a great model for our series of ylides, which have no such delocalization. Nevertheless, the fact that the kinetic acidity of **4** is similar to that of the iodomethylammonium salt, **1a**, allows one to estimate that the pK_as of **1a**–**c** are also probably similar to that of **4**, thus also in the range of 27.

It has been estimated that a trialkylammonium substituent enhances the *thermodynamic* (equilibrium) acidity of an adjacent C–H bond by ~10 pK_a units (as opposed to ~17 pK_a units for a trialkylphosphonium substituent).[21] (The rationale for this difference is, again, generally as discussed above, with hyperconjugative (p→σ*) charge transfer also factored in, in this case.)

Doering and Hoffmann estimated the values of activation free energies $(\Delta G^{\ddagger})_{298}$ for deuteroxide-catalyzed deuterium/hydrogen exchange of $(CH_3)_4N^+$, $(CH_3)_4P^+$, and $(CH_3)_3S^+$ salts to be 36.7, 24.4 and 22.7 kcal mol^{-1} at 25 °C, respectively.[19] The $\Delta G^{\ddagger}$'s calculated [$\Delta G^{\ddagger} = 4.576T(10.319 + \log T - \log k)$ for k at a specific temperature] for **1a**–**c** from the rate constants in Table 1 are 23.3, 23.4 and 24.4 kcal mol^{-1} at 50 °C, respectively. (As indicated by the data for **1c** in Table 2, the value of $\Delta G^{\ddagger}$ has little temperature dependence.) Thus it can be seen that the presence of an α-halo substituent enhances the kinetic acidity of an ordinary $Me_3N^+CH_2$–H bond by 12–13 kcal mol^{-1} [or, *if one were able to equate* $\Delta G°$ *differences with* $\Delta G^{\ddagger}$ *differences*, by ~9 pK_a units (with pK_a and $\Delta G°$ being related by the equation: p$K_a = \Delta G°/4.576T$)].[21] Arbitrarily adding the 10 pK_a units (due to Me_3N^+) to the 9 (due to halogen), and subtracting from the generally accepted pK_a value for CH_4 (49) would give a predicted value of ~30 as the pK_a of the halomethyltrimethylammonium salts, **1a**–**c**. This estimate is not far from the experimental estimate of 27 made on the basis of the correlation with the pK_a of *p*-cyanobenzylammonium compound, **4**.

In this paper we have emphasized the structure–activity issues related to the formation of the respective α-haloammonium ylide species, **2a**, **b**, and **c**. It should be mentioned that such ylides may also have novel *synthetic* applications. Indeed, an interesting condensation process between an α-halo*sulfonium* ylide and ketones was recently reported.[25]

Experimental

The ammonium salts, **1a**–**c**, were synthesized according to literature procedures.[9–11] Sulfonium salt, **5**, was prepared as described in our recent paper.[24] The ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer.

Stability of ammonium salt 1a

A solution of **1a** (0.8 ml, 0.083 M, in D_2O) was sealed in an NMR tube after having been subjected to 3 freeze–pump–thaw cycles. After taking an initial NMR spectrum, the solution was heated at 63 °C for 3.5 hours, and then an NMR spectrum was taken again. No reaction was observed.

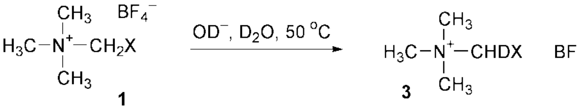
Deuterium exchange reaction of ammonium salt 1a with NaOH

An NMR tube containing 0.8 ml of an 0.083 M solution of **1a** in D_2O, 8 µl of an 8.275 M solution of NaOH in D_2O, and a trace of C_6H_6 as internal standard was subjected to 3 freeze–pump–thaw cycles and sealed. The NMR tube was heated at 63 °C in an oil bath for 6 hours until the exchange reaction was complete. The α-CH_2 group disappeared entirely, whereas the three methyl groups underwent no apparent change according to the integrated area when compared with the signal due to C_6H_6. Therefore, the methyl signal can be used as an internal standard when carrying out the exchange reaction.

When the exchange was complete, the tube was heated at 103 °C in the oil bath for another 3.5 hours, there was no further reaction observed under this condition.

Determination of the rate of deuterium exchange of ammonium salts, 1a–c and 4 (general procedure)

A 0.080 M solution of the salt (**1a**–**c** or **4**) in D_2O was prepared in a volumetric flask. Into an NMR tube with a rubber septum, 0.520 ml of the solution was injected and heated in the probe of the NMR spectrometer at 50 °C for 10 minutes until shimming was stable. A preheated 0.100 ml sample of NaOD (0.4217 M) was then injected into the NMR tube. The disappearance of the peak of the α-CH_2 group with respect to time was then monitored [reaction (4)]. NMR spectra were taken every 600–900 seconds for 3–4.5 hours. The data were analyzed as described below:



(4)

Taking ^{1}H NMR integral A_o, of the CH_2X group of **1** to be a measure of the concentration of **1** at $t = 0$, $[A_o - 2(A_o - A_t)]$ or $[2A_t - A_o]$ can then be taken as a measure of the concentration of **1** remaining at time = t, where A_t is the total integral of the CH_2X/CHDX peaks of **1** and **3**, respectively at time = t.

Thus the pseudo first order rate expression for conversion of **1** to **3** can be represented as eqn. (3):

$$\ln[2A_t - A_o] = -k_{obs}t \qquad (3)$$

Kinetic acidity of chloromethyldimethylsulfonium tetrafluoroborate, 5[24]

The acidity of α-chlorosulfonium salt **5** was measured in a manner similar to that used to obtain the rates for the α-haloammonium salts, **1a**–**c**, except that the molarities of NaOD that were used were 0.0005–0.001 M, the molarities of **5** varied from 0.07 to 0.1 M, and the temperature used was 20 °C. Using these low relative concentrations (~1%) of base relative to **5**, the rate constants were very large and not reproducible, with bimolecular rate constants varying from 3–30 M^{-1} s^{-1}. When the [OD$^-$] was decreased to less than 1% that of **5**, the base was apparently consumed before any exchange could occur.

Acknowledgements

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