Kinetic evidence for a novel, Grob-like substitution/fragmentation mechanism for the reaction of nucleophiles with trialkylammoniomethyl halides

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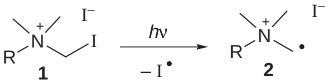
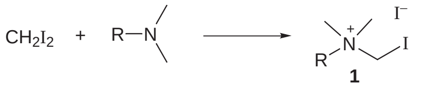
Kinetic evidence is presented in favor of a concerted, bimolecular mechanism for the unusual nucleophilic substitution/fragmentation reactions of iodide ion with (halomethyl)trimethylammonium salts. The relative reactivities of allyl, ethyl and methyl groups for this Grob-like reaction are also determined. Activation parameters are presented for the thermal reactions of 1-iodo-*N*,*N*,*N*-trimethylmethaniminium iodide (log $A = 8.7$, $E_a = 19.0$ kcal mol^{-1}) and 1-iodo-*N*-allyl-*N*,*N*-dimethylmethaniminium iodide (log $A = 14.6$, $E_a = 25.7$ kcal mol^{-1}) in acetonitrile, the latter reaction having an observed second order rate constant 39 times larger than the former at 70 °C. The results are compared with the classic data of Hughes, Ingold and Conant for S_N2 reactions of alkyl halides.

Results from our initial studies of the reactivity of α-ammonio distonic radical cations, **2**, have been reported in two recent papers.[1,2] This work demonstrated that a trialkylammonium substituent imparts electrophilic character and enhanced reactivity to a methyl radical with respect to its 5- and 6-*exo*,*trig* alkenyl cyclizations and its hydrogen abstraction processes.

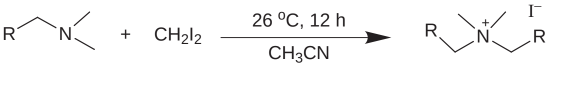


Numerous radicals of type **2** were studied, and the preferred precursors were always the respective iodomethyl compounds, **1**. Such iodomethyl compounds were generally synthesized by the reaction of the appropriate tertiary amine with methylene iodide, as shown for a number of examples below.[3,4]



1a, R = CH_3 (98%); **1b**, R = CH_2=CH(CH_2)$_3$ (55%)
1c, R = PhCH=CH(CH_2)$_3$ (76%); **1d**, R = Ph_2C=CH(CH_2)$_3$ (96%)
1e, R = PhCH=CH(CH_2)$_2$ (95%)

However, in an attempt to prepare **1f** (R = benzyl) and **1g** (R = cinnamyl) anomalous and initially puzzling results were obtained, wherein the only products obtained were *N*,*N*-dibenzyl-*N*,*N*-dimethylammonium iodide (**3**) and *N*,*N*-dicinnamyl-*N*,*N*-dimethylammonium iodide (**4**) in 81 and 85% yield, respectively.

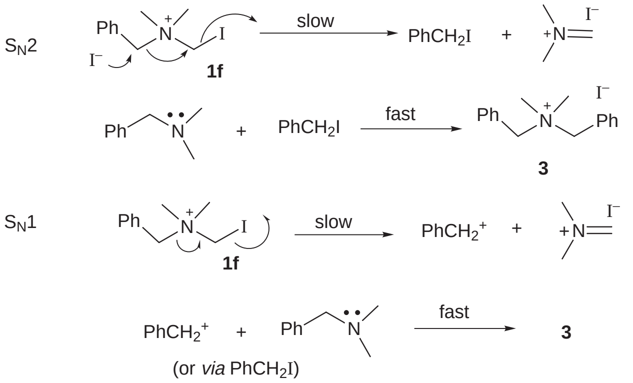


R = Ph and PhCH=CH

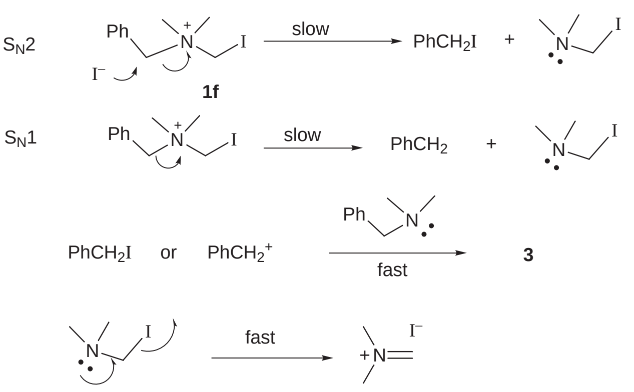
3, R = Ph (81%)
4, R = PhCH=CH (85%)

In hypothesizing a possible pathway for the formation of **3** and **4**, we presumed that expected products **1f** and **g** were *intermediates* in the reactions,[5] but that under the reaction conditions they were converted to **3** and **4**.

Such conversions could occur by any of a number of unimolecular or bimolecular nucleophilic substitution mechanisms that are given in Schemes 1 and 2.

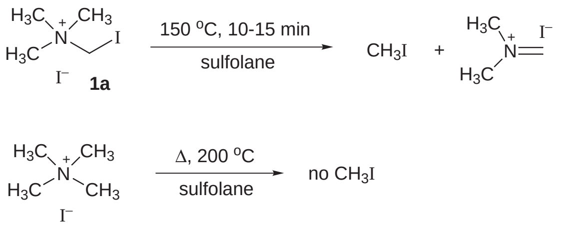


Scheme 1 Concerted mechanisms.



Scheme 2 Stepwise mechanisms.

To our knowledge, there has been but one previously reported example of such a nucleophilic substitution/fragmentation process, that by Eschenmoser in his classic communication on the preparation of what has become known as Eschenmoser's Salt.[6] Eschenmoser proposed a concerted, bimolecular mechanism for this reaction, and consistent with his contention of a Grob-like mechanism,[7] he found that, unlike **1a**, tetramethylammonium iodide did not produce methyl iodide at a significant rate at 200 °C. To our knowledge, no subsequent efforts have been made to further demonstrate and elucidate the mechanism of this unusual transformation.[8]



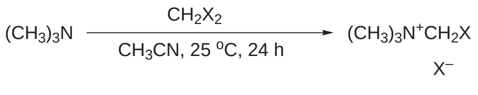
In this paper we present clear kinetic evidence in favor of the concerted, bimolecular mechanism for the nucleophilic substitution/fragmentation reactions of (halomethyl)trimethylammonium salts.

In devising a strategy to distinguish the mechanisms in Scheme 1 and Scheme 2, it was reasoned that if the mechanism were to proceed in a stepwise manner, as in Scheme 2, then, regardless of whether the reaction is bimolecular or unimolecular, the kinetic influence of the halogen substituent of $(CH_3)_3$-N^+CH_2X should derive *only* from its influence on the leaving group ability of the *amine*, $(CH_3)_2NCH_2X$. That is, its influence should depend directly and simply on the *electronegativity* of the halogen. In contrast, if the reaction proceeded by one of the concerted mechanisms in Scheme 1, then the influence of the halogen substituent should depend somewhat on its electronegativity, but primarily upon its *leaving group ability*, *i.e.*, the inverse of its basicity.

Such a distinction is in principle easy to test because halogen substituents have an inverse relationship between their electronegativity and their leaving group ability. Thus, if a stepwise mechanism were operational, one would expect the order of rates for reaction of $(CH_3)_3N^+CH_2X$ with iodide ion to be X = Cl > Br > I, whereas the opposite order of reactivity should be obtained in the event of a concerted mechanism.

Results and discussion

The required 1-halo-*N*,*N*,*N*-trimethylmethanaminium salts, **1a**, **5a** and **6a**, were readily prepared by the reactions of trimethylamine with the appropriate dihalomethane in acetonitrile, using essentially the method of Isaacs.[3]



$$(CH_3)_3N \xrightarrow[CH_3CN,\ 25\ ^\circ C,\ 24\ h]{CH_2X_2} (CH_3)_3N^+CH_2X \quad X^-$$

1a, X = I, 96%
5a, X = Br, 93%
6a, X = Cl, 44%

The kinetic studies were carried out in CD_3CN as solvent, using benzene as an internal standard. Progress of reactions was monitored using ^1H NMR to measure the loss of starting material (CH_3, δ 3.3 ppm). The rates of reaction of the iodo system, **1a**, were measured directly in the probe of the 300 MHz NMR spectrometer, whereas the reactions of bromo and chloro systems, **5b** and **6b**, were carried out in a constant temperature oil bath. Tetrafluoroborate salts **5b** and **6b**, prepared in 90% yield by treatment of **5a** and **6a** with $AgBF_4$ in acetonitrile, were used for their kinetic studies in order to ensure that the counter ion would not compete with iodide in the displacement process. In all cases, such as these, where iodide ion needed to be added, benzyltrimethylammonium iodide was used as the iodide source, because of its good solubility in acetonitrile and its stability at the required reaction temperatures.

Table 1 Rate constants for the reaction of 1-iodo-*N*,*N*,*N*-trimethylmethanaminium iodide, **1a**, in CD_3CN

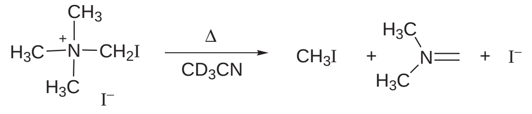
Temperature/°C	65	70	75
Rate/10^{-4} M^{-1} s^{-1}	2.8 (±0.1)	4.1 (±0.2)	6.6 (±0.2)

Log $A = 8.7 \pm 0.2$, $E_a = 19.0 \pm 0.3$ kcal mol^{-1}.

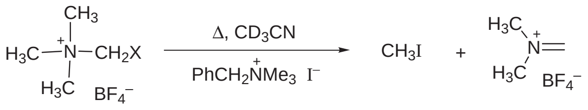
Table 2 Rate constant comparison for the reactions of 1-halo-*N*,*N*,*N*-trimethylmethanaminium iodides or tetrafluoroborates, **1a**, **5b** and **6b**, in CD_3CN at 101 °C

Compound	X	k/M^{-1} s^{-1}	k_{rel}
6b[a]	Cl	$4.8 (\pm 0.1) \times 10^{-6}$	1
5b[a]	Br	$1.9 (\pm 0.1) \times 10^{-5}$	40
1a	I	4.3×10^{-3}[b]	896

[a] One equiv. of $PhCH_2NMe_2^+I^-$ added to provide I^- as nucleophile. [b] Rate extrapolated to 101 °C using the Arrhenius data for **1a**.



1a



5b, X = Br
6b, X = Cl

Rate constants were obtained at three temperatures, and are given in Table 1, for the most reactive substrate, **1a** (X = I), so that an Arrhenius correlation could be obtained and rates then extrapolated to the higher temperatures required for the analogous reactions of substrates **5b** and **6b**.

Rate constants for the reaction of iodide ion with the less reactive bromomethyl and chloromethyl analogs **5b** and **6b** were obtained at 101 °C, and those rates, along with that calculated for the iodomethyl compound, are given in Table 2.

Consistent with these reactions being bimolecular in nature, the second order rate constant for reaction of bromomethyl salt **5b** was observed to remain relatively unchanged when one doubled the concentration of iodide ion [$k = 1.7 (\pm 0.1) \times 10^{-5}$ M^{-1} s^{-1} at 101 °C]. The observed [I^-] dependence is actually somewhat surprising since reactions of negative nucleophiles with positively charged substrates are notorious for exhibiting non-uniform kinetics.[9]

Since the second order rate constants in Table 2 were observed to correlate with the relative leaving group abilities rather than the electronegativities of substituent X, we conclude that the mechanism of these reactions is the bimolecular, Grob-like, concerted substitution/fragmentation mechanism depicted in Scheme 1.

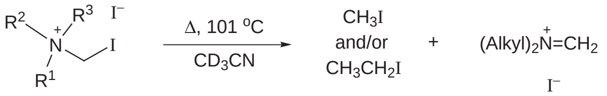
Ethyl *versus* methyl group reactivities

Because of the general lack of data related to the relative susceptibilities of alkyl groups in tetraalkylammonium compounds to undergo nucleophilic attack, and because (iodomethyl)trialkylammonium compounds, such as **1**, have a significantly greater reactivity and propensity to undergo dealkylation processes than do tetraalkylammonium compounds, it was decided to exploit the exceptional S_N2-type of reactivity of such substrates to further examine structure–reactivity factors in this reaction.

With this in mind, the series of methyl- and ethyl-substituted ammoniomethyl iodides (**1a**, **7**, **8** and **9**) was examined, with the intent of obtaining relative rates for displacement at ethyl *versus* methyl.

Table 3 Rate constants for the reaction of 1-iodo-*N*,*N*,*N*-trialkylmethanaminium iodides, **1a**, **7**, **8** and **9** at 101 °C in CD_3CN

Substrate	$k_{overall}$ ($\times 10^{-3}$ M^{-1} s^{-1})	[MeI]/[EtI]	k_{Me} (per methyl)	k_{Et} (per ethyl)
1a	4.3	—	1.4	—
7	12.6 (±0.4)	13.8 (±0.7)	5.9	0.85
8	6.3 (±0.3)	2.9 (±0.4)	4.8	0.81
9	2.79 (±0.05)	—	—	0.93



1a, $R^1 = R^2 = R^3 = CH_3$
7, $R^1 = R^2 = CH_3$, $R^3 = C_2H_5$
8, $R^1 = CH_3$, $R^2 = R^3 = C_2H_5$
9, $R^1 = R^2 = R^3 = C_2H_5$

Although there is an abundance of kinetic data available in the literature regarding the S_N2 reactivity of methyl, ethyl, and other alkyl halide substrates with various nucleophiles (most of the data deriving from the early work of the groups of Hughes, Ingold and Conant),[10,11] there is a relative dearth of quantitative information on the related S_N2 reactivity of tetraalkylammonium compounds. In those days, interest in tetraalkylammonium compounds was mostly related to their E_2 (Hofmann) reactivity, and what little is known about the competition between E_2 and S_N2 and the relative reactivities of alkyl substituents in these systems derives from a short series of papers by Hughes and Ingold.[12–14]

Kinetic studies of the three ethyl-containing 1-iodo-*N*,*N*,*N*-trialkylmethanaminium compounds, **7**–**9**, were carried out in CD_3CN at 101 °C, in the manner described above, except that conversion of starting material was monitored by following the disappearance of each compound's methylene (CH_2I) peak at δ 4.9–5.1 ppm. In this manner were obtained the second order rate constants (in Table 3), which when combined with the ratios of $CH_3I : C_2H_5I$,[15] allowed calculation of the listed partial rate factors that provide a measure of the relative reactivities of the methyl and ethyl groups in this reaction.

Although the data in Table 3 clearly indicate that a methyl group is more reactive than an ethyl group, it appears that the relative Me : Et rate ratios for ammonium dealkylative S_N2 processes are not nearly as large as those that have been observed for S_N2 reactions where *halide* has been the leaving group.

In fact, the relevant Me *vs.* Et S_N2 kinetic data that are in the literature indicate a significant range in values. For example in the classic series of papers by De La Mare, Fowden, Hughes, Ingold and Mackie,[11] the relative rates for the reaction of MeY *versus* EtY with chloride ion in acetone at 25 °C varied from a value of 71 for Y = Cl, to 61 for Y = Br, to 11 for Y = I, indicating a significant leaving group dependence. They also observed relative rates, for $X^- + CH_3Br$ *versus* CH_3CH_2Br, of 140 for X = I, 76 for X = Br, and 61 for X = Cl, indicating a significant dependence of this ratio on nucleophile.

As indicated earlier, there do not appear to be any quantitative data in the literature on Me : Et relative rate ratios for S_N2 reactions of tetraalkylammonium compounds.[11] However, our data are consistent with the conclusion that structure–reactivity relationships in dealkylative S_N2 reactions of 1-halo-*N*,*N*,*N*-trialkylmethaniminium (and indeed *all* tetraalkylammonium) compounds must involve a complex interplay of a number of factors, the most important of which is probably the reactivity of the alkyl group undergoing substitution. However, relief of A-strain (that is relief of ground state non-bonded interactions) must also be playing an important role, as is reflected by the larger partial rate factors for substitution on CH_3 when the leaving group bears at least one ethyl group. Differences in ground state solvation of the various ammonium substrates probably also have an impact on the observed rate constants. The relative importance of each of these factors can not be determined from our limited study.

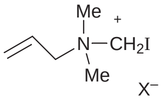
Table 4 Rates of the reaction of 1-iodo-*N*-allyl-*N*,*N*-dimethylmethanaminium iodide, **10a**, in CD_3CN

Temperature/°C	40	50	70
$k/10^{-5}$ s^{-1}	1.2 (±0.1)	4.6 (±0.3)	39 (±2)

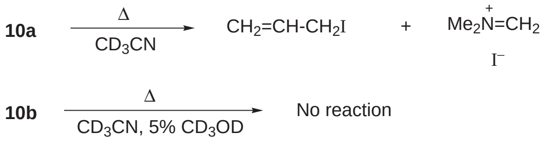
Log $A = 14.6 \pm 1.3$, $E_a = 25.7 \pm 0.2$ kcal mol^{-1}.

Allyl system

Although the putative benzyl intermediate (**1f**) proposed in the overall reaction process in Scheme 1 could not be isolated, presumably because of its high *in situ* reactivity with iodide ion, the analogous allyl derivative (**10**) could be prepared, albeit in lower yield (38%) than for other primary alkyl derivatives. The ability to prepare **10** provided a good opportunity to obtain a quantitative measure of allyl group reactivity in its reaction with iodide ion.



10a, X = I
10b, $X = BF_4$



Rates for the reaction of iodide salt **10a** were obtained in CD_3CN at three temperatures, as shown in Table 4. Unlike the results for displacement of a methyl group discussed above (*i.e.*, for **1a**, **5b** and **6b**), *no* apparent rate dependence on [I^-] was observed for the reaction of **10a**. Second order rate constants of 16, 6.4 and 5.0 × 10^{-2} M^{-1} s^{-1} were observed for 1, 2.4 and 3 equivalents of I^- (0.024, 0.055 and 0.074 molar), respectively. In fact, with calculated pseudo first order rate constants of 3.9, 3.5 and 3.7 × 10^{-4} s^{-1}, the reaction of **10a**, to all extents and purposes, appears to be first order. However, as was pointed out by a referee, and as indicated by the work of Swain and Kaiser on the behavior of trialkylsulfonium compounds towards nucleophiles,[9,16] the apparent absence of a linear dependence of concentration of nucleophile need not indicate an S_N1 mechanism. Indeed, the fact that the reaction of allyl salt **10a** with iodide ion is *bimolecular* was clearly demonstrated by an experiment in which tetrafluoroborate salt **10b** was heated under identical conditions [40 °C for 24 h and 70 °C for 0.5 h in CD_3CN (with 5% CD_3OD added to trap any carbocations formed)], with no reaction of the substrate being detected. When an equivalent amount of benzyltrimethylammonium iodide was added at 70 °C, disappearance of **10b** was observed, with a second order rate constant of 1.02 (±0.02) × 10^{-2} M^{-1} s^{-1}. Therefore, in spite of the observed first order reactivity of **10a** with its counter ion I^-, the mechanism of its nucleophilic displacement must be S_N2, as is the case for other allyl substrates (*i.e.*, halides and tosylates) in their reactions with nucleophiles.[17]

Although the available data are limited, the S_N2 reactivities of allyl halides are similar, perhaps somewhat greater, than those of methyl halides, with allyl halides being 3–4 times less reactive than benzyl halides.[11] Thus, one would have expected iodide displacement on methyl and allyl to have been competitive. In fact, no methyl iodide was observed in our study of **10a**. In this study the observed second order rate constant [$k = 1.6 \times 10^{-2}$ M^{-1} s^{-1}] of **10a** was actually *39 times larger* than that of **1a** [$k = 4.1 \times 10^{-4}$ M^{-1} s^{-1}] at 70 °C. The remarkably different activation parameters for allyl and methyl displacement processes of **10a** and **1a** indicate that there are significant differences in the detailed mechanisms of the two reactions. The exact nature of these differences remains ambiguous. Nevertheless, an interesting artifact of the current study is the finding that the relative reactivity of the allyl group in substrate **10a** towards S_N2 displacement (compared to methyl) is much greater than has been observed in the past for halide displacement reactions.

Conclusions

In conclusion, the reactivities of a series of 1-halo-*N*-alkyl-*N*,*N*-dimethylmethanaminium iodides towards nucleophilic attack by iodide ion have been examined in order to elucidate the mechanism of these novel reactions. On the basis of kinetic data, where the alkyl group is methyl, ethyl and allyl, it was determined that the mechanism of these reactions involves a concerted, S_N2, Grob-like process, such as that proposed originally by Eschenmoser.[6]

Experimental

General method for preparation of iodide salts[3]

In a dry, three-necked, round-bottomed flask, equipped with a magnetic stirrer were added 50% w/w of CH_3CN and CH_2I_2 (4 equivalents), amine (1 equivalent) and a few crystals of hydroquinone. Most reactions were left to stir overnight, after which the precipitated salts were removed by filtration. The salts were washed several times with ether, acetone or ethyl acetate and the desired products were obtained as white solids.

General method for preparation of tetrafluoroborate salts

A stirred solution of the silver tetrafluoroborate (1 equiv.) in MeOH was added dropwise to a suspension of the iodide salt (1 equiv.) in MeOH. After the addition, the mixture was stirred for 2 h at room temperature and then filtered in order to remove the silver iodide. The filtrate was concentrated under reduced pressure to give crude tetrafluoroborate salt. The tetrafluoroborate salts were washed with ether, acetone, ethyl acetate and then recrystallized in either ethanol, ethyl acetate–ethanol or water.

1-Iodo-*N*-allyl-*N*,*N*-dimethylmethaniminium iodide (10a)

10a was synthesized in 38% yield when 1.00 g (11.7 mmol) of allyldimethylamine[18,19] was reacted with 9.44 g (0.353 mol) of diiodomethane in 6 mL of acetonitrile, using the general procedure for the synthesis of iodide salts:[3] mp 101–104 °C; ^{1}H NMR (DMSO-d_6) δ 3.11 (s, 6H), 4.05 (d, J = 7.2 Hz, 2H), 5.11 (s, 2H), 5.68 (m, 2H), 6.00 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 33.07, 50.88, 66.09, 125.40, 128.29; HRMS (LSIMS POS) calcd for $C_6H_{13}NI$: 226.0093; found, 226.0095; CHN analysis calcd for $C_6H_{13}NI_2$: C, 20.42, H, 3.71, N, 3.97; found C, 20.58, H, 3.69, N, 3.91%.

1-Iodo-*N*-allyl-*N*,*N*-dimethylmethanaminium tetrafluoroborate, 10b

Tetrafluoroborate salt **10b** was obtained in the usual manner in 94.0% yield: ^{1}H NMR (DMSO-d_6/TMS) δ 3.09 (s, 6H), 4.04 (d, 2H), 5.10 (s, 2H), 5.68 (m, 2H), 6.00 (m, 1H).

1-Iodo-*N*,*N*,*N*-trimethylmethaniminium iodide (5)[3]

5 was prepared by the general method described above. Trimethylamine (7.4 g, 0.125 mol) was bubbled slowly into the solution of diiodomethane. The desired product was obtained as a white solid in 95.9% yield: mp 235 °C (decomp); ^{1}H NMR (DMSO-d_6) δ 3.22 (s, 9H), 5.24 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 34.80, 53.13.

N,*N*-Dibenzyl-*N*,*N*-dimethylammonium iodide (3)

3 was made using the general procedure for the synthesis of the iodide salts.[3] The salt was obtained in 80.9% yield: mp 185 °C (decomp); ^{1}H (DMSO-d_6) δ 2.91 (s, 6H), 4.72 (s, 4H), 7.59 (m, 10H); ^{13}C (DMSO-d_6) δ 48.05, 66.76, 127.86, 128.85, 130.24, 133.05; HRMS (LSIMS POS) calcd for $C_{16}H_{20}N$: 226.1596; found 226.1577.

N,*N*-Dicinnamyl-*N*,*N*-dimethylammonium iodide (4)

Using the general procedure for the synthesis of iodide salts,[3] the title salt was obtained starting from cinnamyldimethylamine[20] in 84.5% yield: mp 170 °C (decomp); ^{1}H (DMSO-d_6) δ 3.11 (s, 6H), 4.22 (d, J = 7.41 Hz, 4H), 6.58 (dt, J = 15.65 Hz, 2H), 6.98 (d, J = 15.66 Hz, 2H), 7.38 (m, 6H), 7.63 (d, J = 6.87, 2H); ^{13}C (DMSO-d_6) δ 49.09, 64.83, 116.77, 127.18, 128.62, 128.83, 135.28, 140.78; HRMS (LSIMS POS) calcd for $C_{20}H_{24}N$, 278.1909; found, 278.1910.

1-Bromo-*N*,*N*,*N*-trimethylmethaniminium tetrafluoroborate (5b)[3]

5b was synthesized in 90.4% yield when 1.00 g (5.47 mmol) of 1-bromo-*N*,*N*,*N*-trimethylmethaniminium bromide (**5a**) was reacted with one equivalent of silver tetrafluoroborate (1.07 g, 5.47 mmol) following the general procedure for the synthesis of tetrafluoroborate salts: mp 166–167 °C; ^{1}H NMR (DMSO-d_6) δ 3.19 (s, 9H), 5.31 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 51.84, 59.06; HRMS (LSIMS POS) calcd for $C_4H_{11}NBr$: 152.0075; found, 152.0019.

1-Chloro-*N*,*N*,*N*-trimethylmethaniminium tetrafluoroborate (6b)[21]

6b was obtained in 89.9% yield when 1.00 g (7.00 mmol) of 1-chloro-*N*,*N*,*N*-trimethylmethaniminium chloride (**6a**) was reacted with 1.36 g (7.00 mmol) of silver tetrafluoroborate in 10 mL of acetonitrile. The crude product was recrystallized from 6 : 1 ethanol–acetonitrile solvent mixture: mp 221–224 °C; ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 9H), 5.35 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 42.36, 47.13; HRMS (LSIMS POS) calcd for $C_4H_{11}NCl$: 108.0580; found, 108.0575; CHN analysis calcd for $C_4H_{11}NClBF_4$: C, 24.59, H, 5.68, N, 7.17; found C, 24.55, H, 5.57, N, 7.04%.

1-Chloro-*N*,*N*,*N*-trimethylmethaniminium chloride (6a)[3]

Into a gas sampling tube that was cooled to –78 °C, was weighed 3.12 g (52.8 mmol) of trimethylamine gas. The amine was then dissolved with 10 ml acetonitrile and the resulting solution transferred to a 50 mL, three-necked, round-bottomed flask fitted with a magnetic stirrer and a 25 mL pressure-equalizing addition funnel. To the flask was added 11.9 mL (13.5 g, 158 mmol) of dichloromethane in 7 mL acetonitrile over 4 h. The reaction was stirred at −78 °C for 5 h and then allowed to warm up to room temperature over 19 h, with stirring. The white ammonium chloride salt, which was hygroscopic, was filtered from the reaction mixture under nitrogen atmosphere, and then washed with three 10 mL portions of diethyl ether. The crude product was isolated in 44.3% yield: mp 150–153 °C; ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 9H), 5.62 (s, 2H); ^{13}C (DMSO-d_6) δ 50.64, 69.63; HRMS (LSIMS POS) calcd for $C_4H_{11}N_1{}^+Cl$: 108.0580; found 108.0552.

1-Bromo-*N*,*N*,*N*-trimethylmethaniminium bromide (5a)

5a was synthesized using the same methodology described for the synthesis of the iodide salts.[3] One equivalent of trimethylamine gas was reacted with three equivalents of dibromomethane to give the bromide salt in 92.7% yield after recrystallization in absolute ethanol: mp 165–166 °C; ^{1}H NMR

(DMSO-d_6) δ 3.32 (s, 9H), 5.61 (s, 2H); ^{13}C (DMSO-d_6) δ 51.58, 59.05.

General procedure for determination of rates of dealkylation of ammonium salts

A stock solution (~20 mM) of the salt in acetonitrile-d_3 was made with benzene included as an internal standard for concentration. In sealed pyrex NMR tubes, 0.7 mL of the reaction mixture were heated at the appropriate temperature. (Note: for reactions below 80 °C, the tubes were heated in a Varian Gemini 300 spectrometer which was calibrated using neat ethylene glycol as a reference. For reactions above 100 °C, the tubes were heated in a constant temperature oil bath.) The disappearance of the starting materials with respect to time was monitored by proton NMR, with the reactions being generally followed for one half-life. Concomitant formation of iminium ion **3** was indicated by appearance of its characteristic signals in the ^{1}H NMR at δ 3.6 and 8.1 ppm. Pseudo first order rate constants were obtained by plotting the natural logarithm of the concentration (NMR intensity) of the salt with respect to time in seconds, with the observed rate of dealkylation being obtained from the slope of the plot. The observed rate constants were converted to second order rate constants by using the equation: $k_{\text{actual}} = k_{\text{observed}}[\text{iodide salt}]^{-1}$, and Arrhenius parameters were determined by plotting the logarithms of these second order rate constants against the reciprocals of the temperatures in K.

Determination of the rate of deallylation of 10a

Rate constants for the deallylation of 25 mM **10a** were determined at 40, 50 and 70 °C, using the method described above. Spectra were collected every 10 min for 2 h, and the disappearance of the **10a** was monitored by observing the decrease of its methyl peak at δ 3.16 ppm. The data were analyzed as described above and gave excellent first order correlation, and the results are summarized in Table 4. Formation of allyl iodide and methylenedimethylammonium iodide in the reaction was verified by addition of authentic samples to the reaction mixtures and observing the growth of the product peaks. An Arrhenius plot of the data in Table 4 provided the following activation parameters for **10**: $E_a = 25.7$ (±0.2) kcal mol^{-1} and log $A = 14.6 \pm 1.3$.

Reactivity of 10b

The NMR tubes containing 0.7 ml portions of a 24.7 mM solution of **1a** in deuterated acetonitrile (with 5% deuterated methanol) and benzene as internal standard were heated in an oil bath. One tube was heated at 40 °C for 24 h, the other one was heated at 70 °C for 0.5 h. The reaction was monitored by 300 MHz proton NMR spectroscopy. There was no detectable reaction in either case.

Reaction of 10b with iodide ion

A sealed NMR tube containing 0.7 ml of 24.7 mM solution of **10b** and benzyltrimethylammonium iodide in deuterated acetonitrile was heated at 70 °C. The disappearance of starting material was monitored by observation of the decrease of the methylene peak at 4.04 ppm. The pseudo first order rate constant was calculated to be 2.50 (±0.04) × 10^{-4} s^{-1}, and the second order rate constant was calculated to be 1.02 (±0.02) × 10^{-2} M^{-1} s^{-1}.

Determination of the rate of demethylation of 1a

As in the case of **10**, 20 mM solutions of **1b** in deuterated acetonitrile were heated in the Varian Gemini 300 spectrometer at 65, 70 and 75 °C, and the disappearance of the **1a** (*i.e.* its methyl peak at δ 3.3 ppm) was monitored by proton NMR with respect to time. The second order rate constants for the demethylation of **1a** are summarized in Table 1. Formation of methyl iodide was verified by adding authentic methyl iodide to the reaction mixture and observing the growth of the corresponding peak at δ 2.2 ppm. A plot of the data in Table 1 provided Arrhenius parameters for the reaction of **1a**: $E_a = 19.0$ (±0.3) kcal mol^{-1} and log $A = 8.7$ (±0.2).

Determination of the rates of demethylation of 5b and 6b

Solutions of 0.0167 mmol of **5b** and **6b** plus 0.0167 mmol benzyltrimethylammonium iodide in 0.7 mL acetonitrile-d_3 were heated in a constant temperature oil bath at 101 °C for ten minute intervals for a total period of 60 min. The disappearance of the bromide and chloride salts was monitored by observing the decrease of their methyl peaks at δ 3.2 ppm with respect to time. The proton signal for the methyl peak in the iodide salt at δ 3.03 ppm was used as an internal standard. Second order rate constants were obtained by applying the usual rate equation for a situation where the reactants are equal or unequal in concentration [eqn. (1)].

$$1/(a_0 - x) = k_A t + 1/a_0 \quad \text{or} \quad \ln[1 + a_0/a] = a_0 k_A t + \ln 2 \qquad (1)$$

The rate constants for **5b** and **6b** were found to be 18.7 (±0.8) and 4.79 (±0.07) × 10^{-6} M^{-1} s^{-1}, respectively (see Table 2), and when 2 equivalents of iodide were used in a reaction of **5b**, the rate constant was 17 (±1) × 10^{-6} M^{-1} s^{-1}.

1-Iodo-*N*,*N*,*N*-triethylmethaniminium iodide (9)

9 was prepared by the general method described for the trimethyl-substituted salts.[3] Triethylamine (2.0 g, 0.0198 mol) and diiodomethane (15.9 g, 0.0593 mol) were stirred together in 20 mL of ethyl acetate at room temperature for 48 h. The desired product **9** was filtered from the reaction mixture through a glass frit and isolated in 47.7% yield (3.48 g) after recrystallization from absolute ethanol: mp 178 °C (decomp), ^{1}H NMR (DMSO-d_6) δ 1.21 (t, $J = 7.14$ Hz, 9H), 3.34 (q, $J = 7.15$ Hz, 6H), 5.1 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 7.74, 27.86, 53.93; HRMS (LSIMS POS) calcd for $C_7H_{17}NI$, 242.0406; found, 242.0398.

1-Iodo-*N*,*N*-diethyl-*N*-methylmethaniminium iodide (8)

A 25 mL round-bottomed flask fitted with a magnetic stirrer was charged with 10 mL of ethyl acetate. The flask was sealed with a rubber septum. *Via* syringe, 3 mL of diethylmethylamine (2.16 g, 0.0248 mol) were added followed by 3.03 g (0.0113 mol) of diiodomethane with stirring. The reaction mixture was stirred at room temperature for 18 h before adding an additional 10 mL of the amine. The stirring was allowed to continue for an additional 24 h period. The solid product was filtered from the reaction mixture through a glass frit and later recrystallized from absolute ethanol. The product **8** was dried under full vacuum and was isolated in 9.2% yield (0.37 g): mp 146–147.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, $J = 7.15$ Hz, 6H), 3.04 (s, 3H), 3.41 (m, 4H), 5.1 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 7.91, 30.15, 47.65, 57.45; HRMS (LSIMS POS) calcd for $C_6H_{15}NI$, 228.0249; found, 228.0256.

1-Iodo-*N*-ethyl-*N*,*N*-dimethylmethaniminium iodide (7)

7 was prepared in the same manner as its diethyl analog. In this reaction, 1.02 g of dimethylethylamine (0.0139 mol) and 5.53 g (0.0206 mol) of diiodomethane were stirred together in 8 mL of ethyl acetate at room temperature for 25.5 h. To the reaction mixture were added 10 mL extra of the amine and 5 mL of ethyl acetate, after which the reaction mixture was stirred at room temperature for an additional 24 h. The solid product was filtered from the reaction mixture through a glass frit, and then recrystallized from absolute ethanol to give the pure product **7** in 36.8% yield (2.59 g): mp 120–121.5 °C; ^{1}H NMR (DMSO-d_6)

δ 1.25 (t, J = 7.2 Hz, 3H), 3.14 (s, 6H), 3.47 (q, J = 7.2 Hz, 2H), 5.19 (s, 2H); ^{13}C NMR (DMSO-d$_6$) δ 8.16, 32.61, 50.59, 60.06; HRMS (LSIMS POS) calcd for $C_5H_{13}NI$, 214.0093; found, 214.0106.

Determination of the rate of deethylation of 9

A 20 mM stock solution of **9** in deuterated acetonitrile with benzene as an internal standard was used for the kinetic study of **9**, which was carried out in the usual manner, following the disappearance of the methylene peak of the starting material (at δ 5.1 ppm). The pseudo first order rate constant was obtained in the usual way, with the second order rate constant being 2.79 (±0.05) × 10^{-3} M^{-1} s^{-1}. Formation of ethyl iodide was verified by adding authentic ethyl iodide to the reaction mixture and observing the growth of the corresponding peaks at δ 1.8 and 3.3 ppm.

Determinations of the absolute rates for dealkylation of 7 and 8

The determinations were carried out *via* the usual procedure. The reactions were performed using 21 mM stock solutions. Pseudo first order rate constants were obtained in the usual way, and the second order rate constants were 6.3 (±0.3) and 12.6 (±0.4) × 10^{-3} M^{-1} s^{-1}, respectively.

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