The Mechanism of Deamination of Methoxy Substituted Tritylammonium Ions in Methanolic Aqueous Acid

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In methanolic aqueous acid, methoxy-substituted tritylammonium ions undergo heterolysis to give an equilibrium mixture of the substituted trityl cation, the corresponding alcohol (and methyl ether), and the ammonium cation *via* an S_N1 mechanism; the detection of a reaction channel first order in hydronium ions may implicate substituted trityl cation–ammonia (ion–molecule) pairs as reactive intermediates.

The S_N1 is one of the most studied of all organic reaction mechanisms, yet there are still unresolved questions of detail. The archetypal reactant is an alkyl halide or arenesulfonate ester capable of yielding a relatively stable carbenium ion intermediate, and the main focus of ongoing studies of such reactions concerns the nature and lifetime of the ion or ion-pair intermediate.[1] Alcohols corresponding to the alkyl halides and sulfonate esters are not substrates in S_N1 reactions because hydroxide does not act as a good nucleofuge. However, pre-equilibrium protonation of the alcohol under acidic conditions generates a low concentration of its conjugate acid from which water may depart as a nucleofuge and, under these conditions, substitution reactions become possible, for example in the well known Lucas test to distinguish between primary, secondary and tertiary alcohols.[2] In the reaction of an alcohol capable of yielding a relatively stable carbenium ion under acidic conditions, the intermediate cation may be paired, but with a neutral water molecule rather than with a counterion.

In view of the greater basicity of nitrogen compared with oxygen[3] and the lower bond energy of the C–N bond compared with the C–O bond,[4] it is perhaps surprising that the corresponding reactions of amines are not well known. The present interest in cation–molecule chemistry[5] and recent reports of reactions of carbenium ions with amines[6] prompt us to report our initial results on the generation of carbenium ions by heterolysis of alkylammonium cations.

Substituted tritylamines, Ar′Ar′′Ar′′′CNH_2, react in methanolic aqueous acid to give an equilibrium mixture of the corresponding alcohol, Ar′Ar′′Ar′′′COH (and ether, Ar′Ar′′Ar′′′COMe), the carbocation, Ar′Ar′′Ar′′′C^+ and NH_4^+, and the overall reaction is described by Scheme 1 where R = Ar′Ar′′Ar′′′C (the minor formation of the methyl ether in the largely aqueous medium is omitted for clarity). The rate of the reaction and the composition of the final equilibrium depend upon the experimentral conditions and the substituents in the aryl rings. With Ar′ = Ar′′ = Ph and Ar′′′ = 4-$MeOC_6H_4$, the reaction is slow and requires high acid concentrations to generate appreciable concentrations of the carbenium ion at equilibrium. With Ar′ = Ar′′ = Ar′′′ = 4-$MeOC_6H_4$, the reaction is much faster and gives a high yield of the carbenium ion at relatively low acid concentrations. Between these extremes, with Ar′ = Ph and Ar′′ = Ar′′′ = 4-$MeOC_6H_4$, the rate of reaction in acidic MeOH : H_2O (20 : 80 v/v) to give an appreciable yield of the carbenium ion is conveniently measured by monitoring the increase in the visible absorption spectrum at 498 nm. This reaction has been investigated by the method of initial rates[7] and by conventional first-order kinetics in thermostatted spectrophotometric cells,[8] and shown to be first order in the substrate which exists wholly in its protonated form under the acidic conditions employed.[9]

Initial rates increase dramatically as the hydrochloric acid concentration increases, but not in a simple manner, and rates are considerably higher using perchloric acid in place of hydrochloric. The mechanism in Scheme 2 was proposed initially, which leads to the rate law [eqn. (1)] for the formation of the carbenium ion in the absence of chloride or any other nucleophile besides the solvent.

$$\frac{d[\mathrm{R^+}]}{dt} + (k_2 + k_{-2}[\mathrm{H_3O^+}])[\mathrm{R^+}] = k_{-2}[\mathrm{H_3O^+}][\mathrm{RNH_3{}^+}]_0 + [\mathrm{RNH_3{}^+}]_0\,(k_1 - k_{-2}[\mathrm{H_3O^+}])\mathrm{e}^{-k_1 t} \quad (1)$$

The general solution of this linear first-order differential equation is eqn. (2)

$$[\mathrm{R^+}]_t = \frac{\beta}{\alpha}\,(1 - \mathrm{e}^{-\alpha t}) - \frac{\gamma(\mathrm{e}^{-k_1 t} - \mathrm{e}^{-\alpha t})}{(k_1 - \alpha)} \quad (2)$$

where

$\alpha = k_2 + k_{-2}[\mathrm{H_3O^+}]$, $\beta = k_{-2}[\mathrm{H_3O^+}][\mathrm{RNH_3{}^+}]_0$, $\gamma = [\mathrm{RNH_3{}^+}]_0(k_1 - k_{-2}[\mathrm{H_3O^+}])$, $[\mathrm{RNH_3{}^+}]_0$ = initial concentration of the substituted tritylammonium cation, and $[\mathrm{H_3O^+}]$ = the constant hydronium ion concentration.

Using perchloric acid rather than hydrochloric, we have established that 4,4′-dimethoxytrityl alcohol gives the same equilibrium mixture (judged by UV–VIS spectroscopy) much

$$\mathrm{RNH_2 + H_3O^+ \rightleftharpoons RNH_3{}^+ + H_2O}$$
$$\mathrm{RNH_3{}^+ + H_2O \rightarrow ROH + NH_4{}^+}$$
$$\mathrm{ROH + H_3O^+ \rightleftharpoons R^+ + 2\,H_2O}$$

Scheme 1 The deamination of substituted tritylamines in methanolic aqueous acid

$$\mathrm{RNH_3{}^+ \xrightarrow{k_1} R^+ + NH_3}$$
$$\mathrm{R^+ + 2\,H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ROH + H_3O^+}$$
$$\mathrm{NH_3 + H_3O^+ \overset{fast}{\rightleftharpoons} NH_4{}^+ + N_2}$$

Scheme 2 Mechanism for the uncatalysed deamination of substituted tritylammonium cations

Table 1 Rate constants for the deamination of 4,4′-dimethoxytritylammonium perchlorate in 80 : 20 (v/v) water : methanol containing perchloric acid and sodium perchlorate at 25 °C[a]

$[\mathrm{HClO_4}]$ /mol dm^{-3}	$[\mathrm{NaClO_4}]$ /mol dm^{-3}	Total ionic strength /mol dm^{-3}	k_{obs} /10^{-5} s^{-1}
0.2	0.0	0.2	1.93
0.2	0.5	0.7	3.27
0.2	0.8	1.0	4.14
0.5	0.5	1.0	4.64
1.0	0.0	1.0	5.61

[a] Reactions were investigated using a Cecil Instruments model CE 5502 spectrophotometer interfaced with a PC using GraFit Version 3.0 (Erithacus Software Ltd) for calculation of the rate constants. Reactions were carried out between 1 and 4 times using initial substrate concentrations of 10^{-5}–10^{-4} mol dm^{-3} and rate constants were reproducible to about 5%.

$$RNH_3^+ \underset{k_{-1'}}{\overset{k_{1'}}{\rightleftharpoons}} [R^+NH_3]$$

$$[R^+NH_3] \xrightarrow{k_d} R^+ + NH_3$$

$$[R^+NH_3] + H_3O^+ \xrightarrow{k_{1''}} R^+ + NH_4^+ + H_2O$$

$$R^+ + 2\,H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ROH + H_3O^+$$

$$NH_3 + H_3O^+ \overset{\text{fast}}{\rightleftharpoons} NH_4^+ + H_2O$$

Scheme 3 Mechanism of deamination of 4,4′-dimethoxytritylammonium cations

faster than the corresponding amine in the same reaction medium. Under our reaction conditions, therefore, the k_2 and $k_{-2}[H_3O^+]$ steps in Scheme 2 are both much faster than the initial k_1 step, *i.e.* they constitute a 'post-equilibrium' which is maintained much more rapidly than the substrate reacts. In this case, eqn. (2) collapses to the first-order rate law [eqn. (3)], where $K_{R^+} = k_2/k_{-2} = [ROH][H_3O^+]/[R^+]$, and the

$$[R^+]_t = \frac{[RNH_3^+]_0(1 - e^{-k_1 t})}{\left(\dfrac{K_{R^+}}{[H_3O^+]} + 1\right)} \qquad (3)$$

experimentally observed rate constant is equal to k_1 of the mechanism of Scheme 2. The above kinetic analysis of the post-equilibrium mechanism of Scheme 2 also shows that the final equilibrium concentration of the substituted trityl cation is a function of the initial substrate concentration, the acidity of the carbenium ion (expressed as its pK_{R^+}), and the hydronium ion concentration, which is what is observed experimentally.

Using perchloric acid and sodium perchlorate, the results in Table 1 were obtained. These show that the observed rate constant increases with increasing ionic strength at constant perchloric acid concentration and, at constant ionic strength, it increases as sodium ions are replaced by hydronium ions. Extrapolations to zero concentration of sodium perchlorate and of perchloric acid correspond to the reactions of the substituted tritylammonium cation in the absence of each additional solute in turn, and these are clearly appreciable reactions. We can also estimate from these results a rate constant of $1 \times 10^{-5}\ s^{-1}$ for the deamination at $[H_3O^+] = 0$ and zero ionic strength. We have, therefore, identified a reaction of the 4,4′-dimethoxytritylammonium cation in the absence of additional electrolytes, and this reaction has an appreciable kinetic salt effect. Furthermore, we have detected *either* substantial *specific* kinetic salt effects upon the reaction, *or* a route genuinely first order in hydronium ions at constant ionic strength. Replacement of sodium chloride by ammonium chloride in hydrochloric acid, and of sodium perchlorate by lithium perchlorate in perchloric acid had no effect. Consequently, we propose that the modest rate enhancement induced by increasing concentrations of H_3O^+ at constant ionic strength is genuine catalysis by hydronium ions. The rate constant k_1 in the experimental rate law, therefore, needs to be replaced by $(k_0 + k_H[H_3O^+])$ were k_0 and k_H are the experimental rate constants for the uncatalysed and catalysed formation of R^+, and the mechanism of Scheme 2 needs to be expanded to include both uncatalysed and catalysed routes.

The catalytic term in the observed rate law requires that the alkylammonium cation and a hydronium ion (as well as an indeterminate number of solvent molecules) are involved in the rate-determining step of the catalysed reaction. There is clearly no site for direct protonation of the initial substrate, and the simplest reasonable catalytic mechanism to accommodate this finding involves reversible heterolysis of the alkylammonium cation to give the carbenium ion–ammonia (cation–molecule) pair which may undergo dissociation facilitated by protonation of the ammonia molecule as shown by the $k_{1''}$ step in Scheme 3. (The alternative concerted equivalent of this stepwise catalytic mechanism would involve interaction of a hydronium ion directly with the equally charged residue of the alkylammonium ion.) On the reasonable assumption that $k_{-1'} >> k_{1''}[H_3O^+]$ in Scheme 3, *i.e.* the assisted dissociation of the intermediate ion–molecule pair is rate-determining, this catalytic mechanism leads to the observed first-order rate law with $k_H = k_{1''} \times k_{1'}/k_{-1'}$. Scheme 3 also allows us to identify the uncatalysed route as the diffusional separation of the ion–molecule pair intermediate, unassisted by proton transfer, with elementary rate constant k_d. This step will be virtually unidirectional due to the rapid and essentially irreversible trapping of the ammonia by its subsequent protonation. Consequently, the first-order rate constant for the uncatalysed route in the experimental rate law is given by $k_0 = k_d \times k_{1'}/k_{-1'}$.

We are presently investigating further the effects of structural modifications upon reactivity in this system, and the utility of the reaction in general as a mild method of deprotection of substituted trityl-amino groups, especially in nucleoside synthesis.[10]

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