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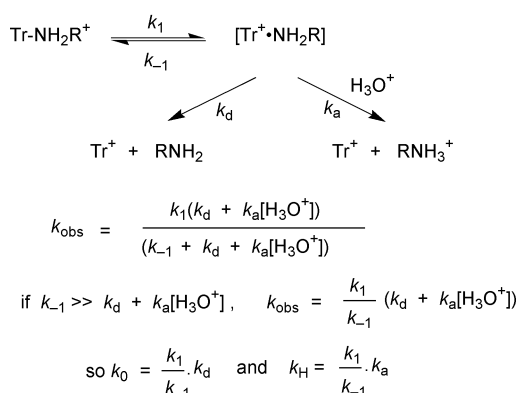The University of Cankırı Karatekin, Cankırı, …
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Substituent effects upon rates of deamination and base strengths of substituted *N*-tritylamines

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Substituted *N*-tritylamines undergo deamination in aqueous acidic solution containing organic cosolvents, and follow a pseudo first-order specific acid-catalysis rate law ($k_{obs} = k_0 + k_H[H_3O^+]$); the products are the corresponding trityl alcohols in equilibrium with the trityl carbenium ions, and ammonium ions. The change from 4,4′-dimethoxy- to 4,4′,4″-trimethoxy-tritylamine increases reactivity by a factor of about 30 in both k_0 and k_H, but *N*-alkyl and *N*-aryl groups have much greater effects (*ca.* 10^6 for both k_0 and k_H for 4,4′-dimethoxytritylamine) which are largely independent of the nature of the *N*-alkyl and *N*-aryl groups. The anions of the catalytic strong acids (perchlorate, chloride, bromide, and nitrate) have only small effects as also does the concentration of acetonitrile as cosolvent; ethanoic acid as cosolvent is mildly rate-enhancing. Substituents in the aniline residue of *N*-(4,4′-dimethoxytrityl)-anilines have virtually no effect upon either k_0 or k_H ($\rho = 0$ for both). The results are interpreted by a mechanism involving a pre-equilibrium heterolysis of the (substituted) tritylammonium ion to give an ion–molecule pair which may undergo diffusional or acid-catalysed dissociation before the (substituted) trityl cation undergoes equilibrium nucleophilic capture by water. Base strengths of some substituted *N*-tritylamines have been measured; the substituted *N*-trityl group causes all amines (aliphatic and aromatic) to be comparably strongly basic (pK_{BH^+} *ca.* 9).

Introduction

The substituted trityl group (triphenylmethyl) has been widely used as a protecting group for hydroxy and amino functions.[1] The parent trityl group is most easily introduced (using trityl chloride) but the least easy to remove, requiring acidic conditions which, in some cases, compromise the integrity of the rest of the molecule.[2] *p*-Methoxy substituted analogues, conveniently prepared using the tetrafluoroborates,[3] are much easier to deprotect. Early work indicated that cleavage of substituted trityl ethers under acidic conditions occurs by pre-equilibrium protonation followed by a simple S$_N$1 cleavage,

Scheme 1 Simplified mechanism for the specific acid-catalysed deprotection of trityl ethers in aqueous solution.

Scheme 1,[4] although later work has shown that ion–molecule pairs are involved.[5–7] The extent of return from the trityl cation and the alcohol will be insignificant in dilute aqueous solution, and k should be independent of $[H_3O^+]$ as has been observed for the closely related cleavage of trityl alcohols;[6,7] but the overall reaction is specific acid-catalysed due to the dependence of the concentration of the reactive intermediate (the protonated substrate) upon $[H_3O^+]$. Thus, in the first-order

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decomposition of (substituted) trityl ethers, which (like the corresponding alcohols) are only weak bases in aqueous solution, $k_{obs} = k_H[H_3O^+]$ as there is no detectable reaction at $[H_3O^+] = 0$. A mechanism for the deprotection of a generic *N*-tritylamine, Tr–NH–R, based upon analogy with the reactions of trityl ethers, is shown in Scheme 2. In the pre-equilibrium,

Scheme 2 Deprotection of a generic *N*-tritylamine under acidic conditions.

however, the initial substituted tritylamine is virtually wholly protonated under the normal reaction conditions (dilute strong acid containing a low concentration of cosolvent) since the amines are strong bases and $[H_3O^+] \gg [\text{tritylamine}]_0$. Also in contrast to the corresponding deprotection of trityl ethers, the departure of the nucleofuge is irreversible regardless of aqueous dilution since the nucleofuge, being a strongly basic amine, will be rapidly trapped by protonation in the acidic medium. According to this mechanism, heterolysis of the protonated amine is the rate-limiting step of an S$_N$1 reaction, and the rate constant of this elementary step, k in Scheme 2, will be the observed overall pseudo first-order rate constant, k_{obs}, *i.e.* $k_{obs} = k$ and is independent of $[H_3O^+]$ as long as $[H_3O^+] \gg [\text{TrNH}_2]_0$. The subsequent nucleophilic capture by water of the substituted trityl carbenium ion and associated deprotonation to give the corresponding substituted trityl alcohol constitute a reversible post-equilibrium. This final post-equilibrium is, of course, exactly the same as in the deprotection of trityl ethers,

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and has been extensively investigated in the past starting from the trityl alcohol. It is the basis of the well known H_R acidity function scale,[8] and comprises steps which are all much more rapid than the deaminations of the substituted primary tritylamines.[6,7,9,10]

Our kinetics study of the deprotection of substituted N-tritylamines was initiated to provide a basis in synthesis to allow improved control in the selective removal of one substituted trityl group in the presence of others that are differently substituted, or of one trityl group in the presence of an identical one but on a different type of amino group in a multi-protected polyamine. We have already reported kinetics results for the deprotection of several substituted N-trityl-N-alkylamines,[9] and a detailed mechanistic investigation of the deamination of 4,4′-dimethoxytritylamine under controlled acidic conditions.[10] This earlier work showed that the simple mechanism of Scheme 2 is inadequate; this reaction, like the cleavage of trityl ethers (but for a quite different reason), is also acid catalysed, $i.e.$ $k_{obs} = k_0 + k_H[H_3O^+]$; these tritylammonium ions are perhaps unique in having no basic site at the reaction centre, yet undergo an acid-catalysed reaction. The simplest mechanism that can accommodate this rate law is shown in Scheme 3. It involves the

$$\text{Tr-NH}_2\text{R}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{Tr}^+ \cdot \text{NH}_2\text{R}]$$

$$\text{Tr}^+ + \text{RNH}_2 \qquad \text{Tr}^+ + \text{RNH}_3^+$$

$$k_{obs} = \frac{k_1(k_d + k_a[H_3O^+])}{(k_{-1} + k_d + k_a[H_3O^+])}$$

if $k_{-1} \gg k_d + k_a[H_3O^+]$, $\quad k_{obs} = \frac{k_1}{k_{-1}}(k_d + k_a[H_3O^+])$

so $k_0 = \frac{k_1}{k_{-1}} \cdot k_d$ and $k_H = \frac{k_1}{k_{-1}} \cdot k_a$

Scheme 3 Mechanism for deprotection of N-tritylamines under acidic conditions.

intermediate formation of an ion–molecule pair which reacts further with and without acid catalysis.[9–11] We have also reported base strengths and crystal structure determinations of several N-trityl-N-alkylamines.[12] We now report results of further pK_a determinations and a kinetics study of deaminations of additional substituted N-trityl-N-alkylamines shown in Fig. 1.

Methods and results

Our substrates were made from the substituted trityl chloride or tetrafluoroborate with amines as appropriate using established methods, and have already been described.[9,12] In all cases, our samples had spectroscopic and other properties in accord with literature values and ascribed structures.

Reaction rates of (N-substituted) monomethoxy-, dimethoxy-, and trimethoxy-tritylamines were measured at 25 °C in water containing a small proportion of acetonitrile for solubility reasons, and concentrations of up to about 1 mol dm^{-3} in perchloric acid; the ionic strength was maintained constant using sodium perchlorate. Initial concentrations of substrates were typically $1-6 \times 10^{-5}$ mol dm^{-3}. Some measurements were made with the parent tritylamine, but a higher temperature and higher acidities (hence a higher ionic strength) had to be used in order to get measurable rate constants. In all cases, rates were measured by monitoring the increase in UV absorbance due to the formation of the (substituted) trityl carbenium ion. In all of these reactions, the terminal absorbance depended upon the concentration of the (substituted) trityl carbenium ion in the final equilibrium mixture which, in turn, depended upon the
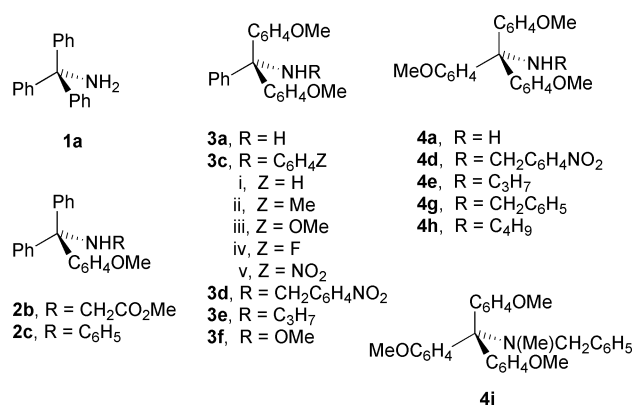
Fig. 1 Structures (all arene substituents are *para*) of **1**–**4**.

equilibrium constant for the reaction between carbenium ion, water, and hydronium ion ($i.e.$ the pK_{R^+} of the particular carbocation), in addition to the initial concentration of the substrate and the acidity of the medium.[13] In a representative case, we established that the final equilibrium under the same experimental conditions was the same starting from equal concentrations of the trityl alcohol and the tritylamine (although the former reacted much faster).

Reactions with half-lives greater than a few minutes were investigated by a conventional UV spectrophotometric method as previously described;[6,7,9,10] faster reactions were investigated using multi-mixing stopped-flow spectrophotometers.[14] All reactions were reproducible and experimental pseudo first-order rate constants, k_{obs}, are believed to be reliable to better than 5%. It was generally observed that the experimental pseudo first-order rate constants, k_{obs}, were linearly dependent upon the hydronium ion concentration (although upward curvature at acidities greater than about 1 mol dm^{-3} was evident). The linear relationship may be expressed as eqn. (1);

$$k_{obs} = k_0 + k_H[H_3O^+] \tag{1}$$

k_H (the second-order rate constant for the acid-catalysed reaction) and k_0 (the first-order rate constant of the uncatalysed reaction) were obtained either graphically or by linear regression.

Values of k_0 and k_H (reliable, we believe, to about 20%) are shown in Table 1 along with the pK_a values of the corresponding tritylammonium ions ($i.e.$ the pK_{BH^+} of the amine)[15] measured in water at constant ionic strength containing sufficient acetonitrile to maintain a homogeneous solution under the reaction conditions. We have already established in representative cases that substituting Li$^+$ or NH$_4^+$ for Na$^+$ at constant perchlorate and hydronium ion concentrations has no appreciable kinetic effect.[9] Rate constants of 4,4′-dimethoxy- and 4,4′,4″-trimethoxy-tritylamines (DMTrNH$_2$ and TMTrNH$_2$) were also measured at other temperatures between 288 and 328 K which allowed determination of the activation parameters shown as footnotes to Table 1. Replacing perchloric acid with other strong acids (hydrochloric, hydrobromic, and nitric) is shown in Table 2 to have little effect upon catalysed and uncatalysed reactions of TMTrNH$_2$ under the conditions employed. The effect of the composition of the aqueous acetonitrile is negligible, and ethanoic acid as cosolvent is slightly rate-enhancing (Table 2); additionally, tetrahydrofuran was tried as a cosolvent but was unsuitable as it did not give a single phase with high concentrations of aqueous electrolytes. The effects of the nature of the cosolvent and its composition with water are similar for DMTrNH$_2$ (Table 3).

A routine pH titration technique was used for determining the pK_a's of the substituted N-tritylalkyl- and N-tritylaryl-ammonium ions.[12,17] Acetonitrile was used as cosolvent to overcome solubility difficulties in water alone and, although this is

Table 1 Acidity constants and rate constants for uncatalysed and acid-catalysed reactions of the conjugate acids of substituted tritylamines in aqueous perchloric acid containing 1–2% acetonitrile; ionic strength (NaClO$_4$) = 1 mol dm^{-3}, 25 °C[a]

Tritylamine	pK_{BH^+} (% CH$_3$CN)	k_0/s^{-1}	k_H/dm^3 mol^{-1} s^{-1}
TrNH$_2$, **1a**	9.2(16)	6.9×10^{-5}[b]	3.8×10^{-5}[b]
MMTrNHCH$_2$CO$_2$Me, **2b**	—	34.0	59.1
MMTrNHPh, **2c**	—	9.25	145
DMTrNH$_2$, **3a**	9.5(28)[c]	3.49×10^{-5}[d]	1.2×10^{-5}[d]
DMTrNHPh, **3c,i**	8.9(39)[e]	41	37
DMTrNHC$_6$H$_4$Me, **3c,ii**	9.2(17)[e]	37	72
DMTrNHC$_6$H$_4$OMe, **3c,iii**	9.5(53)[e]	45	10
DMTrNHC$_6$H$_4$F, **3c,iv**	8.8(17)[e]	43	56
DMTrNHC$_6$H$_4$NO$_2$, **3c,v**	9.3(87)[e]	38	23
DMTrNH(p-NO$_2$Bn), **3d**	—	9	142
DMTrNHC$_3$H$_7$, **3e**	—	48	33
DMTrNHOMe, **3f**	—	0.20[f]	1.3[f]
TMTrNH$_2$, **4a**	9.3(26)[c]	3.81×10^{-4}[g]	1.68×10^{-4}[g]
TMTrNH(p-NO$_2$Bn), **4d**	—	5.8	118
TMTrNHC$_3$H$_7$, **4e**	9.7(26)	4.75	146
TMTrNHBn, **4g**	9.4(32)	4.9	138
TMTrNHC$_4$H$_9$, **4h**	9.7(36)	5.3	143
TMTrN(Me)Bn, **4i**	9.9(20)	5.7	128

[a] pK_{BH^+} values of the bases, *i.e.* the pK_a values of the corresponding alkylammonium ions,[15] were measured in acetonitrile–water solution, ionic strength 1.0 mol dm^{-3} (NaClO$_4$) at 21 °C; all arene substituents are at position 4. [b] 340 K, ionic strength (NaClO$_4$) = 3.5 mol dm^{-3}, 4% MeCN. [c] Ref. 9. [d] $k_0 = 3.1 \times 10^{-5}$ s^{-1} and $k_H = 1.6 \times 10^{-5}$ dm^3 mol^{-1} s^{-1};[9] from rate measurements made between 288 and 328 K, $\Delta H^\ddagger = 105 \pm 5$ and 126 ± 8 kJ mol^{-1}, and $\Delta S^\ddagger = 21 \pm 10$ and 85 ± 15 J K^{-1} mol^{-1}, for k_0 and k_H, respectively. [e] Ref. 12. [f] Ref. 16. [g] $k_0 = 89 \times 10^{-5}$ s^{-1} and $k_H = 50 \times 10^{-5}$ dm^3 mol^{-1} s^{-1};[9] from rate measurements made between 288 and 328 K, $\Delta H^\ddagger = 97 \pm 5$ and 100 ± 5 kJ mol^{-1}, and $\Delta S^\ddagger = 15 \pm 10$ and 19 ± 10 J K^{-1} mol^{-1}, for k_0 and k_H, respectively.

unlikely to have had a significant effect, its proportion changed slightly as the ammonium salts were titrated against standard sodium hydroxide. The initial acidic pH of the solution for titration was chosen to minimise solvolytic deamination of the *N*-tritylalkyl- and *N*-tritylaryl-ammonium ions. Results are included in Table 1.

Discussion

It is evident from the pK_{BH^+} values of the substituted trityl-amines, that the substrates in these deamination reactions under the acidic conditions of the kinetics experiments are actually the corresponding substituted tritylammonium cations.[15] Consequently, although k_H is the rate constant of the real acid-induced reaction of the (substituted) ions, Tr–NH$_3^+$ (or Tr–NH$_2$R$^+$), k_0 corresponds to the hypothetical reaction of these ions at [H$_3$O$^+$] = 0. The insensitivity of the kinetics of deamination of TMTrNH$_2$ to the nature of the strong acid catalyst (Table 2) is in accord with previous studies using DMTrNH$_2$, and is as expected for a specific acid-catalysed mechanism. The absence of a major solvent effect upon the rates of deaminations of both DMTrNH$_2$ and TMTrNH$_2$ shown in Tables 2 and 3 indicates that the choice of cosolvent need be guided only by solubility issues in deprotection reactions in synthesis.

Monomethoxytritylamine (MMTrNH$_2$) is much less reactive than the dimethoxy- analogue,[18] and the parent tritylamine (TrNH$_2$) is even less reactive. Furthermore, trityl and mono-methoxytrityl carbenium ions are much less stable in aqueous solution than dimethoxy- and trimethoxy- analogues. Consequently, it was not possible to obtain reliable rate measurements on TrNH$_2$ and MMTrNH$_2$ under conditions (temperature, acidity, and ionic strength) comparable with those employed for dimethoxy- and trimethoxy- analogues. The similarity in the rate-enhancing effects of the extra 4-methoxy substituent between DMTrNH$_2$ and TMTrNH$_2$ upon both k_0 and k_H (Table 1, a factor of about 30) suggests that the effect is upon the initial pre-equilibrium ionization (k_1/k_{-1}) rather than the subsequent k_d and k_a steps (Scheme 3). This is readily understood as the resonance effect of the extra methoxy substituent upon the stability of the dimethoxytrityl cation. The 4-methoxy substituent effect is much smaller, however, than the effect of

Table 2 Effect of catalytic acids and solvent composition upon rate constants for uncatalysed (k_0) and acid-catalysed (k_H) reactions of 4,4′,4″-trimethoxytritylammonium cation in aqueous solution at 298 K; ionic strength = 1 mol dm^{-3a}

Acid (% cosolvent)	$10^4 k_0$/s^{-1}	$10^4 k_H$/dm^3 mol^{-1} s^{-1}
HClO$_4$ (1% MeCN)	3.81[b]	1.68[b]
HCl (1% MeCN)	2.02	1.80
HBr (1% MeCN)	2.44	0.92
HNO$_3$ (1% MeCN)	2.44	1.21
HClO$_4$ (51% MeCN)	1.74	3.1
HClO$_4$ (78% MeCN)	2[c]	5[c]
HCl (60% AcOH)	8.6	3.6
HCl (95% AcOH)[d]	11	10

[a] The ionic strength was maintained constant with the sodium salt of the catalytic acid. [b] From Table 1. [c] These results are less precise due to the poorer quality of the linear correlation of k_{obs} with [HClO$_4$]. [d] Ionic strength not kept constant.

Table 3 Effect of cosolvent upon rate constants for uncatalysed (k_0) and perchloric acid-catalysed (k_H) reactions of 4,4′-dimethoxy-tritylammonium cation in aqueous solution at 298 K; ionic strength (NaClO$_4$) = 1 mol dm^{-3}

Cosolvent	$10^5 k_0$/s^{-1}	$10^5 k_H$/dm^3 mol^{-1} s^{-1}
1% MeCN[a]	3.49	1.2
60% AcOH	5.5	2.9
95% AcOH[b]	6	7

[a] It was shown that, under otherwise the same experimental conditions at 298 K, k_{obs} increased only from 4.6 to 6.5×10^{-5} s^{-1} as the proportion of MeCN increased from 1 to 60%. [b] Ionic strength not kept constant.

an *N*-alkyl group (a factor of about 10^6 upon both k_0 and k_H for DMTrNH$_2$). Moreover, the rate-enhancements due to resonance of the second and third methoxy substituents virtually disappear in the *N*-alkyl derivatives, *i.e.* the *N*-alkyl has a levelling effect upon the rate-enhancing resonance effect of the second and third 4-MeO groups. Furthermore, comparisons of reactivities of mono-, di-, and tri-methoxy-substituted analogues with a common substituent on the

nitrogen, *e.g.* –NH–Ph, or –NH–CH$_2$CO$_2$Me,[9] do not appear to follow any readily explicable pattern. Within the dimethoxytrityl series, however, all carbon-bonded *N*-substituents lead to similarly large rate enhancements (Table 1), and the alkoxy group of *N*-(dimethoxytrityl)-*O*-methylhydroxylamine has an effect smaller by a factor of only about 200 on k_0 and 50 on k_H compared with the alkyl substituents. Replacement of an alkyl on the nitrogen by an alkoxy yields an α-effect nucleofuge/nucleophile,[19] so there will be a higher proportion of internal return for the hydroxylamine, *i.e.* k_1/k_{-1} in Scheme 3 will be smaller, with an associated reduction in the overall rate constants, k_0 and k_H, compared with the *N*-alkyl analogues.

We reported previously that the effect of substituents upon the base strengths of anilines, $\rho(\sigma^-) = -2.9$,[20] is absent in *N*-tritylanilines;[12] moreover, all the *N*-tritylanilines we investigated were comparable as bases with simple alkylamines, *i.e.* pK_{BH^+} *ca.* 9. We ascribed this to steric inhibition of resonance between the lone pair on the nitrogen and the aryl residue and its *para*-substituents (if present). We now observe that k_0 values for *N*-trityl(aryl)amines are generally higher than for *N*-trityl(alkyl)amines, but independent of the substituent in the arylamine ($\rho = 0$ for k_0), and k_H values are lower than for *N*-alkyl analogues, but again independent of the substituent in the arylamine ($\rho = 0$ for k_H). On the basis that arylamines are poorer nucleophiles and weaker bases than alkylamines, k_{-1} and k_a should be smaller for arylamines than for alkylamines, whereas k_1 should be larger and k_d much the same. It follows (Scheme 3) that k_0 should be larger for *N*-trityl(aryl)amines than *N*-trityl(alkyl)amines but k_H smaller as is observed (Table 1) but only by a factor of about 10 for k_0 and even less for k_H. The absence of an effect by substituents in the aniline moiety upon both k_0 and k_H is more intriguing and, like the origin of the massive rate enhancements caused by *N*-alkyl and *N*-aryl groups, is the subject of ongoing investigations.

Activation parameters for the forward reaction ($K.k$) in Scheme 1 for R = H, have already been reported ($\Delta H^\ddagger = 63$ kJ mol^{-1} and $\Delta S^\ddagger = -19$ J K^{-1} mol^{-1}),[7] and are in accordance with a fast second-order catalytic mechanism (low $\Delta H^\ddagger$ and modestly negative $\Delta S^\ddagger$). This acid-catalysed cleavage of alcohols (and ethers) compares with the k_0 reaction channel in the present investigation (Scheme 3), but with an important difference. In the k_0 reaction channel of Scheme 3, the reactant is already protonated, so the reaction is essentially a first-order unimolecular reaction of an alkylammonium ion. Accordingly, there is no adverse translational component to the entropy of activation, as there is for the second-order bimolecular process, and there is no change in charge type as the reactant proceeds to the transition structure. In the absence of complicating differential solvation effects, therefore, $\Delta S^\ddagger$ for the dissociative unimolecular mechanism should be modestly positive as is observed: $\Delta S^\ddagger$ values for k_0 for DMTrNH$_2$ and TMTrNH$_2$ are 21 and 15 J K^{-1} mol^{-1}, respectively. This entropy effect alone, of course, would lead to the deaminations being faster than the cleavage of ethers and alcohols at [H$_3$O$^+$] = 1 mol dm^{-3}. The major cause, therefore, of the much faster cleavage of the C–O bonds in the protonated alcohols and ethers compared with cleavage of the C–N bond in the deamination of tritylammonium ions is the difference in enthalpies of activation (*ca.* 63 kJ mol^{-1} compared with *ca.* 100 kJ mol^{-1}). There is no reaction channel in the cleavage of the alcohols (or ethers) corresponding to the acid-catalysed deamination. We see, however, that $\Delta H^\ddagger$ values for this k_H process for both DMTrNH$_2$ and TMTrNH$_2$ are virtually the same as for the uncatalysed k_0 reactions.

Experimental

Preparations of compounds have already been described.[9,12] Water was glass distilled and concentrations of stock solutions of perchloric acid were determined by titration against standard sodium hydroxide which had been previously standardised against potassium hydrogen phthalate.

Kinetics

The deamination reactions of the trityl-substituted ammonium cations occur in aqueous perchloric acid (containing 1–2% of acetonitrile to overcome solubility problems) to give equilibrium mixtures of the trityl cations and trityl alcohols. Trityl, 4,4′-dimethoxytrityl, and 4,4′,4″-trimethoxytrityl cations absorb strongly at 432, 495, and 483 nm, respectively, and rates were measured by monitoring increases in absorbances at or close to these wavelengths. Conventional kinetics were measured using a Cecil 5502 double beam spectrophotometer controlled by an Elonex PC-433 and with the cell block thermostatted by water circulating from a Grant W6 water bath. The temperature was monitored with a platinum resistance thermometer in the cell block. Stopped-flow kinetics were carried out using an Applied Photophysics SX-17MV stopped-flow spectrofluorimeter at 25 ± 0.1 °C.[14] Rates of decomposition under acidic conditions were investigated under the usual pseudo first-order conditions. The observed pseudo first-order rate constants (averages of at least six runs) were plotted against [H$_3$O$^+$] to give the second-order catalytic constant from the gradient and the first-order rate constant for the uncatalysed reaction from the intercept.

pK_a Determinations

A pH titration method was used and has already been described.[11] A combined glass electrode coupled to a Metrohm 716 DMS Titrino automatic titrator was used to record the pH during the titration of the conjugated acid of the amine against standard sodium hydroxide. The reported pK_a values were optimised by fitting the experimental results to the appropriate sigmoidal equations derived from the Henderson–Hasselbach equation using a non-linear optimisation algorithm.

References

1 B. Helferich, *Adv. Carbohydr. Chem.*, 1948, **3**, 79; J. F. W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, London and New York, 1973; T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, 3rd edn., New York, 1999.

2 L. Zervas and D. M. Theodoropoulos, *J. Am. Chem. Soc.*, 1956, **78**, 1359; P. T. Gilman and H. G. Khorana, *J. Am. Chem. Soc.*, 1959, **81**, 4647; M. Smith, D. H. Rammler, I. H. Goldberg and H. G. Khorana, *J. Am. Chem. Soc.*, 1962, **84**, 430; H. Schaller, G. Wiemann, B. Lerch and H. G. Khorana, *J. Am. Chem. Soc.*, 1963, **85**, 3821.

3 C. Bleasdale, S. B. Ellwood and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1990, 803; A. P. Henderson, J. Riseborough, C. Bleasdale, W. Clegg, M. R. J. Elsegood and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3407.

4 H. Nicholson and P. A. H. Wyatt, *J. Chem. Soc. (B)*, 1968, 198; M. J. Postle and P. A. H. Wyatt, *J. Chem. Soc., Perkin Trans. 2*, 1972, 474.

5 A. Thibblin, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1195.

6 J. Cugeiras and H. Maskill, *Can. J. Chem.*, 1999, **77**, 530.

7 J. Cugeiras and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 2000, 441.

8 N. C. Deno, J. J. Jaruzelski and A. Schriesheim, *J. Am. Chem. Soc.*, 1955, **77**, 3044; N. C. Deno and A. Schreisheim, *J. Am. Chem. Soc.*, 1955, **77**, 3051; N. C. Deno, H. E. Berkheimer, W. L. Evans and H. J. Peterson, *J. Am. Chem. Soc.*, 1959, **81**, 2344; E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, 1964, **86**, 1564; M. J. Cook, N. L. Dassanayake, C. D. Johnson, A. R. Katritzky and T. W. Toone, *J. Am. Chem. Soc.*, 1975, **97**, 760; R. A. Cox and K. Yates, *Can. J. Chem.*, 1983, **61**, 2225.

9 M. C. Lopez, J. C. Martinez, I. Demirtas, H. Maskill and E. Stix, *Org. React.*, 1997, **30**, 71.

10 C. Bleasdale, B. T. Golding, W. H. Lee, H. Maskill, J. Riseborough and E. Smits, *J. Chem. Soc., Chem. Commun.*, 1994, 93; J. Crugeiras and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1901.

11 R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1992, **114**, 1816.

12 M. Canle L., W. Clegg, I. Demirtas, M. R. J. Elsegood and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 2000, 85.

13 W. H. Lee and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1463.

14 X. L. Armesto, M. Canle L., M. I. Fernández, M. V. García and J. A. Santaballa, *Tetrahedron*, 2000, **56**, 1103.

15 H. Maskill, *The physical basis of organic chemistry*, Oxford University Press, Oxford, 1985.

16 M. Canle L., W. Clegg, I. Demirtas, M. R. J. Elsegood, J. Haider, H. Maskill and P. C. Miatt, *J. Chem. Soc., Perkin Trans. 2*, 2001, preceding paper (DOI: 10.1039/b103569j).

17 A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases. A Laboratory Manual*, John Wiley and Sons, Inc., New York, 1962; E. J. King, *Acid-Base Equilibria*, Pergamon Press, New York, 1965.

18 M. Canle L. and H. Maskill, unpublished results.

19 N. S. Isaacs, *Physical organic chemistry*, Longman, London, 1987; K. R. Fountain, T. W. Dunkin and K. D. Patel, *J. Org. Chem.*, 1997, **62**, 2738; I.-H. Um and E. Buncel, *J. Org. Chem.*, 2000, **65**, 577.

20 A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388; G. N. Okafo, R. Brown and P. Camilleri, *J. Chem. Soc., Chem. Commun.*, 1991, 864.