

Acid-catalysed hydrolysis of methoxy-substituted trityl trifluoroethyl ethers: a kinetic and computational investigation of leaving group effects

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Trityl trifluoroethyl (TFE) ether and its 4-methoxy, 4,4'-dimethoxy-, and 4,4',4''-trimethoxy-substituted analogues have been prepared; the dimethoxy and trimethoxy compounds undergo ready acid-catalysed hydrolysis at constant ionic strength = 1 mol dm⁻³ at 25°C. The monomethoxy compound is less reactive and the parent trityl analogue showed minimal reactivity. Using presently reported and literature kinetics results with pK_a values of protonated substrates, first-order rate constants covering 12 orders of magnitude have been determined for heterolysis/dissociation of 11 protonated dimethoxytrityl derivatives DMTrYH⁺ where YH = H₂O, CF₃CH₂OH, ArNH₂ and RNH₂. There is a good correlation between logarithms of these rate constants and the pK_a values of the conjugate acids (YH₂⁺) of the nucleofuges YH. Enthalpies and corresponding free energies at 25°C for the dissociation of the specifically solvated ions CH₃—YH(H₂O)_n⁺ (YH = MeOH and CF₃CH₂OH, n = 1; H₂O, n = 2; and NH₃, n = 3) have been calculated at the B3LYP/6-31+G* level. Corresponding gas phase calculations have also been carried out for Ph₃C—YH(H₂O)_n⁺ (YH = H₂O, n = 2; MeOH, n = 1; CF₃CH₂OH, n = 1 and NH₃, n = 3) and, in addition, structures for these solvated ions with (YH = H₂O, MeOH and NH₃) have been calculated. The specifically solvated ion Ph₃C—O(H)CH₂CF₃(H₂O)⁺ does not correspond to a stable bonded species in the gas phase, which suggests that acid-catalysed fragmentation of methoxy-substituted analogues of Ph₃C—OCH₂CF₃ in aqueous solution are concerted with proton transfer in which case the hydrolytic cleavage will be general acid catalysed. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

The substituted trityl (triphenylmethyl) group is a common protecting group for hydroxyl and amino functions in the synthesis of a wide range of compounds.^[1,2] *p*-Methoxy-substituted trityl derivatives are much easier to deprotect than the parent trityl compounds although this depends, to some degree, upon the rest of the molecule.^[3–8] The deprotection of a (substituted) tritylated alcohol, that is the aqueous acid-induced cleavage of a (substituted) trityl alkyl ether (Tr'—OR where Tr' represents the parent or 4-methoxy-substituted analogues) is shown in Scheme 1. This reaction is closely similar to the protonation/dissociation of the corresponding alcohols Tr'—OH, Scheme 2.^[9,10] In the ether cleavage, the final equilibrium proportions of the trityl alcohol and trityl carbenium ion are the same as from the trityl alcohol itself under the same conditions. Indeed, the reverse of the mechanism of Scheme 2 (or its concerted equivalent) is an expansion of the final equilibration shown in Scheme 1.

The mechanism of the protonation/dissociation of substituted trityl alcohols has been studied in considerable detail and involves a pre-equilibrium protonation followed by ionisation and dissociation via ion–molecule pairs (or the concerted

equivalent).^[9–12] This reversible reaction shown in Scheme 2 is the basis of the well-known *H*_R acidity function scale where *H*_R relates to *K*_R⁺,^[13–17] and the experimentally observed *pseudo*-first-order rate constant for the overall equilibration, *k*_{obs}, is for the sum of forward and reverse processes (*k*_{obs} = *k*_r + *k*_f [H₃O⁺]) regardless of the initial extent of reaction.^[9,10]

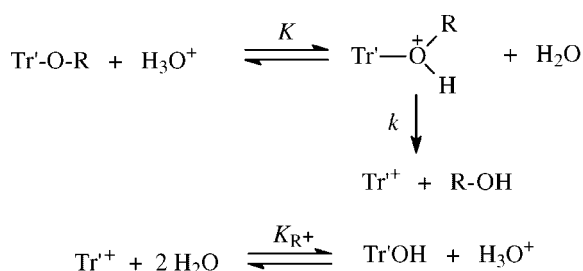
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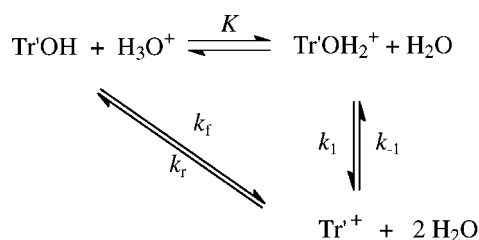
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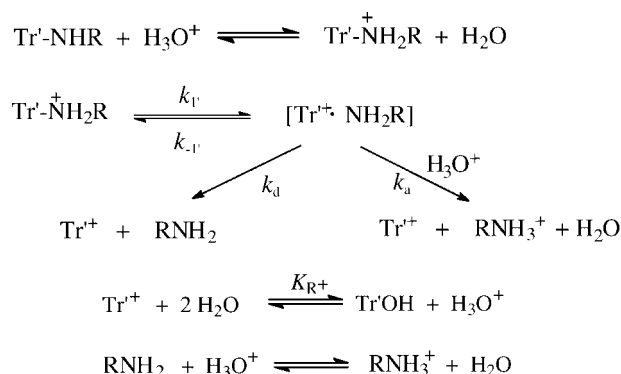
Scheme 1. Heterolytic cleavage of a substituted trityl alkyl ether in dilute aqueous acidic solution and subsequent hydrolysis of the substituted trityl cation



Scheme 2. Reversible protonation/dissociation of substituted trityl alcohols in dilute aqueous acidic solution (the involvement of ion-molecule pairs in the k_1/k_{-1} step^[9,10,12] has been omitted in the interests of brevity)

The anticipated corresponding mechanism for (substituted) trityl alkyl ethers is included in Scheme 1; there should be no appreciable extent of return from the trityl cation and the alcohol ROH in dilute aqueous solution so the reaction is essentially unidirectional. This mechanism leads to a first-order rate dependence on the ether concentration and to specific acid catalysis due to the involvement of the reversibly formed protonated ether as a reactive intermediate.^[18] Thus, for (substituted) trityl alkyl ethers ($\text{Tr}'\text{-OR}$), which are only weak bases in aqueous solution, there should be no detectable reaction at $[\text{H}_3\text{O}^+] = 0$ and, for dilute aqueous solutions, the *pseudo*-first-order rate constants should increase linearly with $[\text{H}_3\text{O}^+]$.

The mechanism for the deprotection of substituted trityl amines, $\text{Tr}'\text{-NHR}$, in aqueous solution has also been studied in detail,^[7,8,19,20] and is characteristically different from the mechanism for the corresponding reaction of substituted trityl alcohols because the amines are strong bases. The initial tritylamine is virtually wholly protonated when $[\text{H}_3\text{O}^+] \gg [\text{tritylamine}]_0$ under the normal reaction conditions (dilute aqueous strong acid containing a low concentration of cosolvent) so the reaction was initially not expected to show acid catalysis. Unexpectedly, the deamination of substituted tritylamines $\text{Tr}'\text{-NH}_3^+$ was found to be specific acid catalysed ($\text{rate} = k_{\text{obs}} [\text{Tr}'\text{NH}_3^+]$ where $k_{\text{obs}} = k_0 + k_{\text{H}} [\text{H}_3\text{O}^+]$) with appreciable reactivity under the hypothetical extrapolated conditions of $[\text{H}_3\text{O}^+] = 0$.^[7,8,19,20] These wholly unprecedented results were accommodated by a mechanism involving ion-molecule pairs, Scheme 3, that is by invoking the distinction between ionisation and dissociation of $\text{Tr}'\text{-NH}_2\text{R}^+$.^[9,10,12] The final equilibrium here in which the (substituted) trityl carbenium ion undergoes reversible nucleophilic capture by water is, of course, exactly the same as in the acid-induced deprotection of trityl ethers,



Scheme 3. Ion-molecule pair mechanism for deprotection of substituted *N*-trityl alkylamines in dilute aqueous acid

Scheme 1, and the protonation/dissociation of trityl alcohols themselves (Scheme 2).

We investigated the effect of alkyl groups, R, upon reactivity in the acid-induced deprotection of (substituted) trityl amines, $\text{Tr}'\text{-NHR}$, and observed huge but very similar rate enhancing effects compared with the deamination of $\text{Tr}'\text{-NH}_2$.^[7,8] If the effect of converting the nucleofuge in Scheme 2 from -OH_2^+ to -O(H)R^+ in Scheme 1 is similar to that of converting -NH_3^+ to $\text{-NH}_2\text{R}^+$ in Scheme 3, rate constants for the hydrolysis of $\text{Tr}'\text{-OR}$ in dilute aqueous acidic solution would be extremely high and possibly beyond the range of quantification by conventional or even stopped flow UV spectrophotometric investigation. To avoid this possible difficulty, we initiated our present investigation by using 2,2,2-trifluoroethyl ethers ($\text{Tr}'\text{-OTFE}$) in the expectation that the CF_3 group would reduce the base strength of the ethers thereby leading to lower concentrations of the putative protonated reactive intermediate. Of course, the CF_3 group should also enhance the nucleofugality of the protonated leaving group, so there will be a balance of two opposing effects.

We report here our experimental kinetics results for the hydrolysis of methoxy-substituted trityl 2,2,2-TFE ethers in dilute acidic aqueous solution at 25°C (the reactivity of the parent $\text{Ph}_3\text{C-OTFE}$ was too low to quantify by our method under these conditions). In addition, we report a computational comparison of the enthalpy and free energy at 25°C of the heterolytic dissociation of the central bond in $\text{CH}_3\text{-YH}^+$ and $\text{Ph}_3\text{C-YH}^+$ (and their specifically solvated analogues) where YH is H_2O , MeOH, $\text{CF}_3\text{CH}_2\text{OH}$ and NH_3 , and computed structures for specifically solvated ions $\text{Ph}_3\text{C-YH(H}_2\text{O)}_n^+$ where YH is H_2O ($n = 2$), MeOH ($n = 1$) and NH_3 ($n = 3$).

METHODS

Experimental

Trityl TFE ethers were made by conventional methods which are described in the experimental section; in all cases, spectral and analytical characterisations were satisfactory although only the parent trityl TFE ether was crystalline. Detritylation of the methoxy-substituted trityl TFE ethers under acidic conditions led to trifluoroethanol and equilibrium mixtures of the substituted trityl carbenium ions and the corresponding alcohols. The kinetics of the detritylations were investigated by our usual

method of monitoring the rate of increase in UV absorption due to the formation of the substituted trityl cation at a suitable wavelength in the thermostatted cell block of a spectrophotometer connected to a PC for data collection.^[7,8,21,22] Rate constants were calculated by nonlinear optimisation from absorbance-time data measured under *pseudo*-first-order conditions using perchloric acid ($[\text{H}_3\text{O}^+] \gg [\text{substrate}]_0$) and low concentrations of acetonitrile to maintain complete solubility at ionic strengths kept constant with sodium perchlorate. Solutions for kinetics were prepared by adding a concentrated solution of the substrate in acetonitrile to the aqueous solution of electrolytes. The clarity of all solutions and the excellent fitting of the data to the first-order rate law of individual runs indicate that the nonlinear correlations of k_{obs} against $[\text{H}_3\text{O}^+]$ for monomethoxytrityl (MMTr) and dimethoxytrityl (DMTr) TFE-ethers are not due to solubility problems. Kinetic runs were carried out at least twice and the expressed uncertainty in tabulated rate constants (k_{obs} in Supplementary Tables S1–S3) indicates reproducibility.

Reactions of the trimethoxytrityl (TMTr) and DMTr TFE-ethers were carried out at perchloric acid concentrations up to 1 mol dm^{-3} , and 1 mol dm^{-3} constant ionic strength. The MMTr analogue was insufficiently reactive under these conditions so this compound was investigated at acid concentrations up to 2.66 mol dm^{-3} and ionic strength constant at 3.0 mol dm^{-3} . However, the kinetic effect of sodium perchlorate is quite appreciable for the ionisation of trityl alcohols^[9,10,23–25] and the deamination of tritylamines.^[20] Consequently, results for MMTrOTFE at ionic strength (I) = 3 mol dm^{-3} are not directly comparable with those for DMTrOTFE and TMTrOTFE at $I = 1 \text{ mol dm}^{-3}$.

Computational

The geometries were fully optimised at the B3LYP/6-31+G* level of theory with normal convergence using the Gaussian 03 programme.^[26] Vibrational normal mode analyses were performed at the same level to ensure that each optimised structure was a true minimum on the potential energy surface and to calculate the thermal correction needed to obtain the Gibbs free energies. Bond dissociation enthalpies in water were also estimated using the Onsager reaction field model at the same level of theory.^[27–29] The $\text{Tr}-\text{YH}^+$ series did not give stable structures in either type of calculation, that is $\text{Tr}-\text{Y}$ bond cleavage occurs without a barrier. Solvated complexes in which acidic hydrogens H-bond with specific water molecules were then calculated. By this method, stable structures were obtained for $\text{Tr}-\text{YH}(\text{H}_2\text{O})_n^+$ with $\text{YH} = \text{NH}_3$ ($n = 3$), H_2O ($n = 2$) and MeOH ($n = 1$); bond dissociation enthalpies were then obtained from the enthalpy of the gas phase reaction of Eqn 1 where n is the number of water molecules in the specifically solvated protonated complexes:



RESULTS

Experimental

The effect of the acidity of the reaction medium is not simply kinetic. The reaction was monitored by following the UV

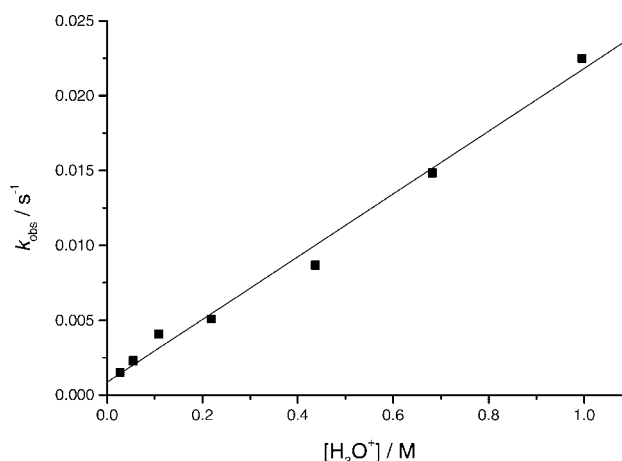


Figure 1. Graph of k_{obs} versus $[\text{H}_3\text{O}^+]$ for 4,4',4'''-trimethoxytrityl trifluoroethyl ether in aqueous solution, $[\text{Substrate}]_0 = 2.11 \times 10^{-5} \text{ mol dm}^{-3}$; ionic strength (NaClO_4) = 1.00 mol dm^{-3} ; $T = 298.0 \text{ K}$; $\lambda = 483 \text{ nm}$; $0.7\% \text{ CH}_3\text{CN}$. $k_o = 8.7 \times 10^{-4} \text{ s}^{-1}$ and $k_H = 2.10 \times 10^{-2} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($R = 0.995$)

absorbance of the carbenium ion which is in equilibrium with the trityl alcohol according to the final equation of Scheme 1. The equilibrium concentration of carbenium ion, therefore, depends upon the acid concentration and the equilibrium constant for the particular system under the particular physical conditions. At low acidities in water at 25°C , the product mixture from the parent trityl TFE ether contains too low a proportion of the carbenium ion in equilibrium with the alcohol for the kinetics of cleavage to be reliably quantified.

Kinetics results for the three methoxy-substituted compounds are illustrated in Figs 1–3 and experimental data are given in the accompanying Supplementary Tables S1–S3. The increase in *pseudo*-first-order rate constants with increasing acid concentration was initially linear, which allowed the determination of second-order rate constants for the hydronium-ion-catalysed reaction (k_H); these are shown in the footnotes to the figures and

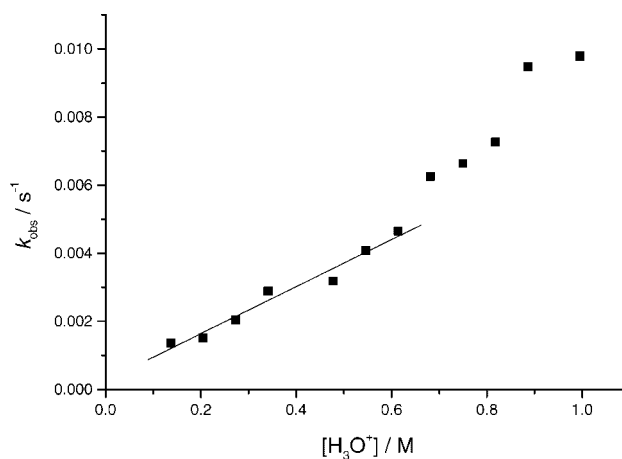


Figure 2. Graph of k_{obs} versus $[\text{H}_3\text{O}^+]$ for 4,4'-dimethoxytrityl trifluoroethyl ether in aqueous solution, $[\text{Substrate}]_0 = 2.82 \times 10^{-5} \text{ mol dm}^{-3}$; ionic strength (NaClO_4) = 1.00 mol dm^{-3} ; $T = 298.0 \text{ K}$; $\lambda = 495 \text{ nm}$; $1\% \text{ CH}_3\text{CN}$. $k_o = 2.3 \times 10^{-4} \text{ s}^{-1}$ and $k_H = 6.9 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($R = 0.98$) from results up to $[\text{HClO}_4] = 0.614 \text{ mol dm}^{-3}$

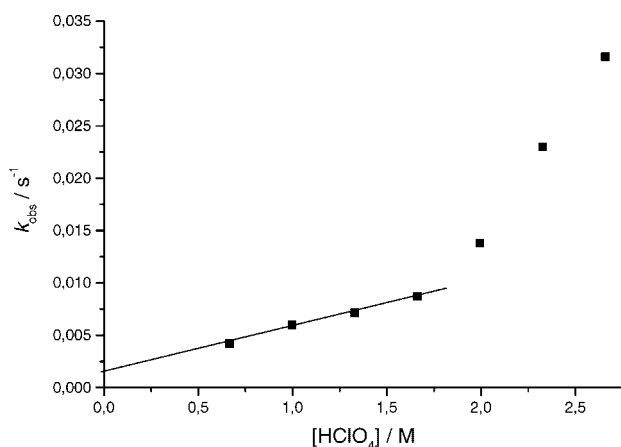


Figure 3. Graph of k_{obs} versus $[\text{H}_3\text{O}^+]$ for 4-methoxytrityl trifluoroethyl ether in aqueous solution, $[\text{Substrate}]_0 = 4.43 \times 10^{-5} \text{ mol dm}^{-3}$; ionic strength (NaClO_4) = 3.00 mol dm^{-3} ; $T = 298.0 \text{ K}$; $\lambda = 471 \text{ nm}$; 1% CH_3CN . $k_0 = 1.4 \times 10^{-3} \text{ s}^{-1}$ and $k_H = 4.4 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ($R = 0.997$) from results up to $[\text{HClO}_4] = 1.66 \text{ mol dm}^{-3}$

tables along with the extrapolated rate constants at $[\text{H}_3\text{O}^+] = 0$ which correspond to the uncatalysed reactions.

Computational

Computational results at the B3LYP/6-31+G* level for the enthalpy of dissociation of the protonated substrates $\text{CH}_3\text{—YH}^+$ ($\text{YH} = \text{H}_2\text{O}$, MeOH , $\text{CF}_3\text{CH}_2\text{OH}$ and NH_3), all of which correspond to stable bonded ions in the gas phase, are shown in Table 1 together with corresponding free energies of dissociation at 25°C . (The electronic energies, enthalpies and free energies of neutrals, complexes and cations are given in Hartrees in the accompanying Supplementary Table S4.) The column headed 'Onsager model' contains results for aqueous solution using a continuum model for the dielectric of the medium;^[27–29] results in the column headed 'Solvated model' are for the gas phase with the ions specifically solvated by n water molecules through hydrogen bonds ($n = 1$ for the protonated ethers, 2 for the protonated alcohol and 3 for the protonated amine).

Table 2. Enthalpies and free energies (25°C) of heterolytic bond dissociation of protonated species $\text{Tr—YH}(\text{H}_2\text{O})_n^+$ calculated at the B3LYP/6-31+G* level

$\text{Tr—YH}(\text{H}_2\text{O})_n^+$	Solvated model ^a	
	ΔH° (kJ mol ^{−1})	ΔG°_{25} (kJ mol ^{−1})
$\text{Tr—OH}_2(\text{H}_2\text{O})_2^+$	11	−54
$\text{Tr—O(H)CH}_3(\text{H}_2\text{O})^+$	−33	−96
$\text{Tr—NH}_3(\text{H}_2\text{O})_3^+$	69	20

^a Standard state = ideal gas at 1 atm.

Table 2 contains the gas phase results for dissociation of $\text{Ph}_3\text{C—YH}(\text{H}_2\text{O})_n^+$ ($\text{YH} = \text{H}_2\text{O}$, MeOH and NH_3) specifically solvated as indicated above for the methyl analogues. Results for $\text{YH} = \text{CF}_3\text{CH}_2\text{OH}$ are not included as $\text{Tr—O(H)TFE}(\text{H}_2\text{O})^+$ does not correspond to a stable bonded ion, that is protonation of Tr—OTFE with one water molecule of solvation led to spontaneous dissociation of the central bond. Thus, Fig. 5 shows the optimised structures of the H-bonded solvated complexes $\text{Tr—YH}(\text{H}_2\text{O})_n^+$ at the B3LY/6-31+G* level ($n = 1$ for $\text{YH} = \text{MeOH}$, $n = 2$ for $\text{YH} = \text{H}_2\text{O}$ and $n = 3$ for $\text{YH} = \text{NH}_3$) whereas the optimised structure for $\text{YH} = \text{CF}_3\text{CH}_2\text{OH}$ ($n = 1$) shows the propeller-shaped trityl carbenium ion to be essentially planar at the central carbon and separated from the dissociated $\text{CF}_3\text{CH}_2\text{OH}$ molecule H-bonded to one water molecule. (Cartesian coordinates of optimised structures of Tr—Y and $\text{Tr—YH}(\text{H}_2\text{O})_n^+$ at the B3LYP/6-31+G* level of theory are given in the accompanying Supplementary Table S5.)

DISCUSSION

Extrapolation of kinetics results to $[\text{H}_3\text{O}^+] = 0$ as shown in Figs 1–3 indicates unexpected reactivity for all three unprotonated methoxy-substituted trityl TFE ethers, that is reaction with trifluoroethoxide as nucleofuge (presumably with electrophilic assistance due to H-bonding with a solvent molecule); we are aware of no other dialkyl ethers which have been shown to

Table 1. Enthalpies and free energies (25°C) of heterolytic bond dissociation of protonated species $\text{CH}_3\text{—YH}^+$ ($\text{YH} = \text{H}_2\text{O}$, MeOH , $\text{CF}_3\text{CH}_2\text{OH}$ and NH_3) calculated at the B3LYP/6-31+G* level

$\text{CH}_3\text{—YH}^+$	Gas phase ^a		Onsager model ^{[27–29]b}		Solvated model ^a	
	ΔH° (kJ mol ^{−1})	ΔG°_{25} (kJ mol ^{−1})	ΔH° (kJ mol ^{−1})	ΔG°_{25} (kJ mol ^{−1})	ΔH° (kJ mol ^{−1})	ΔG°_{25} (kJ mol ^{−1})
$\text{CH}_3\text{—OH}_2^+$	282	241	279	238	458.6	407
$\text{CH}_3\text{—O(H)CH}_3^+$	334	290	331	286	420.1	374
$\text{CH}_3\text{—O(H)CH}_2\text{CF}_3^+$	278	234	326	282	364	316
$\text{CH}_3\text{—NH}_3^+$	441.4	399	445.2	403	550.6	520.1

^a Standard state = ideal gas at 1 atm.

^b Standard state = pure solute at 1 mol dm^{-3} in water.

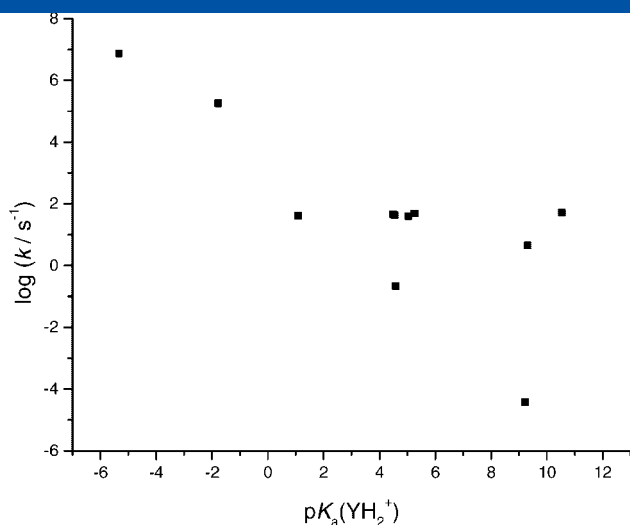


Figure 4. Brønsted-type plot of $\log k$ (s^{-1}) where k represents k , k_1 and k_o in Scheme 4 against the pK_a of the conjugate acid (YH_2^+) of the leaving groups YH in Scheme 4. $\text{YH}_2^+ = \text{NH}_4^+$ ($\text{pK}_a = 9.21$,^[51] $k_o = 3.5 \times 10^{-5} \text{ s}^{-1}$); $\text{CF}_3\text{CH}_2\text{OH}_2^+$ ($\text{pK}_a = -5.6$; $k_o = 7 \times 10^6 \text{ s}^{-1}$); H_3O^+ ($\text{pK}_a = -1.74$,^[18] $k_o = 1.7 \times 10^5 \text{ s}^{-1}$); MeONH_3^+ ($\text{pK}_a = 4.60$,^[52] $k_o = 0.20 \text{ s}^{-1}$); $\text{PhCH}_2\text{NH}_3^+$ ($\text{pK}_a = 9.34$,^[51] $k_o = 4.2 \text{ s}^{-1}$); $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+$ ($\text{pK}_a = 10.53$,^[51] $k_o = 48 \text{ s}^{-1}$); PhNH_3^+ ($\text{pK}_a = 4.62$,^[53] $k_o = 41 \text{ s}^{-1}$); $4\text{-NO}_2\text{C}_6\text{H}_4\text{NH}_3^+$ ($\text{pK}_a = 1.11$,^[53] $k_o = 38 \text{ s}^{-1}$); $4\text{-MeC}_6\text{H}_4\text{NH}_3^+$ ($\text{pK}_a = 5.07$,^[53] $k_o = 37 \text{ s}^{-1}$); $4\text{-MeOC}_6\text{H}_4\text{NH}_3^+$ ($\text{pK}_a = 5.29$,^[53] $k_o = 45 \text{ s}^{-1}$); $4\text{-FC}_6\text{H}_4\text{NH}_3^+$ ($\text{pK}_a = 4.52$,^[53] $k_o = 43 \text{ s}^{-1}$). k_o values from references^[7,8,50]

undergo hydrolysis by an uncatalysed $\text{S}_{\text{N}}1$ mechanism. The uncatalysed route requires incorporation of an extra reaction channel into the mechanism of Scheme 1, and the predicted rate law is then given by

$$\text{Rate} = k_{\text{obs}} [\text{Tr}^+\text{OTFE}] \text{ where } k_{\text{obs}} = k_o + k_{\text{H}} [\text{H}_3\text{O}^+] \quad (2)$$

This allows determination of the catalytic rate constant k_{H} and, according to the mechanism of Scheme 1, $k_{\text{H}} = k/K_a$ where K_a is the acid dissociation constant (acidity constant) of the protonated ether, that is the reciprocal of the equilibrium constant K for the pre-equilibrium shown in Scheme 1. However, the simple linear relationship between the observed *pseudo*-first-order rate constant and hydronium ion concentration, expected on the basis of Scheme 1 and Eqn 2, is observed only for TMTr TFE ether (Fig. 1). Upwards curvature is observed for the dimethoxy analogue (Fig. 2), and is even stronger for MMTr TFE ether (Fig. 3). Absence of a rectilinear correlation between $k_{\text{obs}}/[\text{H}_3\text{O}^+]$ and $[\text{H}_3\text{O}^+]$ for MMTrOTFE (the correlation is an irregularly shaped curve which defied mathematical fitting) established that the upward curvature in Fig. 3 is not simply due to the intrusion of a

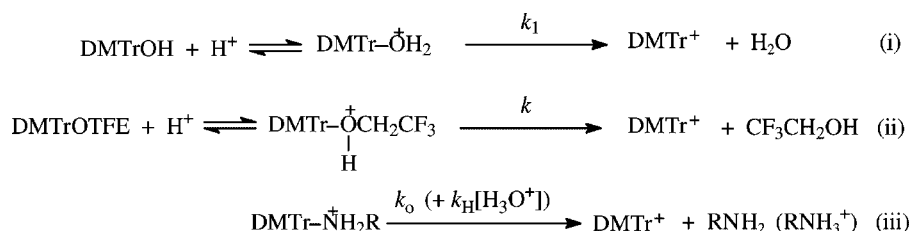
second-order term in the rate law. Our working hypothesis is that this strong curvature is a medium effect (MMTrOTFE was investigated at ionic strength = 3 mol dm^{-3} and $[\text{H}_3\text{O}^+]$ up to 2.66 mol dm^{-3}) and further consideration will be postponed until a proper acidity function analysis is complete.^[17,30]

Leaving group effect upon heterolysis in protonated substituted trityl alcohols, TFE ethers and amines in aqueous solution

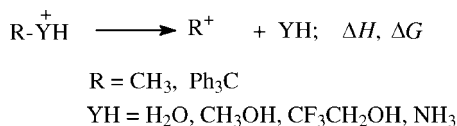
We see from Scheme 2 that $k_{\text{f}} = k_1/K_a$ for the protonation/dissociation of substituted trityl alcohols where k_{f} is the experimental second-order rate constant of the forward reaction and K_a is the acidity constant of the protonated alcohol (equal to the reciprocal of the equilibrium constant K for the pre-equilibrium shown in Scheme 2). Since $k_{\text{obs}} = k_{\text{f}} + k_{\text{f}} [\text{H}_3\text{O}^+]$ for the equilibration of Scheme 2, k_{f} is determinable. We have an experimental value of $k_{\text{f}} = 16.5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for DMTr alcohol (25°C , aqueous perchloric acid, 2% acetonitrile, ionic strength = 1 mol dm^{-3}).^[9,10] From an estimated value of $K_a \approx 10^4 \text{ mol dm}^{-3}$ for the putative DMTr-OH_2^+ in Scheme 2 based upon literature data ($\text{pK}_a = -1.74$,^[18] -1.98 ,^[31] -2.12 ,^[32,33] and -3.8 ,^[34] for OH_3^+ , MeOH_2^+ , EtOH_2^+ and $\text{Me}_3\text{COH}_2^+$, respectively), we estimate $k_1 \approx 1.7 \times 10^5 \text{ s}^{-1}$ for DMTr-OH_2^+ . (This replaces our earlier estimate of 830 s^{-1} based upon a simplistic value for the pK_a of DMTr-OH_2^+).^[7]

To calculate the analogous parameter k in the reaction of DMTrOTFE in Scheme 1, we need an estimate of the acidity constant of its conjugate acid, DMTrO(H)TfE^+ . This can be done stepwise starting from the value for DMTrOH_2^+ ($\text{pK}_a \approx -4$, see above), and incorporating perturbations due to conversion first to $\text{DMTrO(H)CH}_2\text{CH}_3^+$, then to $\text{DMTrO(H)CH}_2\text{CF}_3^+$. From pK_a values of -2.1 and -3.6 for EtOH_2^+ and Et_2OH^+ , respectively,^[32,33,35,36] we estimate $\text{pK}_a \approx -5.5$ for $\text{DMTrO(H)CH}_2\text{CH}_3^+$. Then, from pK_a values for ethanol (15.9)^[37] and trifluoroethanol (12.4),^[38] we arrive at a value of $\text{pK}_a \approx -9$ for DMTrO(H)TfE^+ , that is $K_a \approx 10^9 \text{ mol dm}^{-3}$. Thus, with $k_{\text{H}} = 6.9 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, we obtain $k \approx 7 \times 10^6 \text{ s}^{-1}$ which is only about 40 times greater than the value of $k_1 \approx 1.7 \times 10^5 \text{ s}^{-1}$ for DMTr-OH_2^+ (see above) following the improvement in the nucleofuge by replacing $-\text{OH}_2^+$ by $-\text{O(H)TfE}^+$. However, reduction of the concentration of the protonated reactive intermediate through reduction of the base strength of the substrate (a factor of about 10^5 , see above) more than compensates for this modest rate constant ratio, and DMTrOTFE has a much lower experimental catalytic rate constant than DMTrOH. The ratio for uncatalysed C—O heterolysis reactions of DMTr-OTFE and DMTr-OH is immeasurably high as the latter shows no detectable reactivity in the absence of acid.

Heterolytic cleavage of the C—N bond of $\text{DMTr-NH}_2\text{R}^+$ in Scheme 3 comprises uncatalysed and catalysed channels but



Scheme 4. Comparison of rates of unimolecular heterolyses of DMTr-YH^+ in aqueous solution for $\text{YH} = \text{H}_2\text{O}$, $\text{CF}_3\text{CH}_2\text{OH}$ and NH_3 . k_1 in Eqn (i) $\approx 1.7 \times 10^5 \text{ s}^{-1}$ (see the text); k in Eqn (ii) $\approx 7 \times 10^6 \text{ s}^{-1}$ (see the text); k_o in Eqn (iii) $= 3.67 \times 10^{-5} \text{ s}^{-1}$ for $\text{R} = \text{H}$.^[20]

**Scheme 5.** Dissociation of protonated species $\text{CH}_3\text{-YH}^+$ and Tr-YH^+

only the former is directly comparable with the heterolyses of DMTr-OH_2^+ and DMTr-O(H)TfE^+ , that is the k_o component of Eqn (iii) in Scheme 4. Comparison of Schemes 3 and 4 shows that $k_o = (k_1/k_{21})k_d$, and $k_o = 3.67 \times 10^{-5} \text{ s}^{-1}$ for DMTr-NH_3^+ .^[19,20] Thus, whilst rate constants for heterolyses of DMTr-O(H)TfE^+ and DMTr-OH_2^+ differ only by a factor of about 40, there is a rate ratio of about 4×10^9 for fragmentation of DMTr-OH_2^+ compared with DMTr-NH_3^+ . Figure 4 includes a Brønsted-type plot of $\log(k, k_1 \text{ or } k_o)$ against the pK_a of the conjugate acid of the leaving group for DMTrYH^+ ($\text{YH} = \text{OH}, \text{OTfE}$ and NH_2) together with results reported earlier for eight other substrates: $\text{DMTr-NH}_2\text{R}^+$ (Scheme 3) with $\text{R} = \text{MeO}, \text{PhCH}_2$ and $\text{CH}_3\text{CH}_2\text{CH}_2$, and $4\text{-X-C}_6\text{H}_4$ ($\text{X} = \text{H}, \text{NO}_2, \text{Me}, \text{MeO}$ and F). Literature pK_a values were available for all 11 protonated leaving groups YH_2^+ except TfEOH_2^+ (see Fig. 4). A value of $\text{pK}_a = -5.6$ for TfEOH_2^+ may be estimated from the value for TfEOH (12.4)^[38] assuming that the difference between these two is the same as the difference between values for EtOH_2^+ and EtOH (-2.1 and 15.9),^[32,33,18] similar results are obtained if the difference between pK_a values of H_2O and H_3O^+ is taken or between MeOH and MeOH_2^+ . As seen, results for five substrates which span the whole wide range of reactivity lie on an excellent straight line suggestive of a common mechanism. The high value of the gradient ($-0.79, R = -0.99$) is wholly compatible with the dissociation of Tr'YH^+ involving initial ionisation followed by rate-determining separation of the ion-molecule pair,^[9,10,12] a detail included in Fig. 3 but not in Figs 1, 2 and 4, that is the bond from the trityl residue to the nucleofuge is completely broken in the transition structure for heterolysis/dissociation of Tr'YH^+ . Results for six substrates, however, lie above the linear correlation (two are superimposed), that is these six substrates are more reactive than anticipated. We have at present no explanation of these anomalies but note that four are substituted anilines.

The enormous element effect upon the rate of heterolysis of the ions DMTr-OH_2^+ and DMTr-NH_3^+ is quite remarkable given that the C—O and C—N bond dissociation enthalpies in $\text{CH}_3\text{-OH}$ and $\text{CH}_3\text{-NH}_2$ are 385 and 356 kJ mol^{-1} , respectively.^[39] However, these bond dissociation enthalpies correspond to gas phase homolysis and the present reactions are heterolyses in aqueous solution. Consequently, we have calculated the dissociation enthalpies and free energies for the heterolytic reactions in Scheme 5 to provide a basis for comparison of the kinetic effects being observed.

Computational comparison of leaving group effects upon heterolysis of R-YH^+ where $\text{R} = \text{CH}_3$ and Ph_3C , and $\text{YH} = \text{H}_2\text{O}, \text{CH}_3\text{OH}, \text{CF}_3\text{CH}_2\text{OH}$ and NH_3

Assuming that reactivity parallels thermodynamic driving force for the set of closely related compounds reacting by the same generic mechanism, we anticipated the kinetic reactivity of R-O(H)TfE^+ , R-OH_2^+ and R-NH_3^+ to parallel heterolytic bond

dissociation free energies. In view of the relatively small effect of the methoxy-substituents, we also assumed that computations on the parent trityl compounds ($\text{R} = \text{Ph}_3\text{C}$) would adequately model our experimental results for the 4,4'-dimethoxy derivatives, and, as a preliminary, we investigated the much simpler ions with $\text{R} = \text{CH}_3$ and included R-O(H)Me^+ to model projected experimental results using Tr'-OMe .

All four ions $\text{CH}_3\text{-YH}^+$ correspond to stable bonded species, and the bond dissociation enthalpies and free energies (25°C) are shown in Table 1. For the three analogues of compounds for which we have experimental results, the decreasing order of bond strengths in the gas phase ($\text{NH}_3 \gg \text{H}_2\text{O} > \text{CF}_3\text{CH}_2\text{OH}$), both with and without using the specific solvation model, corresponds very well to the increasing order of reactivity found in solution ($\text{NH}_3 \ll \text{H}_2\text{O} < \text{CF}_3\text{CH}_2\text{OH}$). Agreement using the Onsager model in solution is less satisfactory so this was not considered further.^[27-29] Results predicted for $\text{CH}_3\text{-O(H)CH}_3^+$ in the gas phase indicate reactivity lower than for $\text{CH}_3\text{-OH}_2^+$ (but still much greater than for $\text{CH}_3\text{-NH}_3^+$). Inclusion of specific water molecules of solvation, however, inverts the order for $\text{CH}_3\text{-O(H)CH}_3^+$ and $\text{CH}_3\text{-OH}_2^+$ but $\text{CH}_3\text{-O(H)CH}_3^+$ is still predicted to be more stable (less reactive) than $\text{CH}_3\text{-O(H)CH}_2\text{CF}_3^+$.

For the parent trityl analogues Tr-YH^+ , results using the solvated model for $\text{YH} = \text{H}_2\text{O}, \text{CH}_3\text{OH}$ and NH_3 are given in Table 2; (the ion $\text{Tr-O(H)CH}_2\text{CF}_3^+$ did not correspond to an energy minimum). Heterolytic dissociation of $\text{Tr-NH}_3(\text{H}_2\text{O})_3^+$ is still thermodynamically unfavourable whereas that of $\text{Tr-O(H)CH}_3(\text{H}_2\text{O})^+$ is strongly favourable; between the two lies $\text{Tr-OH}_2(\text{H}_2\text{O})_2^+$ whose dissociation is endothermic (positive ΔH°) but overall favourable (negative ΔG°) when the entropy term is included.

Computed structures of Tr-YH^+ are shown in Fig. 5. Structural parameters for $\text{TrNH}_3(\text{H}_2\text{O})_3^+$ (C—N bond, 1.550 Å; sum of angles at central C, 337.2°) are in excellent agreement with crystallographic values for $\text{TrNH}_3^+\text{Cl}^-$ (1.519 Å and 334.8°) and *N*-tritylglycine ($\text{TrNH}_2^+\text{CH}_2\text{CO}_2^-$, 1.551 Å and 333.6°).^[40] In addition, the computations reproduce the C—N bond length observed experimentally for $\text{Ph}_3\text{C-NH}_2$ (C—N = 1.486 Å computationally compared with 1.481 Å crystallographically)^[41] and the elongation upon protonation of the nitrogen, which lends credibility to the computational protocol. For $\text{Tr-OH}_2(\text{H}_2\text{O})_2^+$, the C—O bond is 1.620 Å (appreciably longer than the value 1.446 Å presently calculated for TrOH , and 1.448 Å obtained crystallographically^[42]), and there is an appreciably greater degree of planarisation (sum of angles at central C = 344.2°) than in the less reactive tritylammonium ion (337.2°) in accordance with the Bürgi–Dunitz principle.^[43-46]

The solvated protonated trityl TFE ether does not correspond to a stable bonded ion and, correspondingly, the computed structure comprises the propeller-shaped trityl carbocation (fully planar at the central carbon) well separated from the trifluoroethanol molecule hydrogen-bonded to a water molecule (the central carbon atom being 3.536 Å from the oxygen). This suggests that the acid-catalysed fragmentation of Tr'-OTfE in aqueous solution is concerted with proton transfer rather than following a pre-equilibrium as shown in Scheme 1. This leads to the prediction of general as opposed to specific acid catalysis. If confirmed experimentally, this would be wholly in line with the observation by Bunton of general acid catalysis in the protonation/dissociation of tropyl alcohol to give the tropylium ion,^[11] and general base catalysis in the hydration of some triarylmethyl carbenium ions.^[47-49]

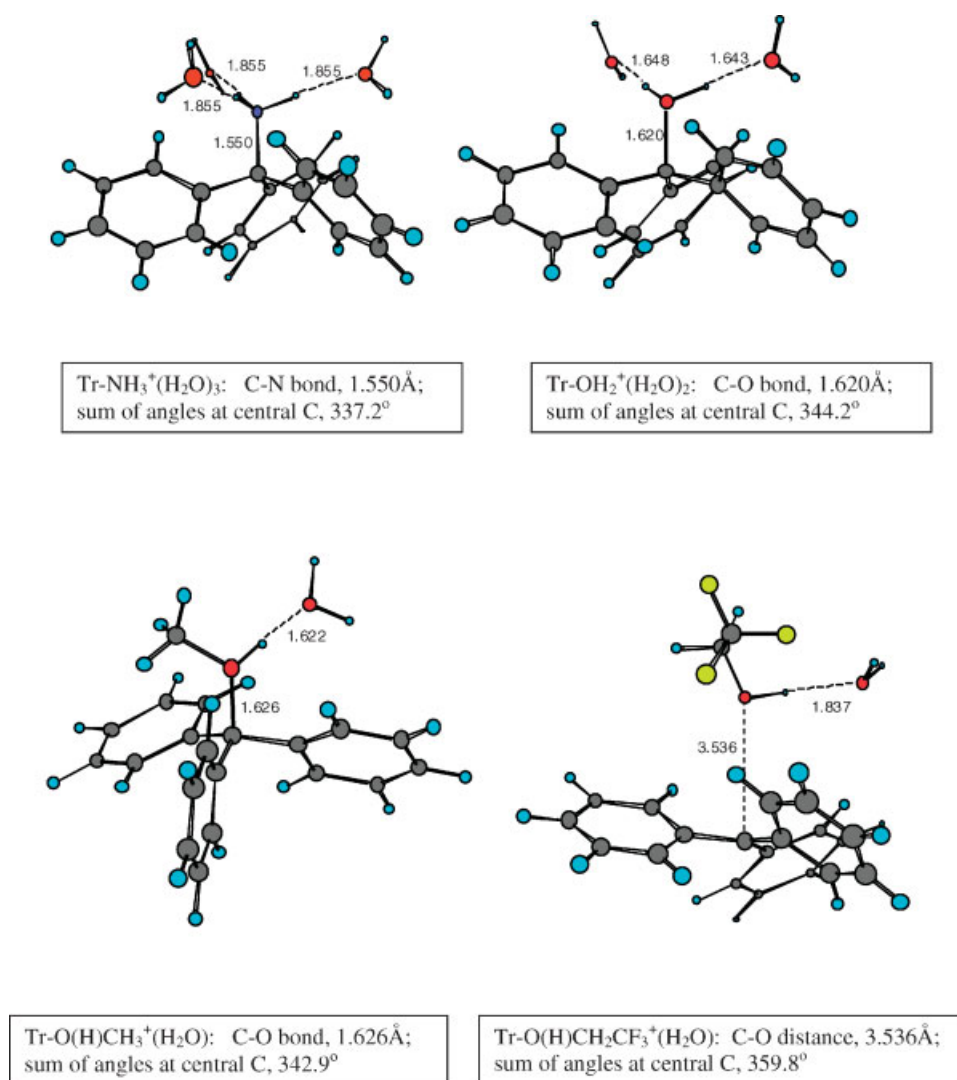


Figure 5. Optimised structures of solvated complexes, Tr-YH(H₂O)_n⁺, at the B3LYP/6-31+G* level.

EXPERIMENTAL

Our kinetics methods, general experimental procedures and instrumentation have already been described.^[7,9,10,20–22]

PREPARATIONS

Trityl 2,2,2-trifluoroethyl ether

Trityl bromide (66 mg, 0.2 mmol) was dissolved in acetone (1 cm³) and 2,2,2-trifluoroethanol (2 cm³) was added. After addition of triethylamine (two drops), the product precipitated out and the mixture was stirred for 1 h at room temperature. The precipitated compound was filtered off and dried *in vacuo* to yield the title compound as white crystals (61 mg, 89%; mp 123–125°C; found: C, 73.46; H, 4.90; C₂₁H₁₇OF₃ requires C, 73.67; H, 5.00; δ_H 3.65 (2H, q, *J* 8.5, CH₂), 7.20–7.40 (15H, m, ArH); δ_C 61.75 (C–O), 62.44 (CH₂), 87.89 (CF₃), 127.56 (C-4'), 128.15 (C-3', C-5'), 128.56 (C-2', C-6'), 142.68 (C-1')).

4-Methoxytrityl 2,2,2-trifluoroethyl ether

4-Methoxytrityl tetrafluoroborate (51 mg, 0.14 mmol) was dissolved in 2,2,2-trifluoroethanol (2 cm³, excess) and triethylamine (two drops) was added. The mixture was stirred overnight at room temperature and then evaporated to dryness. The residue was chromatographed on silica gel (20% ethyl acetate/petrol) to give a colourless oil (40 mg, 76%; δ_H 3.38 (2H, q, *J* 8.5, CH₂), 3.71 (3H, s, OCH₃), 6.77 (2H, d, *J* 9, C-3'H, C-5'H), 7.10–7.40 (12H, m, ArH); δ_C 55.28 (OCH₃), 61.68 (C–O), 62.37 (CH₂), 87.82 (CF₃), 113.45 (C-3, C-5), 127.38 (C-4'), 128.12 (C-3', C-5'), 128.27 (C-2', C-6'), 130.39 (C-2, C-6), 134.22 (C-1), 143.25 (C-1'), 159.03 (C-4)).

4,4'-Dimethoxytrityl 2,2,2-trifluoroethyl ether

4,4'-DMTr tetrafluoroborate (200 mg, 0.62 mmol) was dissolved in 2,2,2-trifluoroethanol (4 cm³, excess) and triethylamine (five drops) was added. The mixture was stirred for 21 h at room temperature and then evaporated to dryness. The residue was

extracted between water (10 cm³) and dichloromethane (10 cm³). The organic phase was separated, dried (Na₂SO₄), filtered and evaporated to give an oil (135 mg, 56%; δ_{H} 3.45 (2H, q, *J* 8.5, CH₂), 3.80 (6H, s, 2 × OCH₃), 6.84 (4H, d, *J* 9, C-3'H, C-5'H), 7.10–7.50 (5H, m, ArH), 7.32 (4H, d, *J* 9, C-2'H, C-6'H); δ_{C} 55.28 (2 × OCH₃), 61.60 (C—O), 62.29 (CH₂), 87.78 (CF₃), 113.23 (C-3, C-5), 127.20 (C-4'), 127.99 (C-3', C-5'), 129.18 (C-2, C-6), 130.03 (C-2', C-6'), 134.81 (C-1), 143.77 (C-1'), 158.88 (C-4)).

4,4',4''-Trimethoxytrityl 2,2,2-trifluoroethyl ether

4,4',4''-TMTTr tetrafluoroborate (29.5 mg, 0.07 mmol) was dissolved in 2 cm³ (excess) of 2,2,2-trifluoroethanol and two drops of triethylamine were added. The mixture was stirred for 6 h at room temperature and then extracted between water (10 cm³) and ether (10 cm³). The organic phase was separated, dried (Na₂SO₄), filtered and evaporated to give an oil (24.19 mg, 80%; δ_{H} 3.40 (2H, q, *J* 8.5, CH₂), 3.75 (9H, s, 3 × OCH₃), 6.80 (6H, d, *J* 9, C-3H, C-5H), 7.25 (6H, d, *J* 9, C-2H, C-6H); δ_{C} 55.27 (3 × OCH₃), 61.54 (C—O), 113.39 (C-3, C-5), 129.73 (C-2, C-6), 135.32 (C-1), 158.75 (C-4)).

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