DOI: 10.1002/chem.200902669

Stabilities of Trityl-Protected Substrates: The Wide Mechanistic Spectrum of Trityl Ester Hydrolyses

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Dedicated to Professor Rudolf Knorr on the occasion of his 75th birthday

Abstract: Ionization rates of *para*-substituted triphenylmethyl (trityl) acetates, benzoates, and *para*-nitrobenzoates have been determined in aqueous acetonitrile and aqueous acetone at 25 °C. Conventional and stopped-flow techniques have been used to evaluate rate constants ranging from 1.38×10^{-5} to $2.15\times10^{2}\,s^{-1}$ by conductimetry and photospectrometry methods. The varying stabilities of the differently substituted tritylium ions account for a gradual change of reaction mechanism. Poorly stabilized carbocations are generated slowly by the ionization of their covalent precursors and trapped fast by water. Better stabilized carbocations are generated more rapidly and accumulate, so that ionization and trapping by water can be observed as separate steps in a single experiment. Finally, highly stabilized tritylium ions do not react with water, and only the rates of their formation could be measured. The ionization rate constants correlate linearly with Winstein's ionizing powers Y; the low slopes ($0.17 < m < 0.58$) indicate non-carbocation-like transition states. While the correlation between the ionization rates and Hammett-Brown's σ^{+} parameters is excellent for symmetrically substituted tritylium derivatives, deviations for unsymmetrically substituted systems are observed. The failing rate–equilibrium relationship between the ionization rates of ionizations ($\log k_{ion}$) and the stabilities of the carbocations in aqueous solution (pK_{R+}) may be explained by the late development of resonance between a *p*-amino group and the carbocationic center of the tritylium ion during the ionization process.

Keywords: kinetics • linear free-energy relationships • protecting groups • solvolysis • tritylium ions

Introduction

The triphenylmethyl (trityl) cation was the first carbocation ever recognized.[1] Since then, the trityl group has found numerous applications in organic chemistry. It has been used as a hydride acceptor[2] and as a catalyst in Lewis acid initiated reactions.[3] Stabilized tritylium ions, covalently bound to nucleosides and peptides, have served as mass tags for improving the sensitivity in MALDI-TOF mass spectrometry.[4]

Most important in synthetic chemistry, however, is their use as protecting groups for OH and NH functionalities.[5–8] The unsubstituted parent residue has long been employed to protect alcohols, carboxylic acids, and amines.[5] Because the cleavage of trityl ethers often requires conditions which also lead to the deprotection of other acid-labile groups, like glycosides, Khorana introduced 4-methoxy- and the 4,4′-dimethoxytrityl derivatives, which are more acid-labile.[6] 4-Methoxy-substituted tritylium systems have been studied extensively by Maskill,[7] who determined rate constants of acidic detritylations of amines[7a] and trifluoroethanol.[7b] Destabilized trityl compounds, like the heptafluorotrityl system, were designed to serve as acid-stable protecting groups, for example, for the γ-carboxy group of glutamic acid.[8]

While the qualitative trend that the cleavage of trityl esters is facilitated by electron-donating substituents and impeded by acceptor groups is well-known, there are only a few kinetic studies on the solvolyses of donor-substituted tritylium derivatives, probably because many of these reactions proceed very quickly and require special experimental techniques, which were not generally available in the period when most kinetic investigations of solvolysis reactions were being performed.

Swain and co-workers determined solvolysis rates of trityl acetate in aqueous alcohols and acetone at 25 °C.[9] Bunton

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902669.

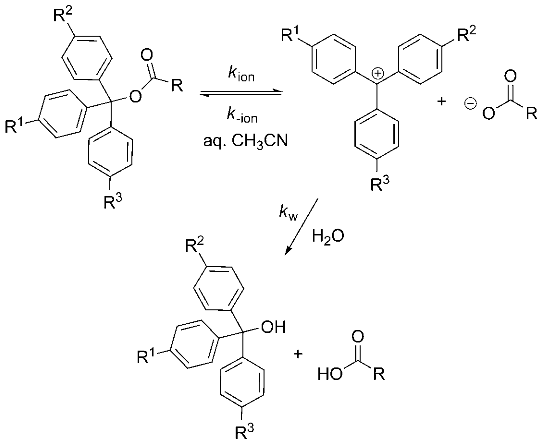
proved that the alkyl–oxygen bond (rather than the acyl–oxygen bond) is cleaved in the rate-determining step during the hydrolysis of trityl acetate.[10] Hammond reported rates of solvolysis of trityl benzoate in ethanolic ethyl methyl ketone at 55 °C, and found the exclusive formation of the ethyl trityl ether.[11] Smith studied the decomposition of tris-(*p*-tolyl)methyl benzoate in ethanolic methylene chloride, and detected strong common ion rate depression.[12] In the course of their work on ion pairs, Swain[13] and Winstein[14] investigated the rate of equilibration of carbonyl-^{18}O-labeled trityl benzoate in pure acetone.

In view of the thousands of kinetic investigations of S_N1 reactions yielding less stabilized carbenium ions, we were surprised that no systematic investigation concerning the heterolyses of donor-substituted trityl esters had yet been undertaken. Because such information is essential for selecting trityl derivatives with tailor-made stabilities, we set out to study the ionization rates of trityl carboxylates, including dimethylamino- and methoxy-substituted derivatives, which are of particular importance as protecting groups (Table 1).

Table 1. The tritylium systems studied in this work with corresponding pK_{R+} values.

R^1, R^2, R^3[a]	Abbreviation	pK_{R+}[b]
H, H, H	Tr^+	−6.63
Me, H, H	$MeTr^+$	−5.41
Me, Me, H	Me_2Tr^+	−4.71
Me, Me, Me	Me_3Tr^+	−3.56
MeO, H, H	$(MeO)Tr^+$	−3.40
MeO, MeO, H	$(MeO)_2Tr^+$	−1.24
MeO, MeO, MeO	$(MeO)_3Tr^+$	0.82
Me_2N, H, H	$(Me_2N)Tr^+$	3.88[c]
Me_2N, MeO, H	$(Me_2N)(MeO)Tr^+$	4.86[d]
Me_2N, Me_2N, H	$(Me_2N)_2Tr^+$	6.94[d]

[a] For the location of the substituents see Scheme 1. [b] From ref. [16]. [c] From ref. [17]. [d] From ref. [18].



Scheme 1. Hydrolysis of a trityl acetate (R = Me), benzoate (R = Ph), or *p*-nitrobenzoate (R = *p*-$NO_2C_6H_4$).

Kinetic methods: If acyl cleavage is excluded, the hydrolyses of trityl esters follow Scheme 1, which includes four scenarios (A to D, below) depending on the relative magnitudes of k_{ion} and k_w. As discussed later, common ion return, k_{-ion}, does not occur in the concentration range of interest, and will therefore be neglected in the following discussion.

A) $k_{ion} \ll k_w$. In the classical S_N1 reaction, carbocations are generated as short-lived intermediates, which are trapped immediately by the solvent. The progress of the reactions can be followed conveniently by conductimetry.

B) $k_{ion} \approx k_w$. When the formation and consumption of the intermediates proceed with comparable rates, small concentrations of the tritylium ions are detectable, and the course of the reaction can be followed by conductimetry or photospectrometry.

C) $k_{ion} \gg k_w$. In the so-called S_N2C^+ mechanism, which was first proposed by Ingold and co-workers,[15] carbocations are formed in a fast ionization process and trapped in a slow subsequent reaction. Because the intermediate carbocations are generated almost quantitatively before they are trapped by water, both steps of the reaction sequence can easily be followed by photospectrometry.

D) k_{ion} fast, k_w not detectable. The solvolysis scheme is reduced to the ionization step, because the generated tritylium ions are so stable that they do not react with water under the reaction conditions. Photospectrometry is a convenient method for monitoring the ionization.

Results

Only triphenylmethyl acetate, benzoate, and *p*-nitrobenzoate, that is, the unsubstituted parent compounds, have been isolated as pure substances. Because of their low stability, the esters of the donor-substituted tritylium systems were generated in acetonitrile directly before the kinetic measurements by mixing the colored tritylium tetrafluoroborates with tetra-*n*-butylammonium acetate or benzoate. Usually, one equivalent of the ammonium carboxylate was sufficient to decolorize the solution. As mentioned above, different kinetic methods were employed depending on the relative magnitudes of k_{ion} and k_w.

Scenario A, $k_{ion} \ll k_w$: Because CH_3CO_2H, $PhCO_2H$, and *p*-nitrobenzoic acid, which were generated in the hydrolyses, are weak acids, tertiary amines (usually triethylamine) were added to increase the sensitivity of the conductimetric measurements by forming ionic ammonium carboxylates. Only relative conductivities κ_{rel} were needed for the evaluation of the kinetic experiments, and we did not calibrate the conductivity cell to determine absolute values of κ. In order to examine the relationship between reaction progress and conductivity of the solution, a stock solution of (MeO)Tr–OAc in acetonitrile was added portionwise to 50:50 (v/v) acetonitrile/water containing triethylamine (→Et_3NH^+ AcO^-). The solvolysis was complete within a few seconds after each addition, and the resulting conductivities were plotted against the concentrations of the dissolved trityl ester. The linear correlation in the relevant concentration range of the kinetic runs (Figure 1) allowed us to directly relate the conductivity and the progress of the hydrolysis.

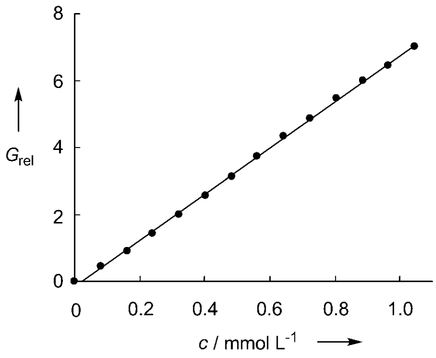


Figure 1. Plot of relative conductivities G_{rel} versus concentrations of $(\mathrm{MeO})\mathrm{Tr{-}OAc}$; 50:50 (v/v) acetonitrile/water, 25 °C, $[\mathrm{Et_3N}] = 4.62 \times 10^{-3}$ mol L^{-1}.

Figure 2 shows a typical exponential increase of conductivity due to the rate-determining ionization of a trityl ester. Analogous first-order kinetics were observed for the hydrolyses of all other trityl carboxylates, implying that common ion return did not take place.[19] First-order rate constants k_{ion} were evaluated by least-squares fitting of the curves to the mono-exponential function $G_t = G_0(1-e^{-kt}) + C$.

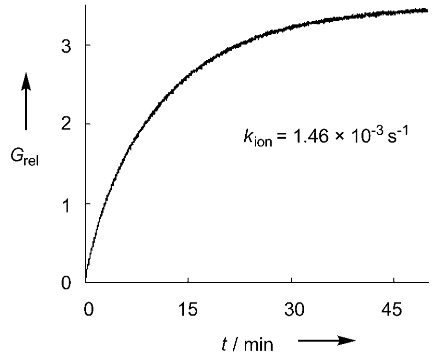


Figure 2. Conductivity G_{rel} versus time for the solvolysis of $\mathrm{MeTr{-}OAc}$ ($c_0 = 1.06 \times 10^{-3}$ mol L^{-1}) in 60:40 (v/v) acetonitrile/water at 25 °C, 5 equiv of $\mathrm{NEt_3}$.

Scenario B, $k_{\mathrm{ion}} \approx k_{\mathrm{w}}$: The similarities of the rates of ionization and quenching of the carbocation during the hydrolyses of $(\mathrm{MeO})_3\mathrm{Tr{-}OAc}$ and $(\mathrm{MeO})_3\mathrm{Tr{-}OBz}$, gave rise to substantial transient concentrations of $(\mathrm{MeO})_3\mathrm{Tr}^+$, which could be visualized by photospectrometry. No amine was added in the experiments of Figure 3. Numerical treatment of the time-dependent concentrations of $(\mathrm{MeO})_3\mathrm{Tr}^+$ with the help of the computer program GEPASI[20] delivered individual rate constants for both steps, k_{ion} and k_{w}. In all cases the measured curves could be reasonably fitted (Tables 2 and 3; for details see the Supporting Information).

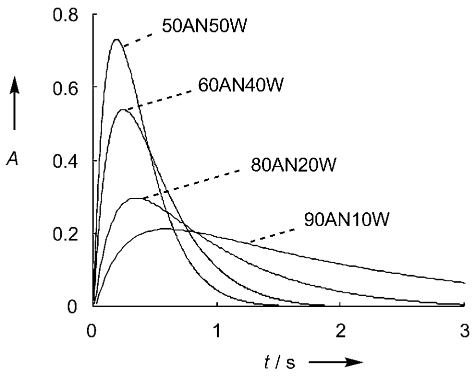


Figure 3. Time-dependent absorption of $(\mathrm{MeO})_3\mathrm{Tr}^+$ during the solvolyses of $(\mathrm{MeO})_3\mathrm{Tr{-}OAc}$ ($c_0 = 6.66 \times 10^{-5}$ mol L^{-1}) in aqueous acetonitrile (stopped-flow photospectrometry, $\lambda = 484$ nm, 25 °C).

At the maxima of the curves shown if Figure 3, ionization and trapping proceeded with the same rate. Whereas the ionization of $(\mathrm{MeO})_3\mathrm{Tr{-}OAc}$ was accelerated by a factor of eight when going from 90AN10W (90:10 (v/v) acetonitrile/water) to 50AN50W, the trapping rate only increased by a factor of 1.4. This trend leads to a higher, as well as earlier, maximum absorbance in 50AN50W, in which the maximum carbocation concentration (25 % of initial substrate) was reached after 0.22 s. In 90AN10W, the maximum of the carbocation concentration was reached after 0.63 s, and corresponded to 7.2 % of the initial substrate.

Table 2. Rate constants for the solvolyses of $(\mathrm{MeO})_3\mathrm{Tr{-}OAc}$ in aqueous acetonitrile at 25 °C; determined by conductimetry and photometric monitoring of the intermediate carbocation.

solvent[a]	From conductivity in the presence of piperidine k_{ion} [s^{-1}]	From Gepasi-Fit of the absorbance of $(\mathrm{MeO})_3\mathrm{Tr}^+$ k_{ion} [s^{-1}]	k_{w} [s^{-1}]
90AN10W	6.80×10^{-1}	5.15×10^{-1}	5.01
80AN20W	1.58	1.13	7.13
60AN40W	3.86	2.50	7.12
50AN50W	5.56	4.09	7.22

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, etc.

Table 3. Rate constants for the solvolyses of $(\mathrm{MeO})_3\mathrm{Tr{-}OBz}$ in aqueous acetonitrile at 25 °C; determined by conductimetry and photometric monitoring of the intermediate carbocation.

Solvent[a]	From conductivity in the presence of piperidine k_{ion} [s^{-1}]	From Gepasi-Fit of the absorbance of $(\mathrm{MeO})_3\mathrm{Tr}^+$ k_{ion} [s^{-1}]	k_{w} [s^{-1}]
90AN10W	3.79	2.34	5.08
80AN20W	6.45	3.94	6.99
60AN40W	1.12×10^{1}	6.18	7.46
50AN50W	1.38×10^{1}	9.01	8.01

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, etc.

When the solvolyses of $(MeO)_3Tr{-}OAc$ and $(MeO)_3Tr{-}OBz$ were carried out in the presence of piperidine, the intermediate carbocations were trapped immediately by the amine;[21] a transient absorption was not detectable. From the mono-exponential increase of conductivity, the first-order rate constants listed in the second columns of Tables 2 and 3 were obtained. The independence of k_{obs} of the concentration of piperidine (Table 4) proved the ionization step to be rate-determining. Tables 2 and 3 show that the conductimetrically determined ionization rate constants in the presence of piperidine are generally 1.3 to 1.8 times bigger than those derived from the absorbance of the intermediate carbocations.

Table 4. Ionization rate constants of $(MeO)_3Tr{-}OAc$ ($c_0 = 8.33 \times 10^{-4}$ mol L^{-1}) in the presence of variable amounts of piperidine (stopped-flow conductimetry, 90:10 (v/v) acetonitrile/water, 25 °C).

piperidine [mol L^{-1}]	k_{obs} [s^{-1}]
5.18×10^{-3}	6.74×10^{-1}
1.04×10^{-2}	6.79×10^{-1}
1.55×10^{-2}	6.65×10^{-1}
2.07×10^{-2}	6.80×10^{-1}

Scenario C, $k_{ion} \gg k_w$: The esters of $(Me_2N)Tr$ ionized very rapidly compared to the reaction of the carbenium ion with water, as shown in Figure 4. Both the increase and decrease of the absorbance were separated by a relatively large time gap, which allowed us to evaluate ionization rate constants by fitting the first parts of the curves according to the mono-exponential function $A_t = A_0(1-e^{-kt})+C$. However, conversion to the alcohol only went to completion when an excess of carboxylate was used to quench the generated protons, and thus suppress the reionization of the triarylcarbinol. Table 5 shows that an excess of AcO^- did not affect the ionization rates.

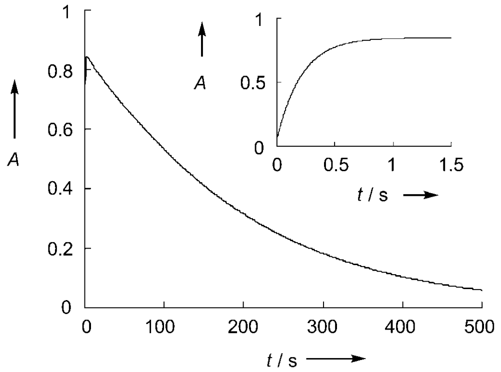


Figure 4. Solvolysis of $(Me_2N)Tr{-}OAc$ ($c_0 = 2.79 \times 10^{-5}$ mol L^{-1}) in 60:40 (v/v) acetonitrile/water, stopped-flow photospectrometry, $\lambda = 461$ nm, 25 °C; $[(nBu)_4N^+OAc^-] = 3.18 \times 10^{-4}$ mol L^{-1}. The insert magnifies the first stage of the reaction.

Scenario D, k_{ion} fast and k_w not detectable: As illustrated in Figure 5, the ionizations of $(Me_2N)(MeO)Tr{-}OAc$ in aqueous acetonitrile of different compositions gave solutions of the tritylium ion according to the rate law $A_t = A_0\,(1-e^{-kt})+C$. While the resulting solutions of the carbocations are fairly stable in the absence of base, a slow reaction with water takes place in the presence of carboxylate ions, converting this system into a scenario C case.

Table 5. Ionization rates of $(Me_2N)Tr{-}OAc$ ($c_0 = 6.00 \times 10^{-5}$ mol L^{-1}) in aqueous acetonitrile in the presence of variable amounts of $(nBu)_4N^+AcO^-$ (stopped-flow photospectrometry, $\lambda = 461$ nm, 25 °C).

$(nBu)_4N^+AcO^-$ [mol L^{-1}]	k_{ion} [s^{-1}] 50AN50W[a]	k_{ion} [s^{-1}] 90AN10W[a]
1.32×10^{-4}	7.40	1.08
3.21×10^{-4}	7.41	1.07
1.87×10^{-3}	7.29	1.02
3.73×10^{-3}	7.34	1.04
6.78×10^{-3}	7.32	1.03
1.01×10^{-2}	7.22	1.05
1.35×10^{-2}	7.22	1.04

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, 50AN50W = 50:50 (v/v) acetonitrile/water.

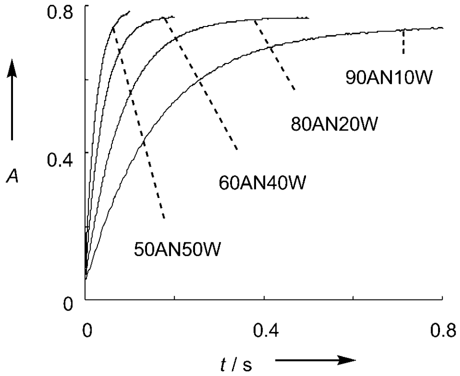


Figure 5. Time-dependent absorbance A for the ionization of $(Me_2N)(MeO)Tr{-}OAc$ ($c_0 = 5.03 \times 10^{-5}$ mol L^{-1}) in aqueous acetonitrile solutions (stopped-flow photospectrometry, $\lambda = 506$ nm, 25 °C).

For the synthesis of $(Me_2N)_2Tr{-}OAc$, an ester of malachite green, a large excess of $(nBu)_4N^+AcO^-$ was needed. Its ionization proceeded so rapidly, however, that the kinetics of these reactions could only be followed by a stopped-flow device in solvents of low ionizing power, that is, in 90AN10W and 80AN20W, but not in 60AN40W. Due to the pK_{R+} value of 6.94, the subsequent reaction with water would have needed strongly basic conditions, and could not be observed even in the presence of high carboxylate concentrations.

Salt effects: When the trityl esters used for the kinetic studies were generated by combining tritylium tetrafluoroborates with tetra-*n*-butylammonium carboxylates, $(nBu)_4N^+BF_4^-$ was produced as a byproduct. In order to examine the influence of this additional salt on the ionization rates,[19,22] a series of experiments with variable concentration of $(nBu)_4N^+BF_4^-$ was performed. Table 6 shows that even large amounts of this salt did not affect the rates of ionization. We therefore conclude that tetraalkylammonium salts do not exert a positive salt effect. This finding is in line with Hojo's investigations of the solvolyses of adamantyl halides in 50:50 (v/v) sulfolane/water, showing that small concentrations of tetraalkylammonium salts hardly affected the ionization rates, while larger concentrations (up to 1 mol L^{-1}) caused slight retardations of the solvolyses.[23]

Table 6. Ionization rate constants of $(Me_2N)(MeO)Tr{-}OAc$ ($c_0 = 5.03 \times 10^{-5}$ mol L^{-1}) in the presence of variable amounts of $(nBu)_4N^+BF_4^-$ (photospectrometry, $\lambda = 506$ nm, 90:10 (v/v) acetonitrile/water, 25 °C).

$(nBu)_4N^+BF_4^-$ [mol L^{-1}]	k_{ion} [s^{-1}]
0	6.23
6.07×10^{-4}	6.37
1.75×10^{-3}	6.13
3.17×10^{-3}	6.27
4.53×10^{-3}	6.19

Summary of rate constants: Although a variety of differently substituted trityl acetates (Table 7) and benzoates (Table 8) have been investigated in aqueous acetonitrile, triphenylmethyl *p*-nitrobenzoate is the only ester of *p*-nitrobenzoic acid that we have studied kinetically (Table 9).

Figure 6 illustrates the consistency of the different series of rate constants, and shows that the ionization rates of differently substituted trityl acetates in 50AN50W and 90AN10W correlate linearly with the ionization rates of the corresponding trityl benzoates. The converging correlation lines indicate that the difference in rates between the two solvents decreases when better stabilized carbocations are employed (Hammond effect). Solvolytic studies in aqueous acetone were only performed with esters of the unsubstituted triphenylmethanol (Table 10).

Table 9. Ionization rate constants of trityl *para*-nitrobenzoate in aqueous acetonitrile (25 °C).

Solvent[a]	k_{ion} [s^{-1}]
90AN10W	1.57×10^{-3}
80AN20W	4.19×10^{-3}
60AN40W	9.68×10^{-3}
50AN50W	1.82×10^{-2}

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, etc.

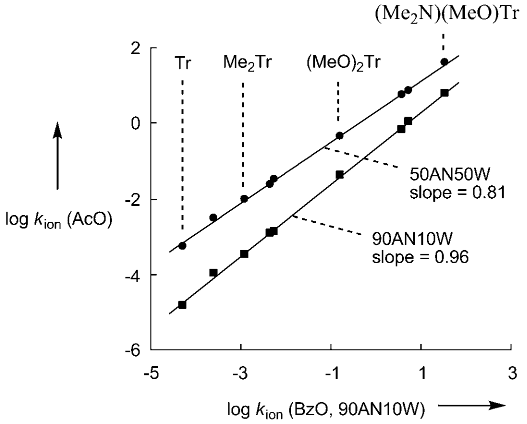


Figure 6. Correlation of ionization rates of trityl acetates in different solvents with those of trityl benzoates in 90:10 (v/v) acetonitrile/water, 25 °C.

Table 7. Ionization rate constants of trityl acetates in aqueous acetonitrile[a] (25 °C).

	k_{ion} [s^{-1}]				Scenario
	90AN10W	80AN20W	60AN40W	50AN50W	
Tr	1.47×10^{-5}	5.88×10^{-5}	2.70×10^{-4}	5.57×10^{-4}	A
MeTr	1.03×10^{-4}	3.59×10^{-4}	1.46×10^{-3}	3.01×10^{-3}	A
Me_2Tr	3.23×10^{-4}	1.21×10^{-3}	5.62×10^{-3}	9.59×10^{-3}	A
Me_3Tr	1.30×10^{-3}	4.98×10^{-3}	1.77×10^{-2}	3.33×10^{-2}	A
(MeO)Tr	1.20×10^{-3}	4.53×10^{-3}	1.50×10^{-2}	2.40×10^{-2}	A
$(MeO)_2Tr$	4.04×10^{-2}	1.15×10^{-1}	3.06×10^{-1}	4.41×10^{-1}	A
$(MeO)_3Tr$	6.80×10^{-1}	1.58	3.86	5.56	B
$(Me_2N)Tr$	1.08	2.00	4.51	7.40	C
$(Me_2N)(MeO)Tr$	6.23	1.22×10^{1}	2.49×10^{1}	3.93×10^{1}	D
$(Me_2N)_2Tr$	1.28×10^{2}	2.15×10^{2}[b]	–[c]	–[c]	D

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, etc. [b] Reaction was very fast, approximate value. [c] Reaction was too fast to be measured.

Table 8. Ionization rate constants of trityl benzoates in aqueous acetonitrile[a] (25 °C).

	k_{ion} [s^{-1}]				Scenario
	90AN10W	80AN20W	60AN40W	50AN50W	
Tr	5.34×10^{-5}	1.67×10^{-4}	5.14×10^{-4}	9.99×10^{-4}	A
MeTr	2.56×10^{-4}	8.08×10^{-4}	2.78×10^{-3}	5.01×10^{-3}	A
Me_2Tr	1.26×10^{-3}	3.55×10^{-3}	1.05×10^{-2}	1.71×10^{-2}	A
Me_3Tr	5.43×10^{-3}	1.51×10^{-2}	4.55×10^{-2}	6.97×10^{-2}	A
(MeO)Tr	4.45×10^{-3}	1.30×10^{-2}	3.86×10^{-2}	5.56×10^{-2}	A
$(MeO)_2Tr$	1.61×10^{-1}	3.34×10^{-1}	6.67×10^{-1}	9.30×10^{-1}	A
$(MeO)_3Tr$	3.79	6.45	1.12×10^{1}	1.38×10^{1}	B
$(Me_2N)Tr$	5.37	8.35	1.40×10^{1}	2.04×10^{1}	C
$(Me_2N)(MeO)Tr$	3.36×10^{1}	4.70×10^{1}	6.95×10^{1}	1.02×10^{2}	D

[a] 90AN10W = 90:10 (v/v) acetonitrile/water, etc.

Discussion

As expected,[25] trityl benzoates always ionized faster than the corresponding acetates (cf. Tables 7, 8, and 10). The high polarity of water caused an increase of ionization rates with increasing amounts of water in all solvent mixtures. Whereas Tr–OAc, Tr–OBz, and Tr–PNB solvolyzed more slowly in aqueous acetone than in aqueous

Table 10. Ionization rate constants of several trityl esters in aqueous acetone[a] (25 °C).

	k_{ion} [s^{-1}]			
	90A10W	80A20W	60A40W	50A50W
Tr−OAc	–	$1.38\times10^{-5[c]}$	1.99×10^{-4}	6.40×10^{-4}
Tr−OBz	9.31×10^{-6}	$3.50\times10^{-5[d]}$	2.87×10^{-4}	6.95×10^{-4}
Tr−PNB[b]	3.63×10^{-4}	1.49×10^{-3}	1.08×10^{-2}	3.25×10^{-2}

[a] 90A10W = 90:10 (v/v) acetone/water, etc. [b] PNB = *p*-nitrobenzoate. [c] A rate constant of 1.45×10^{-5} s^{-1} has been reported in ref. [9]. [d] A rate constant of 3.33×10^{-5} s^{-1} has been reported in ref. [24].

acetonitrile when the water portion was low (10 vol % water), the opposite reactivity order was found in solvents with a high fraction of water (50 vol %). In line with the larger dependence of Winstein–Grunwald's ionizing power *Y* (see later) on the percentage of water in aqueous acetone than in aqueous acetonitrile, the ionization rates of the trityl esters depend more strongly on the composition of acetone/water than of acetonitrile/water mixtures.

Hammett analysis: The Hammett–Brown parameters σ_p^+ were designed for reactions with a positively-charged center developing at a position which is in conjugation with the substituents under consideration.[26] Figure 7 shows that the three symmetrical systems Tr, Me$_3$Tr, and (MeO)$_3$Tr, correlate perfectly linearly with $\Sigma\sigma_p^+$, and deviations from the correlation line are most significant for systems which are unsymmetrically substituted with strong electron-donating groups. The small value of the reaction constant ($\rho = -1.99$) is due to the propeller-like arrangement of the phenyl rings, which inhibits full conjugation of the carbocationic center with all three aryl rings. Most significantly, tritylium ions containing one or two dimethylamino groups deviate positively from the correlation line. The problem of the additivities of σ^+ parameters in di- and triarylcarbenium ions has been discussed in detail previously.[27,28]

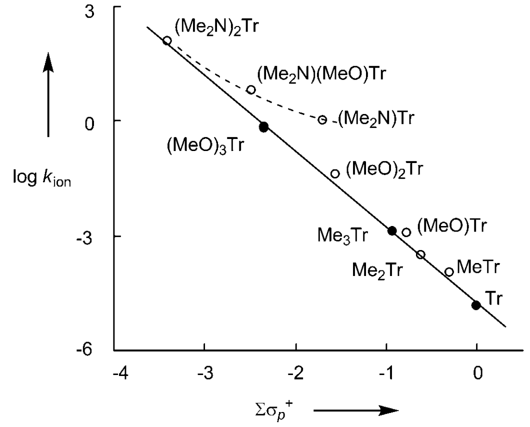


Figure 7. Plot of log k_{ion} versus $\Sigma\sigma_p^+$ for ionizations of substituted trityl acetates in 90:10 (v/v) acetonitrile/water, 25 °C; the line is drawn through filled circles, log $k_{ion} = -1.99\ \Sigma\sigma_p^+ - 4.80$, $R^2 = 0.9995$; $\sigma_p^+ = 0$ (H), −0.31 (*p*-Me), −0.78 (*p*-OMe), and −1.70 (*p*-NMe$_2$) from reference [29].

Winstein–Grunwald analysis: The ionizing power *Y* of a solvent was introduced by Winstein and Grunwald.[30] In Equation (1) the parameter *m* is a measure of the sensitivity of the rate of solvolysis to a change of the solvent; it has often been used as a criterion for the determination of the mechanism of a solvolysis reaction. Values below 0.5 were considered as evidence for S$_N$2 reactions, whereas values close to 1 are usually found for typical S$_N$1 reactions.[31]

$$\log k_{ion} = \log k_0 + mY \tag{1}$$

In Figures 8 and 9, ionization rate constants of trityl acetates and benzoates are plotted against the ionizing powers *Y* of aqueous acetonitrile.[32] The slopes of the linear correlations represent the *m* parameters as defined by Equation (1). It can easily be seen that *m* decreases with increasing solvolysis rates, that is, with increasing stabilization of the carbocation. This trend may be explained by a Hammond shift[33] towards the reactants as the exothermicity of the reactions is increased. The remarkably small *m* parameters, particularly in the case of donor-substituted systems, indicate non-carbocation-like transition states, which is supported by the full free-energy diagrams in Figure 11 of the subsequent paper in this issue.[39] A similar behavior has recently been found for the ionizations of benzhydryl carboxylates.[25] The fact that the ionization rates of trityl benzoates

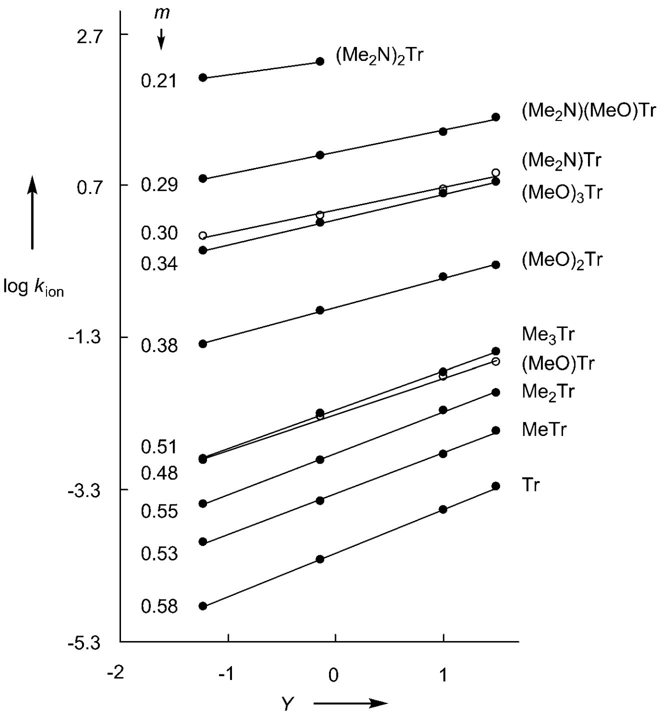


Figure 8. Plot of log k_{ion} of trityl acetates versus ionizing powers *Y* of aqueous acetonitrile, 25 °C; $Y = -1.23$ (90AN10W), −0.14 (80AN20W), 1.00 (60AN40W) and 1.50 (50AN50W) from ref. [32].

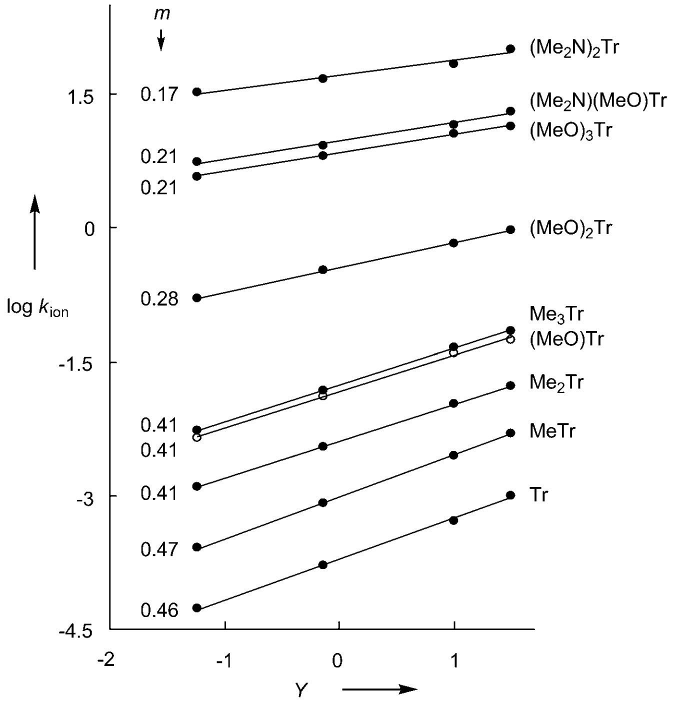


Figure 9. Plot of $\log k_{\text{ion}}$ of trityl benzoates versus ionizing powers Y of aqueous acetonitrile, 25 °C.

are generally less sensitive to solvent polarity than those of trityl acetates may also be attributed to earlier transition states of the benzoate hydrolyses.

Figure 10 shows that the m value of triphenylmethyl p-nitrobenzoate is considerably smaller than that of the corresponding benzoate, which seems to exclude the rationalization of the different m parameters by steric arguments, but supports an explanation by electronic effects. However, because trityl p-nitrobenzoates and benzoates have similar m values in aqueous acetone, much smaller than trityl acetates (Figure 11), an unambiguous rationalization for the absolute magnitude of the m values appears not to be possible.

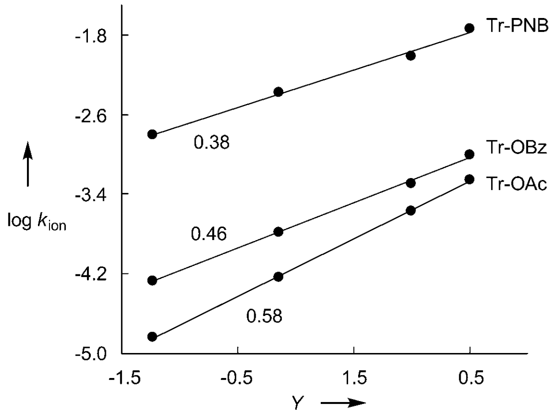


Figure 10. Plot of $\log k_{\text{ion}}$ of trityl esters versus ionizing powers Y of aqueous acetonitrile, 25 °C.

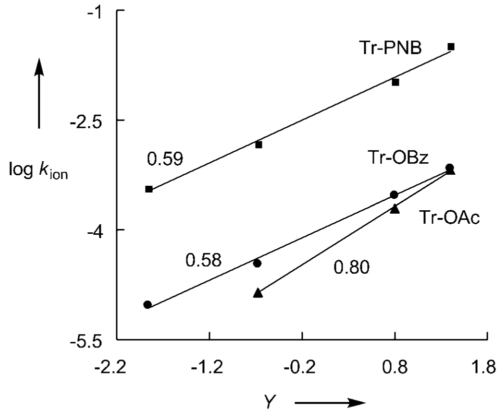


Figure 11. Plot of $\log k_{\text{ion}}$ of trityl esters versus Y of aqueous acetone, 25 °C; $Y = -1.856$ (90A10W), -0.673 (80A20W), 0.796 (60A40W), and 1.398 (50A50W) from reference [34].

Rate-equilibrium relationships: Intuitively, one would expect a good correlation between the ionization rates of trityl esters and the stabilities of the corresponding tritylium ions in aqueous solution, pK_{R^+}. Such a correlation has been reported for solvolyses of benzhydryl chlorides by Deno.[35]

As can be seen in Figure 12, there are two separate correlation lines between $\log k_{\text{ion}}$ and pK_{R^+}, one for the methyl- and methoxy-substituted compounds, and one for the dimethylamino-substituted systems. From the slope of the correlation for the methyl- and methoxy-substituted compounds (0.62) one might infer that more than half of the carbocation character is developed in the solvolysis transition states. Consideration of the full data set shows, however, that this conclusion is too simplistic. Although $(MeO)_3Tr^+$ and $(Me_2N)Tr^+$ differ by a factor of 1.1×10^3 in their thermodynamic stabilities in water (from pK_{R^+}), the ionization rates of the corresponding carboxylates are almost identical. The unexpected low reactivities of the dimethylamino-substituted trityl derivatives indicate that the product-stabilizing resonance of the amino group develops late on the reaction coordinate, and contributes only slightly to the stabilization of

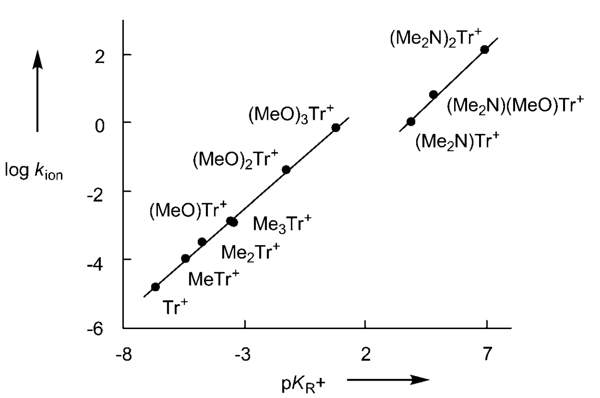


Figure 12. Plot of $\log k_{\text{ion}}$ for trityl acetates in 90:10 (v/v) acetonitrile/water, 25 °C, versus pK_{R^+}.

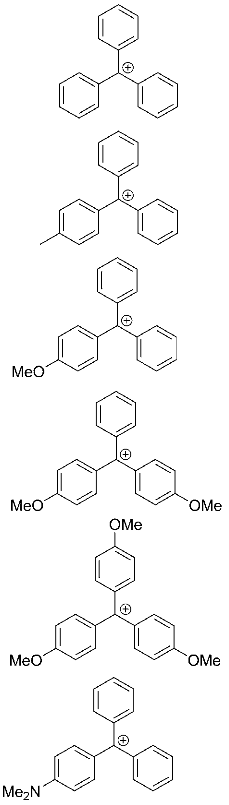
the transition state. This is another example of Bernasconi's "Principle of Non-Perfect Synchronization",[36] and emphasizes the role of intrinsic barriers for these reactions.

Conclusion

Hydrolyses of donor-substituted tritylium carboxylates in aqueous acetonitrile and acetone cover a wide mechanistic spectrum: from conventional S_N1 reactions with slow ionization and rapid trapping of the intermediate carbocations by water, through reactions in which the carbocations can be observed by the appearance and disappearance of color (carbocation watching),[37] to reactions where the carbocations are formed as persistent species. From the small Winstein *m* values one can derive non-carbocation-like transition states despite the fact that we are dealing with well-defined ionization processes.

Most important for the use of tritylium ions as tailor-made protecting groups in organic syntheses is the finding that the well-known thermodynamic stability parameters pK_{R+} cannot be used to predict kinetic stability and the ease of deprotection of strongly donor-substituted derivatives. While the relative hydrolysis rates of methyl- and methoxy-substituted tritylium esters correlate well with pK_{R+}, the expected further acceleration from the trimethoxy- to the dimethylamino-substituted system is not observed. The *p*-(dimethylamino)trityl protecting group is released at almost the same rate as the tri-*p*-methoxytrityl group, although the latter tritylium ion is less stabilized by a factor of 1.1×10^3 in aqueous solution. According to Scheme 2, a correlation exists between the reaction times τ_{99} for 99% ionization of trityl acetates and the semiquantitative reaction times reported for complete detritylations of 5′-*O*-trityluridines (τ_{uridine}).[6a]

Because Tables 7 and 8 provide a quantitative comparison of the ionization rates of all *p*-methyl- and methoxy-substituted trityl systems, it is now possible to fine-tune the stabilities of trityl-protected OH and NH functionalities. We are currently extending our investigations on the nucleofugalities of various O-, N-, and S-centered leaving groups,[38] which will be combined with the data of the present investigation in order to provide absolute lifetimes for differently substituted trityl ethers, esters, and amides in solvents of different ionizing powers. A quantitative basis for the use of tritylium ions as protecting groups in bioorganic chemistry is thus emerging.



pK_{R+}	k_{rel}[a]	τ_{99}[b]	τ_{uridine}[c]
-6.63	1.0	2.3 h	48 h
-5.41	5.4	25 min	-
-3.40	43	3.2 min	2 h
-1.24	7.9×10^2	10 s	15 min
0.82	1.0×10^4	0.8 s	1 min
3.88	1.3×10^4	0.6 s	-

Scheme 2. Detritylation times for acetates and uridines. [a] Relative rate constants for the ionizations of acetates in 50:50 (v/v) acetonitrile/water, 25 °C. [b] Time for 99% ionization of trityl acetate in 50:50 (v/v) acetonitrile/water at 25 °C. [c] Time for "complete" hydrolysis of 5′-protected uridine derivatives in 80% AcOH at RT, from reference [6a].

Experimental Section

Chemicals: Acetonitrile (VWR, ≥99.9%), acetone (VWR, ≥99.8%), tetra-*n*-butylammonium acetate (Fluka, ≥99%) and tetra-*n*-butylammonium benzoate (Fluka, ≥99%) were used as purchased. Water was purified by using a Millipore MilliQ (final specific resistance ≥18.2 MΩ cm). Trityl alcohols and tritylium tetrafluoroborates, as well as trityl acetate, benzoate, and *p*-nitrobenzoate, were synthesized according to standard procedures (see Supporting Information). All synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy and melting points.

Kinetics: Typically, each run was repeated at least once, the reported rate being the arithmetic mean. The error was usually less than 3%. The temperature in all runs was kept constant at 25 °C using a circulating water bath. For conductimetry, reactions with half-times >10 s were followed by conventional conductimetry using a Tacussel CD810 or a Radiometer MeterLab CDM230, both instruments being equipped with Pt electrodes. Reactions with half-times <10 s were followed by a Hi-Tech Scientific SF-61 DX2 stopped-flow device (cell volume 21 μL, Pt electrodes), controlled by the Hi-Tech KinetAsyst3 software. Initial concentrations of substrates were between 10^{-4} and 10^{-3} mol L^{-1}, and 5 to 15 equivalents of triethylamine were used as additive. In the case of tri(*p*-methoxy)trityl ester solvolyses, 16 to 18 equivalents of piperidine were added. For photospectrometry, an Applied Photophysics SX.18MV-R stopped-flow reactor was used. Initial concentrations of substrates were between 10^{-5} to 10^{-4} mol L^{-1}.

Acknowledgements

We thank Dr. Armin Ofial for help during the preparation of this manuscript. Financial support by the Deutsche Forschungsgemeinschaft (Ma 673/20-3) and the Fonds der Chemischen Industrie is gratefully acknowledged.

[1] Historic reviews: a) G. A. Olah in *Carbocation Chemistry* (Eds.: G. A. Olah, G. K. S. Prakash), Wiley-Interscience, Hoboken, **2004**, pp. 7–41; b) C. N. Nenitzescu in *Carbonium Ions, Vol. 1* (Eds.: G. A. Olah, P. von R. Schleyer), Wiley-Interscience, New York, **1973**, Chapter 1; c) H. H. Freedman in *Carbonium Ions, Vol. 4* (Eds.: G. A. Olah, P. von R. Schleyer), Wiley-Interscience, New York, **1973**, Chapter 28.

[2] a) H. Volz, *Angew. Chem.* **1963**, *75*, 921; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 622; b) H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon, D. L. Pearson, *J. Am. Chem. Soc.* **1957**, *79*, 4557–4558; c) D. Mandon, L. Toupet, D. Astruc, *J. Am. Chem. Soc.* **1986**, *108*, 1320–1322; d) C. I. F. Watt, *Adv. Phys. Org. Chem.* **1988**, *24*, 57–112; e) T.-Y. Cheng, R. M. Bullock, *Organometallics* **1995**, *14*, 4031–4033; f) J. Chojnowski, L. Wilczek, W. Fortuniak, *J. Organomet. Chem.* **1977**, *135*, 13–22; g) J. Chojnowski, W. Fortuniak, W. Stańczyk, *J. Am. Chem. Soc.* **1987**, *109*, 7776–7781; h) C. A. Mullen, M. R. Gagné, *J. Am. Chem. Soc.* **2007**, *129*, 11880–11881.

[3] a) J. P. Kennedy, E. Maréchal *Carbocationic Polymerization*, Wiley, New York, **1982**, p. 94; b) C. Schade, H. Mayr, *Makromol. Chem. Rapid Comm.* **1988**, *9*, 477–482; c) T. Mukaiyama, H. Iwakari, *Chem. Lett.* **1985**, 1363–1366.

[4] a) A. V. Ustinov, V. V. Shmanai, K. Patel, I. A. Stepanova, I. A. Prokhorenko, I. V. Astakhova, A. D. Malakhov, M. V. Skorobogatyi, P. L. Bernad, Jr., S. Khan, M. Shahgholi, E. M. Southern, V. A. Korshun, M. S. Shchepinov, *Org. Biomol. Chem.* **2008**, *6*, 4593–4608; b) M. S. Shchepinov, R. Chalk, E. M. Southern, *Tetrahedron* **2000**, *56*, 2713–2724.

[5] P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley-Interscience, Hoboken, **2007**.

[6] a) M. Smith, D. H. Rammler, I. H. Goldberg, H. G. Khorana, *J. Am. Chem. Soc.* **1962**, *84*, 430–440; b) H. Schaller, G. Weimann, B. Lerch, H. G. Khorana, *J. Am. Chem. Soc.* **1963**, *85*, 3821–3827; c) C. Bleasdale, S. B. Ellwood, B. T. Golding, *J. Chem. Soc. Perkin Trans. 1* **1990**, 803–805; d) M. Sekine, T. Mori, T. Wada, *Tetrahedron Lett.* **1993**, *34*, 8289–8292; e) M. Sekine, T. Hata, *J. Org. Chem.* **1987**, *52*, 946–948; f) A. P. Henderson, J. Riseborough, C. Bleasdale, W. Clegg, M. R. J. Elsegood, B. T. Golding, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3407–3414.

[7] a) M. C. López, I. Demirtas, H. Maskill, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1748–1752; b) M. C. López, I. Demirtas, H. Maskill, M. Mishima, *J. Phys. Org. Chem.* **2008**, *21*, 614–621; c) M. C. López, W. Clegg, I. Demirtas, M. R. J. Elsegood, J. Haider, H. Maskill, P. C. Miatt, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1742–1747; d) M. C. López, W. Clegg, I. Demirtas, M. R. J. Elsegood, H. Maskill, *J. Chem. Soc. Perkin Trans. 2* **2000**, 85–92.

[8] B. Löhr, S. Orlich, H. Kunz, *Synlett* **1999**, 1136–1138.

[9] C. G. Swain, T. E. C. Knee, A. MacLachlan, *J. Am. Chem. Soc.* **1960**, *82*, 6101–6104.

[10] C. A. Bunton, A. Konasiewicz, *J. Chem. Soc.* **1955**, 1354–1359.

[11] G. S. Hammond, J. T. Rudesill, *J. Am. Chem. Soc.* **1950**, *72*, 2769–2770.

[12] S. G. Smith, *Tetrahedron Lett.* **1970**, *11*, 4547–4549.

[13] C. G. Swain, G. Tsuchihashi, *J. Am. Chem. Soc.* **1962**, *84*, 2021–2022.

[14] S. Winstein, B. R. Appel, *J. Am. Chem. Soc.* **1964**, *86*, 2720–2721.

[15] E. Gelles, E. D. Hughes, C. K. Ingold, *J. Chem. Soc.* **1954**, 2918–2929.

[16] R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait, S. Steenken, *J. Am. Chem. Soc.* **1989**, *111*, 3966–3972.

[17] R. A. Diffenbach, K. Sano, R. W. Taft, *J. Am. Chem. Soc.* **1966**, *88*, 4747–4749.

[18] C. D. Ritchie, *Can. J. Chem.* **1986**, *64*, 2239–2249.

[19] For common ion rate depression, see: S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, G. C. Robinson, *J. Am. Chem. Soc.* **1956**, *78*, 328–335.

[20] a) P. Mendes, *Comput. Appl. Biosci.* **1993**, *9*, 563–571; b) P. Mendes, *Trends Biochem. Sci.* **1997**, *22*, 361–363; c) P. Mendes, D. Kell, *Bioinformatics* **1998**, *14*, 869–883; further information about GEPASI: http://www.gepasi.org.

[21] N. Streidl, A. Antipova, H. Mayr, *J. Org. Chem.* **2009**, *74*, 7328–7334.

[22] For salt effects see: L. C. Manege, T. Ueda, M. Hojo, M. Fujio, *J. Chem. Soc. Perkin Trans. 2* **1998**, 1961–1965.

[23] M. Hojo, T. Ueda, E. Ueno, T. Hamasaki, D. Fujimura, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 751–760.

[24] K.-T. Liu, M.-Y. Kuo, Y. Wang, *J. Phys. Org. Chem.* **1988**, *1*, 241–245.

[25] H. F. Schaller, A. A. Tishkov, X. Feng, H. Mayr, *J. Am. Chem. Soc.* **2008**, *130*, 3012–3022.

[26] Y. Okamoto, H. C. Brown, *J. Org. Chem.* **1957**, *22*, 485–494.

[27] a) M. K. Uddin, M. Fujio, H.-J. Kim, Z. Rappoport, Y. Tsuno, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1371–1379; b) Y. Tsuno, M. Fujio, *Adv. Phys. Org. Chem.* **1999**, *32*, 267–385.

[28] a) S. I. Miller, *J. Am. Chem. Soc.* **1959**, *81*, 101–106; b) M. O'Brien, R. A. More O'Ferrall, *J. Chem. Soc. Perkin Trans. 2* **1978**, 1045–1053.

[29] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[30] E. Grunwald, S. Winstein, *J. Am. Chem. Soc.* **1948**, *70*, 846–854.

[31] T. W. Bentley, G. Llewellyn, *Prog. Phys. Org. Chem.* **1990**, *17*, 121–158.

[32] T. W. Bentley, J. P. Dau-Schmidt, G. Llewellyn, H. Mayr, *J. Org. Chem.* **1992**, *57*, 2387–2392.

[33] G. S. Hammond, *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

[34] A. H. Fainberg, S. Winstein, *J. Am. Chem. Soc.* **1956**, *78*, 2770–2777.

[35] N. C. Deno, A. Schriesheim, *J. Am. Chem. Soc.* **1955**, *77*, 3051–3054.

[36] a) C. F. Bernasconi, *Acc. Chem. Res.* **1987**, *20*, 301–308; b) C. F. Bernasconi, *Acc. Chem. Res.* **1992**, *25*, 9–16.

[37] H. F. Schaller, H. Mayr, *Angew. Chem.* **2008**, *120*, 4022–4025; *Angew. Chem. Int. Ed.* **2008**, *47*, 3958–3961.

[38] See Figure 4 in: B. Denegri, A. R. Ofial, S. Jurić, A. Streiter, O. Kronja, H. Mayr, *Chem. Eur. J.* **2006**, *12*, 1657–1666.

[39] Succeding paper in this issue: M. Horn, H. Mayr, *Chem. Eur. J.* **2010**, *16*, DOI: 10.1002/chem.200902670</.

Received: September 28, 2009
Revised: February 24, 2010