PERKIN 2

Competing base-promoted E2 and E1 reactions of an acidic tertiary substrate†

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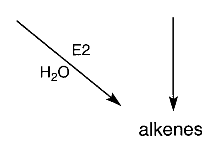
Received (in Cambridge, UK) 21st January 2002, Accepted 18th April 2002
First published as an Advance Article on the web 29th May 2002

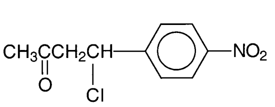
The solvolysis of 4-chloro-4-(4′-nitrophenyl)pentan-2-one (**1-Cl**) in aqueous acetonitrile yields the alcohol 4-hydroxy-4-(4′-nitrophenyl)pentan-2-one (**1-OH**) and the elimination products 4-(4′-nitrophenyl)-2-oxopent-4-ene (**2**), (*E*)-4-(4′-nitrophenyl)-2-oxopent-3-ene (**3**), and (*Z*)-4-(4′-nitrophenyl)-2-oxopent-3-ene (**4**). Addition of thiocyanate ion does not increase the total reaction rate in 25 vol% acetonitrile in water, but gives rise to the substitution products **1-SCN** and **1-NCS**, at the expense of **1-OH**, and a small increase in the fraction of alkene **3**. Addition of acetate ion and other weak bases gives rise to base-promoted E2 (or E1cB) to give alkene **3** (and **4**). The Brønsted parameter for this reaction was measured as $\beta = 0.76$. Water-promoted E2 (or E1cB) reaction was not observed.

Introduction

It has been shown in some recent reports on solvolysis reactions that solvent-promoted elimination can be the predominant pathway to alkenes for acidic substrates which undergo slow ionization to carbocation intermediates (Scheme 1).[1–7] For example, the solvolysis of the secondary substrate 4-chloro-4-(4′-nitrophenyl)butan-2-one (**5**) in aqueous solvent provides alkene by a water-promoted E2 or E1cB reaction in competition with ion-pair formation giving alcohol and alkene.[7] The reasons for the predominant solvent-promoted elimination reaction are the acidic β-hydrogen (activation by the carbonyl group) and the relatively slow ionization of the secondary substrate.



Scheme 1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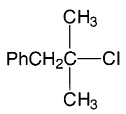
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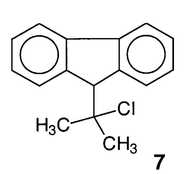
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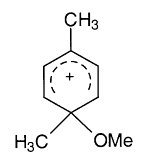
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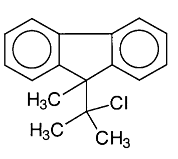
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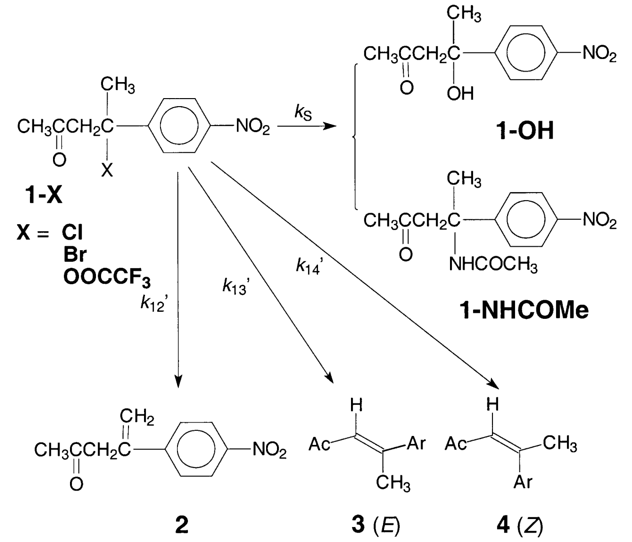
We have now extended the studies of solvent-promoted elimination to tertiary substrates by introducing a methyl group on the α-carbon (**1-Cl**, Scheme 2). This makes the carbocation route more competitive owing to faster ionization, and to somewhat slower E2 or E1cB reaction.[8] The mechanistic details of the elimination and substitution reactions are discussed.



Scheme 2

Results

The alcohol 4-hydroxy-4-(4′-nitrophenyl)pentan-2-one (**1-OH**) was synthesized in low yield (20%) by condensation of 4-nitroacetophenone with acetone. This alcohol was used as a precursor for the other compounds.

The solvolysis of 4-chloro-4-(4′-nitrophenyl)pentan-2-one (**1-Cl**) or 4-bromo-4-(4′-nitrophenyl)pentan-2-one (**1-Br**) in aqueous acetonitrile yields the alcohol **1-OH** and the elimination products 4-(4′-nitrophenyl)-2-oxopent-4-ene (**2**), (*E*)-4-(4′-nitrophenyl)-2-oxopent-3-ene (**3**), along with traces of (*Z*)-4-(4′-nitrophenyl)-2-oxopent-3-ene (**4**). Reaction with the acetonitrile component of the solvent gives rise to a small amount of the substitution product **1-NHCOMe** (Scheme 2). The reaction of **1-Cl** in 50 vol% methanol in water affords the methyl ether 4-methoxy-4-(4′-nitrophenyl)pentan-2-one (**1-OMe**), substitution product ratio [**1-OMe**]/[**1-OH**] = 0.54. The ester 4-(trifluoroacetoxy)-4-(4′-nitrophenyl)pentan-2-one

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† Electronic supplementary information (ESI) available: the effect of base concentration on rate constant and product composition. See http://www.rsc.org/suppdata/p2/b2/b200758d/

DOI: 10.1039/b200758d

Table 1 Rate constants and product compositions for the reactions of **1-Br** and **1-Cl** in aqueous acetonitrile

			mol%				
Temp./°C	MeCN/vol%	10^6k_{obs}[b]/s^{-1}	**1-OH**	**1-NHCOMe**	**2**	**3**	**4**
1-Br[a]							
25	25	720					
40	25	3644					
1-Cl[a]							
25	25	23.7	81.8	0.5	13.2	4.5	Trace
40	15	426	85.8	0.3	10.1	3.8	Trace
40	20	238	83.3	0.4	11.9	4.4	Trace
40	25	146	80.3	0.5	14.3	4.9	Trace
40	30	80.3	78.1	0.6	16.1	5.2	Trace
40	35	46.6	74.9	0.6	18.3	6.2	Trace

[a] Substrate concentration: 0.05–0.10 mM. [b] Estimated maximum error: ±5%.

Table 2 The effects of added salts on the rate constants and product compositions for the reaction of **1-Cl**[a] in 25 vol% acetonitrile in water at 40 °C

		mol%					
Salts	10^6k_{obs}[b]/s^{-1}	**1-OH**	**1-NHCOMe**	**2**	**3**	**4**	**1-Nu**
None	146	80.3	0.5	14.3	4.9	Trace	
0.75 M $NaClO_4$	177	79.6	0.7	14.3	5.4	Trace	
0.75 M NaCl	143	78.1	0.5	15.3	6.1	Trace	
0.75 M NaBr	173	77.3	0.5	15.8	6.4	Trace	
0.75 M NaSCN	168	58.2	0.4	14.6	6.8	Trace	20.0[c]
0.625 M NaSCN 0.125 M $NaClO_4$	172	61.3	0.4	14.5	6.7	Trace	17.1[c]
0.50 M NaSCN 0.25 M $NaClO_4$	178	65.1	0.5	14.2	5.9	Trace	14.3[c]
0.375 M NaSCN 0.375 M $NaClO_4$	176	68.4	0.5	14.2	5.9	Trace	11.0[c]
0.25 M NaSCN 0.50 M $NaClO_4$	173	71.8	0.6	14.3	5.5	Trace	7.8[c]
0.75 M NaSCN[d]	31.3	56.5	0.5	13.5	6.6	Trace	22.9[c]
0.675 M NaOAc[e]	145	51.3	0.3	9.0	26.6	12.1	0.7
0.625 M NaO_2CCH_2OMe[e]	113	69.2	0.5	13.2	12.9	3.0	1.2
0.563 M NaO_2CCH_2CN[e]	118	75.5	0.4	~16.6	7.5	Trace	Trace
0.625 M NaO_2CCF_3	111	77.9	0.5	15.1	5.5	Trace	1.0
0.0179 M $NaOCH(CF_3)_2$[f]	13845	1.2			55.6	43.2	

[a] 0.05–0.10 mM. [b] Estimated maximum error ±5%. [c] The sum of **1-SCN** and **1-NCS**. [d] At 25 °C. [e] Buffered with 10% of the corresponding acid. [f] Buffered with 18% of $(CF_3)_2CHOH$.

(**1-OOCCF$_3$**) reacts quickly to give **1-OH** which is not accompanied by any significant amount of other products, not even in the presence of 0.75 M sodium acetate. Solvolysis of **1-OOCCF$_3$** in 50 vol% methanol in water provides only traces of the methyl ether indicating that the ester reacts predominantly by acyl-oxygen cleavage.

The kinetics of the reactions were studied either by UV spectrophotometry or by a sampling high-performance liquid chromatography procedure. The latter technique was also used for measuring the product compositions of the reactions. The rate constants and product compositions measured for **1-Cl** and **1-Br** at 25 and 40 °C, and with various fractions of acetonitrile in the reaction solution, are recorded in Table 1. The analytical HPLC column did not give a complete baseline separation of the alkenes **2** and **4** and it was therefore difficult to accurately measure traces of alkene **4**. The products were found to be stable under the reaction conditions used for the solvolysis studies. The alcohol **1-OH** decomposes to 4-nitroacetophenone under basic conditions.

The effect of different salts on the rate of disappearance of **1-Cl** was found to be small (Table 2). Addition of the sodium salts of perchlorate ion, thiocyanate ion and bromide ion, respectively, give a rate increase of about 15–20%. Addition of chloride or acetate ions does not have any significant effect on the reaction rate.

Nucleophilic salts give rise to substitution products. The strongly reactive, ambident nucleophile thiocyanate ion yields two products, **1-SCN** and **1-NCS**. There is no bimolecular reaction of **1-Cl** with this powerful nucleophile (Fig. 1). The thiocyanate adducts are formed at the expense of the alcohol

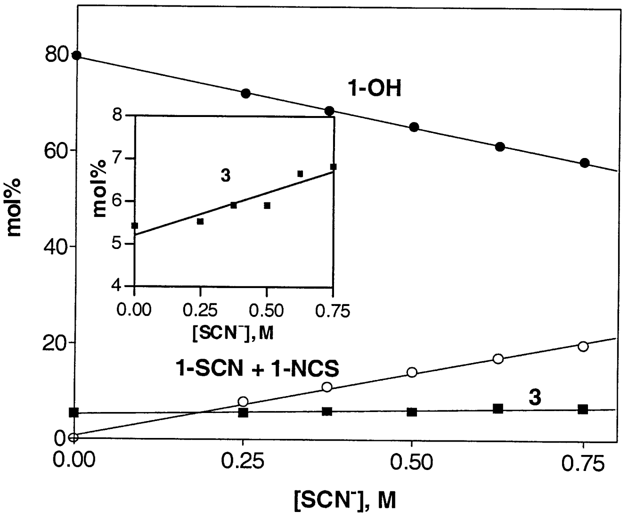


Fig. 1 The effect of added sodium thiocyanate on the product composition for the reaction of **1-Cl** in 25 vol% acetonitrile in water at 40 °C; ionic strength 0.75 M, maintained with sodium perchlorate. Inset: enlargement of the plot for alkene **3**.

1-OH. There is also a slight increase in the fraction of alkene **3** with increasing thiocyanate concentration (Fig. 1). We did not detect any significant change in the yield of **2** or **4**, but this may be due to the bad separation of these two products in the HPLC analysis. In fact, a slight decrease in the yield of **2** may be hidden by a slight increase in **4**. The stabilities of **1-SCN** and **1-NCS** are relatively high. They undergo a very slow decomposition under the reaction conditions. No quantitative results were obtained with azide ion owing to overlapping HPLC peaks and significant decomposition of the azide adduct **1-N$_3$**.

The observed product ratio of **1-Nu** to **1-OH** is a measure of the competition between added nucleophile (Nu$^-$) and water for reaction with the substrate and/or carbocation intermediate(s). The dimensionless second-order rate constant ratio k_{Nu}/k_{HOH} could be used to compare the reactivity of different nucleophiles:

$$k_{Nu}/k_{HOH} = ([\mathbf{1\text{-}Nu}]/[\mathbf{1\text{-}OH}])([H_2O]/[Nu^-]) \qquad (1)$$

Addition of bases

Added bases increase the fraction of the two alkenes **3** and **4** at the expense of **1-OH** and alkene **2**. A trace of the substitution product with the carboxylate ion is also formed. Data for the solvolysis of **1-Cl** in the presence of substituted acetate ions are given in Table 2. The effect of product composition as a function of acetate ion is shown in Fig. 2. Similar results were obtained with the less basic $NCCH_2COO^-$ and $MeOCH_2COO^-$ ions. Plots of the product ratios [**3**]/[**1-OH**] *versus* base concentration are shown in Fig. 3 for acetate and substituted acetate ions. The stronger base $(CF_3)_2CHO^-$ gives rise to bimolecular reaction with **1-Cl** as shown in Fig. 4.

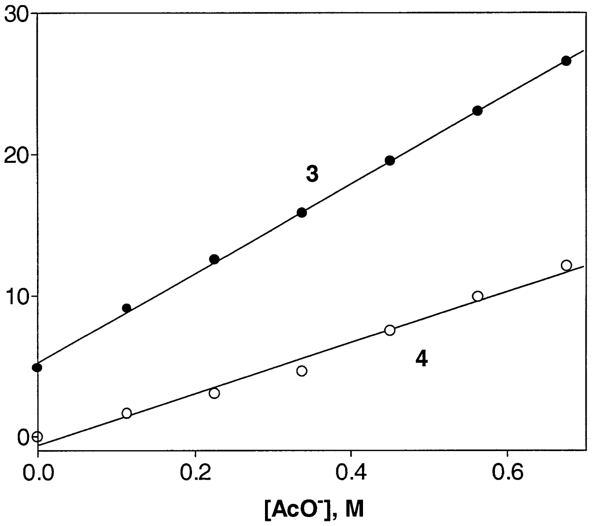


Fig. 2 The effect of added acetate ion on the alkene formation for the reaction of **1-Cl** in 25 vol% acetonitrile in water at 40 °C buffered with 10% of acetic acid.

Discussion

The solvolysis of **1-Cl** is about 200 times faster than the solvolysis of the corresponding secondary substrate **5** and approximately 12 times slower than the solvolysis of 2-chloro-2-methyl-1-phenylpropane (**6**).[7,9] The rate constant for the disappearance of the substrate as well as all the separate phenomenological rate constants are very sensitive toward the solvent ionizing power as shown in Fig. 5. The measured parameter for k_{obs} is m_{obs} = 1.16. A carbocation-like transition state is consistent with these data. The alcohol formation shows a greater sensitivity to solvent ionizing power than the elimination reactions in accord with previous results for solvolysis reactions.[10]

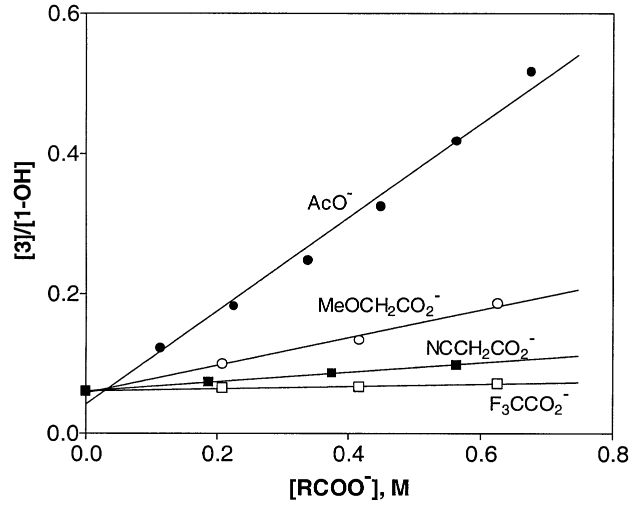


Fig. 3 The effect of added carboxylate ion on the product ratio [**3**]/[**1-OH**] for the reaction of **1-Cl** in 25 vol% acetonitrile in water at 40 °C buffered with 10% of the free acid. The slopes of the lines are 0.668, 0.198, 0.0674, and 0.0164 M^{-1}, respectively.

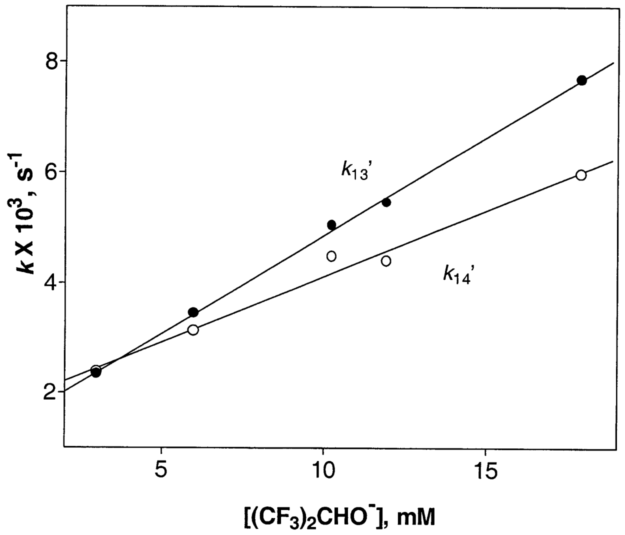


Fig. 4 The effect of added sodium hexafluoroisopropoxide on the rate constants k_{13}' and k_{14}' for reaction of **1-Cl** to give alkenes **3** and **4**, respectively. Reaction conditions: **1-Cl** in 25 vol% acetonitrile in water at 40 °C, buffered with 18% of the corresponding alcohol.

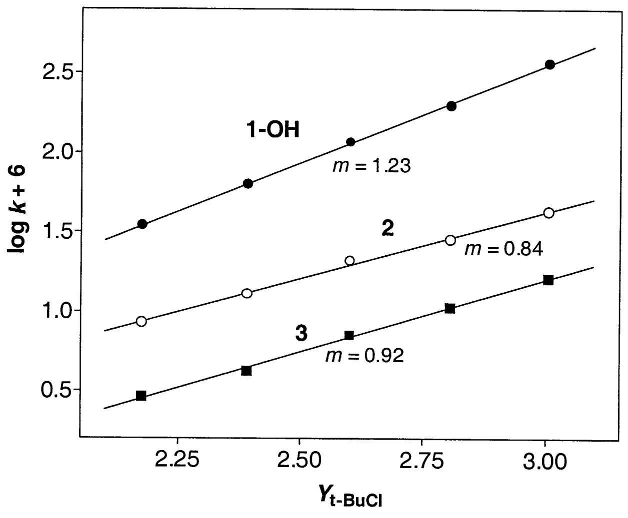


Fig. 5 Grünwald–Winstein plots for the solvolysis of **1-Cl** in acetonitrile–water mixtures at 40 °C. The *Y* values are from the reports of Bunton and coworkers.[29]

The effect of different salts on the rate of disappearance of **1-Cl** was found to be small (Table 2). Addition of the sodium salts of perchlorate ion, thiocyanate ion and bromide ion, respectively, gives a rate increase of about 15–20%. Addition of chloride ions or acetate ions does not have any significant effect on the reaction rate of **1-Cl** in contrast to the usual rate-retarding effect of these ions. For example, the solvolysis of Ph_2CHX, where X is Cl or 4-nitrobenzoate,[11] in 25 vol% acetonitrile in water is retarded 48 and 52%, respectively, by addition of 0.75 M sodium acetate and the solvolysis of **7** is retarded 48%.[12,13] The effect of 0.75 M sodium chloride is smaller, about 17%.[11–13]

There is no second-order substitution reaction with the added strong nucleophile thiocyanate ion. The rate of disappearance of the substrate at constant ionic strength (maintained with sodium perchlorate) does not change significantly with increasing concentration of the nucleophile (Table 1). The increase in the fraction of the two substitution products **1-SCN** and **1-NCS** is compensated by a decrease in the fraction of **1-OH** (Fig. 1). Thus, there is no indication of reversible ionization or competing one-step S_N2 reaction with this powerful nucleophile.

The product composition data of Table 2 indicate a very unstable intermediate; thiocyanate is only 19 times more reactive than a water molecule toward the carbocation. The lifetime of the carbocation intermediate might be estimated by the "azide-clock" method.[14,15] However, owing to the instability of **1-N₃**, we have used thiocyanate ion instead of azide ion as the trapping reagent. The thiocyanate ion should react with the carbocation by diffusion-controlled addition having a rate constant in aqueous acetonitrile of about 5×10^9 M^{-1} s^{-1} (at 25 °C).[16] This diffusional rate constant value combined with $k_{SCN}/k_w = 19$ (eqn. (1)) yields a rate constant for reaction of water with the carbocation of $k_w = 1.1 \times 10^{10}$ s^{-1}. This clearly indicates that the carbocation intermediate is relatively unstable and it should not be a fully solvent-equilibrated species since diffusional separation of an ion pair should have a rate constant of about 2×10^{10} s^{-1}. Accordingly, $k_w = 1.1 \times 10^{10}$ s^{-1} is presumably an underestimate. The rate constant for water addition is similar to that estimated in the reaction of 2-chloro-2-methyl-1-phenylpropane (**6**).[9]

Addition of the acetonitrile component to the carbocation intermediate provides a small amount of **1-NHCOMe** through the initial formation of the nitrilium ion.[17] The formation of this product reflects the highly reactive character of the carbocation showing a very small discrimination between different nucleophiles. Solvolysis reactions through more stable carbocations do not show this type of product in neutral solution. A further indication of the very unstable character of the carbocation is the measured small discrimination between methanol and water in 50 vol% methanol in water, $k_{MeOH}/k_{HOH} = 1.2$ (ratio of second-order rate constants, eqn. (1)).

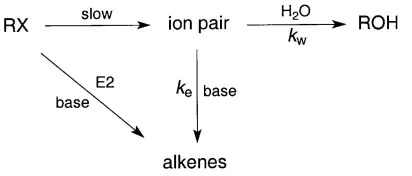
There is a small increase in the fraction of **3** with increasing thiocyanate ion concentration (Fig. 1). This apparent thiocyanate ion-promoted elimination could be attributed to elimination either from the carbocation intermediate or directly from the substrate. The latter base-promoted reaction is a viable possibility since the increase in the fraction of **3** is small and could not significantly change the total reaction rate. Base-promoted E2 (or E1cB) reactions with this weak base ($pK_{HSCN} = 0.23$)[18] in aqueous acetonitrile have been reported previously for acidic substrates. The pK_a of the β-hydrogens adjacent to the carbonyl group should be high, close to that of acetone ($pK_a = 19.3$).[19]

Added acetate ion does not have a rate-depressing effect on the disappearance of the substrate as expected for a reaction through a carbocation intermediate. We would expect an approximately two-fold rate decrease for 0.75 M acetate ion for a reaction proceeding entirely *via* carbocation intermediates (*vide supra*). This estimate is based upon the observed rate-depressing effects measured in the same solvent mixture for some other solvolysis reactions which occur through carbocation intermediates.[9,12–14] We therefore suggest that the rate-depressing effect of the carbocation formation, giving mainly alcohol **1-OH**, is compensated by an acetate ion-promoted E2 (or E1cB) reaction giving **3** and **4**. With the much stronger base $(CF_3)_2CHCO^-$ ($pK_a = 9.3$),[18] there is a significant fraction of competing E2 reaction (Fig. 4).

Let us now consider the two extreme mechanistic possibilities of alkene **3** formation.

Alternative 1: alkene 3 is formed exclusively through the carbocation intermediate with acetate ion and other weak bases

The assumption that the rate constant k_w for formation of **1-OH** from the common carbocation intermediate (Scheme 3)



Scheme 3

is not affected by the base addition implies that the measured product ratio [**3**]/[**1-OH**] could be used for measuring the Brønsted parameter for the dehydronation‡ (k_e) of the intermediate (Fig. 6). The slope of this plot, $\beta = 0.35$, is much higher than expected for the dehydronation of a very unstable carbocation intermediate. For example, the more stable cumyl carbocation $PhCMe_2^+$ shows a Brønsted parameter of $\beta = 0.13$ under similar conditions,[20] and the dehydronation of the much more stable carbocation **8⁺** exhibits a sensitivity to base strength of $\beta = 0.28$.[21] We therefore conclude that the alkene **3** is formed partly or exclusively through another reaction path, *viz.* the base-promoted E2 (or E1cB) reaction.

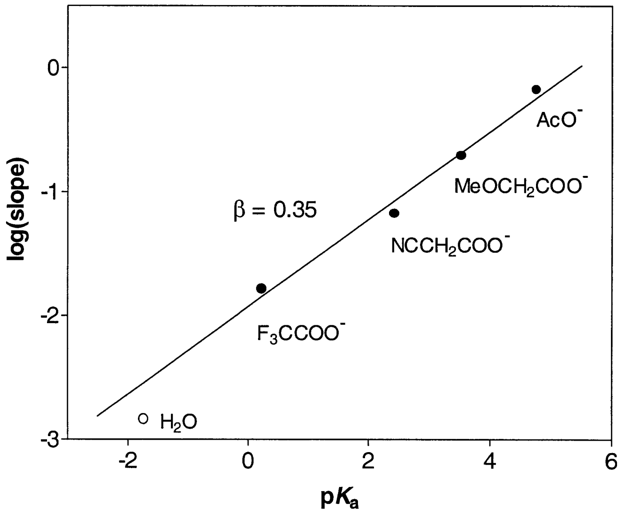


Fig. 6 Brønsted plot for the solvolysis of **1-Cl** in 25 vol% acetonitrile in water at 40 °C assuming that the alkene **3** is formed exclusively by dehydronation of the ion pair. Thus, the plotted slopes (see Fig. 3), represent the apparent catalysis of the bases on k_e (Scheme 3). The pK_a values refer to water at 25 °C.[18,26]

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‡ *Hydron* and *hydronation* are the generalnames, to be used without regard to the nuclear mass of the hydrogen entity, recommended by IUPAC, Organic Chemistry Division, Commission on Physical Organic Chemistry, 1984.

Alternative 2: alkene 3 is formed exclusively through a base-promoted E2 (or E1cB) reaction

Fig. 7 shows the Brønsted plot that corresponds to elimination involving dehydronation of the substrate in an E2 or irreversible E1cB reaction. The slope is large, $\beta = 0.76$. The regression line for the substituted acetate ions alone has a slope of $\beta = 0.51$. The Brønsted parameter for the reaction of the corresponding secondary substrate **5** with substituted acetate ions has been reported as $\beta = 0.67$.[7]

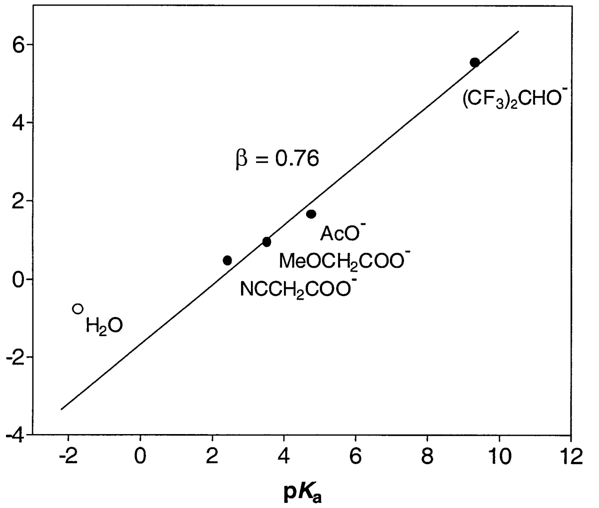

Fig. 7 Brønsted plot for the elimination reaction of **1-Cl** to give alkene product **3** (with the second-order rate constant k_{13}) in 25 vol% acetonitrile in water at 40 °C. The pK_a values refer to water at 25 °C.[18,26]

We expect the putative water-promoted E2 elimination reaction to be slower than predicted by the Brønsted line for the negatively charged bases in accord with previous studies of E2 reactions.[1–4,6,7] Dehydronation of carbocation intermediates shows similar behavior.[12,15,20–22] Negative deviations of water-catalyzed reactions are well-known for hydron transfer to and from carbon in which H_2O and HO^- are the hydron donor and acceptor, respectively.[23] The low catalytic activity of water as a hydron acceptor in E2 reactions probably reflects some kind of solvation effect. Therefore, the positive deviation (166-fold) from the Brønsted plot suggests that the alkene **3** is formed by another reaction path, *i.e.*, through the ion pair (Scheme 3). This reaction path is the major elimination route to alkene **3** in the absence of added bases. In fact, we conclude that there is no experimental evidence for any significant water-promoted E2 (or E1cB) reaction with **1-Cl** despite the large acidity of the substrate. This is in contrast to the solvolysis of the corresponding secondary chloride **5** which shows E2 (or E1cB) reaction with solvent water.[7] These reactions are also expected to be faster for a secondary than for a tertiary substrate.[8]

The same result was obtained previously for less acidic, fluorene-activated tertiary substrates. For example, the solvolysis of 9-(2-X-2-propyl)fluorene (X = Cl (**7**) or Br) does not give a significant amount of the alkene 9-isopropylidenefluorene despite a pK_a of about 22.5.[12,13] The reaction predominantly gives 9-(2-propenyl)fluorene, the less stable alkene product, by elimination of one of the methyl hydrons of the ion pair. Obviously, the β-hydrogens have to be very acidic, otherwise the E2 reaction is too slow compared to the ionization of tertiary substrates. However, the corresponding secondary fluorene substrate 9-(2-X-2-ethyl)fluorene ionizes more slowly and therefore the water-promoted E2 reaction becomes competitive.[1,2,4,5]

The products of the base-promoted elimination reactions are **3** and **4**, *i.e.* the more stable products which are formed by abstraction of one of the two acidic hydrons adjacent to the carbonyl group. In contrast, the uncatalyzed elimination reaction through the ion pair yields predominantly the less stable alkene **2**. This result is in accord with previous studies on solvolytic elimination reactions of specifically deuterated substrates that demonstrated the importance of hyperconjugative stabilization of the carbocationic transition state.[12,13] The relatively high kinetic acidity of the hydrogens of the methyl group is attributed to this hyperconjugative weakening of the carbon–hydrogen bonds in the methyl group.

Chloride-promoted elimination *via* the ion pair?

Addition of sodium chloride provides a small increase in the fraction of alkenes (Table 2). This result is in accord with previous reports for solvolysis reactions through unstable carbocation intermediates. For example, the solvolysis reactions of **7** and **9** exhibit an enhanced fraction of elimination products when chloride ion is present in the reaction solution.[10,12] Also a more stable tertiary carbocation has been found to react more efficiently with chloride ion than with solvent water.[22] For **7**, this apparent catalysis from the chloride ion ($pK_{HCl} = -6.3$)[26] is fairly well described by the Brønsted correlation of the rate constants for dehydronation by substituted acetate ions ($\beta = 0.05$).[12] For **9**, the catalysis is more efficient, chloride ion shows a 3-fold positive deviation from the Brønsted line ($\beta = 0.07$).[10] Thus, chloride ion shows the same efficiency as trifluoroacetate ion in abstracting a hydron from the ion pair that may reflect a specific solvent effect.

It has been suggested that the chloride leaving group of the ion pair may function as the hydron-abstracting base in solvolytic elimination reactions.[10,24,25,27,28] The thermodynamic basicity of chloride ion is not high in water but its kinetic basicity may be relatively high owing to incomplete solvation of the leaving group in the ion pair. This proposal may account for the fact that tertiary chlorides generally give larger fractions of elimination than substrates with uncharged, neutral leaving groups. Moreover, as discussed above, the catalytic effect of water is lower than predicted by the pK_a of H_3O^+.

Experimental

General procedures

NMR spectra were recorded at 20 °C on a Varian Unity 300 or 400 spectrometer, for ^1H at 300 or 400 MHz and for ^{13}C at 75.4 MHz. Chemical shifts were indirectly referenced to TMS *via* the solvent signal (chloroform-d_1 7.26 and 77.16 ppm). The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on an Inertssil 3 ODS-3 (3 × 100 mm) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature maintained with a HETO 01 PT 623 thermostat bath. The kinetic studies were also carried out employing a Kontron Uvicon 930 spectrophotometer, equipped with an automatic cell changer kept at constant temperature with water from the thermostat bath.

Materials

Merck silica gel 60 (240–400 mesh) was used for flash chromatography. Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from sodium and benzophenone. Dichloromethane was dried over calcium chloride and freshly distilled. Methanol and acetonitrile were of HPLC grade. All other chemicals were of reagent grade and used without further purification.

4-Hydroxy-4-(4′-nitrophenyl)pentan-2-one (1-OH). This was synthesized from 4-nitroacetophenone and acetone by a slight modification of the procedure used for the secondary analogue.[7] To a solution of 4-nitroacetophenone (10 g) in 102 ml of acetone were added 7 ml of a 1% aqueous KOH solution at 0 °C. Stirring was continued at 0 °C for 1 h. The reaction was then quenched by addition of 16 ml of saturated NH_4Cl and concentrated. The residue was dissolved in 100 ml of water and extracted with ether (3 × 100 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuum*. The crude product contained only about 20% of the alcohol (NMR). The rest was mainly unconverted 4-nitroacetophenone, half of which could be recovered by recrystallization from ether. The resulting residue after recrystallization was separated by flash chromatography on a silica column with CH_2Cl_2 as eluent. The combined components containing **1-OH** were further purified by repeated recrystallization from pentane–ether, affording a slightly yellow crystal: mp 64.3–65.6 °C (Found: C, 59.25; H, 5.9; N, 6.3. $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%); ^{1}H NMR (300 MHz), δ 8.19 (m, 2 H), 7.60 (m, 2 H), 4.67 (s, 1 H), 3.20 (d, J = 17.7 Hz, 1 H), 2.94 (d, J = 17.7 Hz, 1 H), 2.13 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR, δ 210.2, 155.0, 147.0, 125.6, 123.8, 73.37, 53.60, 31.83, 30.59.

4-Chloro-4-(4′-nitrophenyl)pentan-2-one (1-Cl). A solution of **1-OH** (1.0 g) in dichloromethane (40 ml) containing anhydrous calcium chloride and lithium chloride was cooled to 0 °C. Dry hydrogen chloride was bubbled through the solution for 10 h. After filtration, the resulting slightly yellow solution was concentrated with a stream of nitrogen. The residue was purified by flash chromatography on a silica column using 40–60 vol% ether in pentane. The product is a colourless liquid, which is stable for several weeks in organic solvents, such as diethyl ether or $CDCl_3$, at −25 °C. ^{1}H NMR (300 MHz), δ 8.20 (m, 2 H), 7.72 (m, 2 H), 3.50 (d, J = 17.0 Hz, 1 H), 3.39 (d, J = 17.0 Hz, 1 H), 2.14 (s, 3 H), 2.10 (s, 3 H); ^{13}C NMR, δ 203.6, 151.2, 147.2, 127.2, 123.6, 67.82, 57.84, 31.50, 31.15.

(*E*)-4-(4′-Nitrophenyl)-2-oxopent-3-ene (3). The alkene **3** was formed as the main product when **1-Cl** (neat) was decomposed at room temperature. The resulting black solid was purified by flash chromatography on a silica column using 40% ether in pentane, followed by repeated recrystallization from diethyl ether affording yellowish crystals: mp 104.1–105.8 °C (Found: C, 64.35; H, 5.4; N, 6.8. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83%); ^{1}H NMR (400 MHz), δ 8.24 (m, 2 H), 7.61 (m, 2 H), 6.53 (d, J = 1.2 Hz, 1 H), 2.53 (d, J = 1.2 Hz, 3 H), 2.33 (s, 3 H); ^{13}C NMR, δ 198.7, 151.0, 149.1, 148.0, 127.5, 126.9, 123,9, 32.41, 18.39.

(*Z*)-4-(4′-Nitrophenyl)-2-oxopent-3-ene (4). The alkene **4** is formed in a small amount when **1-Cl** is decomposed. The alkene **4** eluted after the alkene **3** when separation was carried out by flash chromatography on a silica column (conditions as above). The isolated yellowish oil contained *ca.* 5% of **3** (NMR): ^{1}H NMR (400 MHz), δ 8.21 (m, 2 H), 7.33 (m, 2 H), 6.29 (q, J = 1.2 Hz, 1 H), 2.18 (d, J = 1.2 Hz, 3 H), 2.03 (s, 3 H); ^{13}C NMR, δ 197.8, 150.7, 148.3, 147.4, 128.1, 127.8, 123,7, 31.14, 27.05.

4-Bromo-4-(4′-nitrophenyl)pentan-2-one (1-Br). A solution of **1-OH** (0.83 g) in dry dichloromethane (3 ml) was added to 2.5 ml of concentrated HBr solution saturated with $ZnBr_2$ in a separatory funnel. The mixture was shaken for 15 s and the reaction was quenched by addition of dry CH_2Cl_2. After separation, the organic phase was washed 3 times with water and once with brine and dried over $MgSO_4$. Filtering and evaporation with a nitrogen stream afforded a lightly coloured liquid that contained *ca.* 50% of **1-Br** (NMR, the rest being mainly the alkene **3**). Owing to the instability of **1-Br**, purification was not successful. Therefore, this crude product was directly used in kinetic measurements. ^{1}H NMR (300 MHz), δ 8.21 (m, 2 H), 7.72 (m, 2 H), 3.83 (d, J = 17.5 Hz, 1 H), 3.59 (d, J = 17.5 Hz, 2 H), 2.38 (s, 3 H), 2.10 (s, 3 H).

4-(2′,2′,2′-Trifluoroacetoxy)-4-(4′-nitrophenyl)pentan-2-one ($\mathbf{1\text{-}OOCCF_3}$). Alcohol **1-OH** (0.53 g) was dissolved in dry dichloromethane (20 ml), and dry pyridine (2 ml) and trifluoroacetic anhydride (1 ml) were added. The mixture was stirred at room temperature overnight, and then most of the solvent was evaporated. Ether was used to extract the crude product, followed by washing twice with 0.5 M HCl, once with Na_2CO_3 (sat.) and twice with water, and then drying over magnesium sulfate. Evaporation of the solvent gave a viscous oil (0.5 g), which was purified by flash chromatography on a silica column using 40–60 vol% ether in pentane. The purity (>99%) was confirmed with NMR and HPLC. ^{1}H NMR (400 MHz), δ 8.24 (m, 2 H), 7.57 (m, 2 H), 3.42 (d, J = 16.8 Hz, 1 H), 3.38 (d, J = 16.8 Hz, 1 H), 2.10 (3 H, s), 2.09 (3 H, s); ^{13}C NMR, δ 202.9, 155.5 (q, J = 42.2 Hz), 148.3, 147.7, 126.1, 124.0, 114.3 (q, J = 285.0 Hz), 86.1, 52.9, 31.6, 24.4.

4-(4′-Nitrophenyl)-2-oxopent-4-ene (2). A solution of the crude product **1-Br** (0.37 g) dissolved in 75 vol% acetonitrile in water (100 ml) was stirred at room temperature for 4 days. Extraction with CH_2Cl_2 (3 × 100 ml), drying ($MgSO_4$), and flash chromatography (conditions as above) afforded the pure colorless alkene: mp 52.0–54.7 °C (Found: C, 64.35; H, 5.4; N, 6.75. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83%). ^{1}H NMR (300 MHz), δ 8.18 (m, 2 H), 7.53 (m, 2 H), 5.73 (s, 1 H), 5.40 (s, 1 H), 3.66 (s, 2 H), 2.18 (s, 3 H).

Kinetics and product studies

Reactions at 25 °C were monitored by an HPLC procedure. The reaction solutions were prepared by mixing acetonitrile with water or aqueous salt solution at room temperature, *ca.* 22 °C. The solvolysis experiments were run at pH < 6.5. The reaction vessel was a 2-ml HPLC vial, sealed with a gas-tight PTFE septum, which was placed in an aluminium block kept at a constant 25 °C with water from the thermostat bath. The concentration of the substrate in the reaction solution was in the range 0.05–0.10 mM. The volume of reaction solution was usually 1.2 ml. The reactions were initiated by fast addition of a few microliters of the substrate dissolved in acetonitrile by means of a syringe. At appropriate intervals, samples were analyzed using the HPLC apparatus. The reactions were followed by monitoring the decrease in the peak area of the substrate and the rate constants were calculated from plots of the peak area *versus* time by means of a non-linear regression computer program. The separate rate constants for the elimination and substitution reactions were derived by combination of product composition data, obtained from the peak areas and the relative response factors determined in separate experiments, with the observed rate constants. The HPLC peaks of **2** and **4** were not fully separated.

Reactions at 40 °C were followed by monitoring the increase in the absorbance at 320 nm with a spectrophotometer. The reaction solutions were prepared by mixing acetonitrile with water at room temperature, *ca.* 22 °C. The reaction vessel was a 3-ml tightly stoppered UV cell. The concentration of the substrate in the reaction solution was in the range 0.05–0.10 mM. The volume of reaction solution was usually 2.4 ml. The reaction was initiated by fast addition of a few microliters of the substrate dissolved in acetonitrile by means of a syringe. The reactions were followed for about 10 half-lives. The product ratios were then obtained by HPLC analyses as described above for the reactions carried out at 25 °C.

The reaction products **2**, **3** and **4** were stable under the reaction conditions. The substitution products **1-SCN** and **1-NCS** undergo a very slow decomposition to give alkenes but this is not significant during the time of a solvolysis experiment. The alcohol **1-OH** affords 4-nitroacetophenone in basic solution but is stable below pH 6.5.

Determination of relative HPLC response factors. The relative response factors for **1-OH** and alkenes **2** and **3** were measured by HPLC analysis of a mixture of the three components, prepared by weighing. The relative response factor for alkene **3** and alkene **4** was determined by a combination of NMR analysis and HPLC analysis. A mixture of appropriate amounts of the two alkenes, **3** and **4**, was dissolved in chloroform-d_1 and analysed by ^{1}H NMR. The peak areas of the well-resolved signals, such as methyl signals or alkenyl signals, were integrated and used to calculate the relative molar ratio of the two components, assuming that the NMR integrals exactly corresponded to the expected number of protons. A few microliters of this solution were transferred to a 2-ml HPLC flask. The solvent was evaporated under a stream of nitrogen. The residue was dissolved in acetonitrile and analyzed by HPLC. The response factors of the other substitution products were assumed to be the same as that of **1-OH**.

The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors.

Acknowledgements

We thank the Swedish Natural Science Research Council for supporting this work.

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