Competing solvolytic elimination and substitution reactions *via* very short-lived ion-pair intermediates

Xiaofeng Zeng and Alf Thibblin *

Institute of Chemistry, University of Uppsala, P.O. Box 531, Uppsala, SE-751 21, Sweden

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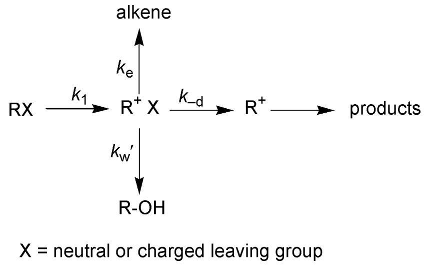
The solvolysis of 9-methyl-9-(2-X-2-propyl)fluorene (X = Cl, Br, or $OOCCF_3$) (**1-X**) in aqueous acetonitrile or aqueous 1,1,1-trifluoroethanol (TFE) yields the alkene, 9-methyl-9-(propen-2-yl)fluorene (**2**), and the alcohol, 9-methyl-9-(2-hydroxy-2-propyl)fluorene (**1-OH**), accompanied by a small amount of substitution product from the reaction with the organic component of the solvent mixture. The fraction of elimination product increases with decreasing fraction of water in the solvent mixture as well as by addition of general bases, which can be expressed by a Brønsted parameter of $\beta = 0.07$ for the reaction of **1-Cl**, measured with substituted acetate anions. Also, the addition of chloride ions increases the fraction of alkene. The kinetic deuterium isotope effects on the reactions of the hexadeuterated substrates vary with solvent composition in a way which is *not* consistent with a common carbocation intermediate which has time to choose between dehydronation and addition of a solvent water molecule. A stepwise preassociation mechanism is proposed for the elimination reaction.

Introduction

Solvolysis reactions of substrates having a hydrogen in the β-position generally give both substitution and 1,2-elimination products in aqueous solvents. The alcohol product usually has a greater thermodynamic stability and is for that reason often the predominant product. There seems to be a consensus that the elimination from simple tertiary substrates occurs directly through the ion pair before dissociation occurs.[1–3] Accordingly, the leaving group may catalyze the carbocation by acting as a general Brønsted base. It has been reported, for example, that even neutral leaving groups catalyze the alkene formation from cumyl derivatives.[4] The leaving group in simple, more unstable carbocations, is expected to function in a similar way. Also the addition of water to simple tertiary carbocation intermediates has been suggested to occur before dissociation (Scheme 1).[5,6]



Scheme 1

The role of the chloride ion leaving group in the elimination process is, however, not clear.[2,5] Does it act as a general base that abstracts a β-hydron from the cation, or is a water molecule of the solvation shell the active species? It has been argued that the chloride ion is a very weak base, much weaker than water, and therefore, is not able to compete with water as the hydron-abstracting base.[5] In contrast, it has been proposed that incomplete solvation of the chloride ion in the contact ion pair makes the chloride ion a much stronger base than that implied by the pK_a of HCl.[2] It is also plausible that the carbocation–chloride ion pair is so short-lived that the elimination occurs through a stepwise preassociation mechanism with water or an added base already correctly positioned for abstracting a hydron from the carbocation intermediate. A concerted unimolecular pericyclic mechanism has also been proposed in which the leaving group acts as the hydron acceptor in elimination reactions of tertiary substrates.[5,7] This mechanism requires *syn* stereochemistry. However, it was more recently shown that both the elimination of hydrochloric acid from a very unstable tertiary carbocation ion pair and the elimination of 4-nitrobenzoic acid from a cumyl-like substrate occur by *anti* stereochemistry.[2]

We report here a study of the competition between elimination and substitution and the kinetics of the solvolysis of the tertiary substrates **1-X** (Scheme 2) as a function of leaving group, solvent composition, and β-deuterium substitution. We have previously studied the solvolysis of the corresponding substrate with a hydrogen instead of a methyl group at the 9-position of the fluorene moiety (**A-X**, Scheme 2).[8–10] It was found that, without the presence of a strong base, the terminal alkene and the alcohol are the predominant products. It was proposed that the solvolysis involves irreversible rate-limiting ionization to give a common ion-pair intermediate for the elimination and substitution reactions. The measured kinetic deuterium isotope effects and the small Brønsted parameters supported this conclusion. Excluding the acidic hydrogen makes the analysis of the reaction products somewhat easier since only one alkene is accompanying the substitution products (Scheme 2), and there is no isomerization of alkenes.

We have frequently employed kinetic deuterium isotope effect measurements as a probe of reaction branching through a common intermediate, both for carbanionic[11] and carbocationic reactions.[1,8–18] However, the kinetic deuterium isotope effect measurements do not indicate a common intermediate for the reactions of **1-X**. The mechanistic implications will be discussed.

Results

The solvolysis of 9-methyl-9-(2-X-2-propyl)fluorene (**1-X**, X = Cl, Br, $OOCCF_3$) in aqueous acetonitrile or in aqueous 2,2,2-trifluoroethanol (TFE) provides the alkene 9-methyl-9-(propen-2-yl)fluorene (**2**) and the substitution products 9-methyl-9-(2-hydroxy-2-propyl)fluorene (**1-OH**) along with a

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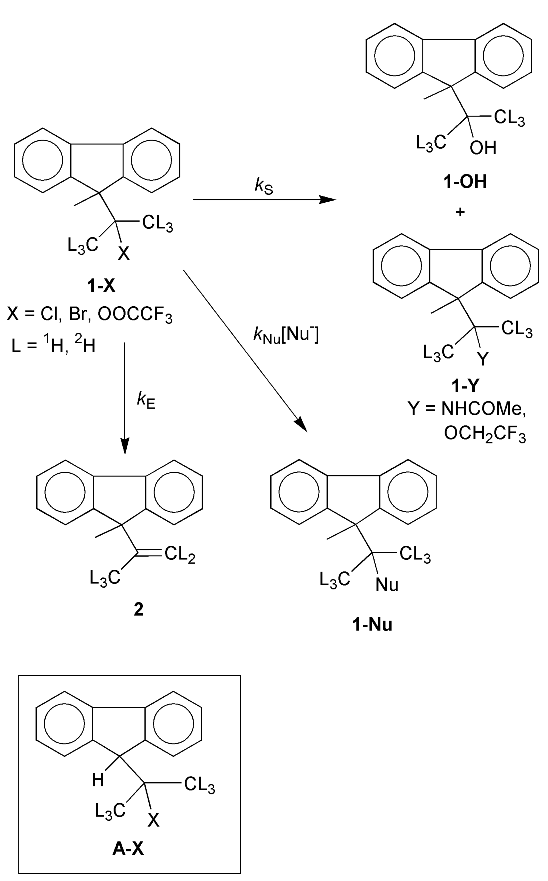


Scheme 2

small amount of 9-methyl-9-(2-acetamido-2-propyl)fluorene (**1-NHCOMe**) or 9-methyl-9-[2-(2′,2′,2′-trifluoroethoxy)-2-propyl]fluorene (**1-OCH$_2$CF$_3$**), respectively (Scheme 2). The kinetics of the solvolysis reactions of **1-Cl** and **1-OOCCF$_3$** were studied at 25 °C by a sampling high-performance liquid-chromatography procedure. The kinetics of the reactions of **1-Br** were studied by following the change in absorption at 409 nm in the presence of added 4-nitrophenolate anion (see Experimental section). The reaction rates and product compositions are strongly dependent on the nature of the leaving group and reaction media. The measured rate constants and reaction conditions for **1-Cl**, **1-Br**, and **1-OOCCF$_3$** are shown in Tables 1, 2, and 3, respectively. The separate rate constants for the elimination and substitution reactions were derived from the measured product compositions. Tables 1 and 3 also give the kinetic data for reactions in 50 vol% methanol, but, owing to overlapping HPLC peaks for **1-OMe** and **2**, only rate constants for the disappearance of the substrates (k_{obs}) are reported.

The observed product ratio of **1-Nu** to **1-OH** is a measure of the competition between added nucleophile (Nu$^-$) and water for the reaction with substrate and/or ion pair. The second-order rate-constant ratios k_{Nu}/k_w in Tables 1–3 were derived from the measured product ratios according to eqn. (1).

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

The effect of solvent polarity has been studied by measuring Grünwald–Winstein parameters for the reactions of **1-Cl**, **1-Br**, and **1-OOCCF$_3$** in aqueous acetonitrile, as shown in Figs. 1–3.[19–21] The Y values are from reports of Bunton and coworkers.[22,23]

Added basic salts increase the elimination-to-substitution ratio. The effect is most significant in aqueous acetonitrile (Table 1). There is an approximately linear dependence between base concentration and k_E/k_S as shown for **1-Cl** with two of the bases, AcO$^-$ and CF$_3$COO$^-$ (Fig. 4).

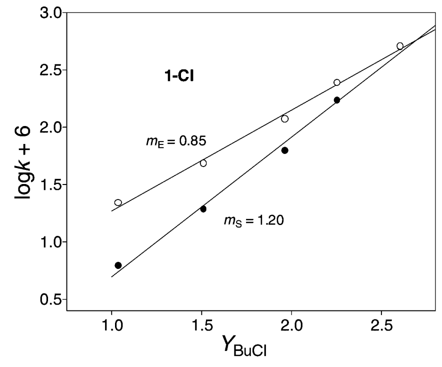


Fig. 1 Grünwald–Winstein plot for the solvolysis of **1-Cl** in acetonitrile–water mixtures at 25 °C.

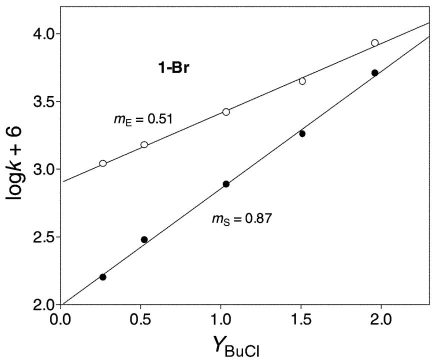


Fig. 2 Grünwald–Winstein plot for the solvolysis of **1-Br** in acetonitrile–water mixtures at 25 °C.

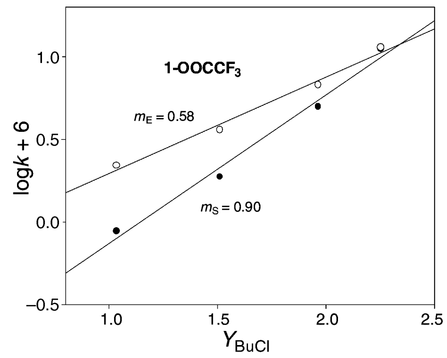


Fig. 3 Grünwald–Winstein plot for the solvolysis of **1-OOCCF$_3$** in acetonitrile–water mixtures at 25 °C.

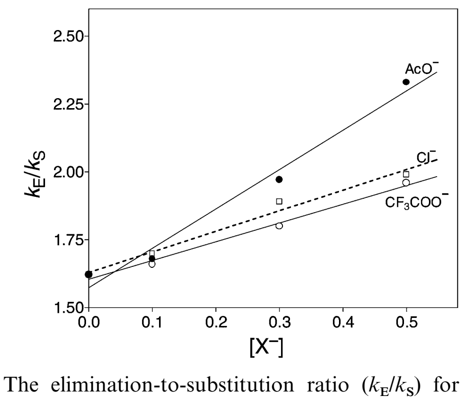


Fig. 4 The elimination-to-substitution ratio (k_E/k_S) for **1-Cl** as a function of [AcO$^-$] (●), [Cl$^-$] (□), and [CF$_3$COO$^-$] (○), respectively, at constant ionic strength of 0.5 M, maintained with sodium perchlorate at 25 °C.

The deuterated substrates 9-methyl-9-[2-X-2-(1′,1′,1′,3′,3′,3′-^{2}H$_6$)propyl]fluorene (X = Cl, Br, OOCCF$_3$) yield lower reaction rates and smaller alkene fractions. The measured kinetic deuterium isotope effects for solvolysis of these deuterated substrates are given in Table 4.

Table 1 Rate constants for the reactions of **1-Cl**[a] in aqueous solvents at 25 °C

Solvent[b]	Salt	$10^6k_{obs}{}^c/s^{-1}$	$10^6k_E{}^d/s^{-1}$	$10^6(k_S + k_{Nu}[Nu^-])^d/s^{-1}$	k_E/k_S	k_{Nu}/k_w
25% MeCN	None	1001	499	502	0.99	
33.3% MeCN	None	417	245	172	1.42	
40% MeCN	None	181	118	62	1.90	
50% MeCN	None	67.7	48.4	19.2	2.52	
60% MeCN	None	28.1	21.9	6.2	3.54	
40% MeCN	0.50 M $NaClO_4$	236	146	90	1.62	
40% MeCN	2.66 M $NaClO_4$	413	245	168	1.46	
40% MeCN	0.50 M NaCl	109	72	36	1.99	
40% MeCN	0.50 M NaBr	165	109	56	1.93	
40% MeCN	0.50 M NaI	243	158	85	1.85	
40% MeCN	0.50 M NaN_3	160	106	54	1.95	3.4[e]
40% MeCN	0.50 M NaSCN	221	139	81	1.71	5.1[f]
40% MeCN	0.45 M NaOAc	82.2	57.5	25.7	2.33	
40% MeCN	0.45 M NaO_2CCH_2CN	127	87	41	2.14	
40% MeCN	0.45 M NaO_2CCF_3	164	108	55	1.96	
50% MeOH	None	470				
50% TFE	None	1492	852	640	1.33	
75% TFE	None	1070	674	396	1.70	
50% TFE	0.50 M $NaClO_4$	2127	1115	1012	1.10	
50% TFE	0.50 M NaCl	1893	1081	812	1.33	
50% TFE	0.50 M NaBr	1679	951	728	1.31	
50% TFE	0.45 M NaOAc	1389	810	579	1.40	
50% TFE	0.50 M NaN_3	1635	920	715	1.29	4.9[e]
50% TFE	0.50 M NaSCN	1910	1030	880	1.17	11[f]

[a] 0.04–0.12 mM. [b] By volume. [c] $k_{obs} = k_E + k_S + k_{Nu}[Nu^-]$, see Scheme 2: estimated maximum error ± 3 %. [d] Estimated maximum error ± 6%. [e] Approximate since the product HPLC peak of **1-N$_3$** overlaps partially with that of alkene **2**. [f] The ratio is based upon the sum of the products **1-SCN** and **1-NCS**.

Table 2 Rate constants for the reactions of **1-Br**[a] in aqueous acetonitrile at 25 °C

Solvent[b]	Salt	$10^9k_{obs}{}^c/s^{-1}$	$10^9k_E{}^d/s^{-1}$	$10^9(k_S + k_{Nu}[Nu^-])^d/s^{-1}$	k_E/k_S	k_{Nu}/k_w
40% MeCN	None	13.7	8.52	5.19	1.64	
50% MeCN	None	6.28	4.46	1.81	2.46	
60% MeCN	None	3.42	2.64	0.78	3.39	
70% MeCN	None	1.81	1.51	0.30	4.98	
75% MeCN	None	1.26	1.10	0.16	6.91	
40% MeCN	0.50 M $NaClO_4$	24.4	14.2	10.2	1.39	
40% MeCN	0.50 M NaCl	10.1	6.6	3.5	1.87	
40% MeCN	0.50 M NaBr	13.9	8.85	5.05	1.75	
40% MeCN	0.50 M NaI	23.0	14.5	8.5	1.71	
40% MeCN	0.50 M NaSCN				1.46	4.8[f]
50% MeCN	0.50 M NaSCN				2.14	4.1[f]
40% MeCN	0.50 M NaN_3				1.83	1.8[e]
50% MeCN	0.50 M NaN_3				2.71	1.8[e]
40% MeCN	0.45 M NaO_2CCH_2CN				1.99	
40% MeCN	0.45 M NaO_2CCF_3				1.81	
50% MeCN	0.45 M NaO_2CCF_3				1.95	
50% MeCN	0.50 M $NaClO_4$	9.91	6.61	3.30	2.00	
50% MeCN	0.50 M NaBr	5.36	3.88	1.48	2.63	
50% MeCN	0.50 M NaI	8.15	5.86	2.29	2.56	
50% MeCN	0.35M NaCl	4.39	3.19	1.20	2.66	

[a] 0.04–0.12 mM. [b] By volume. [c] $k_{obs} = k_E + k_S + k_{Nu}[Nu^-]$, see Scheme 2; estimated maximum error ± 3%. [d] Estimated maximum error ± 6%. [e] Approximate since the product HPLC peak of **1-N$_3$** overlaps partially with that of alkene **2**. [f] The ratio is based upon the sum of the products **1-SCN** and **1-NCS**.

Discussion

Carbocationic transition states

The methyl substituent of the fluorene moiety has a rate-acceleration effect. Thus, the solvolyses of **1-Cl** and **1-Br** are both about seven times faster than the corresponding reactions of **A-Cl** and **A-Br**, respectively, but the effect on the product ratio is small (Scheme 2).[8,9] The difference in reactivity of **1-X** and **A-X**, corresponding to 1.2 kcal mol^{-1}, is attributable to the increased strain in the reactant caused by the methyl group. The strain is partially relieved in the rate-limiting ionization step.

The effect of the leaving group on the reaction rate is substantial. The bromide reacts 122 times faster than the chloride, and 1110 times faster than the ester in 60 vol% acetonitrile (Tables 1–3). The reaction rates of the three substrates are also very sensitive to the ionization power of the solvent. The slopes of the Grünwald–Winstein plots for the solvolysis in acetonitrile–water mixtures are shown in Figs. 1–3. The slopes (m_{obs}) of the plots for the total reaction of the different substrates are all smaller than unity; there is a decrease in the Grünwald–Winstein parameter in the order m_{obs} = 0.97, 0.70, and 0.60 for **1-Cl**, **1-OOCCF$_3$**, and **1-Br**, respectively. The trend in the parameter value should reflect a difference in solvation of the three leaving groups, which parallels the extent of charge development on the carbon in the rate-limiting transition state. Bentley and Roberts have found the following trend in solvation effect with different leaving groups: Cl > Br > I.[24] Accordingly,

Table 3 Rate constants for the reactions of **1-OOCCF$_3$**[a] in aqueous solvents at 25 °C

Solvent[b]	Salt	$10^6k_{obs}{}^c$/s^{-1}	$10^6k_E{}^d$/s^{-1}	$10^6(k_S + k_{Nu}[Nu^-])^d$/s^{-1}	k_E/k_S	k_{Nu}/k_w
33.3% MeCN	None	22.6	11.4	11.2	1.02	
40% MeCN	None	11.8	6.8	5.0	1.35	
50% MeCN	None	5.50	3.6	1.9	1.93	
60% MeCN	None	3.08	2.2	0.9	2.49	
40% MeCN	0.50 M NaClO$_4$	16.3	9.0	7.3	1.24	
50% MeCN	0.32 M NaClO$_4$	6.93	4.4	2.5	1.73	
50% MeCN	0.32 M NaCl	4.12	2.9	1.2	2.32	
50% TFE	None	26.5	14.0	12.5	1.13	
50% TFE	0.50 M NaClO$_4$	30.5	15.4	15.0	1.03	
50% TFE	0.50 M NaCl	25.6	13.9	11.7	1.19	
50% TFE	0.50 M NaBr	29.8	16.2	13.6	1.19	
50% TFE	0.50 M NaN$_3$	28.8	16.2	13.5	1.20	4.0[e]
50% TFE	0.50 M NaSCN	29.7	14.4	13.3	1.07	11.2[f]
50% MeOH	None	29.5				

[a] 0.04–0.12 mM. [b] By volume. [c] $k_{obs} = k_E + k_S + k_{Nu}[Nu^-]$, see Scheme 2; estimated maximum error ± 3%. [d] Estimated maximum error ± 6%. [e] Approximate since the product HPLC peak of **1-N$_3$** overlaps partially with that of alkene **2**. [f] The ratio is based upon the sum of the products **1-SCN** and **1-NCS**.

Table 4 Kinetic deuterium isotope effects for **1-Cl**, **1-Br** and **1-OOCCF$_3$** in aqueous media at 25 °C

Substrate	Solvent	$k_{obs}{}^H/k_{obs}{}^{D6}$	$k_E{}^H/k_E{}^{D6}$	$k_S{}^H/k_S{}^{D6}$
1-Cl	25% MeCN	1.76	3.5	1.2
1-Cl	40% MeCN	1.97	3.2	1.2
1-Cl	60% MeCN	2.46	3.2	1.3
1-Cl	40% MeCN, 0.50 M NaClO$_4$	1.84	3.1	1.1
1-Cl	40% MeCN, 0.50 M NaCl	2.29	3.4	1.2
1-Cl	40% MeCN, 0.45 M NaOAc	2.41	3.5	1.4
1-Cl	50% TFE	1.91	3.5	1.2
1-Br	40% MeCN	2.03	3.2	1.3
1-Br	50% MeCN	2.16	3.2	1.2
1-Br	60% MeCN	2.47	3.3	1.4
1-Br	70% MeCN	2.45	3.0	1.3
1-OOCCF$_3$	33.3% MeCN	2.03	3.8	1.4
1-OOCCF$_3$	50% TFE	2.15	3.7	1.5
1-OOCCF$_3$	50% TFE, 0.50 M NaClO$_4$	1.98	3.6	1.4

different Y-parameters for different leaving groups have been proposed.

For the separate reactions of **1-X**, the following parameter values were measured: $m_E = 0.85$, 0.58, and 0.51 for **1-Cl**, **1-OOCCF$_3$**, and **1-Br**, respectively, and $m_S = 1.20$, 0.90, and 0.87, respectively. A substrate parameter m close to unity is expected for a classical S$_N$1 reaction and reactions of S$_N$2 type usually exhibit m values in the range 0.25–0.35.[25] However, as has been pointed out previously,[26] the value of m is not a good mechanistic tool for distinguishing S$_N$1 and S$_N$2 reactions since it has been shown that bimolecular substitution reactions can exhibit large values.[26]

The effect of added salts on the kinetics is rather large (Tables 1–3). Addition of the large polarizable anions ClO_4^-, SCN^-, and I^- all give an increase in the total reaction rate. The effects are larger in aqueous acetonitrile than in aqueous TFE. In aqueous acetonitrile there is also a considerable rate-depressing effect of added Cl^- and AcO^-. All these salt effects in mixed water–organic solvents are similar to those observed previously,[8,9,12–18,26] and could be attributed to a salt-induced medium effect.[27]

Substitution reactions

It has recently been proposed that simple tertiary carbocations react with water from the surrounding solvation shell faster than the ion pair undergoes dissociation.[5,6] The tertiary carbocation $\mathbf{1}^+$ is more unstable than a simple tertiary carbocation and the direct reaction of the undissociated ion pair $\mathbf{1}^+\mathbf{X}^-$ is expected to be even more favoured relative to dissociation. Thus, the rate-limiting process of the addition of a solvent molecule should be the rotation of the nucleophile into a reactive position which should have a rate constant similar to that for rotational relaxation of a water molecule, *i.e.*, $k_w' \sim 1 \times 10^{11}$ s^{-1}.

Since the diffusion of a dilute nucleophile into the reaction position is much slower, the azide-clock method for measuring the lifetime of the intermediate does not work. The small amounts of **1-N$_3$**, **1-SCN**, and **1-NCS** formed in the presence of the strongly nucleophilic anions (*e.g.*, discrimination ratios of $k_{N_3}/k_w = 3.4$ and $k_{SCN}/k_w = 5.1$ were measured with **1-Cl** in 40 vol% acetonitrile, Table 1), should therefore originate from a preassociation reaction mechanism and/or a “pool” mechanism in which the nucleophiles close to the ion pair are reacting. The measured discrimination values are similar to those measured with the corresponding fluorene derivatives without the 9-methyl group (**A-X**, Scheme 2).[8,9]

The extremely small nucleophilic selectivity is also manifested in the formation of a substitution product with the acetonitrile component of the solvent. Initially, nucleophilic attack by MeCN on the ion pair gives the nitrilium ion **1-N≡CMe$^+$** with subsequent hydrolysis by water providing the amide.[28] The amide **1-NHCOMe** (Scheme 2) is formed not very much slower than the alcohol, $k_{MeCN}/k_w = 0.2$–0.5, despite the large difference in nucleophilicity of acetonitrile and water. The nucleophilicity of acetonitrile is expected to be low because the basicity of acetonitrile in water is very low, $pK_{MeCNH^+} = -10$.[29]

The competition between elimination and substitution

Lower polarity of the solvent increases the fraction of elimination products in accord with what is usually seen in solvolytic elimination/substitution reactions. This is illustrated by the Grünwald–Winstein plots (Figs. 1–3) which all show $m_S > m_E$. Obviously, the two product-forming transition states following

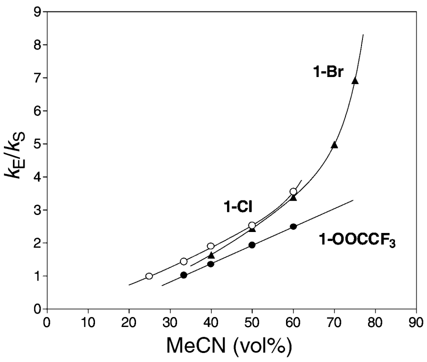


Fig. 5 The elimination-to-substitution ratio (k_E/k_S) as a function of vol% acetonitrile in acetonitrile–water mixtures at 25 °C.

a postulated common ion-pair intermediate show different sensitivities to solvent polarity, suggesting a more localised charge on the carbon in the addition step than in the elimination step.

The effect of solvent composition on the elimination-to-substitution ratio k_E/k_S is shown in Fig. 5. All three substrates show a considerable increase in the product ratio with increasing fraction of acetonitrile in the solvent. Similar behaviour was found for the closely related substrates **A-X** (Scheme 2) which do not have the 9-methyl substituent.[8,9]

Added basic salts increase the elimination-to-substitution ratio. The effect is most significant in aqueous acetonitrile (Table 1). There is an approximately linear dependence between base concentration and k_E/k_S as shown for the two bases AcO$^-$ and CF$_3$COO$^-$ in Fig. 4.

A plausible explanation for this behaviour is that the base abstracts a hydron from the carbocation. The assumption that the addition of solvent to the ion pair to provide a substitution product is not affected by the general base, implies that a Brønsted parameter for this catalysis could be derived by employing the slope of k_E/k_S *versus* base concentration for the Brønsted plot. Such a plot is shown in Fig. 6 for the reactions with substituted acetate ions. A slope of $\beta = 0.07$ is obtained, which suggests a very early transition state with very little hydron transfer to the hydron-abstracting base. A parameter value of $\beta = 0.05$ has previously been reported for **A-Cl**.[8] The more stable ion pair formed from cumyl chloride has a Brønsted parameter of $\beta = 0.13$.[14] The chloride ion, which is a very weak base, also increases the k_E/k_S ratio, approximately to the same extent as the trifluoroacetate ion. However, owing to the low pK_a, the chloride ion shows an approximately three-fold positive deviation from the Brønsted plot (Fig. 6). Water, on the other hand, shows a *ca.* 10-fold negative deviation. Consistent with the apparent catalytic effect of chloride ions on k_E/k_S is the observation that the substrate **1-Cl** yields a higher k_E/k_S ratio than the ester **1-OOCCF$_3$** (Fig. 5), despite the difference in pK_a of the leaving groups.

The question concerning the possible role of Cl$^-$ as a general base has recently been addressed.[2,5] It was pointed out that an important driving force of the ionization is of course the solvation of the chloride ion but it is not expected to be complete at the contact ion-pair stage.[2] In addition to this positive effect for chloride ion as a base, there is a low catalytic activity of water as a hydron acceptor (Fig. 6), in accord with what has been observed previously for E1 reactions and water-promoted E2 reactions;[8,16,17,30,31] Brønsted plots generally show a negative deviation for water as a base of about one order of magnitude.

It has been concluded that even substrates which solvate to give relatively stable carbocations in mostly aqueous solution still produce most of the alkene from the ion pair.[32] Moreover, Bunton and coworkers have found that, even in highly aqueous solvents, added Cl$^-$ promotes elimination from relatively stable carbocations.[33]

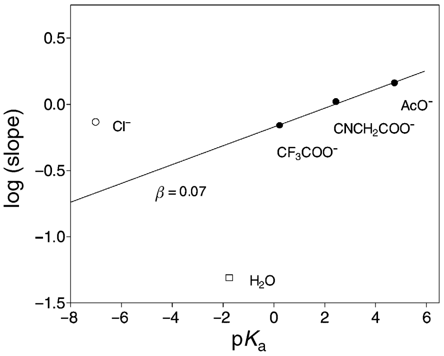


Fig. 6 Brønsted plot for the dehydronation of the ion-pair intermediate formed in the solvolysis of **1-Cl** in 40% acetonitrile in water; ionic strength 0.50 M, maintained with sodium perchlorate at 25 °C. The pK_a values refer to those in water (see ref. 39).

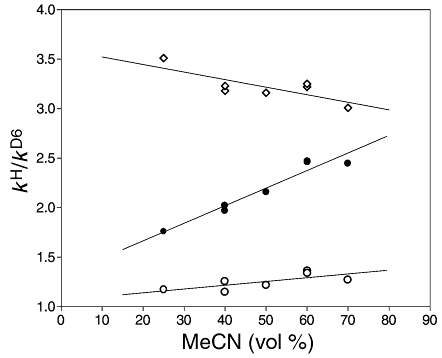


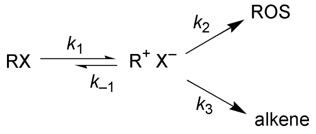
Fig. 7 The kinetic deuterium isotope effects for **1-Cl** and **1-Br** as a function of vol% acetonitrile in acetonitrile–water mixtures at 25 °C. Key: k_{obs}^H/k_{obs}^{D6} (●), k_E^H/k_E^{D6} (◇), k_S^H/k_S^{D6} (○).

Isotope effects

The measured kinetic deuterium isotope effect on the total reaction (k_{obs}^H/k_{obs}^{D6}) for the reactions without added salts (Table 4) *versus* the fraction of acetonitrile in the solvent is plotted in Fig. 7. There is a significant increase in isotope effect with increase in the fraction of the organic solvent that parallels the increase in k_E/k_S (Fig. 5). The data for the two substrates **1-Cl** and **1-Br** are very similar and are adequately described by a single linear regression line (Fig. 7). Added salts, which affect k_E/k_S, also have a corresponding effect on k_{obs}^H/k_{obs}^{D6} (Table 4). The change in the isotope effect may be explained by a small amount of internal return that increases slightly with increasing fraction of the organic solvent (*vide infra*).

The isotope effects on the separate reactions, k_E and k_S, respectively, are also very similar for the leaving groups Cl$^-$ and Br$^-$. There is a slight decrease in k_E^H/k_E^{D6} and a slight increase in k_S^H/k_S^{D6}, with an increasing fraction of acetonitrile in the solvent (Fig. 7).

Are the measured isotope effects consistent with a branched mechanism with a common ion-pair intermediate for the elimination and substitution reactions (Scheme 3)? Let us analyse the isotope expressions in some detail. The mechanistic model corresponds to the following relationships between phenomenological and microscopic rate constants [eqns. (2)–(4)]. The expressions for the isotope effects are given by eqns. (5)–(7).



Scheme 3

$$k_S = k_1k_2/(k_{-1} + k_2 + k_3) \quad (2)$$

$$k_E = k_1k_3/(k_{-1} + k_2 + k_3) \quad (3)$$

$$k_S + k_E = k_1(k_2 + k_3)/(k_{-1} + k_2 + k_3) \quad (4)$$

$$k_S^H/k_S^{D6} = (k_1^H/k_1^{D6})(k_2^H/k_2^{D6})(k_{-1}^{D6} + k_2^{D6} + k_3^{D6})/(k_{-1}^H + k_2^H + k_3^H) \quad (5)$$

$$k_E^H/k_E^{D6} = (k_1^H/k_1^{D6})(k_3^H/k_3^{D6})(k_{-1}^{D6} + k_2^{D6} + k_3^{D6})/(k_{-1}^H + k_2^H + k_3^H) \quad (6)$$

$$(k_S^H + k_E^H)/(k_S^{D6} + k_E^{D6}) = (k_1^H/k_1^{D6})[(k_2^H + k_3^H)/(k_2^{D6} + k_3^{D6})][(k_{-1}^{D6} + k_2^{D6} + k_3^{D6})/(k_{-1}^H + k_2^H + k_3^H)] \quad (7)$$

Reaction branching may cause enlarged and attenuated isotope effects as will be discussed below. Let us assume for simplicity that internal return is negligible ($k_{-1} << k_2, k_3$). The isotope effect on the ionization step, k_1^H/k_1^{D6}, is a secondary isotope effect caused by hyperconjugative weakening of the bonds to the six β-hydrogens. A maximum β-deuterium isotope effect of $1.15/^2H$, *i.e.*, a value of $k_{obs}^H/k_{obs}^{D6} < 2.31$ for six deuteriums is expected.[34] Also k_2^H/k_2^{D6} is a secondary isotope effect; the value should be close to unity. The primary isotope effect k_3^H/k_3^{D6}, on the other hand, should have a substantial value since it is a primary isotope effect which includes a small secondary isotope effect (with an expected value >1).

It can be inferred from eqn. (6) that the isotope effect on the elimination reaction attains a maximum value of $k_E^H/k_E^{D6} = (k_1^H/k_1^{D6})(k_3^H/k_3^{D6})$ when elimination is much slower than substitution ($k_3^H << k_2^H$). The isotope effect on the substitution reaction [eqn. (5)] attains under these conditions a maximum value of $k_S^H/k_S^{D6} = k_1^H/k_1^{D6}$. On the other hand, fast elimination, *i.e.* $k_3^H >> k_2^H$, yields a minimum elimination isotope effect of $k_E^H/k_E^{D6} = k_1^H/k_1^{D6}$, and a minimum substitution isotope effect given by eqn. (8),

$$k_S^H/k_S^{D6} = (k_1^H/k_1^{D6})(k_2^H/k_2^{D6})(k_3^{D6}/k_3^H) \quad (8)$$

which can be approximated as $k_S^H/k_S^{D6} = (k_1^H/k_1^{D6})(k_3^{D6}/k_3^H)$. Branching as the cause of unusually large and unusually small isotope effects on competing reactions has been discussed previously for carbocation [1,8–18] and carbanion reactions,[11] and has also been generalized and reviewed.[1,11]

Fast internal return ($k_{-1} >> k_2, k_3$) yields eqn. (9),

$$k_E^H/k_E^{D6} = (k_1^H/k_1^{D6})(k_3^H/k_3^{D6})\ (k_{-1}^{D6}/k_{-1}^H) \quad (9)$$

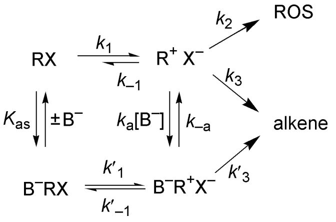
i.e., $k_E^H/k_E^{D6} \approx (k_1^H/k_1^{D6})(k_3^H/k_3^{D6})$, and $k_S^H/k_S^{D6} \approx (k_1^H/k_1^{D6})(k_2^H/k_2^{D6})$. This has the same effect on the elimination isotope effect as fast substitution. Thus, the observed elimination isotope effect is enlarged owing to multiplication by a factor larger than unity.

As discussed above, a small and changing amount of internal return has to be included in the mechanistic interpretation of the results (Scheme 3). The slight decrease in k_E^H/k_E^D with increasing fraction of the organic solvent component is also consistent with this interpretation. However, the slight increase in the isotope effect k_S^H/k_S^{D6} with increasing acetonitrile fraction of the solvent does not seem possible to accommodate into the mechanism of Scheme 3. The introduction of two parallel pathways, however, removes this inconsistency (see next section).

Previous reported results for the closely related **A-X** system showed an approximately constant ionization isotope effect k_{obs}^H/k_{obs}^{D6} and changes in the isotope effects for the separate rate constants are in accord with irreversible ionization *via* a common intermediate (Scheme 3, $k_{-1} << k_2, k_3$).[8–10]

Preassociation mechanism

Scheme 4 shows various reaction paths available for alkene formation. The rate constant k_3 represents elimination promoted by the leaving group and/or by the solvent. This can occur by rotation of the leaving group or a solvent water molecule into a reaction position, processes with expected rate constants of ~1 × 10^{11} s^{-1}.[35–37] A concerted pericyclic reaction is not reasonable; evidence that disqualifies this mechanism has recently been reported.[2] Another possible pathway is through preassociation of the base with the substrate, followed by ionization to give the triple ion complex $B^-R^+X^-$. This stepwise preassociation route is preferred for elimination when collapse of the triple ion complex to B^-RX is faster than B^- diffusing away, *i.e.*, $k_{-1}' > k_{-a}$. If the apparent slight catalysis by Brønsted bases is real (and not just a specific salt effect), it must occur by this preassociation route because the ion pair is so short-lived that diffusion is slower than the reaction of the intermediate with the solvent or leaving group. A water molecule is less effective as a base than the substituted acetate anions; the deviation from the Brønsted line is one order of magnitude as discussed above (Fig. 6). The apparent slight general base catalysis of $\beta = 0.07$ suggests that there is a barrier for the dehydronation of the ion pair. Accordingly, the elimination does not occur through an enforced uncoupled concerted mechanism.



Scheme 4

There is no competing concerted E2 reaction with the solvent because the much stronger base, the hydroxide ion, does not give any bimolecular elimination. The solvent-promoted E2 reaction is significant for the closely related, more slowly ionizing, secondary substrates, 9-(1-X-ethyl)fluorene, which have an acidic hydrogen in the 9-position of the fluorene moiety.[16,38]

The incomplete consistency of the measured isotope effects with the common ion-pair mechanisms of Scheme 3 suggests that the ion pair is very unstable and does not have time to choose between dehydronation and addition of a solvent water molecule. This supports the conclusion that the preassociation route is significant for the elimination reaction.

Experimental

General procedures

NMR spectra were recorded at 20 °C on a Varian Unity 300 spectrometer, for ^{1}H NMR at 300 MHz and for ^{13}C NMR at 75.45 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 Inertsil 5 ODS-2 (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 kept at 25.00 ± 0.03 °C. A Kontron Uvicon 930 spectrophotometer equipped with an automatic cell changer kept at constant temperature with water from the thermostat bath was used for some of the kinetic studies. The mass spectrometry experiments were performed on a Finnigan MAT GCQ instrument.

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. Methanol and acetonitrile were of HPLC grade and 2,2,2-trifluoroethanol (TFE) was of GC grade. All other chemicals were of reagent grade and used without further purification.

9-Methylfluorene. Synthesised according to a literature procedure.[40]

9-Methyl-9-(2-hydroxy-2-propyl)fluorene (1-OH). A solution of *n*-butyllithium (7.36 ml of a 1.6 M solution in hexane) was added to 9-methylfluorene (1.929 g) dissolved in dry THF (52 ml) at −78 °C under nitrogen. The resulting red solution was stirred for 40 min at −78 °C, and then dry acetone (0.8 ml) was added. The reaction mixture was stirred for 1 h, and then poured into a saturated NH_4Cl solution. The mixture was extracted 3 times with ether. The combined ether fractions were washed with water 3 times to neutrality, followed by washing with brine and drying over magnesium sulfate. After removal of the solvent, the crude product was purified by flash chromatography (silica gel) with ether–pentane as eluent. Recrystallization twice from hexane gave pure material: mp 70–71.5 °C (lit. 67–70 °C);[41] ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, $J = 6.84$ Hz), 7.57 (2H, d, $J = 6.87$ Hz), 7.25–7.41 (4 H, m), 1.74 (1 H, s), 1.63 (3 H, s), 1.06 (6 H, s).

9-Methyl-9-(2-hydroxy-2-[1′,1′,1′,3′,3′,3′-$^2H_6$]propyl)fluorene. Prepared from 9-methylfluorene and 1,1,1,3,3,3-($^2H_6$)-acetone (>99.5 atom% ^{2}H, Ciba-Geigy) according to the method described above. The ^{2}H content of the crystalline material was measured by ^{1}H NMR as >99.7 atom%.

9-Methyl-9-(2-chloro-2-propyl)fluorene (1-Cl). A solution of **1-OH** (0.56 g) in dichloromethane (43 ml) containing anhydrous calcium chloride and lithium chloride was cooled to 0 °C. Dry hydrogen chloride was bubbled through the solution for 12 h. After filtration, the solvent was removed. Recrystallization from pentane several times gave pure material: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.67–7.75 (4 H, m), 7.24–7.41 (4 H, m), 1.79 (3 H, s), 1.45 (6 H, s); *m*/*z* 256, 258 (M^+).

9-Methyl-9-(2-chloro-2-[1′,1′,1′,3′,3′,3′-$^2H_6$]propyl)fluorene. Prepared from the deuterated alcohol according to the method described above. The ^{2}H content of the crystalline material was measured by ^{1}H NMR as >99.5 atom%.

9-Methyl-9-(2-bromo-2-propyl)fluorene (1-Br). A solution of **1-OH** (0.2 g) in dry dichloromethane (3 ml) was added to 2.5 ml of concentrated HBr solution saturated with $ZnBr_2$ in a separating funnel. The mixture was shaken for 15 s and the reaction was quenched by the addition of pentane. After separation, the organic phase was washed 3 times with water. After evaporation the residue was purified by repeated recrystallization (6 times) from pentane giving the pure **1-Br**: mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (2 H, d, $J = 7.56$ Hz), 7.69 (2 H, d, $J = 7.44$ Hz), 7.39 (2 H, t, $J = 7.44$ Hz), 7.28 (2 H, t, $J = 7.48$ Hz), 1.83 (3 H, s), 1.67 (6 H, s); *m*/*z* 300, 302 (M^+).

9-Methyl-9-(2-bromo-2-[1′,1′,1′,3′,3′,3′-$^2H_6$]propyl)fluorene. Prepared from the deuterated alcohol according to the method described above. The ^{2}H content of the crystalline material was measured by ^{1}H NMR as >99.3 atom%.

9-Methyl-9-(2-trifluoroacetoxy-2-propyl)fluorene (1-OOCCF$_3$). Alcohol **1-OH** (0.4 g) was dissolved in dry dichloromethane (16 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 3 times with 0.5 M HCl and then 3 times with water and drying over magnesium sulfate. Evaporation of the solvent gave a viscous oil. NMR and HPLC confirmed the purity. ^{1}H NMR ($CDCl_3$) δ 7.74 (2 H, d, $J = 7.59$ Hz), 7.59 (2 H, d, $J = 7.44$ Hz), 7.40 (2 H, t, $J = 7.44$ Hz), 7.31 (2 H, t, $J = 7.59$ Hz), 1.83 (3 H, s), 1.67 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 156.0 (q, $J = 41.3$ Hz), 148.5, 141.2, 128.1, 127.4, 125.3, 120.0, 114.8 (q, $J = 287.5$ Hz), 93.2, 58.1, 21.0, 19.5; *m*/*z* 334 (M^+).

9-Methyl-9-(2-trifluoroacetoxy-2-[1′,1′,1′,3′,3′,3′-$^2H_6$]propyl)fluorene. Prepared according to the method above. The ^{2}H content of the viscous oil was measured by ^{1}H NMR as >99.6 atom%.

9-Methyl-9-(propen-2-yl)fluorene (2). Accidentally obtained in an attempt to purify crude 9-methyl-9-(2-bromo-2-propyl)fluorene (**1-Br**). The bromide (0.5 g) was completely decomposed on the column (silica gel, 70 g) to give **2** as the first fraction using CH_2Cl_2–C_5H_{12} (10 : 90) as eluent: ^{1}H NMR ($CDCl_3$) δ 7.42 (2 H, m), 7.26–7.40 (6 H, m), 5.35 (1 H, s), 5.07 (1 H, t, $J = 1.38$ Hz), 1.57 (3 H, s), 1.07 (3 H, s); *m*/*z* 220 (M^+).

Kinetics and product studies

Reactions with 1-Cl and 1-OOCCF$_3$. The reaction solutions were prepared by mixing acetonitrile, methanol, or 2,2,2-trifluoroethanol with water at room temperature, *ca.* 23 °C. The reaction vessel was a 1.5 ml HPLC vial, sealed with a gas-tight PTFE septum, which was placed in an aluminium block kept at 25 °C with water from the thermostat bath. The concentration of the substrate in the reaction solution was in the range of 0.04–0.12 mM. The volume of the 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 analysed using the HPLC apparatus. The reactions involving the substrate **1-Cl** were followed by monitoring the increase in the peak area of the product **1-OH**, and the rate constants were calculated from plots of peak area *versus* time by means of a nonlinear regression computer program. The rate constant for the disappearance of the substrate **1-OOCCF$_3$** was calculated from plots of substrate peak area *versus* time by means of the same computer program. All product ratios were constant throughout the reaction progress. 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, and the observed rate constants.

Reactions with 1-Br. The solvolytic reactions of the bromide in aqueous acetonitrile were too fast to be followed by the above HPLC procedure, especially in more than 50 vol% aqueous media. Instead, a spectrophotometric method based on monitoring the decrease in the absorbance of added 4-nitrophenolate anion at 409 nm was used. The reaction solutions were prepared by mixing acetonitrile with water at room temperature, *ca.* 23 °C, and a few microliters of sodium 4-nitrophenolate in 50 vol% acetonitrile in water were added. The reaction vessel, a 3 ml tightly stoppered UV cell, was kept at 25 °C. The concentration of the substrate in the reaction solution (2 ml) was in the range 0.04–0.12 mM, while that of the indicator was usually 2–3 times higher. The reaction was initiated by fast addition of a few microliters of the substrate dissolved in CH_2Cl_2 by means of a syringe. The reactions were followed for about 10 half lives. The product ratios were obtained by HPLC analyses as described above for **1-Cl** and **1-OOCCF$_3$**.

The relative HPLC response factors for **1-OH** and alkene **2** were measured from the HPLC analysis of a mixture of the two components, prepared by weighing and dissolved in acetonitrile. The response factors for the other 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. The maximum errors of the directly measured quantities were thus allowed to propagate as systematic errors into derived quantities, *e.g.*, reaction rate constants.

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References

1 A. Thibblin, *Chem. Soc. Rev.*, 1993, **22**, 427.
2 Q. Meng and A. Thibblin, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1397.
3 J. P. Richard, T. L. Amyes, S.-S. Lin, A. M. C. O'Donoghue, M. M. Toteva, Y. Tsuji and K. B. Williams, *Adv. Phys. Org. Chem.*, 2000, **35**, 67.
4 A. Thibblin and Y. Saeki, *J. Org. Chem.*, 1997, **62**, 1079.
5 M. M. Toteva and J. P. Richard, *J. Am. Chem. Soc.*, 1996, **118**, 11434.
6 Z. S. Jia, X. Zeng and A. Thibblin, submitted for publication.
7 T. L. Amyes and J. P. Richard, *J. Am. Chem. Soc.*, 1991, **113**, 8960.
8 A. Thibblin, *J. Am. Chem. Soc.*, 1987, **109**, 2071.
9 A. Thibblin and H. Sidhu, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1423.
10 H. Sidhu and A. Thibblin, *J. Phys. Org. Chem.*, 1994, **7**, 578.
11 A. Thibblin and P. Ahlberg, *Chem. Soc. Rev.*, 1989, **18**, 209.
12 A. Thibblin and H. Sidhu, *J. Am. Chem. Soc.*, 1992, **114**, 7403.
13 A. Thibblin, *J. Chem. Soc., Perkin Trans. 2*, 1986, 321.
14 A. Thibblin, *J. Phys. Org. Chem.*, 1989, **2**, 15.
15 A. Thibblin, *J. Am. Chem. Soc.*, 1989, **111**, 5412.
16 Q. Meng and A. Thibblin, *J. Am. Chem. Soc.*, 1995, **117**, 9399.
17 Q. Meng and A. Thibblin, *J. Am. Chem. Soc.*, 1997, **119**, 4834.
18 Q. Meng, B. Du and A. Thibblin, *J. Phys. Org. Chem.*, 1999, **12**, 116.
19 E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, 1948, **70**, 846.
20 S. Winstein, E. Grunwald and H. W. Jones, *J. Am. Chem. Soc.*, 1951, **73**, 2700.
21 A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 2770.
22 C. A. Bunton, M. M. Mhala and J. R. Moffatt, *J. Org. Chem.*, 1984, **49**, 3637.
23 C. A. Bunton, M. M. Mhala and J. R. Moffatt, *J. Org. Chem.*, 1984, **49**, 3639.
24 T. W. Bentley and K. Roberts, *J. Org. Chem.*, 1985, **50**, 1985.
25 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, Germany, 1988.
26 J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1383.
27 E. Grunwald and A. F. Butler, *J. Am. Chem. Soc.*, 1960, **82**, 5647; E. F. J. Duynstee, E. Grunwald and M. L. Kaplan, *J. Am. Chem. Soc.*, 1960, **82**, 5654.
28 J. Bartl, S. Steenken, H. Mayr and R. A. McClelland, *J. Am. Chem. Soc.*, 1990, **112**, 6918 and references therein.
29 A. Gervasini and A. Auroux, *J. Phys. Chem.*, 1993, **97**, 2628.
30 J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1373.
31 A. Thibblin and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 4963.
32 A. Thibblin, *J. Phys. Org. Chem.*, 1992, **5**, 367.
33 C. A. Bunton, N. Carrasco, N. Cully and W. E. Watts, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1859.
34 K. C. Westaway, *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, Amsterdam, 1987, ch. 5.
35 Y. Chiang and A. J. Kresge, *J. Am. Chem. Soc.*, 1985, **107**, 6363.
36 C. Paradisi and J. F. Bunnett, *J. Am. Chem. Soc.*, 1985, **107**, 8223.
37 K. Giese, U. Kaatze and R. Pottel, *J. Phys. Chem.*, 1970, **74**, 3718; U. Kaatze, *J. Chem. Eng. Data*, 1989, **34**, 371; U. Kaatze, R. Pottel and A. Schumacher, *J. Phys. Chem.*, 1992, **96**, 6017.
38 Q. Meng, A. Gogoll and A. Thibblin, *J. Am. Chem. Soc.*, 1997, **119**, 1217.
39 W. P. Jencks and J. Regenstein, *Handbook of Biochemistry and Molecular Biology*, ed. G. D. Fasman, CRC Press, Cleveland, USA, 3rd. edn., 1976; A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen and Co., London, 1962.
40 D. W. Robertson, J. H. Krushinski, E. E. Beedle, J. D. Leander, D. T. Wong and R. C. Rathbun, *J. Med. Chem.*, 1986, **29**, 1577.
41 D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, 1963, **85**, 1249.