Stepwise and Concerted Solvolytic Elimination and Substitution Reactions: E1 Reaction via a Primary Carbocation

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Abstract: Solvolysis of 9-(X-methyl)fluorene (**1-X**, X = I, Br, OBs) in 25 vol % acetonitrile in water gives the elimination product 9-methylidenefluorene and the substitution products 9-(hydroxymethyl)fluorene (**1-OH**) and 9-(acetamidomethyl)fluorene (**1-NHCOMe**). Kinetic studies of the corresponding ring-substituted compounds **2-X** and **3-X** show that the rate of elimination increases with increasing acidity of the substrate, Brønsted α > 0. The small kinetic deuterium isotope effects measured for the elimination reactions of the brosylates **1-OBs** and **3-OBs,** $k^H/k^D = 2.0 \pm 0.1$ and 2.8 ± 0.1, respectively, suggest significant amounts of E1 reaction. The bimolecular reactions of the brosylates with added bases may be of irreversible E1cB type in contrast to the reactions of the halides which exhibit E2 reaction with added bases as well as with solvent water.

Introduction

In some recent papers we have reported results on concerted solvent-promoted elimination reactions.[1−5] These E2 reactions with water as the hydron-abstracting base require relatively acidic substrates. For example, it was found that 9-(1-X-ethyl)-fluorene (X = I, Br) in a highly aqueous solvent reacts by a solvent-promoted E2 reaction in competition with a minor reaction through the ion pair.[2,3] In contrast, the corresponding brosylate gives stable alkene mainly via the ion pair as shown in Scheme 1.

We now report on a study in which we have decreased the stability of the putative ion pair by removing the methyl group of the exocyclic carbon (Scheme 2). Does this primary ion pair exist, i.e., does it have a significant lifetime, under solvolytic conditions? Our results indicate that it has a significant lifetime and that the solvolytic elimination of the brosylates occurs through the ion pair. There seems to be no precedence for E1 reaction of a primary substrate. The reasons for this surprisingly high stability of the primary carbocation are discussed. The paper also addresses the question about the mechanism of the competing solvent-promoted elimination of the brosylate: is it of E2 type or of irreversible E1cB type?

Results

The solvolysis of 9-(X-methyl)fluorene (**1-X**, X = I, Br, OBs) in 25 vol % acetonitrile in water provides the alkene 9-methylidenefluorene and the substitution products 9-(hydroxymethyl)fluorene (**1-OH**) and 9-(acetamidomethyl)fluorene (**1-NHCOMe**, Scheme 2). Solvolysis in mixtures of water with methanol affords 9-(methoxymethyl)fluorene (**1-OMe**) instead of the amide. The solvolyses of 2-bromo-9-(X-methyl)fluorene (**2-X**, X = Br, OBs) and 2,7-dibromo-9-(X-methyl)fluorene (**3-X**, X = Br, OBs) yield analogous products. The kinetics of the reactions were studied by a sampling-quench high-

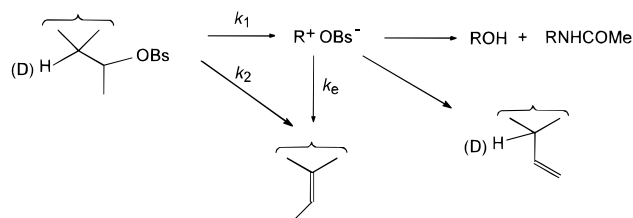[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.
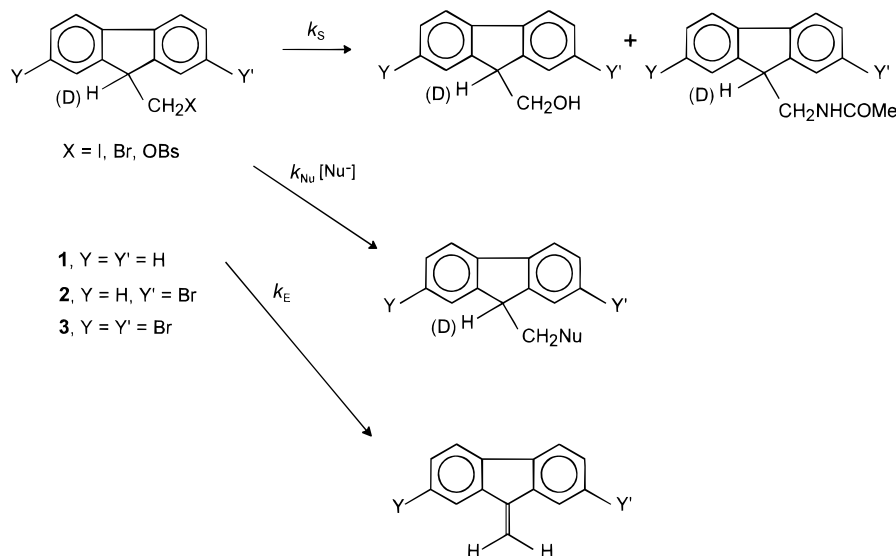(1) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1995,** *117,* 1839−1840.
(2) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1995,** *117,* 9399−9407.
(3) Meng, Q.; Gogoll, A.; Thibblin, A. *J. Am. Chem. Soc.* **1997,** *119,* 1217−1223.
(4) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1997,** *119,* 1224−1229.
(5) Meng, Q.; Thibblin, A. *J. Chem. Soc., Chem. Commun.* **1996,** 345−346.

Scheme 1

Table 1. Rate Constants for the Solvolyses of **1-X**, **2-X**, and **3-X** in 25 vol % Acetonitrile in Water[a] at 70 °C

substrate[b]	$10^6 k_{obs}$, s^{-1}	$10^6 k_S$, s^{-1}	$10^6 k_E$, s^{-1}
1-I	44.5		44.5
1-Br	8.11	0.38	7.73
1-OBs	32.7	29.9	2.77
2-Br	21.7	0.25	21.4
2-OBs	12.5	9.3	3.24
3-Br	68.0		68.0
3-OBs	17.3	5.0	12.3

[a] [HClO$_4$] = 1 mM. [b] Substrate concentration 0.01−0.1 mM.

performance liquid chromatography procedure. The product compositions are strongly dependent on the nature of the leaving group. For example, **1-Br** and **3-Br** yield 95% and almost 100% elimination, respectively, but **1-OBs** and **3-OBs** give 8% and 71% elimination, respectively. The measured rate constants and reaction conditions are shown in Table 1.

Table 2 shows kinetic data for the reactions with added buffer bases. The fast reactions with strong base at 25 °C were studied by following the increase in absorbance at 308 nm by UV spectrophotometry using the stopped-flow technique. The kinetic data are presented in Table 2.

The deuterated substrates 9-(X-methyl)(9-^{2}H)fluorene (**1-X-d**), 2-bromo-9-(X-methyl)(9-^{2}H)fluorene (**2-X-d**), and 2,7-di-bromo-9-(X-methyl)(9-^{2}H)fluorene (**3-X-d**) react slower to give alkene. The measured kinetic deuterium isotope effects for solvolysis and base-promoted reactions of these deuterated substrates are given in Table 3.

Perchlorate anion has a small rate-enhancing effect on the solvolysis reaction of **1-OBs** which mainly reacts through the ion pair. Addition of more efficient nucleophiles (Nu$^-$)

Scheme 2

1, Y = Y' = H
2, Y = H, Y' = Br
3, Y = Y' = Br

Table 2. Rate Constants for the Reactions of **1-X**, **2-X**, and **3-X** with Bases/Nucleophiles

| substrate[a]	base	temp, °C	$10^6 k_{Nu}$, $M^{-1} s^{-1}$	k_E/[base], $M^{-1} s^{-1}$
		25 vol % Acetonitrile in Water		
1-Br[b,c]	$NCCH_2COO^-$	70		2.47×10^{-4}
1-Br[c,d]	$MeOCH_2COO^-$	70		8.98×10^{-4}
1-Br[c,e]	AcO^-	70		3.34×10^{-3}
1-Br[f]	HO^-	25		3.11
1-OBs[b,c]	$NCCH_2COO^-$	70	27.5	7.02×10^{-6}
1-OBs[c,d]	$MeOCH_2COO^-$	70	31.3	1.17×10^{-4}
1-OBs[c,e]	AcO^-	70	44.6	5.02×10^{-4}
1-OBs[f]	HO^-	25		1.16
2-Br[c,d]	$MeOCH_2COO^-$	70		3.77×10^{-3}
2-Br[c,g]	AcO^-	70		1.37×10^{-2}
2-Br[f]	HO^-	25		8.59
2-OBs[c,h]	AcO^-	70	41.6	3.50×10^{-3}
2-OBs[f]	HO^-	25		7.91
3-Br[c,i]	CF_3COO^-	70		1.40×10^{-4}
3-Br[b,c]	$NCCH_2COO^-$	70		3.36×10^{-3}
3-Br[c,d]	$MeOCH_2COO^-$	70		1.62×10^{-2}
3-Br[c,g]	AcO^-	70		6.60×10^{-2}
3-Br[f]	HO^-	25		36.3
3-OBs[c,g]	AcO^-	70		2.39×10^{-2}
3-OBs[b,c]	$NCCH_2COO^-$	70		1.02×10^{-3}
3-OBs[c,d]	$MeOCH_2COO^-$	70		4.80×10^{-3}
3-OBs[c,i]	CF_3COO^-	70		31.6
3-OBs[f]	HO^-	25		35.2
		Methanol		
1-Br[f]	MeO^-	25		5.67
1-OBs[f]	MeO^-	25		3.75
2-Br[f]	MeO^-	25		54.6
2-OBs[f]	MeO^-	25		38.7
3-Br[f]	MeO^-	25		368
3-OBs[f]	MeO^-	25		314

a Substrate concentration 0.01–0.1 mM. *b* Measured with cyanoacetate, 0.025–0.25 M. *c* The ionic strength was maintained (0.75 M) with sodium perchlorate. *d* Measured with methoxyacetate buffer ([MeOCH₂COO⁻]/[MeOCH₂COOH] = 1), 0.025–0.25 M. *e* Measured with acetate buffer, 0.025–0.20 M ([NaOAc]/[HOAc] = 4). *f* Base concentration 1–25 mM. *g* Measured with acetate buffer, 0.025–0.20 M ([HOAc]/[NaOAc] = 4). *h* Measured with acetate buffer, 0.05–0.20 M ([NaOAc]/[HOAc] = 1). *i* Measured with CF₃COO⁻, 0.10–0.65 M.

significantly increases the overall reaction rate by opening up a bimolecular reaction route to substitution product **1-Nu** (Scheme 2) as shown with acetate ion in Figure 1. Acetate ion also functions as a general base catalyst for the elimination reaction.

Table 3. Kinetic Deuterium Isotope Effects for the Reactions of **1-X** and **3-X**

substrate[a]	base	temp, °C	k_{obs}^H/k_{obs}^D	k_S^H/k_S^D	k_E^H/k_E^D
1-Br[b]	solvent	70	3.7 ± 0.2	1.12 ± 0.08	4.1 ± 0.3
1-Br[c,d]	AcO^-	70			4.7 ± 0.4
1-Br[e]	HO^-	25			6.0 ± 1.2
1-Br[f]	MeO^- [h]	25			6.9 ± 0.8
1-OBs[b]	solvent	70	1.09 ± 0.08	1.05 ± 0.08	2.0 ± 0.1
1-OBs[c,d]	AcO^-	70			3.7 ± 0.2
1-OBs[e]	HO^-	25			7.6 ± 0.8
1-OBs[f]	MeO^- [h]	25			6.6 ± 0.7
3-OBs[b]	solvent	70	1.9 ± 0.1	1.04 ± 0.08	2.8 ± 0.1
3-OBs[d,g]	AcO^-	70			4.9 ± 0.4
3-OBs[e]	HO^-	25			7.5 ± 0.8
3-OBs[f]	MeO^- [h]	25			5.5 ± 0.6

a Substrate concentration 0.01–0.1 mM. *b* [HClO₄] = 1 mM. *c* Measured with acetate buffer, 0.025–0.20 M ([NaOAc]/[HOAc] = 4). *d* The ionic strength was maintained (0.75 M) with sodium perchlorate. *e* Measured with 1–25 mM sodium hydroxide. *f* Measured with 1–10 mM sodium methoxide. *g* Measured with acetate buffer, 0.025–0.20 M ([HOAc]/[NaOAc] = 4). *h* In methanol.
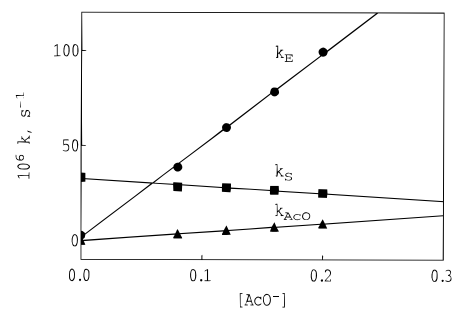
Figure 1. Dependence of the rate constants for solvolysis of **1-OBs** on acetate anion concentration in 25 vol % acetonitrile in water at 70 °C (ionic strength 0.75 M, maintained with sodium perchlorate).

The observed product ratio of **1-Nu** to **1-OH** is a measure of the competition between the nucleophile (Nu⁻) and water for reaction with the substrate and/or ion pair. The nucleophilic selectivities were calculated from the product ratios by treating the substitution reaction with solvent water as a second-order reaction. The nucleophilic selectivities were calculated from the measured product ratios by using eq 1. The nucleophilic selectivity parameters k_{Nu}/k_{HOH} and k_{MeOH}/k_{HOH} are thus dimensionless ratios of second-order rate constants. The measured values are given in Table 4.

Table 4. Nucleophilic Selectivities Expressed as Ratios of Second-Order Rate Constants for Reactions of **1-OBs**[a] at 70 °C

nucleophile	$n_{Me I}$[h]	k_{Nu}/k_{HOH}	nucleophile	$n_{Me I}$[h]	k_{Nu}/k_{HOH}
MeCN		0.20	AcO⁻ [d]	4.30	73
Cl⁻ [b]	4.37	81	N₃⁻ [e]	5.78	1.8×10^3
Br⁻ [b]	5.79	0.22×10^3	MeOH[f]	0	1.9
SCN⁻ [b]	6.70	0.98×10^3	H₂O	−0.27	1
F⁻ [c]	2.7	9.6	CF₃CH₂OH[g]	−2.8	0.30

[a] Substrate concentration 0.01−0.1 mM. [b] Using 0.75 M sodium salt. [c] Using 0.32 M NaF ([F⁻]/[HF] = 6). [d] Using 0.50 M NaOAc ([AcO⁻]/[HOAc] = 100). [e] Using 0.614 M NaN₃ ([N₃⁻]/[HN₃] = 9]). [f] 50 vol % methanol in water. [g] 50 vol % 2,2,2-trifluoroethanol in water. [h] Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319−326. The nucleophilicity of water has been estimated as $n = -0.27$: Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4549−4555.

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

Discussion

Stepwise Reactions through Ion Pairs. A carbocationic reaction path for the solvolysis of the bromides and the brosylates is strongly indicated by the formation of the substitution product **1-NHCOMe** with the acetonitrile component of the solvent mixture. It reasonably cannot be the result of an S$_N$2 reaction. The corresponding secondary substrates 9-(1-X-ethyl)fluorene, and the 2-bromo and the 2,7-dibromo derivatives, solvolyze to give terminal alkene in addition to amide that was concluded to be a further support for stepwise reaction through an ion pair (cf. Scheme 1).[1−3] The amides have been suggested to be formed by nucleophilic substitution with the acetonitrile component of the solvent. The reaction should occur within a pool of solvent molecules that are present when the carbocation is born. We have suggested that the unexpectedly high reactivity of acetonitrile with very short-lived carbocationic intermediates reflects the high dipole moment of acetonitrile (11.8 compared to 5.9 for water).[6] Accordingly, charge−dipole interactions between the carbocation and acetonitrile are assumed to be of importance in stabilizing the carbocation−acetonitrile pair.

Another indication for carbocation reactions is the gradual decrease in the solvent substitution rate constant k_S with increasing acidity of the substrate as shown for the brosylates in Figure 2. The effect, which is quantitatively expressed by a Brønsted parameter of $\alpha = -0.17$, is expected for carbocationic reactions because an enhanced acidity should decrease the stability of the carbocation-like transition state of the ionization step. The fact that the solvent substitution rate constant for **1-OBs** is about 80 times larger than that of **1-Br** (Table 1) may be further support for stepwise reactions because brosylates generally show faster stepwise reactions than bromides.

The small kinetic deuterium isotope effects on the elimination reactions of **1-OBs** and **3-OBs** of $k_E^H/k_E^D = 2.0 \pm 0.1$ and 2.8 ± 0.1, respectively (Table 3), indicate that elimination products are also formed from the ion pairs. We expect much larger isotope effects for water-promoted reactions of the E2 type or of the irreversible E1cB type (*vide infra*).[7] However, the isotope effects on the disappearance of the substrates (k_{obs}^H/k_{obs}^D, Table 3) are too large to attribute the elimination solely to irreversibly formed ion pairs; a maximum isotope effect k_{obs}^H/k_{obs}^D of about 1.15 is expected for such a mechanism.[8]

The small elimination isotope effects may be the consequence of two competing, parallel reactions: E2 with the solvent acting
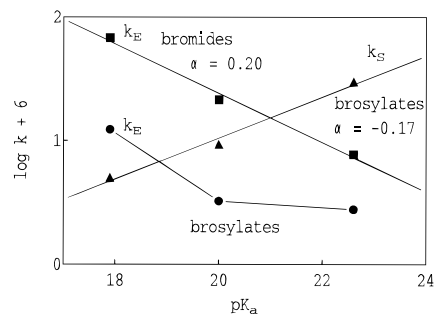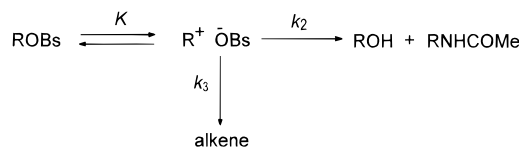
Figure 2. Brønsted plots for solvolytic elimination (k_E) and substitution (k_S), respectively, in 25 vol % acetonitrile in water at 70 °C: bromides (squares), brosylates (circles and triangles). The pK_a values refer to those of the parent fluorenes.[27]

Scheme 3

$$ROBs \underset{}{\overset{K}{\rightleftharpoons}} R^+ \ ^-OBs \xrightarrow{k_2} ROH + RNHCOMe$$

with k_3 branch to alkene

as the base and E1 through an irreversibly formed ion pair. However, a closer analysis of the data shows that a branched ion-pair mechanism in which all or the major part of the substitution products with the solvent originate from an irreversibly formed intermediate is not consistent with all the measured isotope effects. The simplest way to account for the results with the brosylates is therefore a single reaction path to alkene via an ion-pair mechanism involving branching from a reversibly formed intermediate (Scheme 3).[9]

The steady-state approximation applied to Scheme 3 yields the following rate and isotope effect expressions:

$$k_S = Kk_2 \qquad (2)$$

$$k_E = Kk_3 \qquad (3)$$

$$k_{obs} = k_S + k_E = K(k_2 + k_3) \qquad (4)$$

$$k_S^H/k_S^D = (K^H/K^D)(k_2^H/k_2^D) \qquad (5)$$

$$k_E^H/k_E^D = (K^H/K^D)(k_3^H/k_3^D) \qquad (6)$$

$$k_{obs}^H/k_{obs}^D = (K^H/K^D)(k_2^H + k_3^H)/(k_2^D + k_3^D) \qquad (7)$$

Let us assume the following reasonable values for the microscopic isotope effects: $K^H/K^D = 1.04$, $k_2^H/k_2^D = 1.0$, and $k_3^H/k_3^D = 2.7$.[9] This gives a good account of the measured isotope effects for **3-OBs** (Table 3); the relative rate constants used for the calculation of k_{obs}^H/k_{obs}^D are taken from Table 1:

$$k_S^H/k_S^D = 1.04 \times 1.0 = 1.04$$

$$k_E^H/k_E^D = 1.04 \times 2.7 = 2.8$$

$$k_{obs}^H/k_{obs}^D = 1.04(5.0 + 12.3)/(5.0/1.0 + 12.3/2.7) = 1.9$$

The results for the less acidic substrate **1-OBs** are also consistent with the Scheme 3 model if a relatively small isotope

(6) Sidhu, H.; Thibblin, A. *J. Phys. Org. Chem.* **1994**, *7*, 578−584.

(7) A reviewer suggests a solvent-promoted E2 reaction with a very E1-like transition state as an alternative to the carbocation mechanism.

(8) Westaway, K. C. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, Chapter 5.

(9) Reaction branching as the cause of unusually large and unusually small kinetic isotope effects has been reviewed: (a) Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* **1989**, *18*, 209−224. (b) Thibblin, A. *Chem. Soc. Rev.* **1993**, *22*, 427−433.

effect is assumed for the dehydronation step. The small elimination isotope effects and the fact that k_E^H/k_E^D is larger for the more acidic substrate **3-OBs** indicate product-like transition states with extensive hydron transfer from the brosylate ion pairs.

Apparently, the carbocation has a short but significant lifetime. Thus, the ion pair either undergoes reaction with a solvent molecule that is present when the carbocation is born or is dehydronated by the leaving group or by a solvent water molecule. A reasonable explanation of the stability of the primary carbocation is that π-orbitals of the fluorenyl moiety assist the ionization by interaction with the developing p-orbital on the backside of the reaction center. Theoretical calculations by MNDO methods support this conclusion. Thus, it has been reported that the energy level of the HOMO of the fluorenyl-methyl carbocation is -12.3 eV, which is 3.7 eV below that of the HOMO of fluorene.[10] The lifetime of the carbocation is further discussed at the end of this paper.

Consistently, the closely related secondary substrates (*R,R*)- and (*R,S*)-9-(1-X-ethyl)fluorene (X = OBs) solvolyze to give about 90% retention of configuration with solvent water as the nucleophile.[3] With added nucleophiles the secondary substrates show bimolecular kinetics with mainly inversion of configuration, but the amount of inversion decreases with the leaving group in the following order: I > Br > OBs.[3]

Neighboring-group participation has also been observed for the solvolysis of (*R,R*)- and (*R,S*)-1-(1-X-ethyl)indene (X = I, Br, Cl, OBs).[5] The result of the homoallylic participation is that the substitution reaction with solvent water shows a very high retention of configuration.

The curvature of the log k_E plot of the solvolytic elimination for the brosylates versus pK_a of the substrate as shown in Figure 2, the bromides do not show such a behavior, may suggest a carbocation elimination mechanism. The α value for the corresponding secondary system is slightly negative in contrast to the positive α value for the bromides, which has been concluded to be strong evidence for solvolytic E1 reactions of the secondary brosylates.[3]

Further support of the ion-pair mechanism for the solvolytic elimination is that water shows roughly a 14-fold positive deviation from the Brønsted plot ($\beta = 0.79$) for **1-OBs** with substituted acetate anions. The positive deviation could be attributed to a change in mechanism: the reactions with substituted acetate anions are E2 reactions, but the reaction without added base is of the E1 type. The E1 reaction of **3-OBs** is slower and the base-promoted E2 reaction of this substrate is favored by its higher acidity, which give rise to a negative deviation (10-fold) from the Brønsted plot ($\beta = 0.64$). This is also the normal behavior of water as a catalyst in E2 reactions as shown in the Brønsted plots for **1-Br** ($\beta = 0.49$) and **3-Br** ($\beta = 0.60$): the catalytic constant for water as a base falls below the Brønsted line for the substituted acetate anions by factors of 13 and 6, respectively. Similar negative deviations for E2 reactions have been observed before.[2,3] Dehydronation of carbocation intermediates shows similar behavior.[11–13] 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.[14] The low catalytic activity of water as a hydron acceptor in E2 reactions probably

reflects some kind of solvation effect. However, the absence of a negative charge is favorable in the E2 transition state because there is an unfavorable electrostatic interaction between a negatively charged base and the developing partial negative charge on the β-carbon.

Solvent- and Base-Promoted Elimination Reactions. The solvolytic elimination reactions of 9-(1-X-ethyl)fluorene (X = Br, I) have been concluded to be of the water-promoted E2 type.[1–3] This conclusion is based on the measured large kinetic deuterium isotope effects, the substantial Brønsted β values, and the low sensitivity to solvent ionizing power. The solvolytic elimination reaction of the primary substrate **1-Br** shows similar behavior.

(i) The large isotope effect of $k_{obs}^H/k_{obs}^D = 3.7 \pm 0.2$ for the disappearance of the substrate at 70 °C (Table 3) implies that the alkene formation does not proceed via an irreversibly formed carbocationic intermediate, since an isotope effect of $k^H/k^D \leq 1.15$ at 25 °C is expected for such a mechanism.[8] A reversibly formed intermediate which undergoes rate-limiting hydron transfer has been ruled out for the secondary bromide since it is unreasonable that such a short-lived ion pair would undergo a bimolecular reaction to yield exclusively the stable alkene at a low concentration of added base.[2]

(ii) Another, independent, strong indication against a carbocation mechanism for the elimination reaction of the primary substrate **1-Br** is the measured Brønsted parameter ($\beta = 0.49$). A very small β value is expected for a mechanism involving rate-limiting dehydronation of a very unstable carbocation intermediate.[12] Accordingly, the data exclude reactions through an ion pair, either coupled with the substitution reactions or as a separate reaction. However, they indicate the E2 or the irreversible E1cB mechanism.

(iii) The fact that the fraction of elimination to give the stable alkene is larger for I$^-$ than for Br$^-$ as leaving group, the opposite of what is expected for a stepwise carbocationic mechanism in which the leaving group of the ion pair acts as the hydron acceptor, is further support of the E2 mechanism. Thus, the corresponding tertiary substrates 9-(2-X-propyl)fluorene, which have been concluded to react stepwise, provide more terminal alkene from the chloride ion pair than from the bromide ion pair.[12,15] The element effect is substantial, $k_E^I/k_E^{Br} = 5.8$ (Table 1), which may support the E2 mechanism in favor of the irreversible E1cB mechanism. However, this is not conclusive evidence because hyperconjugative stabilization from the leaving group may be important in irreversible E1cB reactions.[16]

The tertiary bromide only exhibits E2 reaction in the presence of strong bases.[12,15,17] The decreased reactivity of the secondary substrate 9-(1-X-ethyl)fluorene (X = Br, I) to ionization shifts the major reaction pathway from stepwise solvolysis to solvent-promoted E2 reaction. The presence of bromo substituents in the 2 and 7 positions of the fluorene ring makes this reaction even more competitive due to the increased acidity of the β-hydron.[3] The decreased reactivity of the primary substrate **1-Br** to ionization should further favor the E2 mechanism. However, a minor fraction of the alkene may be produced through the ion pair.

The solvolysis substitution rate constant k_S for **1-Br** is 27 times smaller than that for the corresponding secondary substrate.[2] The solvolytic elimination rate constants of **1-X** (X = I, Br) are also smaller than those of the corresponding secondary analogs, e.g., 3 times smaller with bromide as leaving group. This is reasonable because the secondary system has

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(14) Thibblin, A.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 4963–4973 and references therein.

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(16) Thibblin, A. *Chem. Scr.* **1980**, *15*, 121–127 and references therein.

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one more methyl substituent to stabilize the E2 elimination transition state in which a significant extent of double bond character has been developed. However, with the stronger base HO^-, the primary bromide reacts 4.6 times faster than the secondary one, and with acetate anion the ratio is 1.8. This is consistent with the variable transition state theory which predicts an E2 transition state having less bond cleavage to the leaving group with a stronger base (*vide infra*). Even less $C-X$ bond cleavage is expected for OBs^-. Accordingly, the primary brosylate reacts 8.7 times faster with HO^- than the corresponding secondary derivative. Rate depression effects of α-methyl substituents have been observed previously by More O'Ferrall and co-workers for methoxide-promoted dehydrohalogenation reactions of fluorene derivatives.[18]

All the studied substrates show bimolecular kinetics with added bases as exemplified for **1-OBs** in Figure 1. The Brønsted plots for the general base catalysis of the elimination reactions all show substantial slopes: the β-values are 0.64 (**3-OBs**), 0.79 (**1-OBs**), 0.60 (**3-Br**), and 0.49 (**1-Br**). Consistently, the primary kinetic isotope effects on the elimination reactions with added bases are substantial (Table 3). The eliminations also exhibit significant sensitivity to changes in the acidity of the β-hydron. The Brønsted parameters for the bromides and the brosylates with acetate anion at 70 °C of $\alpha = 0.27$ and $\alpha = 0.36$, respectively, are slightly larger than those measured with hydroxide anion as base at 25 °C, $\alpha = 0.22$ (bromides) and $\alpha = 0.32$ (brosylates), respectively (plots not shown). Methoxide ion in methanol at 25 °C gives somewhat larger values, $\alpha = 0.39$ (bromides) and $\alpha = 0.41$ (brosylates).

The corresponding secondary substrates show a lower sensitivity to the acidity of the substrate; e.g., with bromide and brosylate leaving groups and acetate anion as the base, the α values are 0.21 and 0.27, respectively.[3] This is reasonable because the primary substrates are expected to react through transition states involving more hydron transfer.

The characteristics of the transition state of β-elimination reactions are conveniently described by More O'Ferrall–Jencks diagrams.[17,19] For example, the above-discussed change in transition state caused by the removal of the α-methyl group can be considered to be the effect of increasing the energy of the carbocation intermediate in the upper left-hand corner and the elimination product in the upper right-hand corner of the diagram. This corresponds to a change in the transition-state position as shown in Figure 3, resulting in a more carbanion-like transition state with a larger β value. Accordingly, the Brønsted parameter for the bromides increases from $\beta = 0.43$ to $\beta = 0.49$. Figure 3 can also be used to describe the effect of a poorer leaving group: the upper edge will increase in energy, and the result will be similar.

The assignment of the E2 mechanism to the base-promoted elimination reactions of the halides is in accord with the studies of More O'Ferrall and co-workers who proposed that the methoxide ion-promoted eliminations of these compounds in methanol are of the E2 type.[18] The main argument was the observation of elimination rates being larger than the estimated ionization rates. With less efficient leaving groups, such as carboxylate anions or tertiary amines, elimination was concluded to be of the irreversible E1cB type.[20]
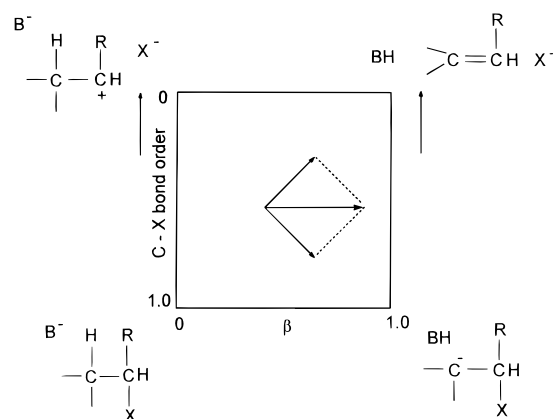

Figure 3. Reaction coordinate–energy diagram (More O'Ferrall–Jencks diagram) for alkene-forming 1,2-elimination.[17,19] The horizontal and vertical axes describe the amounts of hydron removal and cleavage of the bond to the leaving group as measured by the Brønsted β and $C-X$ bond order, respectively. The energy contour lines are omitted. The effect of removal of the α-methyl group of the substrate is a raising of the energy of the upper edge of the diagram. The result for a predominantly diagonal reaction coordinate is a shift to the right and an increase in β as indicated.
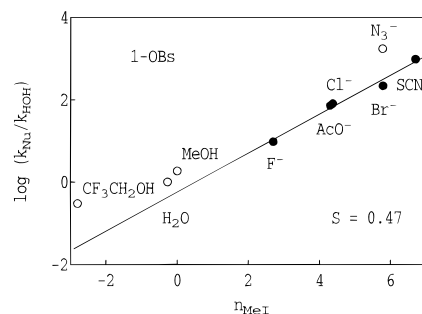

Figure 4. Swain–Scott plot for the reaction of **1-OBs** with nucleophiles in 25 vol % acetonitrile in water at 70 °C.

All the observed changes in the measured β values seem to be consistent with the changes in the characteristics predicted by the More O'Ferrall–Jencks diagram for central, diagonal transition states, with one exception. Thus, the *decrease* in β from 0.79 for **1-OBs** to 0.64 for **3-OBs** may indicate a shift from an E2 reaction to an irreversible E1cB reaction for the more acidic brosylate; an *increase* is predicted for the E2 mechanism with a diagonal transition state. However, an E2 transition state with a large horizontal component, corresponding to hydron transfer, is an alternative rationalization of the results.

Bimolecular Substitution Reactions (S_N2). The presence of a weak base/nucleophile such as acetate anion gives rise to competing bimolecular elimination and substitution reactions as shown for **1-OBs** in Figure 1. This substrate exhibits, as expected, a higher sensitivity to nucleophilicity than the corresponding secondary brosylate. The Swain–Scott parameters are $s = 0.47$ (Figure 4) and $s = 0.28$,[2] respectively. The transition state formed from the primary substrate requires more stabilizing interactions with the nucleophile than the secondary substrate in which the methyl group stabilizes the slightly carbocationic reaction center. This is reflected in the Swain–Scott parameters.

Water, methanol, and 2,2,2-trifluoroethanol show positive deviations from the Swain–Scott plot (Figure 4). This is

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consistent with, but does not require, nucleophilic assistance from the solvent. There is a positive deviation of 6-fold for the reaction of azide ion, consistent with an S_N2 transition state possessing some carbocationic character. Similar deviations have been observed for the corresponding secondary system as well as for other systems.[2,21,22]

The less carbocationic transition state of the primary brosylate is also reflected in a larger product ratio, [**1-SCN**]/[**1-NCS**] = 72, compared with 5 for the secondary derivative.[2] A gradual increase in the reactivity of S relative to N of the thiocyanate in the order of increasing acidity of the β-hydron has also been noticed.[3]

The relative large nucleophilic selectivity ratio of k_{MeOH}/k_{HOH} = 1.9 for the primary brosylate may reflect S_N2 reaction with methanol. The value measured for the secondary derivative is 1.0,[2] and the tertiary chloride, which does not react by an S_N2 mechanism with methanol, shows a selectivity value as low as 0.6.[12] The very short lifetime of the tertiary chloride ion pair is also indicated by the selectivity ratio of $k_{N3}/k_{HOH} \approx 5$, which has been used to estimate a lifetime of roughly 1×10^{-11} s.[12] The lifetime of the primary carbocation should be, of course, even shorter. However, it is not possible to semiquantitatively estimate the lifetime by trapping experiments owing to the appearance of a second-order reaction with good nucleophiles as discussed above.

Experimental Section

General Procedures. NMR spectra were recorded for CDCl$_3$ solutions at 25 °C with a Varian Unity 400 spectrometer, for ^{1}H at 400 MHz and for ^{13}C at 100.6 MHz. Chemical shifts are indirectly referenced to TMS via the solvent signal (chloroform-d_1, 7.26 and 77.0 ppm). The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on a C18 (5 μm, 3 × 100 mm) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature in a HETO 01 PT 623 thermostat bath. UV spectrophotometry was performed with a Kontron Uvicon 930 spectrophotometer equipped with an automatic cell changer kept at constant temperature with water from the thermostat bath. The fast reactions were studied in the spectrophotometer with the stopped-flow technique by using an Applied Photophysics RX 1000 rapid kinetics spectrometer accessory. The pH was measured using a Radiometer PHM82 pH meter with an Ingold micro glass electrode.

Materials. Merck silica gel 60 (240−400 mesh) was used for flash chromatography. Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium and benzophenone. Pyridine and methylene chloride were distilled under nitrogen from calcium hydride. 9-(Hydroxymethyl)fluorene and 2-bromofluorene were purchased from Lancaster. Methanol and acetonitrile were of HPLC grade. All other chemicals were of reagent grade and used without further purification. The deuterium content of all the deuterated compounds was measured by ^{1}H NMR to be >99 atom % ^{2}H in the 9 position of the fluorene moiety. The deuterated compounds 2-bromo-9-(X-methyl)(9-^{2}H)-fluorene and 2,7-dibromo-9-(X-methyl)(9-^{2}H)fluorene (X = OH, Br, OBs) were synthesized using the same method used for the corresponding nondeuterated analogs.

2-Bromo(9,9-^{2}H$_2$)fluorene and 2,7-Dibromo(9,9-^{2}H$_2$)fluorene were prepared by the same method as has been used for the synthesis of (9,9-^{2}H$_2$)fluorene.[2,23]

9-(Hydroxymethyl)(9-^{2}H)fluorene (1-OH-d) was prepared from (9,9-^{2}H$_2$)fluorene following Ahlberg's procedure for the corresponding indenyl alcohol.[24] The crude product was purified by flash chroma-

tography (silica gel) with 25% ethyl acetate−pentane as eluent. Recrystallization twice from CH$_2$Cl$_2$−pentane (1:2) gave pure material: mp 101−102 °C.

2-Bromo-9-(hydroxymethyl)fluorene (2-OH) was prepared from 2-bromofluorene as described above. The crude product was purified by flash chromatography (silica gel) with 10−20% ethyl acetate in pentane as eluent. Recrystallization twice from CH$_2$Cl$_2$−pentane (1: 1) gave pure material: mp 115−116 °C.

2,7-Dibromo-9-(hydroxymethyl)fluorene (3-OH) was prepared from 2,7-dibromofluorene as described above. The crude product was purified by flash chromatography (silica gel) with ethyl acetate−pentane (20:80) as eluent. Recrystallization twice from ethyl acetate−pentane (1:10) gave pure material: mp 168−169 °C (lit.[25] mp 154 °C).

9-(Bromomethyl)fluorene (1-Br) was prepared by treatment of the alcohol **1-OH** with ZnBr$_2$−HBr in chloroform. Recrystallization twice from ethanol−pentane (1:2) gave pure material: mp 65−66 °C.

9-(Iodomethyl)fluorene (1-I) was prepared from **1-OH** with ZnI$_2$− HI in chloroform in a way similar to that described above. Purification by flash chromatography (silica gel) with ethyl acetate−pentane (3: 97) as eluent, followed by recrystallization from hexane, gave pure material: mp 93−94 °C.

2-Bromo-9-(bromomethyl)fluorene (2-Br) was prepared as described above. Recrystallization twice from ethanol−pentane (1:3) gave pure material: mp 89−90 °C.

2,7-Dibromo-9-(bromomethyl)fluorene (3-Br) was prepared by following a general bromination procedure.[26] To a magnetically stirred solution of *N*-bromosuccinimide (0.13 g) in tetrahydrofuran (4 mL) was added dropwise a solution of triphenyl phosphite (0.23 g) in THF. This was followed by adding **3-OH** (0.15 g). The mixture was stirred at room temperature for 15 h. The solvent was removed, and the residue was dissolved in a minimum amount of dichloromethane. Purification by flash chromatography (silica gel) with 3% ethyl acetate−pentane as eluent, followed by recrystallization from ethanol−pentane (1:1), gave pure material: mp 154−156 °C.

9-((((4′-Bromophenyl)sulfonyl)oxy)methyl)fluorene (1-OBs) was synthesized by stirring a mixture of **1-OH** (0.25 g), dry dichloromethane (5 mL), dry pyridine (2 mL), and *p*-bromobenzenesulfonyl chloride (0.75 g) at room temperature. The reaction mixture was quenched after 1 h (ca. 50% reaction) by addition of 2 M hydrochloric acid. The water phase was extracted with dichloromethane. The combined organic phases were washed with water and brine, and dried over sodium sulfate. Evaporation of the solvent and separation with flash chromatography on silica gel with ethyl acetate−pentane (5:95), followed by recrystallization from chloroform−ethanol−pentane (1:1: 2), gave pure **1-OBs**: mp 143−145 °C.

2-Bromo-9-((((4′-bromophenyl)sulfonyl)oxy)methyl)fluorene (2-OBs) was prepared as described above: mp 149−151 °C.

2,7-Dibromo-9-((((4′-bromophenyl)sulfonyl)oxy)methyl)fluorene (3-OBs) was prepared as described above: mp 173−175 °C.

Kinetics and Product Studies. The reaction solutions were prepared by mixing acetonitrile or methanol with water at room temperature, ca. 22 °C. A few microliters of substrate dissolved in tetrahydrofuran was added. Aliquots of this reaction mixture (∼500 μL) were transferred to several 2 mL HPLC flasks, which were sealed with gas-tight PTFE septa and placed in an aluminum block in the water thermostat bath. The concentration of the substrate in the reaction solution was usually about 0.01−0.1 mM. At appropriate intervals, samples were taken out and analyzed using the HPLC apparatus. The rate constants for the disappearance of the substrates were calculated from plots of substrate peak area versus time by means of a nonlinear regression computer program. Very good pseudo-first-order behavior was seen for all the reactions studied. The separate rate constants for the elimination and substitution reactions were calculated 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.

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The alkene products were found to be stable under the solvolytic reaction conditions for at least 20 half-lives.

The fast reactions with sodium hydroxide in 25 vol % acetonitrile in water or sodium methoxide in methanol were studied with the stopped-flow technique by following the appearance of the elimination product at 308 nm with UV spectrophotometry.

Determination of Relative HPLC Response Factors. Pure **1-OBs**, **1-Br**, **2-OBs**, **2-Br**, **3-OBs**, or **3-Br** in acetonitrile (1 mM $HClO_4$) was injected onto the high-performance liquid chromatograph at least five times. Then, 500 μL of this solution was transferred to a 2 mL measuring flask and 0.5 M aqueous sodium hydroxide solution (500 μL) was added. After 20 min, 1 M acetic acid (500 μL) was added, the volume adjusted to 2 mL with acetonitrile, and the sample analyzed again. The data were used to calculate the relative response factors for the substrates and the corresponding alkene products.

The relative response factors for **1-OBs** and **1-OH**, **2-OBs** and **2-OH**, and **3-Br** and **3-OH**, respectively, were calculated from HPLC analysis of a mixture of the two components, prepared by weighing, dissolved in acetonitrile (1 mM $HClO_4$). The response factors for **1-OMe**, **1-Nu**, and the amides were assumed to be the same as for the corresponding alcohols.

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

Supporting Information Available: Brønsted plots for the elimination reactions of **1-OBs**, **1-Br**, **3-OBs**, and **3-Br** with substituted acetate anions, Brønsted plots for the acetate anion-promoted elimination reactions of the bromides and the brosylates, and NMR data of the compounds (5 pages). See any current masthead page for ordering and Internet access instructions.

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