

# COMPETING SOLVOLYTIC SUBSTITUTION AND ELIMINATION REACTIONS VIA A COMMON IRREVERSIBLY FORMED ION–MOLECULE PAIR INTERMEDIATE

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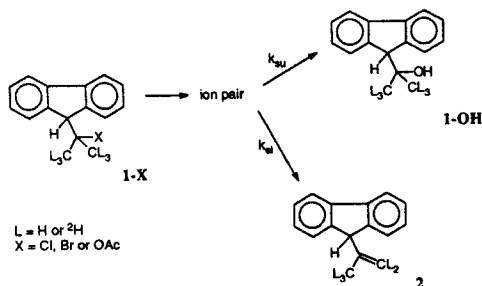
The acid-catalysed solvolysis of 9-(2-phenoxy-2-propyl)fluorene in mixtures of water with acetonitrile or methanol at 25 °C provides 9-(2-hydroxy-2-propyl)fluorene, 9-(2-propenyl)fluorene, and 9-(2-acetamido-2-propyl)fluorene or 9-(2-methoxy-2-propyl)fluorene, respectively. The overall kinetic deuterium isotope effects for the reactions of the hexadeuterated analogue 9-(1,1,1,3,3,3- $\text{D}_6$ )-9-(2-phenoxy-2-propyl)fluorene in 90 vol.% acetonitrile in water were measured as  $(k_E^H + k_S^H)/(k_E^D + k_S^D) = 1.54 \pm 0.05$ , which is composed of the isotope effect  $k_S^H/k_S^D = 1.4 \pm 0.1$  for formation of the substitution products and  $k_E^H/k_E^D = 4.0 \pm 0.2$  for production of 9-(2-methoxy-2-propyl)fluorene. Similar isotope effects were measured in other solvent mixtures. The results strongly indicate a branched mechanism involving rate-limiting formation of a common carbocation–molecule pair (with a secondary isotope effect of 1.54), which either undergoes nucleophilic attack by a solvent molecule (with a secondary isotope effect of *ca* 1), or is dehydrated (isotope effect *ca* 2.8) by the leaving group or by the solvent. The ion–molecule pair shows very low selectivities. Thus, in 50 vol.% acetonitrile in water, an acetonitrile molecule is as efficient as a water molecule as a nucleophile towards the ion–molecule pair,  $k_{\text{MeCN}}/k_{\text{H}_2\text{O}} \geq 1$  (ratio of second-order rate constants). The discrimination between methanol and water is anomalously small,  $k_{\text{MeOH}}/k_{\text{H}_2\text{O}} = 0.7$ .

## INTRODUCTION

We are interested in the role of ion–molecule pairs as intermediates in solvolytic reactions.<sup>1</sup> Intermediates of this type have also been described as ion–dipole pairs and encumbered carbocations. Few reports of results which are discussed in terms of such intermediates have been published.<sup>1–3</sup> Ion–molecule pairs are formed, for example, by stepwise solvolysis of a substrate with a neutral leaving group. This type of complex has most often been ignored in discussions of reaction mechanisms, presumably because it has been assumed to undergo diffusional separation much faster than reaction (or collapse). However, the intermediacy of ion–molecule pairs having significant lifetimes has been indicated in several studies. For example, a 1,3-rearrangement reaction and an ‘aromatization’ reaction have been employed as ion–molecule pair probes.<sup>1a,b</sup> One recent report discusses the role of ion–molecule pairs in solvolytic elimination reactions.<sup>1g</sup> Gas-phase reactions can also proceed through ion–molecule complexes.<sup>4</sup>

This work was started with the intention of studying

the difference in reactivity of a potential, very short-lived, ion–molecule pair intermediate formed from **1-OHPh**<sup>+</sup> and the analogous ion–pair intermediates formed from **1-X** (X = Br, Cl, OAc, Scheme 1), which have been studied previously.<sup>5,6</sup> The evidence for a branched mechanism with a common contact ion–pair intermediate was the measured kinetic deuterium isotope effects for the competing elimination and substitution reactions, which indicate a common intermediate, and the observed extremely small discrimination between added nucleophiles. The carboca-



Scheme 1

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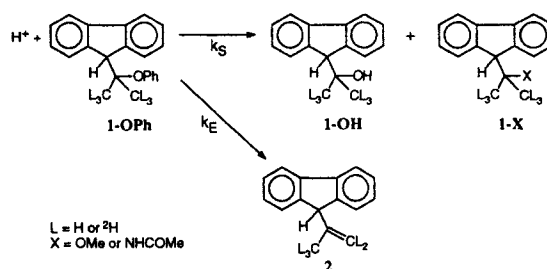
tionic intermediate  $1^+\text{Cl}^-$  was estimated to react to products with rate constants  $k_{\text{el}}$  and  $k_{\text{su}}$  of  $ca\ 7 \times 10^{10}$  and  $ca\ 4 \times 10^{10}\ \text{s}^{-1}$ , respectively (Scheme 1).<sup>5</sup> These rate constants are larger than the estimated rate constant for diffusional separation and, accordingly, indicate that the intermediate is of contact ion-pair type. The lifetime is in fact so short that the ion pair  $1^+\text{Cl}^-$  is expected to react within a pool of solvent molecules and nucleophiles/bases which are present when the ion pair is formed.

It has been found previously that the aforementioned negatively charged leaving groups abstract a hydron within the ion pair.<sup>5,6</sup> This process competes with elimination promoted by added general bases (Brønsted  $\beta = 0.05$ ) and by solvent. Does the leaving group PhOH, which is very weakly basic, also abstract a hydron within the ion-molecule pair? What is the lifetime of the ion-molecule pair  $1^+\text{OHPh}$ ? These are some of the issues discussed in this paper.

In aqueous acetonitrile, nucleophilic substitution occurs not only with water but also with the weakly nucleophilic acetonitrile to give the nitrilium ion  $1\text{-N}\equiv\text{CMe}^+$ . This product is unstable and reacts rapidly with water to give the acetamide  $1\text{-NHCOMe}$  as the final product. An unexpectedly large fraction of this product was obtained; possible reasons are discussed.

## RESULTS

The acid-catalysed solvolysis of 9-(2-phenoxy-2-propyl)fluorene (**1-OPh**) in mixtures of water and acetonitrile at 25 °C provides the alkene 9-(2-propenyl)-



fluorene (**2**) in addition to the substitution products 9-(2-hydroxy-2-propyl)fluorene (**1-OH**) and 9-(2-acetamido-2-propyl)fluorene (**1-NHCOMe**) (Scheme 2). More of the amide **1-NHCOMe** is formed in solutions containing a greater fraction of acetonitrile. Reaction in methanol-water solutions provides 9-(2-methoxy-2-propyl)fluorene (**1-OMe**) instead of the amide. No trace of 9-isopropylidenefluorene is formed in these reactions. The kinetics of the reactions were studied by a sampling-quench high-performance liquid chromatography procedure. The measured rate constants and reaction conditions are shown in Table 1.

The acid-catalysed solvolysis of the alcohol **1-OH** to give **1-NHCOMe** and **2** is slow. The acid-catalysed hydration of **2**, which is accompanied by formation of **1-NHCOMe** in water-acetonitrile, is also slow (Table 1). The amide **1-NHCOMe** is stable under the reaction conditions.

Table 1. Rate constants and rate-constant ratios for the reactions of **1-OPh**<sup>a</sup> at 25 °C<sup>b</sup>

Substrate	Solvent <sup>c</sup>	$10^6 k_{\text{obs}}/[\text{H}^+]$ ( $\text{l mol}^{-1}\ \text{s}^{-1}$ )	$10^6 k_{\text{E}}/[\text{H}^+]$ ( $\text{l mol}^{-1}\ \text{s}^{-1}$ )	$10^6 k_{\text{S}}/[\text{H}^+]$ ( $\text{l mol}^{-1}\ \text{s}^{-1}$ )	$k_{\text{E}}/k_{\text{S}}$	$k_{\text{MeCN}}/k_{\text{HOH}}^{\text{d}}$ or $k_{\text{MeOH}}/k_{\text{HOH}}^{\text{d}}$
<b>1-OPh</b>	50% MeCN <sup>e</sup>	1.49 (0.94)	0.32 (0.09)	1.17 (0.85)	0.27	$\geq 1.0$
<b>1-OPh</b>	90% MeCN <sup>f</sup>	34.6 (22.4)	5.2 (1.3)	29.4 (21.1)	0.18	$\geq 0.26$
<b>1-Br</b>	90% MeCN <sup>f</sup>				4	$\geq 0.14$
<b>1-Br</b> <sup>g</sup>	90% MeCN	39.3 <sup>g</sup>	37.2 <sup>g</sup>	2.1 <sup>g</sup>	18 <sup>g</sup>	$\geq \{0.04\}$
<b>1-OH</b>	50% MeCN <sup>e</sup>	0.006	0.003	0.002	1.5	
<b>1-OH</b>	90% MeCN <sup>f</sup>	0.82	0.34	0.48	0.7	
<b>2</b>	50% MeCN <sup>e</sup>	0.095				$\geq 0.4$
<b>2</b>	90% MeCN <sup>f</sup>	0.89				$\geq 0.4$
<b>1-OPh</b>	70% MeOH <sup>h</sup>				0.4	0.7
<b>1-Br</b> <sup>g</sup>	70% MeOH	671 <sup>g</sup>	481 <sup>g</sup>	190 <sup>g</sup>	2.5 <sup>g</sup>	0.7 <sup>g</sup>
<b>2</b>	70% MeOH <sup>h</sup>					$\sim 0.9$

<sup>a</sup> Substrate concentration 0.2 mM.

<sup>b</sup> The values in parentheses refer to reactions of **d<sub>6</sub>-1-OPh**.

<sup>c</sup> By volume in water.

<sup>d</sup> Dimensionless ratio of second-order rate constants, cf. equation (1).

<sup>e</sup> With acid,  $[\text{H}_2\text{SO}_4] = 2.00\ \text{M}$ .

<sup>f</sup> With acid,  $[\text{H}_2\text{SO}_4] = 0.85\ \text{M}$ .

<sup>g</sup> Without acid, pseudo-first-order rate constants in  $\text{s}^{-1}$  (Ref. 6).

<sup>h</sup> With acid,  $[\text{H}_2\text{SO}_4] = 2.1\ \text{M}$ .

Table 2. Kinetic deuterium isotope effects for the reactions of **1-OPh** at 25°C<sup>a</sup>

Solvent <sup>b</sup>	$(k_E^H + k_S^H)/(k_E^{D6} + k_S^{D6})$	$k_E^H/k_E^{D6}$	$k_S^H/k_S^{D6}$
50% MeCN <sup>c</sup>	$1.59 \pm 0.05$	$3.6 \pm 0.2$	$1.4 \pm 0.1$
90% MeCN <sup>d</sup>	$1.54 \pm 0.05$	$4.0 \pm 0.2$	$1.4 \pm 0.1$

<sup>a</sup> The rate constants are recorded in Table 1.<sup>b</sup> By volume in water.<sup>c</sup> [H<sub>2</sub>SO<sub>4</sub>] = 2.00 M.<sup>d</sup> [H<sub>2</sub>SO<sub>4</sub>] = 0.85 M.

The discrimination between reaction of the carbocation intermediate with water and the other nucleophilic component (X) of the binary solvent mixture was calculated from the measured product ratio by using the equation

$$k_X/k_{\text{HOH}} = ([1\text{-X}]/[1\text{-OH}])([\text{H}_2\text{O}]/[\text{X}]) \quad (1)$$

The values obtained, which are ratios of second-order rate constants, are given in Table 1. The reported selectivities for reaction with acetonitrile and water are minimum values since reaction of the nitrilium ion **1-N≡CMe**<sup>+</sup> to amide **1-NHCOMe** is not necessarily fast compared with its reaction to alcohol **1-OH** and alkene **2**. The product ratios  $[1\text{-NHCOMe}]/[1\text{-OH}]$  are approximately constant during the reactions. The selectivity value of  $k_{\text{MeCN}}/k_{\text{HOH}} \approx 0.9$  measured for the alkene **2** is approximate owing to the relatively fast interconversion of the two products **1-OH** and **1-Ome**.

Relative to **1-OPh**, the corresponding deuterated analogue 9-(1,1,1,3,3,3-<sup>2</sup>H<sub>6</sub>)-9-(2-phenoxy-2-propyl)-fluorene (**d<sub>6</sub>-1-OPh**) reacts more slowly and gives smaller fractions of elimination product **2** (Table 1). The measured isotope effects are given in Table 2.

Scheme 2 can be extended to also include the slow interconversion reactions of the products in water–acetonitrile (Scheme 3,  $k_S = k_W + k_M$ ). The reactions at constant pH follow the rate laws shown in equations (2)–(5).

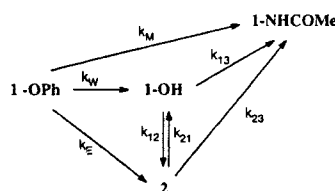
$$d[1\text{-OPh}]/dt = -(k_E + k_W + k_M)[1\text{-OPh}] \quad (2)$$

$$d[2]/dt = k_E[1\text{-OPh}] + k_{12}[1\text{-OH}] - (k_{21} + k_{23})[2] \quad (3)$$

$$d[1\text{-OH}]/dt = k_W[1\text{-OPh}] - (k_{12} + k_{13})[1\text{-OH}] + k_{21}[2] \quad (4)$$

$$d[1\text{-NHCOMe}]/dt = k_M[1\text{-OPh}] + k_{13}[1\text{-OH}] + k_{23}[2] \quad (5)$$

However, the evaluation of the individual rate constants  $k_E$ ,  $k_W$  and  $k_M$  is facilitated by the fact that the product ratio  $[1\text{-OH}]/[1\text{-NHCOMe}]$  is approximately constant during two to three half-lives. Thus, Scheme 8, which is a good approximation of Scheme 3, has been used for computer simulation of the rate constants (see Experimental).

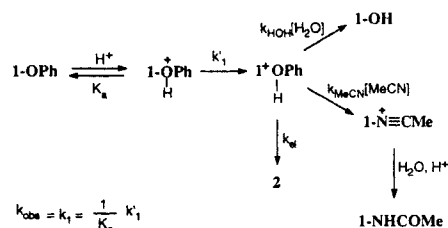


Scheme 3

## DISCUSSION

The solvolysis of **1-OPh** requires acidic conditions; no reaction occurs without addition of strong acid. The acid-catalysed solvolysis in acetonitrile–water can be rationalized with the mechanistic scheme shown in Scheme 4. Accordingly, the hydronated ether undergoes a carbon–oxygen cleavage, which will be called ionization in the following, to give an ion–molecule pair. This intermediate is attacked both by water and by the weakly nucleophilic acetonitrile. The product of the latter is a nitrilium ion, which in a subsequent step is hydrolysed to the amide. Dehydration of the ion–molecule pair intermediate yields the elimination product **2**.

This mechanistic scheme is analogous to what has been proposed for the solvolysis of the related substrates with negatively charged leaving groups **1-Br**, **1-Cl** and **1-OAc** through irreversibly formed ion-pair intermediates (Scheme 1).<sup>5,6</sup> The measured kinetic deuterium isotope effects with these substrates show



Scheme 4

that the ionization step is slow. Thus, the isotope effect for the disappearance of **1-Br** is constant,  $k^H/k^{D6} = 2.3$ , when the solvent composition changes from 70 vol.% methanol or acetonitrile in water up to 100 vol.% of the organic solvent.<sup>6</sup> The elimination-to-substitution ratio varies from 2.5 to infinity (for 100% acetonitrile).<sup>6</sup> These results strongly suggest that formation of the ion-molecule pair **1<sup>+</sup>OHPH** is irreversible since this species is expected to undergo return even more slowly than the ion pairs owing to the relatively low nucleophilicity of PhOH.

The measured isotope effects on the separate reactions  $k_E$  and  $k_S$  (Scheme 2) are consistent with reaction branching. Let us discuss the effect of branching by using Scheme 5, which is a simplified version of Scheme 4. The corresponding rate constant expressions and isotope effect equations are given in equations (6)–(8).

$$k_E = k_1 k_{el} / (k_{-1} + k_{su} + k_{el}) \quad (6)$$

$$k_S = k_1 k_{su} / (k_{-1} + k_{su} + k_{el}) \quad (7)$$

$$k_S + k_E = k_1 (k_{su} + k_{el}) / (k_{-1} + k_{su} + k_{el}) \quad (8)$$

If  $k_{-1} \ll k_{su}, k_{el}$  the following equations are valid:

$$k_E^H/k_E^{D6} = (k_1^H/k_1^{D6})(k_{el}^H/k_{el}^{D6})(k_{su}^{D6} + k_{el}^{D6}) / (k_{su}^H + k_{el}^H) \quad (9)$$

$$k_S^H/k_S^{D6} = (k_1^H/k_1^{D6})(k_{su}^H/k_{su}^{D6})(k_{su}^{D6} + k_{el}^{D6}) / (k_{su}^H + k_{el}^H) \quad (10)$$

$$(k_S^H + k_E^H) / (k_S^{D6} + k_E^{D6}) = (k_1^H/k_1^{D6}) \quad (11)$$

$$= k_E^H/k_E^{D6} > (k_E^H + k_S^H) / (k_E^{D6} + k_S^{D6}) > k_S^H/k_S^{D6} \quad (12)$$

The competition between substitution ( $k_{su}$ ) and elimination ( $k_{el}$ ), which are expected to have a very small secondary  $\beta$ -deuterium isotope effect close to unity and a primary  $\beta$ -deuterium isotope effect, respectively, gives rise to amplification and attenuation of the observed isotope effects (the isotope effect  $k_E^H/k_E^{D6}$  is not a purely primary isotope effect; because there is more than one  $\beta$ -deuterium,  $k_E^H/k_E^{D6}$  includes a small secondary isotope effect with an expected value of  $>1$ ). Thus, the elimination isotope effect  $k_E^H/k_E^{D6}$  is enlarged owing to the competition [cf. equation (9)] and the substitution isotope effect  $k_S^H/k_S^{D6}$  is attenuated [equation (10)] relative to the large secondary isotope effect on the ionization step. A maximum elimination isotope effect  $k_E^H/k_E^{D6}$  is obtained when the fraction of substitution is

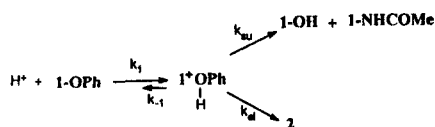
much larger than elimination, i.e.  $k_{su} > k_{el}$ . Under these conditions a maximum isotope effect  $k_S^H/k_S^{D6}$  is measured. Competition as the cause of enlarged and attenuated isotope effects has been discussed in several reports and reviews.<sup>1d,5,6,7</sup>

An isotope effect on the elimination step of the intermediate of  $k_{el}^H/k_{el}^{D6} \approx 2.8$  is consistent with the measured isotope effects on  $k_{obs}$  ( $= k_E + k_S$ ),  $k_E$  and  $k_S$ . An elimination isotope effect  $k_{el}^H/k_{el}^{D6}$  of the same size was estimated for the elimination of HCl from the ion pair **1<sup>+</sup>Cl<sup>-</sup>**.<sup>5</sup> Consistently, the Brønsted parameter was found to be very small,  $\beta = 0.05$ .<sup>5</sup>

The observed isotope effect  $k_{obs}^H/k_{obs}^{D6}$  ( $= k_1^H/k_1^{D6}$ ) (Table 2) for the disappearance of **1-OPh** contains not only the isotope effect on the ionization step, but also an isotope effect on the pre-equilibrium step. The complete expression is  $k_{obs}^H/k_{obs}^{D6} = [(1/K_a^H)/(1/K_a^{D6})] (k_1^H/k_1^{D6})$  (Scheme 4). The isotope effect on the pre-equilibrium step should be slightly larger than unity. Accordingly, the ionization isotope effect  $k_1^H/k_1^{D6}$  is smaller than the corresponding isotope effects for **1-Cl** and **1-Br**, which were measured as 2.2 and 2.3, respectively. The reason for the smaller isotope effect for **1-OPh** is not known.

Why is the common intermediate an ion-molecule pair and not a free carbocation? The answer to this question is that the ion-molecule pair complex is expected to be very reactive. The reactivity should be so large that the diffusional separation of the complex is slower than or comparable to the rate of reaction to elimination and substitution products. Experimental support for this conclusion is the high reactivity of the ion pair **1<sup>+</sup>Cl<sup>-</sup>** (Scheme 1);<sup>5</sup> rate constants of  $k_{el} = 7 \times 10^{10} \text{ s}^{-1}$  and  $k_{su} = 4 \times 10^{10} \text{ s}^{-1}$  have been estimated from competition experiments with added azide ion (the 'azide-clock method'<sup>8</sup>) in water-acetonitrile. It is reasonable to assume a similar or even larger rate constant  $k_{su}$  for the ion-molecule pair. The elimination rate constant  $k_{el}$ , on the other hand, should be smaller for the ion-molecule pair than for the ion pair owing to the low basicity of PhOH. Consistently, small  $k_E/k_S$  values are measured for **1-OPh** (Table 1). The leaving groups  $\text{Cl}^-$  and  $\text{Br}^-$  are efficient in promoting elimination within the ion pairs.<sup>5,6</sup> Hydron abstraction by the solvent is probably slow, but it is not possible to estimate the relative importance of hydron abstraction by the PhOH leaving group and by the solvent.

It was pointed out recently that classical  $E1$  reactions, defined as elimination exclusively from a free carbocation, are presumably not common for solvolytic reactions of substrates with leaving groups which are negatively charged or are neutral but efficient bases.<sup>7a,9</sup> Thus, it has been found that the leaving group of an ion pair is often very efficient in promoting elimination by abstraction of a  $\beta$ -hydron, even for substrates which form relatively stable carbonations in highly aqueous media.<sup>7a,9</sup> The high efficiency of the leaving group as a



Scheme 5



## EXPERIMENTAL

**General.** The  $^1\text{H}$  NMR analyses were performed with a Varian XL 300 spectrometer. The high-performance liquid chromatography (HPLC) analyses were carried out with a Hewlett-Packard Model 1090 liquid chromatograph equipped with a diode-array detector on a  $\text{C}_8$  ( $5\ \mu\text{m}$ ,  $100 \times 3\ \text{mm}$  i.d.) 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. Semi-preparative HPLC separations were carried out with a Hewlett-Packard Model 1084B HPLC apparatus using a semi-preparative  $\text{C}_8$  column ( $7\ \mu\text{m}$ ,  $250 \times 8\ \text{mm}$  i.d.) with methanol–water as mobile phase. The IR spectra were recorded on a Perkin-Elmer Model 1605 Fourier transform (FT) apparatus.

**Materials.** Acetonitrile (Riedel de Haën) and methanol (Baker or Merck) were of HPLC grade and were used without further purification. All other chemicals were of reagent grade and were used without further purification.

**9-(2-Phenoxy-2-propyl)fluorene (1-OPh).** Phenol (35 g, 370 mmol) was added to a solution of 9-(2-bromo-2-propyl)fluorene<sup>5</sup> (1 g, 35 mmol) in 20 ml of toluene. After addition of  $\text{Ag}_2\text{CO}_3$  (12 g, 3.5 mmol) the reaction mixture was shaken by hand for 2 min and then quenched by dilution with 40 ml of pentane, filtered and washed several times with water and twice with brine. The solution was dried over magnesium sulphate and the solvent was evaporated. The product mixture contained three products: 53% of **1-OPh**, 42% of alkene **2** and 5% of **1-OH**. The ether was purified by semi-preparative HPLC. Recrystallization from 1:1 ethanol–pentane gave pure material, m.p.  $105\text{--}107^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ),  $\delta$  7.57 (m, 5 H), 7.2–6.8 (m, 8 H), 4.2 (s, 1 H), 0.9 (s, 6 H).

**9-(1,1,1,3,3,3- $^2\text{H}_6$ )-9-(2-Phenoxy-2-propyl)fluorene (d<sub>6</sub>-1-OPh).** This compound was prepared from 9-(1,1,1,3,3,3- $^2\text{H}_6$ )-9-(2-bromo-2-propyl)fluorene<sup>5</sup> by the same method as for the unlabelled compound. The deuterium content was found to be  $98.1 \pm 1.0\ \text{atom}\%$ .

**9-(2-Acetamido-2-propyl)fluorene (1-NHCOMe).** In 8 ml of acetonitrile, **1-OPh** (100 mg, 0.35 mmol) was dissolved and 2 ml of 10 M  $\text{H}_2\text{SO}_4$  were added. The reaction was quenched with a solution containing 2 M sodium acetate (2.5 ml), acetonitrile (2.5 ml) and water (4.5 ml) and extracted with tetrachloromethane. The tetrachloromethane solution was washed with distilled water several times and once with brine, dried ( $\text{MgSO}_4$ ) and the solvent was evaporated. Semi-preparative HPLC followed by recrystallization from a mixture of dichloromethane–pentane gave pure material, m.p.

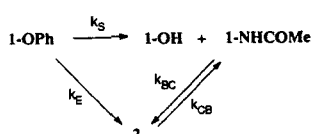
$252\text{--}254^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  7.73 (d, 2 H), 7.50 (d, 2 H), 7.36 (t, 2 H), 7.25 (t, 2 H), 5.55 (s, 1 H), 5.05 (s, 1 H), 2.15 (s, 3 H), 1.2 (s, 6 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  169.8, 144.7, 142.2, 127.2, 126.4, 126.0, 119.6, 56.5, 52.9, 25.2, 24.8; FT-IR (thin film), 3434, 1674,  $1508\ \text{cm}^{-1}$ .

**9-(2-Propenyl)fluorene (2).** Compound **2** was isolated from a product mixture obtained from an unsuccessful synthesis of **1-OPh**; use of  $\text{Ag}_2\text{SO}_4$  instead of  $\text{Ag}_2\text{CO}_3$  gave 93% of **2**. Pure alkene was obtained by recrystallization from 1:1 ethanol–pentane.

**Kinetics and product studies.** The reaction solutions were prepared by mixing acetonitrile or methanol with water at room temperature ( $ca\ 22^\circ\text{C}$ ). The reaction flask was a 2 ml HPLC flask, sealed with a gas-tight PTFE septum, which was placed in an aluminium block in the water thermostat bath. Fluorene was used as an internal standard. The reactions were initiated by fast addition, by means of a syringe, of a few microlitres of the substrate dissolved in acetonitrile. The concentration of the substrate in the reaction solution was usually about 0.2 mM. At appropriate intervals, quenched samples were analysed using the HPLC apparatus. The quenching was done by diluting 100- $\mu\text{l}$  aliquots of the reaction solution with 950  $\mu\text{l}$  of a solution comprising 2 M NaOAc (250 parts), acetonitrile (250 parts) and water (450 parts). The rate constants for the disappearance of the substrates were calculated from logarithmic plots of the ratio of the substrate peak area to fluorene peak area versus time by means of a linear least-squares regression computer program. Very good pseudo-first-order behaviour was seen for all of the reactions studied. The separate rate constants for the elimination ( $k_E$ ) and substitution ( $k_S$ ) reactions of **1-OPh** were evaluated by a computer simulation based on the product composition data, obtained from the peak areas and the relative response factors determined in separate experiments, and the rate-constant equations corresponding to the phenomenological reaction scheme shown in Scheme 8, where  $k_{BC} = k_{12}$  ( $[\text{1-OH}]/([\text{1-OH}] + [\text{1-NHCOMe}])$ ) and  $k_{CB} = k_{21} + k_{23}$  (cf. Scheme 3).

When starting from pure **1-OPh**, the concentrations of **1-OPh**, **2**, and **1-OH** + **1-NHCOMe** are described by the following equations:<sup>12</sup>

$$\begin{aligned}\text{mol}\% \text{ 1-OPh} &= 100e^{-(k_E + k_S)t} \\ \text{mol}\% \text{ 2} &= 100[(k_{CB}/(k_{CB} + k_{BC}))(1 - e^{-(k_{BC} + k_{CB})t}) \\ &\quad + (k_S - k_{CB})/(k_{BC} + k_{CB} - k_E - k_S) \\ &\quad \times (e^{-(k_E + k_S)t} - e^{-(k_{BC} + k_{CB})t})] \\ \text{mol}\% (\text{1-OH} + \text{1-NHCOMe}) &= 100 - \text{mol}\% \text{ 1-OPh} - \text{mol}\% \text{ 2}\end{aligned}$$



Scheme 8

The reaction of deuterated **1-OPh** was simulated using the following approximations:  $k_{BC}^D = k_{BC}^H/4$  and  $k_{CB}^D = k_{CB}^H$ . The results of the simulations show minor sensitivities to small changes in these rate constants.

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

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