Mechanisms of Solvent- and Base-Promoted Imine-Forming Elimination Reactions

Qingshui Meng and Alf Thibblin*

Contribution from the Institute of Chemistry, University of Uppsala, P.O. Box 531, S-751 21 Uppsala, Sweden

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Abstract: Solvolysis of 9-(*N*-chloro-*N*-methylamino)fluorene (**1-Cl**) in 25 vol % acetonitrile in water gives the imine fluorenylidenemethylamine (**3**) as the sole product. The kinetic deuterium isotope effect was measured with the deuterated analogue (9-^{2}H)-9-(*N*-chloro-*N*-methylamino)fluorene as $k^H/k^D = 4.8 \pm 0.2$ (50 °C) without base and $k^H/k^D = 6.7 \pm 0.2$ (25 °C) with hydroxide anion. The solvent- and base-promoted reactions of **1-Cl** are concluded to be of E2 type. The corresponding substrates 9-(*N*-4-Y-benzenesulfonyl-*N*-methylamino)fluorene (**2-Y**, Y = OMe, Me, or Br), with very poor leaving groups, show reversible E1cB reactions with added bases. The strongly activated substrate 9-(*N*-4-nitrobenzenesulfonyl-*N*-methylamino)fluorene (**2-NO$_2$**) does not give any elimination; it exclusively undergoes intramolecular nucleophilic aromatic substitution involving rate-limiting hydron transfer.

Introduction

We are interested in the borderline between stepwise and one-step alkene-forming elimination reactions and have discussed this subject in a number of recent papers.[1−9] Such questions as what can induce a change in mechanism from a stepwise route involving an intermediate of carbocationic or carbanionic type to a one-step, concerted process have been addressed.

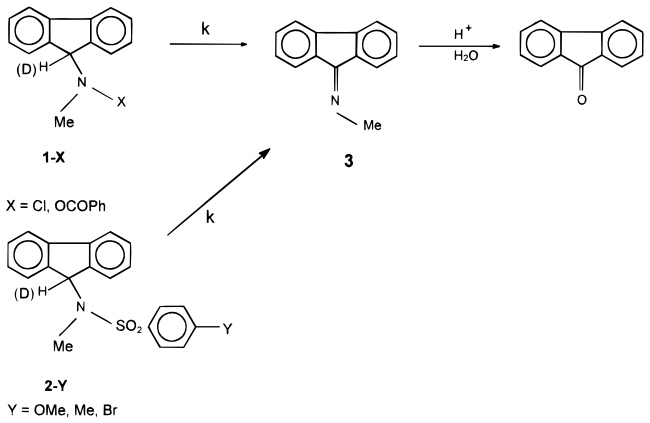
We have now extended the study to imine-forming elimination reactions. Such reactions are less complex in the sense that they generally provide the elimination product exclusively which can facilitate kinetic studies. However, this can be a disadvantage in mechanistic studies because branching from a common intermediate can often give valuable mechanistic information.[3,10]

In the present paper we report results of studies on elimination reactions that form carbon−nitrogen double bonds from substrates which have the β-hydrogen substantially activated. In the corresponding alkene-forming elimination reactions of fluorenyl-activated substrates, depending on the substrate structure and the leaving group, E1cB$_R$, E1cB$_I$, and E2 reactions are possible in addition to E1 elimination through an ion-pair intermediate. Moreover, the first conclusive evidence for the solvent-promoted E2 elimination mechanism was reported recently for secondary halides in a highly aqueous solvent.[6−9] What are the possible mechanisms of imine-forming elimination reactions? A review by Hofmann, Bartsch, and Cho discusses one-step, concerted base-promoted imine-forming reactions,[11] but there seems to be no report on stepwise carbanionic imine-forming reactions in the literature.

We now report results for solvent- and base-promoted imine-forming elimination reactions which show that with very poor leaving groups the reaction occurs through the expulsion of the leaving group from a reversibly formed carbanion intermediate (E1cB$_R$). A change to a more efficient leaving group changes the mechanism to E1cB$_I$ or to E2. With the efficient chloride ion leaving group, the very weakly basic solvent (water) is able to abstract a hydron from the substrate giving water-promoted elimination.

This report also includes a study of the base-catalyzed reaction of **2-NO$_2$** which does not give elimination, but reacts by intramolecular nucleophilic aromatic substitution by a reaction with rate-limiting hydron transfer.

Scheme 1



Results

The solvolysis of 9-(*N*-chloro-*N*-methylamino)fluorene (**1-Cl**) in 25 vol % acetonitrile in water at 50 °C yields exclusively the elimination product fluorenylidenemethylamine (**3**) (Scheme 1). The reaction in the aqueous solvent as well as in methanol is catalyzed by general bases. The kinetics was studied by a sampling high-performance liquid chromatography (HPLC) procedure or by following the decrease in absorbance at 275 nm by UV spectrophotometry. The ester 9-(*N*-benzoyloxy-*N*-methylamino)fluorene (**1-OCOPh**) is less reactive. Its reaction with bases in methanol affording the imine **3** as the main product (about 99% with the amines and about 70% with methoxide ion) has been studied by the same techniques. The rate constants

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Table 1. Rate Constants for the Reactions of **1-X** and **2-Y**

substrate[a]	base	base conc, M	$10^6 k_{obs}$, s^{-1} [k]	$10^6 k$, $M^{-1}\ s^{-1}$ [k]
		25 vol % Acetonitrile in Water		
1-Cl	solvent[b]		402 (84.5)[l]	
1-Cl	solvent[b,c]		123 (24.7)[l]	
1-Cl	HO^- [e]	0.0025	4800	1.92 (0.287)[l] × 10^6
2-Br	HO^- [e,j]	0.75	1140	1530
2-Me	HO^- [e,j]	0.75	343	457
2-OMe	HO^- [e,j]	0.75	317	423
		Methanol		
1-Cl	MeO^- [e]	0.00137	4100	3.00 (0.468)[l] × 10^6
1-Cl	HFIP[e,g]	0.0025−0.01		3.68 × 10^5
1-Cl	quinuclidine[e]	0.00497−0.02024		3.01 × 10^5
1-Cl	DABCO[e,h]	0.02−0.10		5.60 × 10^4
1-Cl	HMTA[e,i]	0.10−0.50		1810
1-OCOPh	MeO^- [e]	0.00137	243	1.22 (0.234)[l] × 10^5
1-OCOPh	quinuclidine[e]	0.0575−0.115		1.39 × 10^4
1-OCOPh	DABCO[e,h]	0.50	1010	2020 (326)[l]
1-OCOPh	HMTA[e,i]	0.20−0.50		46.7
2-Br	MeO^- [f]	1.37	1160	847 (841)[l]
2-Me	MeO^- [f]	1.37	280	204 (204)[l]
2-OMe	MeO^- [f]	1.37	228	166
2-NO_2	MeO^- [e]	0.0137	745	5.44 (0.942)[l] × 10^4
2-NO_2	quinuclidine[d]	0.0023−0.0092		2.39 × 10^4
2-NO_2	DABCO[d,h]	0.05−0.20		986

[a] Substrate concentration 0.01−0.1 mM. [b] 50 °C. [c] In the presence of 1 mM $HClO_4$. [d] 70 °C. [e] 25 °C. [f] 35 °C. [g] $(CF_3)_2CHO^-/(CF_3)_2CHOH = 1$. [h] Diazabicyclo[2.2.2]octane. [i] Hexamethylenetetramine. [j] The ionic strength was maintained constant (0.75 M) with sodium perchlorate. [k] Estimated maximum error is ±5%. [l] Rate constant with the corresponding 9-(^{2}H) compound.

Table 2. Kinetic Deuterium Isotope Effects for the Reactions of **1-X** and **2-Y**

substrate[a]	solvent	base	k^H/k^D
1-Cl	25% MeCN[d]	solvent[b,c]	5.0 ± 0.3
1-Cl	25% MeCN[d]	HO^- [e]	6.7 ± 0.3
1-Cl	MeOH	MeO^- [e]	6.4 ± 0.3
1-OCOPh	MeOH	MeO^- [e]	5.2 ± 0.3
1-OCOPh	MeOH	DABCO[e,g]	6.2 ± 0.3
2-Br	MeOH	MeO^- [f]	1.0 ± 0.1
2-Me	MeOH	MeO^- [f]	1.0 ± 0.1
2-NO_2	MeOH	MeO^- [e]	5.8 ± 0.3

[a] Substrate concentration 0.01−0.1 mM. [b] 50 °C. [c] In the presence of 1 mM $HClO_4$; the isotope effect without acid addition is 4.8 ± 0.2. [d] By volume in water. [e] 25 °C. [f] 35 °C. [g] Diazabicyclo[2.2.2]octane.

for the reactions are shown in Table 1 which also includes the rate constants for the reactions of the (9-^{2}H)-substituted analogues. The kinetic deuterium isotope effects are collected in Table 2. Attempts to prepare the bromide and the arylsulfonyloxy derivatives have not been successful, probably owing to the very high reactivity of these compounds.

The byproduct (ca. 30%) obtained from the methoxide-promoted reaction with **1-OCOPh** is probably the hydroxylamine derivative formed by ester cleavage. Consistently, the UV spectrum of this product is very similar to that of the ester. The product is not stable but reacts to give another product with a quite different UV spectrum.

The much slower reactions of **2-OMe**, **2-Me**, and **2-Br** to give the imine **3** as the sole product (Scheme 1) were studied with strong base, methoxide, or hydroxide anion (Table 1). The reactions exhibit apparent third-order kinetics, first-order in substrate and second-order in base, as shown in Figures 1 and 2. However, this behavior may be a medium effect because it is difficult mechanistically to account for third-order kinetics (see Discussion). ^{1}H NMR analysis showed complete incorporation of ^{1}H in the 9-position of the deuterated substrate **d-2-Me** after one half-life with methoxide ion in methanol. Thus, these reactions are accompanied by complete deuterium-protium exchange with the solvent and they show no kinetic deuterium isotope effects.

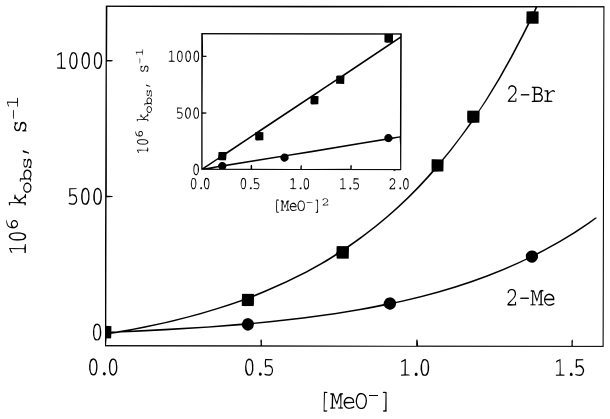


Figure 1. The rate constants for the imine-forming reactions as a function of methoxide ion concentration in methanol at 35 °C: **2-Br** (■) and **2-Me** (●).

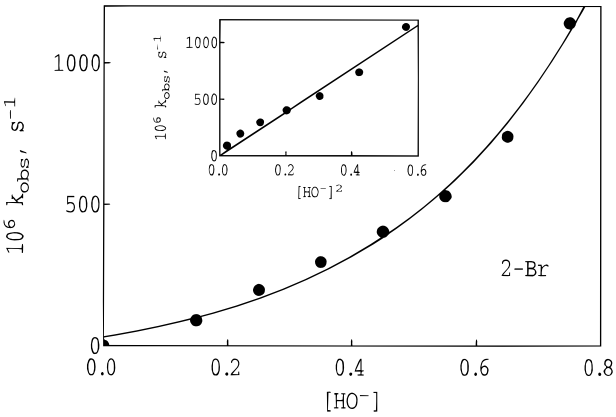
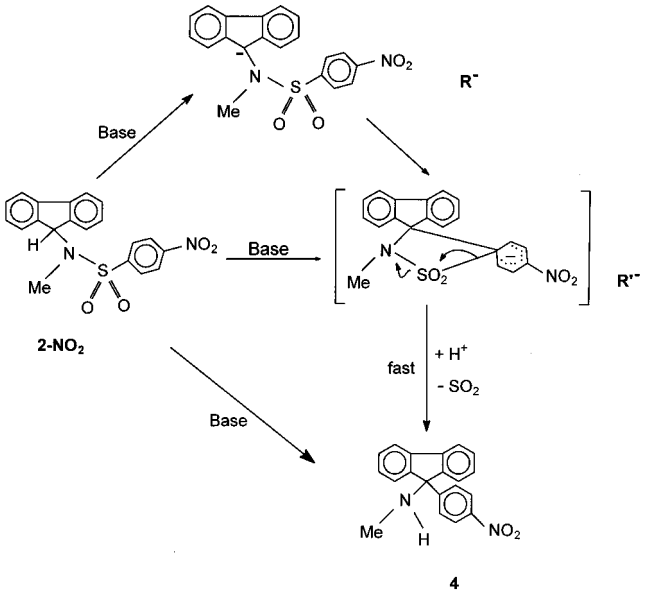


Figure 2. The rate constants for the imine-forming reaction of **2-Br** as a function of hydroxide ion concentration in 25 vol % acetonitrile in water at 25 °C; ionic strength maintained constant (0.75 M) with sodium perchlorate.

The compound **2-NO_2** does not undergo elimination with strong bases; it exclusively yields **4** (Scheme 2). This intramolecular nucleophilic aromatic substitution reaction is general base

Scheme 2



catalyzed. The measured rate constants and kinetic deuterium isotope effect are presented in Tables 1 and 2, respectively.

Discussion

Solvent- and Base-Promoted Elimination. The elimination reactions of **1-Cl** and **1-OCOPh** are catalyzed by general bases. The Brønsted parameters of $\beta = 0.49$ and 0.53 for catalysis by tertiary amines in methanol (Figure 3) indicate substantial amounts of hydron transfer in the rate-limiting transition state. Consistently, the kinetic deuterium isotope effects are large (Table 2). These results strongly indicate E2 and E1cB$_I$ mechanisms since very small β values and small kinetic deuterium isotope effects are expected for a mechanism in which a nitrenium ion or ion pair is dehydronated in the rate-limiting step.

The base-promoted alkene-forming dehydrochlorination of 9-(1-chloroethyl)fluorene has been concluded to be of E2 type.[6,7,9] A nitrogen−chlorine bond is weaker than a bond between carbon and chlorine. Thus, **1-Cl** should undergo a facile cleavage of the nitrogen−chlorine bond, and we suggest that this reaction also occurs by an E2 mechanism. Consistently, the imine-forming reaction of **1-Cl** with hydroxide anion is about 24 times faster than the corresponding alkene-forming reaction. The methoxide-promoted imine-forming elimination from *N*-chloro-*N*-methylbenzylamine proceeds 10^4 times faster than that from the corresponding alkene-forming elimination from 2-chloro-1-phenylpropane under comparable conditions.[11] The much larger rate ratio for the benzyl substrates is due to a large amount of N−Cl bond cleavage in the E1-like E2 transition state of the imine-forming reaction; the alkene-forming reaction has a more E1cB-like transition state. In contrast, the imine- and alkene-forming reactions of the fluorene derivatives both have E1cB-like E2 mechanisms with relatively small amounts of cleavage of the bond to the chlorine in the transition states.

The substrate **1-OCOPh** reacts, as expected owing to the less efficient leaving group, more slowly with bases to give the imine (about 20−40 times, Table 1). These reactions may be classified also as E2 reactions as will be shown in the following. More O'Ferrall−Jencks diagrams of the type shown in Figure 4 have been used frequently for mapping the characteristics of the

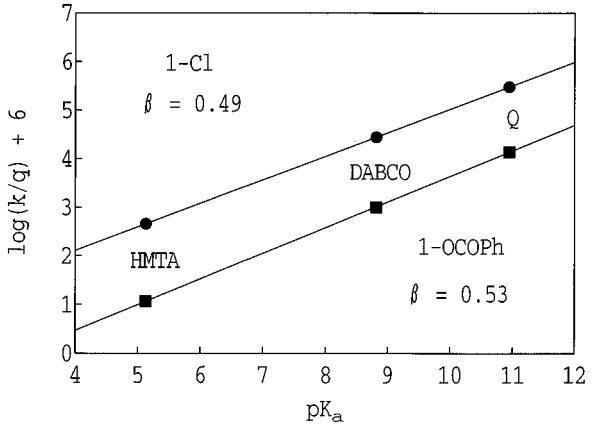


Figure 3. Brønsted plots for the reactions of **1-Cl** (●) and **1-OCOPh** (■) with tertiary amines in methanol at 25 °C. The slopes are $\beta = 0.49$ and $\beta = 0.53$, respectively. The pK_a values refer to water.[20] The rate constants for hexamethylenetetramine (HMTA) and diazobicyclo-[2.2.2]octane (DABCO) have been statistically corrected.

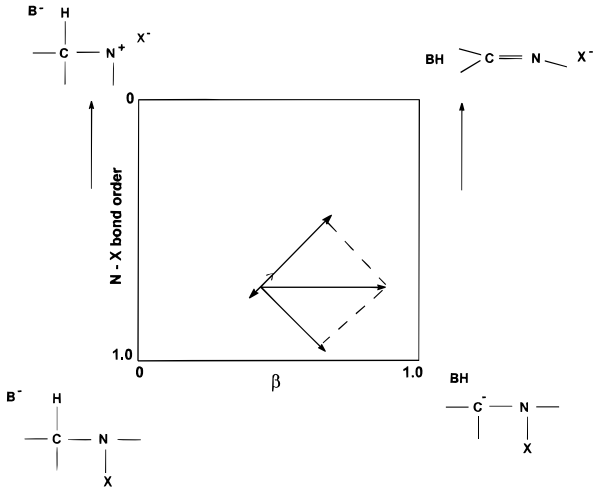


Figure 4. More O'Ferrall−Jencks diagram for imine-forming elimination.[12] The effect of change in leaving group from chloride ion to the less efficient benzoate ion is a raising of the energy of the upper edge of the diagram. The result is a shift to the right and an increase in β as indicated.

transition state of β-elimination reactions.[12] The effect of a less good leaving group is to increase the energy level at the upper edge of the diagram. This results in movement of the transition state uphill toward the product and downhill perpendicular to the original reaction coordinate. This corresponds to a shift to the right and an increase in β as indicated by the arrows in Figure 4. The small increase in β from 0.49 for **1-Cl** to 0.53 for **1-OCOPh** is in accord with this model. However, it cannot be excluded that the mechanism has changed from E2 to E1cB$_I$.

The most significant result with **1-Cl** is the spontaneous elimination reaction observed in the absence of added base. The substrate should have a pK_a not far from zero since it has been found that the chloro substituent has a very large acidifying effect; e.g., the pK_a of *N*-chlorodimethylamine is 0.47.[13] Thus, in neutral solution the compound exists in its unhydronated form. Strong support for a solvent-promoted E2 mechanism for **1-Cl**

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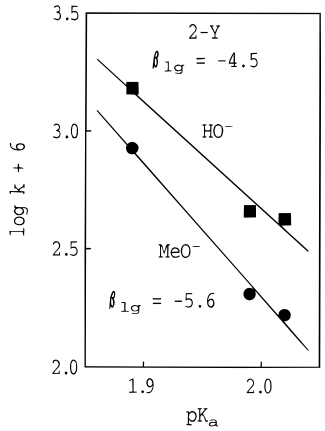

Figure 5. Brønsted plot (using the second-order rate constants reported in Table 1) for the imine-forming reaction of the *para*-substituted benzenesulfonamides **2-Br**, **2-Me**, and **2-OMe** with 0.75 M NaOH in 25 vol % acetonitrile in water and 1.37 M NaOMe in methanol, respectively. The pK_a values refer to water.[20]

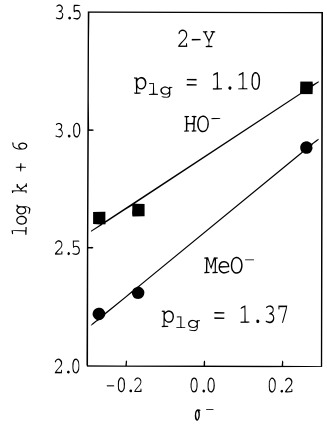

Figure 6. Hammett plot (using the second-order rate constants reported in Table 1) for the imine-forming reactions of the *para*-substituted benzenesulfonamides **2-Br**, **2-Me**, and **2-OMe** with 0.75 M NaOH in 25 vol % acetonitrile in water and 1.37 M NaOMe in methanol.

is the large kinetic isotope effect measured with the 9-deuterated analogue of $k^H/k^D = 5.0 \pm 0.2$ (Table 2), which, using the same arguments as above, is not consistent with a stepwise route through an ion or through ion pairs. The reaction is, as expected, faster than that of 9-(1-chloroethyl)fluorene, which has been concluded to be of the solvent-promoted E2 type.

Generally, it is possible in base-promoted alkene-forming elimination reactions to change the mechanism from a concerted E2 or an irreversible carbanion mechanism, E1cB$_I$, to a reversible mechanism, E1cB$_R$, by changing to a less efficient leaving group. We have used the very poor arylsulfinate leaving groups in this study to ensure a shift in mechanism. Thus, the reactions of **2-Me** and **2-Br** with methoxide anion in methanol do not show any kinetic deuterium isotope effects and they show complete exchange of the 9-deuterium with protium from the solvent, which strongly indicate the E1cB$_R$ mechanism.

The kinetics of the reactions of the substrates with the very poor leaving groups, arylsulfinate, seem to be second-order in methoxide-ion concentration (Figure 1). We also see this effect with hydroxide anion at constant ionic strength (Figure 2) which indicates that the effect of methoxide-ion concentration is not an effect of ion-pairing of the base. However, it is diffcult to see how the base could assist the departure of the leaving group. Therefore, the most likely explanation is medium effects.

A large β_{lg} is expected for the E1cB$_R$ mechanism. The reaction rates of the arylsulfonyl derivatives show an unusually large sensitivity to the pK_a of the leaving group, with a Brønsted slope of $\beta_{lg} = -4.5$ in the aqueous solvent and -5.6 in methanol (Figure 5). The corresponding Hammett parameters for the effect of *para* substitution in the aromatic ring of the leaving group have modest slopes of $\rho_{lg} = 1.1$ and 1.4, respectively (Figure 6), indicating some negative charge on the departing group in the rate-limiting transition state.

An unusually large sensitivity to the pK_a of the leaving group does not explain reasonably why the chloride **1-Cl** reacts so much more quickly than **2-Me**; a rate ratio of about 10^5 can be estimated from the data of Table 1. This large ratio could be ascribed to the difficulty in breaking a nitrogen−sulfur bond. A nitrogen−chlorine bond is much easier to cleave. The barrier for departure of the chloride leaving group from the putative carbanion intermediate should be extremely small. In fact, we believe that there is no barrier for departure of the chloride anion from the carbanion. This corresponds to an uncoupled concerted E2 reaction. However, the hydron transfer and the cleavage of the nitrogen−chlorine bond should be coupled in the E1cB-like E2 transition state (*vide supra*).

Sulfonamides are among the most stable of the nitrogen protecting groups and drastic deprotection conditions are generally required. For example, arylsulfonamides are cleaved by sodium in liquid ammonia or by strong acid at high temperature.[14,15] However, the presence of an acidic hydron on the β-carbon atom can result in a relatively facile cleavage of the nitrogen−sulfur bond through an imine-forming elimination reaction occurring via the reversibly formed carbanion.

Intramolecular Nucleophilic Aromatic Substitution. The substrate **2-NO$_2$** is more activated and is expected to give imine product faster than the other three aryl-substituted derivatives. However, no elimination product is formed; the sole product is compound **4** (Scheme 2). The large isotope effect of $k^H/k^D = 5.8$ (Table 2) shows that the transfer of the hydron occurs in the rate-limiting transition state. Consistently, the Brønsted parameter obtained with quinuclidine and DABCO is large, $\beta = 0.50$. Possible mechanisms are shown in Scheme 2 ($\mathbf{R}^-$ may be an intermediate or a transition state). The simplest mechanism to account for the results is a concerted formation of **4** directly from **2-NO$_2$**. Another, more likely, mechanism is the formation of the carbanion $\mathbf{R}^-$ in a rate-limiting step followed by a concerted or stepwise reaction to give the product. Alternatively, the anion $\mathbf{R'}^-$ is formed directly from the substrate followed by fast formation of the product **4**. This reaction route may be facilitated by participation of the aromatic ring in the ionization.

Experimental Section

General. The NMR spectra were recorded with a Varian 400 spectrometer: ^{1}H at 400 and ^{13}C at 100.5 MHz using the solvent, chloroform-d_1 (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C), as an internal standard. Infrared spectra were measured with a Perkin-Elmer 1600 FT-IR spectrometer. The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on a Asahipak (5 μm, 4 × 125 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. The 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 pH was measured using a Radiometer PHM82 pH meter with an Ingold micro glass electrode. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany.

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Merck silica gel 60 (249−400 mesh) was used for flash chromatography. Methylene chloride and toluene were distilled under nitrogen from calcium hydride. Methanol and acetonitrile were of HPLC grade. Chloroform was dried over 4 Å molecular sieves. Diazabicyclo[2.2.2]-octane (DABCO) was recrystallized twice from hexane. Quinuclidine was sublimed twice at reduced pressure. All other reagents were of reagent grade and were used without further purification. A stock solution of NaOMe was prepared by adding freshly cut pieces of pure sodium to dry methanol. The concentration was determined by titration of aliquots of this stock solution with 1 M HCl. All the deuterated compounds have at least >98.5 atom % ^{2}H in the 9-position as measured by ^{1}H NMR analysis.

The deuterated compounds (9-^{2}H)-9-(*N*-chloro-*N*-methylamino)-fluorene (**d-1-Cl**), (9-^{2}H)-9-(*N*-*p*-toluenesulfonyl-*N*-methylamino)fluorene (**d-2-Me**), (9-^{2}H)-9-(*N*-benzoyloxy-*N*-methylamino)fluorene (**d-1-OCOPh**), (9-^{2}H)-9-(*N*-4-bromobenzenesulfonyl-*N*-methylamino)-fluorene (**d-2-Br**), and (9-^{2}H)-9-(*N*-4-nitrobenzenesulfonyl-*N*-methylamino)fluorene (**d-2-NO$_2$**) were prepared from (9-^{2}H)-fluorenylmethylamine as described for the respective protium compound.

Fluorenylidenemethylamine (3) was prepared by a slight modification of a previously published method.[16] Methylamine gas was bubbled through a solution of 9-fluorenone (5.4 g, 15 mmol) dissolved in toluene (40 mL) at 0 °C for 20 min. Titanium tetrachloride (30 mmol) in dichloromethane (15 mL) was added dropwise from a syringe. After addition, methylamine gas was bubbled through the reaction mixture again until the red color had disappeared. The reaction mixture was warmed to room temperature and stirred for 2 h. Then, it was poured into water and extracted with ethyl acetate, followed by washing with water and brine, and drying over sodium sulfate. The solvent was removed and the residue recrystallized from ether−hexane (1:2) which gave a yellow solid (5.2 g, 90%): mp 51−52 °C (lit.[17] 110−111 °C); ^{1}H NMR δ 7.94 (m, 1 H), 7.77 (dt, J = 7.5, 1.0 Hz, 1 H), 7.68 (ddd, J = 7.5, 1.2, 0.8 Hz, 1 H), 7.59 (dt, J = 7.5, 1.0 Hz, 1 H), 7.44 (td, J = 7.5, 1.2 Hz, 1 H), 7.40 (td, J = 7.5, 1.2 Hz, 1 H), 7.30 (tt, J = 7.5, 1.2 Hz, 2 H), 3.98 (s, 3 H); ^{13}C NMR δ 164.68, 143.48, 140.97, 138.30, 131.92, 131.16, 130.73, 128.35, 127.90, 127.74, 122.14, 120.30, 119.34, 41.17.

Fluorenylmethylamine.[18] Sodium cyanoborohydride ($NaBH_3CN$, 0.4 g, 6.4 mmol) and acetic acid (1 mL) were added to fluorenylidenemethylamine (0.6 g, 3.2 mmol) dissolved in methanol (25 mL). The mixture was heated at 40 °C for 1 h. Methanol was removed and 2 M sodium hydroxide (10 mL) was added to the residue, followed by extraction with ethyl acetate, washing with water and brine, and drying over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in dry dichloromethane (20 mL) and stored in the refrigerator under nitrogen. The compound was used to prepare **1-X** and **2-Y**; the total yields of these two-step syntheses were 50−80% based on fluorenylidenemethylamine.

(9-^{2}H)-Fluorenylmethylamine was prepared from fluorenylidenemethylamine by reduction with sodium borodeuteride in MeOD but otherwise as described above. The washing of the extract was done with D_2O.

9-(*N*-Chloro-*N*-methylamino)fluorene (1-Cl). The solution of fluorenylmethylamine in dichloromethane from the previous step (5 mL, 0.8 mmol) was cooled to 0 °C and *N*-chlorosuccinimide (0.107 g, 0.8 mmol) was added. The mixture was stirred at 0 °C for 1 h. The solvent was removed and the residue was extracted with hexane twice. Recrystallization from ethanol−pentane (1:1) gave pure material: mp 80−81 °C (decomposes to an orange solid of the corresponding imine); ^{1}H NMR δ 7.84 (m, 2 H), 7.69 (dt, J = 7.5, 1.0 Hz, 2 H), 7.43 (tdd, J = 7.5, 1.2, 0.6 Hz, 2 H), 7.33 (td, J = 7.5, 1.2 Hz, 2 H), 5.37 (s,1 H), 2.53 (s, 3 H).

9-(*N*-Benzoyloxy-*N*-methylamino)fluorene (1-OCOPh). To the solution of fluorenylmethylamine in chloroform (10 mL, 1.07 mmol) were added dibenzoyl peroxide (0.24 g, 1.07 mmol) and potassium carbonate (0.52 g).[19] The mixture was refluxed for 2.5 h at 65 °C. The mixture was filtered and the chloroform phase was washed twice with saturated sodium carbonate solution and with water, followed by drying over sodium sulfate. The solvent was removed to give a yellow oil, which was purified by flash chromatography with 5% ethyl acetate in pentane as eluent. After removal of solvent, the residue was recrystallized from diethyl ether−pentane (1:2) giving a white solid: mp 112−113 °C; ^{1}H NMR δ 8.07−7.43 (m, 11 H), 7.35 (dt, J = 7.5, 1.2 Hz, 2 H), 5.60 (s, 1 H), 2.50 (s, 3 H); ^{13}C NMR δ 164.97, 141.40, 141.00, 133.09, 129.50, 129.40, 128.85, 128.56, 127.44, 126.58, 119.96, 71.59, 38.96.

9-(*N*-*p*-Toluenesulfonyl-*N*-methylamino)fluorene (2-Me). A solution of fluorenylmethylamine in dichloromethane (5 mL, 0.8 mmol) was cooled to 0 °C and *p*-toluenesulfonic anhydride (0.261 g, 0.8 mmol) was added. Then, triethylamine (0.08 g, 0.8 mmol) in 2 mL of dichloromethane was added to the reaction mixture. The mixture was stirred for 1 h. It was washed with water and the water phase was extracted with dichloromethane. The combined organic phases were washed with water and brine, dried over magnesium sulfate, and concentrated. Flash chromatography with 50% pentane−acetate gave a pure white solid: mp 162−163 °C; ^{1}H NMR δ 7.94 (m, 2 H), 7.66 (dt, J = 7.5, 0.9 Hz, 2 H), 7.42 (m, 2 H), 7.37 (m, 2 H), 7.22 (td, J = 7.5, 1.1 Hz, 2 H), 7.11 (m, 2 H), 6.00 (s, 1 H), 2.52 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR δ 143.53, 141.40, 140.64, 137.81, 129.95, 128.86, 127.60, 127.32, 125.16, 119.99, 62.55, 29.25, 21.59.

9-(*N*-4-Methoxybenzenesulfonyl-*N*-methylamino)fluorene (2-OMe) was synthesized as described above with fluorenylmethylamine and 4-methoxybenzenesulfonyl chloride. Recrystallization from ethanol−chloroform−pentane (2:1:2) gave pure material: mp 195−196 °C; ^{1}H NMR δ 7.98 (m, 2 H), 7.67 (dt, J = 7.6, 0.9 Hz, 2 H), 7.37 (tdd, J = 7.5, 1.1, 0.6 Hz, 2 H), 7.23 (td, J = 7.5, 1.1 Hz, 2 H), 7.15 (dq, J = 7.6, 0.9 Hz, 2 H), 7.09 (m, 2 H), 5.99 (s, 1 H), 3.94 (s, 3 H), 2.28 (s, 3 H).

9-(*N*-4-Bromobenzenesulfonyl-*N*-methylamino)fluorene (2-Br) was synthesized as described above with fluorenylmethylamine and 4-bromobenzenesulfonyl chloride. Recrystallization from ethanol−chloroform−pentane (2:1:2) gave pure material: mp 155−156 °C; ^{1}H NMR δ 7.91 (m, 2 H), 7.77 (m, 2 H), 7.67 (dt, J = 7.6, 0.9 Hz, 2 H), 7.38 (tdd, J = 7.5, 1.1, 0.6 Hz, 2 H), 7.24 (td, J = 7.5, 1.1 Hz, 2 H), 7.11 (dq, J = 7.6, 0.9 Hz, 2 H), 5.99 (s, 1 H), 2.29 (s, 3 H); ^{13}C NMR δ 141.05, 140.66, 139.84, 132.66, 129.05, 128.76, 127.74, 127.67, 125.00, 120.13, 62.64, 29.30.

9-(*N*-4-Nitrobenzenesulfonyl-*N*-methylamino)fluorene (2-NO$_2$) was synthesized as described above from fluorenylmethylamine and 4-nitrobenzenesulfonyl chloride. Recrystallization from ethanol−chloroform−pentane (2:1:2) gave pure material: mp 182−183 °C; ^{1}H NMR δ 8.49 (m, 2 H), 8.24 (m, 2 H), 7.69 (dt, J = 7.5, 1.0 Hz, 2 H), 7.40 (tdd, J = 7.5, 1.1, 0.9 Hz, 2 H), 7.24 (td, J = 7.5, 1.1 Hz, 2 H), 7.09 (dq, J = 7.5, 1.0 Hz, 2 H), 6.02 (s, 1 H), 2.35 (s, 3 H); ^{13}C NMR δ 150.09, 146.62, 140.71, 140.65, 129.27, 128.36, 127.86, 124.79, 124.68, 120.29, 62.82, 29.42. Anal. Calcd for $C_{20}H_{16}N_2O_4S$: C, 63.14; H, 4.24; N, 7.37; S, 8.41. Found: C, 62.89; H, 4.22; N, 7.36; S, 8.46.

9-(4-Nitrophenyl-9-*N*-methylamino)fluorene (4). 9-(*N*-4-Nitrobenzenesulfonyl-*N*-methylamino)fluorene (**2-NO$_2$**, 50 mg) was dissolved in a solution of 1 M NaOMe (40 mL) in methanol. The mixture was stirred at room temperature for 1 h and the solvent was removed. The residue was dissolved in ether and the solution was washed with water and brine and dried over magnesium sulfate. Evaporation of the ether gave a pure yellow solid material: mp 159−160 °C; ^{1}H NMR δ 8.07−7.20 (m, 12 H), 2.06 (s, 3 H), 1.91 (s, 1 H); ^{13}C NMR: δ 152.33, 148.31, 146.99, 140.56, 128.71, 128.11, 127.27, 124.53, 123.49, 120.24, 73.54, 30.12; IR ($CDCl_3$) 3326, 3065, 2949, 2797, 1604, 1594, 1517, 1489, 1474, 1449, 1349, 1109, 852 cm^{-1}. Anal. Calcd for $C_{20}H_{16}N_2O_2$: C,75.93; H, 5.10; N, 8.85. Found: C, 75.77; H, 5.24; N, 8.75.

Kinetics and Product Studies. The reaction solution was prepared by mixing acetonitrile with water at room temperature, ca. 22 °C. It was transferred into 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,

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samples were analyzed using the HPLC apparatus. For the reaction of **2-NO$_2$** with sodium methoxide, the samples were quenched with an aqueous solution of acetic acid (1 M) before analysis. The rate constants for the disappearance of the substrates were calculated from plots of substrate-peak area vs time by means of a nonlinear regression computer program. Very good pseudo-first-order behavior was seen for all of the reactions studied.

The fast reactions of **1-X** and **2-Y** with strong bases were followed for at least 10 half-lives by monitoring the decrease in absorbance at 275 nm by using thermostated 3-mL quartz cells as reaction vessels. After complete reaction, the reaction mixture was quenched with acetic acid (1 M aqueous solution). Analysis by HPLC showed that fluorenone is the only product. The relative response factors of **2-Me**, **1-OCOPh**, and fluorenone were determined by weighing both of them into a flask, dissolving in acetonitrile, and analyzing by HPLC.

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

Hydrogen-Exchange Experiments. The deuterated substrate **d-2-Me** (3 mg) was dissolved in a solution of NaOMe (10 mL, 1.37 M) in MeOH. The mixture was stirred at room temperature for 2 h (ca. 1 half-life). The reaction solution was quenched with 15 mL of 2 M sulfuric acid. The mixture was extracted with diethyl ether, washed with water and brine, and dried over sodium sulfate. Ether was removed and the residue was dissolved in chloroform-d_1. ^{1}H NMR analysis showed that the ^{2}H in 9-position of the starting material (**d-2-Me**) had been exchanged completely.

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