β-Elimination of 9-(Dimethylaminomethyl)fluorene; Buffer Catalysis and pH Dependence indicating a Zwitterion Intermediate

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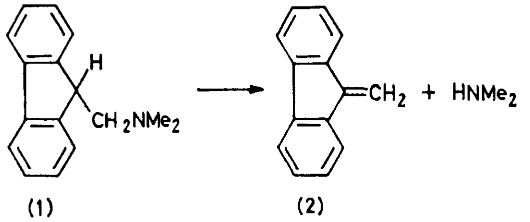
In aqueous sodium hydroxide and tertiary amine buffers at 25° 9-(dimethylaminomethyl)fluorene eliminates dimethylamine to form dibenzofulvene. Between 0.02 and 0.2M-OH⁻ the reaction is first order in hydroxide with a rate constant expected of ionisation to a fluorenyl anion. Above 0.2M the order in hydroxide falls, consistent with a change in rate-determining step to loss of the leaving group. Below 0.02M the order also falls and in buffer solutions the reaction shows general acid catalysis, as expected of rate-determining attack of hydroxide and buffer base on protonated substrate. Buffer saturation is observed with a limiting rate constant close to that at high hydroxide concentrations, again indicating a change in rate-determining step. In weakly basic buffers the saturation rate becomes pH dependent and a pK_a of 8.54 is calculated for the substrate. A stepwise mechanism is proposed with formation of a zwitterion intermediate preceded respectively at high pH by a fluoren-9-yl anion and at low pH by a dimethylammonium cation. The behaviour is compared with that of Mannich bases, β-arylsulphonylalkylamines and carbonyl forming eliminations of amines. Relative to carbonyl reactions the rate of expulsion of the amine leaving group appears slow, and there is no evidence of a ' proton switch ' between β-carbon atom and leaving group.

A β-FLUORENYL group is sufficiently strongly activating in β-eliminations that poor leaving groups react under quite mild conditions,[1-3] and in this paper we report elimination of dimethylamine (Scheme 1) in dilute aqueous hydroxide and buffer solutions at 25°. Eliminations of amines have been observed in other activated systems, for example β-ketoalkylamines [4-6] (Mannich bases) and β-arylsulphonylalkylamines,[7,8] and the reverse reaction, addition of an amine to an activated double bond, is well known,[9] and has been studied in detail by Rappoport, especially for 1,1-dicyano-olefins in aprotic solvents.[10] When the addition is at a double bond bearing a suitable leaving group it may be followed by elimination leading to overall substitution.[10,11] In the substitution mode the reaction is also important in aromatic substrates,[12] although the protonation and deprotonation steps of strict addition–elimination normally do not take place.

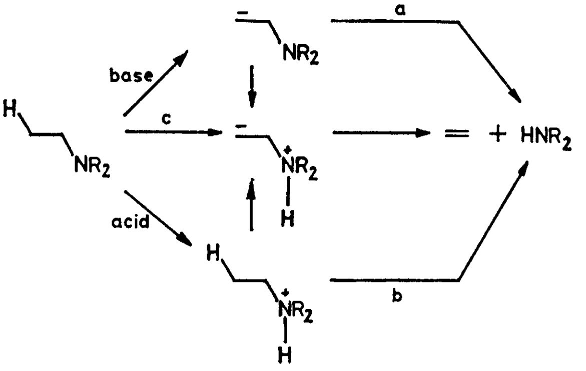


SCHEME 1

Elimination reactions of amines are of interest in requiring both base catalysis for removal of a β-hydrogen and acid catalysis for separation of the leaving group. The catalytic steps may be separated, in which case the reaction proceeds through both a singly charged and a zwitterionic intermediate, or they may be concerted and the zwitterion avoided (Scheme 2). The possibilities of bifunctional or intramolecular catalysis, converting the amine directly to the zwitterion *via* a proton switch,[13,14] or completing reaction in a single step, also exist.

The mechanistic possibilities have been less extensively investigated in olefin-forming eliminations than in additions and eliminations at the carbonyl group, in amide hydrolysis,[15-18] ester aminolysis,[14] and related reactions,[19,20] but especially carbinolamine-forming additions to aldehydes and ketones.[21-24] There are important differences between olefinic and carbonyl reactions,[16] notably the presence of a lone pair of electrons on the oxygen atom and the low intrinsic barrier to proton transfer to or from oxygen which makes proton transfer in carbonyl reactions diffusion controlled; [16] but comparisons of the two reactions and the question of to what extent carbonyl reactions are analogues of olefinic eliminations of substrates possessing an acidic β-hydrogen are clearly of interest. Sayer and Jencks have recently made a detailed comparison of concerted mechanisms of elimination forming olefins and imines.[25]

A practical advantage of studying eliminations of fluorenylmethylamines over most related systems is that no prior or subsequent reactions of the reactant or substrate hinder investigation of the elimination itself.



SCHEME 2 a, Concerted acid catalysis; b, concerted base catalysis; c, proton switch

RESULTS

In aqueous sodium hydroxide and tertiary amine buffers at 25° reaction of 9-(dimethylaminomethyl)fluorene (1) gives exclusively dibenzofulvene (2) recognisable from its

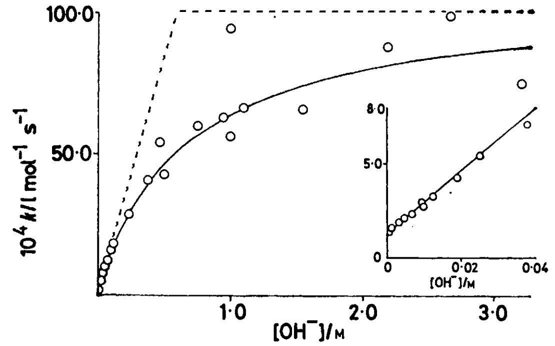


FIGURE 1 Plot of first-order rate constants for elimination of 9-(dimethylaminomethyl)fluorene against [OH$^-$]. The calculated curve is based on equation (1). The straight lines show limiting slopes at high and low hydroxide concentrations

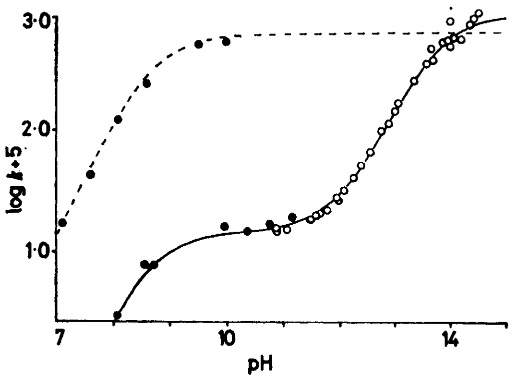


FIGURE 2 Plot of log k *versus* pH for elimination of 9-(dimethylaminomethyl)fluorene. Full line, zero buffer concentration; dashed line, infinite buffer concentration; ○, from measurements with NaOH; ●, extrapolated from buffer measurements

TABLE 1

First-order rate constants for reaction in aqueous sodium hydroxide at 25° [a]

[OH$^-$]/ M	10^4k/ s^{-1}	[OH$^-$]/ M	10^4k/ s^{-1}	[OH$^-$]/ M	10^4k/ s^{-1}
0.000 78	1.60	0.025	5.41	0.505	42.9
0.000 80	1.48	0.0375	7.05	0.754	60.0
0.001 17	1.60	0.0589	10.7	0.943	63.2
0.003 13	1.89	0.075	12.6	1.00	56.3
0.004 00	2.04	0.100	16.1	1.00	94.6
0.004 69	2.14	0.100	16.0	1.10	66.5
0.006 25	2.31	0.100	15.0 [b]	1.54	65.8
0.009 38	2.93	0.118	18.6	2.19	88.4
0.0100	2.76	0.236	28.8	2.67	98.6
0.0125	3.27	0.377	40.8	3.21	75.8
0.0188	4.25	0.472	54.2		

[a] Ionic strength 0.1 except for [OH$^-$] > 0.1M and as indicated. [b] Ionic strength 1.0M.

u.v. absorption spectrum.[2] The reaction is first order in substrate and in the concentration range 0.02—0.2M-sodium hydroxide, first order in hydroxide ion. At higher and lower base concentrations the order in hydroxide falls towards zero, as is shown by the plots of pseudo-first-order rate constants against [OH$^-$] in Figure 1 and its inset and by the log$k$–pH profile of Figure 2, in which hydroxide rate constants are shown as open circles. Observed first-order rate constants are listed in Table 1 and could be fitted to equation (1) with $k_1 = 1.66 \times 10^{-2}$ l mol^{-1}

$$k_{\text{obs}} = k_{\text{min.}} + \frac{k_1[\text{OH}^-]}{1 + k_1[\text{OH}^-]/k_{\text{max.}}} \qquad (1)$$

s^{-1}, $k_{\text{max.}} = 1.02 \times 10^{-2}$ s^{-1}, and $k_{\text{min.}} = 1.36 \times 10^{-4}$ s^{-1}, where k_1, $k_{\text{max.}}$, and $k_{\text{min.}}$ are respectively rate constants for reaction of hydroxide ion and for the maximum and minimum pH independent reactions. The quality of fit is indicated by the calculated curve in Figure 1. The straight lines correspond to $k_{\text{min.}} + k_1$ [OH$^-$], and $k_{\text{max.}}$

Measurements with triethylamine buffers showed that the pH independent reaction extends to the pH range 11.5—10.0 and is subject to catalysis by the acid component of the buffer, BH$^+$, as seen in the plots of k_{obs} against [BH$^+$] in Figure 3a. The buffer rate constants are independent of pH and in the Figure the ordinate scales for different buffer ratios are shifted to avoid superposition of the plots. Values of k_{obs} are listed together with rate constants for other buffers in Table 2 and were used to evaluate rate constants k and k_{o} from equation (2). Values of k_{o} for different buffer

$$k_{\text{obs}} = k_{\text{o}} + k[\text{BH}^+] \qquad (2)$$

ratios are given in Table 3 and can be seen to be close to $k_{\text{min.}}$ from equation (1).

At lower pH values, in N-methyldiethanolamine buffers, the buffer dependence is still that of equation (2) but with k_{o} and k now dependent upon pH, with larger values at higher pHs. This is seen in Figure 3b and is consistent with rate-determining attack of buffer base on a protonated substrate of pK_{a} less than that of triethylamine (10.72) but close to or greater than that of N-methyldiethanolamine (8.52).

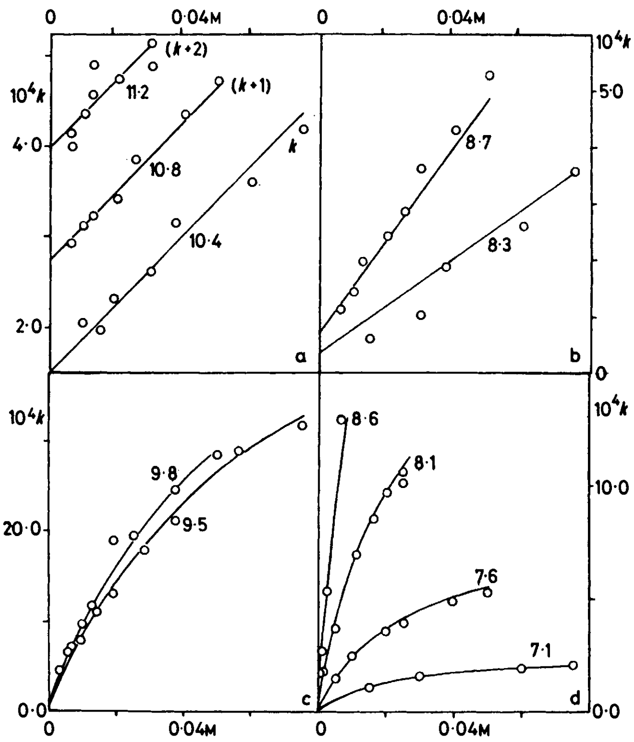


FIGURE 3 Plots of observed rate constants (10^4k/l mol^{-1} s^{-1}) *versus* buffer acid concentration for elimination of 9-(dimethylaminomethyl)fluorene at various buffer ratios and pH values indicated. (a) Triethylamine: plots of 10^4k, $10^4(k + 1)$, $10^4(k + 2)$ at different buffer ratios; (b) N-methyldiethanolamine; (c) trimethylamine; (d) N-methylmorpholine

TABLE 2

First-order rate constants for reaction in aqueous buffers at 25° for various buffer ratios (R) [a]

N-Methylmorpholine

$10^2[BH^+]$ M	10^4k_{obs} s^{-1}
(R 1/9, pH 8.58)	
0.025	1.10
0.10	1.77
0.25	3.57
1.0	8.64
(R 1/3, pH 8.08)	
0.175	1.18
0.50	2.46
1.125	4.64
1.625	5.70
2.0	6.47
2.5	7.06
2.5	6.75
(R 1, pH 7.60)	
0.50	0.98
1.00	1.64
2.00	2.38
2.50	2.59
4.00	3.27
5.00	3.55
(R 3, pH 7.10)	
1.50	0.72
3.00	1.04
6.00	1.28
7.50	1.38

Trimethylamine

$10^2[BH^+]$ M	10^4k_{obs} s^{-1}
(R 1, pH 9.97)	
0.313	4.68
0.625	7.16
0.938	9.57
1.250	11.67
1.875	18.9
2.50	19.4
3.75	24.4
5.00	28.3
(R 2, pH 9.51)	
0.468	3.97
0.938	7.82
1.406	10.9
1.875	13.0
2.813	17.8
3.75	21.2
5.625	28.8
7.50	31.7
Triethylamine	
(R 1/3, pH 11.17)	
0.625	2.00
0.625	2.15
1.00	2.36
1.25	2.91
1.25	2.58
2.00	2.74
2.50	2.89
2.50	3.14

Triethylamine

$10^2[BH^+]$ M	10^4k_{obs} s^{-1}
(R1, pH 10. 75)	
0.625	1.93
1.00	2.11
1.25	2.23
2.00	2.42
2.50	2.86
4.00	3.36
5.00	3.73
(R 3, pH 10.38)	
0.938	2.04
1.50	1.96
1.875	2.31
3.00	2.61
3.75	3.15
6.00	3.80
7.50	4.20
N-Methyldiethanolamine	
(R 1, pH 8.74)	
0.625	1.32
1.00	1.62
1.25	1.97
2.00	2.43
2.50	2.85
4.00	4.30
5.00	5.27
(R 3, pH 8.26)	
1.50	0.61
3.00	1.02
3.75	1.87
6.00	2.60
7.50	3.58

[a] $R = [BH^+]/[B]$, the ratio of buffer acid to buffer base concentrations.

Buffer catalysis by triethylamine and *N*-methyldiethanolamine is rather weak. For the more strongly catalytic trimethylamine and *N*-methylmorpholine the rate dependence on buffer acid concentration is no longer linear but shows marked buffer saturation (Figures 3c and d) with rate constants described by

$$k_{obs} = \frac{k_0 + k[BH^+]}{1 + (k/k_\infty)[BH^+]} \qquad (3)$$

in which k_∞ is the limiting rate constant at high buffer concentrations. For trimethylamine, values of k_∞ (Table 3) are independent of pH and not very different from $k_{max.}$ at high hydroxide concentrations from equation (1). For the less basic *N*-methylmorpholine (pK_a 7.41), however, k_∞ is strongly pH dependent with lower values at lower pHs as is evident from Table 3 and Figure 3d. This is again consistent with reaction of a protonated substrate of ionisation constant ($K_{SH_2^+}$) comparable with or greater than that of the buffer, and the dependence was analysed in terms of expression (4), to obtain p$K_{SH_2^+}$ = 8.54 and a pH

$$k_\infty = k_{max.}\left\{\frac{K_{SH_2^+}}{[H^+] + K_{SH_2^+}}\right\} \qquad (4)$$

independent rate constant, $k_{max.} = 7.3 \times 10^{-3}$ s^{-1}. The less accurate values of k_0 show a qualitatively similar dependence upon pH, and for the individual buffers so do values of k, while k/k_∞ remains approximately constant. Calculated dependences of k_{obs} upon $[BH^+]$ shown in Figures 3c and d were based on equation (5) where k_{BH^+} is

$$k_{obs} = \frac{(k_{min.} + k_{BH^+}[BH^+])}{\{1 + (k_{BH^+}/k_{max.})[BH^+]\}}\left\{\frac{K_{SH_2^+}}{[H^+] + K_{SH_2^+}}\right\} \qquad (5)$$

the rate constant for catalysis by the acidic component of the buffer and $k_{min.}$ is close to the limiting rate constant at low pH for hydroxide catalysis. Values of k_{BH^+} are shown in Table 3. For *N*-methyldiethanolamine k_{BH^+} was obtained from equation (2) with $k = k_{BH^+}/(1 + K_{SH_2^+}/[H^+])$. Details of calculations of rate and equilibrium constants are given below

TABLE 3

Rate constants [a] from buffer measurements

Buffer	$[BH^+]/[B]$	pH	10^4k_0 s^{-1}	10^4k_∞ s^{-1}	$10^4k_{BH^+}/t^{-1}$ A [b]	$10^4k_{BH^+}/t^{-1}$ B [b]
N-Methyl-morpholine	3.0	7.10	*c*	1.70	3 020 [d]	3 024 [e]
	1.0	7.60	*c*	4.41		
	0.333	8.08	0.28	13.63		
	0.111	8.58	0.79	26.96		
N-Methyl-diethanolamine	3.0	8.27	*c*			160
	1.0	8.74	0.77			
Trimethylamine	3.0	9.50	*c*	58.8	1 080 [d]	1 020 [e]
	1.0	9.97	1.65	61.0		
Triethylamine	3.0	10.38	1.58			36.3
	1.0	10.75	1.78			
	0.333	11.17	2.01			

[a] Based on $1/k^2_{obs}$ weighting. [b] *Cf.* methods A and B under Data Analysis. [c] Negative values obtained. [d] Based on $k_{max.} = 6.7 \times 10^{-3}$ s^{-1}. [e] Based on $k_{max.} = 7.3 \times 10^{-3}$ s^{-1}.

Values of k_0 from the buffer measurements are included in Figure 2 as closed circles and extend the log$k$–pH profile to show the downward break at the pK_a of the substrate. This break is also shown by the corresponding plot of log k

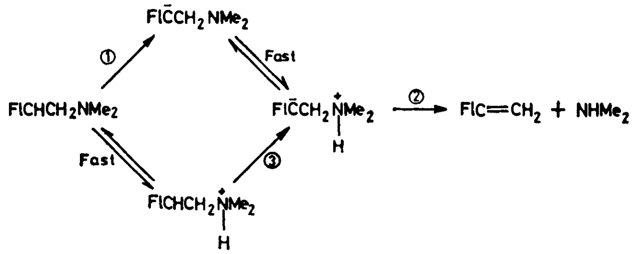
versus pH for rate constants at infinite buffer concentration. At zero buffer the calculated pH dependence was based upon equation (6) with $k_1 = 1.60 \times 10^{-2}$ s^{-1}, $k_{\text{min.}} =$

$$k_{\text{calc}} = \frac{k_{\text{min.}} K_{\text{SH}_2^+}}{[\text{H}^+] + K_{\text{SH}_2^+}} + \frac{k_1[\text{OH}^-]}{1 + k_1[\text{OH}^-]/k_{\text{max.}}} \qquad (6)$$

1.52×10^{-4} s^{-1}, and $k_{\text{max.}} = 1.03 \times 10^{-2}$ s^{-1}, while that at infinite buffer was based upon equation (4) with $k_{\text{max.}} = 7.3 \times 10^{-3}$ s^{-1}. The different values of $k_{\text{max.}}$ reflect the difference in extrapolated rate constants at high hydroxide and high buffer concentrations. The rate constants differ slightly from those of equation (1) because they are calculated from the extrapolated buffer independent rate constants k_0 as well as from measurements with sodium hydroxide.

DISCUSSION

Reaction Mechanism.—Elimination of 9-(dimethylaminomethyl)fluorene in aqueous hydroxide and amine buffers may be understood in terms of reaction *via* a zwitterion intermediate, with formation of the zwitterion occurring by one of the two paths shown in Scheme 3.



SCHEME 3

Under sufficiently basic conditions initial ionisation of the substrate yields a fluoren-9-yl anion which protonates on the dimethylamine nitrogen, as in the upper path; under more acidic conditions protonation of nitrogen precedes ionisation of the hydrogen, as in the lower path. Loss of dimethylamine from the zwitterion gives the product, dibenzofulvene.

The first-order dependence on hydroxide concentration in moderately dilute sodium hydroxide is sensibly interpreted as rate determining ionisation of the neutral substrate (step 1 of Scheme 3). The rate constant (1.60×10^{-2} l mol^{-1} s^{-1}) is, as might be expected,[1] a little larger than that from tritium and deuterium exchange measurements corrected for isotope effects for ionisation of 9-hydroxymethylfluorene[2] (5.5×10^{-3} l mol^{-1} s^{-1}).

Above *ca.* 0.2M-hydroxide, however, the order in hydroxide falls, as Figure 1 and the log$k$–pH profile of Figure 2 show. In aqueous solution the change in order is associated with some experimental scatter of rate constants because high rates and salting out by hydroxide hinder kinetic measurements. In methanolic sodium methoxide however a similar kinetic dependence upon base concentration is observed but with a smaller rate maximum and there the change from first to zero order was found to occur quite smoothly, both for the present substrate and for other fluoren-9-ylmethyl tertiary amines.

The fall in kinetic order points to a change in rate determining step to a later step in the reaction. Since protonation of the dimethylamino nitrogen should be diffusion controlled and, at high pH, thermodynamically favoured in the reverse direction, the only likely possibility is loss of the leaving group (Scheme 3, step 2). In terms of the molecular rate constants of equation (7),

$$\text{SH} \xrightleftharpoons{k_1[\text{OH}^-]} \text{S}^- \rightleftharpoons \text{SH}^\pm \xrightarrow{k_3} \text{P} \qquad (7)$$

in which SH and SH$^+$ denote the substrate and zwitterion respectively, the kinetic dependence upon hydroxide ion concentration would be given by equation (8)

$$\text{d[P]/d}t = \frac{k_1[\text{OH}^-][\text{SH}]}{1 + (k_1[\text{OH}^-]/k_3K^\pm)} \qquad (8)$$

where $K^\pm$ denotes the equilibrium constant for formation of the zwitterion, [SH$^\pm$]/[SH]. This indeed is the behaviour observed, with the limiting rate constant for rate-determining loss of the leaving group, $k_3K^\pm$, corresponding to $k_{\text{max.}}$ ($= 1.02 \times 10^{-2}$ s^{-1}) of equation (1).

At low concentrations of sodium hydroxide the order in hydroxide also falls and the rate of reaction approaches a lower pH independent value with rate constant $k_{\text{min.}} = 1.36 \times 10^{-4}$ s^{-1} (inset of Figure 1). This represents an ' upward break ' in the pH profile and shows that an alternative more favourable path has become available for reaction. One infers that this is the lower path of Scheme 3 and that the pH independence arises from rate-determining attack of hydroxide upon the *N*-protonated substrate (step 3). In terms of equation (9), the kinetic expression now becomes (10) with $K_{\text{SH}_2^+}$ the ionisation constant of the protonated substrate.

$$\text{H}^+ + \text{SH} \rightleftharpoons \text{SH}_2{}^+ \xrightarrow{k'_2[\text{OH}^-]} \text{SH}^\pm \xrightarrow{k_3} \text{P} \qquad (9)$$

$$\frac{\text{d[P]}}{\text{d}t} = \frac{k'_2[\text{OH}^-][\text{H}^+][\text{SH}]}{K_{\text{SH}_2^+}} = \frac{k'_2K_\text{w}[\text{SH}]}{K_{\text{SH}_2^+}} \qquad (10)$$

Measurements with buffers confirm this interpretation. With triethylamine buffers the limiting rate constants at zero buffer concentration, k_0 in Table 3, still have the value $k_{\text{min.}}$, while at finite buffer concentrations the reaction is subject to general acid catalysis (Figure 3a) consistent with attack of buffer base on protonated substrate. Replacement of OH$^-$ in (10) by B gives as rate constant for buffer catalysis $k_2K_\text{a}/K_{\text{SH}_2^+}$, where K_a is the ionisation constant of the buffer acid BH$^+$.

More significantly, for the less basic and more kinetically effective trimethylamine, plots of observed first-order rate constants against buffer acid concentration show marked buffer saturation (Figure 3c). Evidently, increasing the concentration of buffer acid so increases the rate of zwitterion reprotonation (the reverse of step 3) that again there is a change in rate-determining step to loss of the leaving group. Equation (9) may be extended to (11) to take account of this, and the corresponding rate expression is (12). Thus, while at low concentrations of buffer acid, or for sufficiently basic buffers, a plot of observed first-order rate constants against [BH$^+$]

$$\mathrm{H^+ + SH \rightleftharpoons SH_2^+ \xrightleftharpoons[k_{-2}[BH^+]]{k'_2[OH^-] + k_2[B]} SH^{\pm} \xrightarrow{k_3} P} \quad (11)$$

$$\frac{\mathrm{d[P]}}{\mathrm{d}t} = \frac{(k'_2K_\mathrm{w} + k_2K_\mathrm{a}[\mathrm{BH^+}])[\mathrm{SH}]}{(1 + k_{-2}[\mathrm{BH^+}]/k_3)K_{\mathrm{SH_2^+}}} \quad (12)$$

should approach linearity with the normal slope $k_{\mathrm{BH^+}} = k_2K_\mathrm{a}/K_{\mathrm{SH_2^+}}$, at sufficiently high concentrations of BH$^+$ a buffer independent rate with rate constant $k_2k_3/k_{-2}K_{\mathrm{SH_2^+}} = k_3K^{\pm}$ is expected.

The limiting rate at high buffer concentrations should be the same as that for the alternative conditions under which loss of the leaving group becomes rate determining, at high hydroxide concentrations. Analysis of the curvature of the trimethylamine buffer plots using equation (3) as empirical counterpart of equation (12) gave a limiting rate constant k_∞ of 6.0×10^{-3} s^{-1} (Table 3) compared with $k_{\mathrm{max.}}$ of 1.02×10^{-2} s^{-1} from measurements with sodium hydroxide [equations (1) and (6)]. Considering the uncertainty of the extrapolations and the probability of salt effects upon rate constants at high concentrations of hydroxide the agreement is satisfactory.

Buffer saturation in the less basic *N*-methylmorpholine buffers (pK_a 7.41) reveals a further feature of the reaction. As shown by the plots at different buffer ratios in Figure 3d and the values of k in Table 3 the saturation rate constants now depend strongly upon pH. This is the behaviour expected when protonated substrate is present in greater than steady state concentrations and it suggests that the pK_a of the substrate is comparable to or greater than that of *N*-methylmorpholine. The buffer dependence is still quantitatively described by equation (12), but with [SH] replaced by [SH] + [SH$_2^+$] and $K_{\mathrm{SH_2^+}}$ by ($K_{\mathrm{SH_2^+}}$ + [H$^+$]), with the consequence that the rate constant for catalysis by buffer acid and the limiting rate constants at zero and infinite buffer concentrations are reduced by the factor $K_{\mathrm{SH_2^+}}/(K_{\mathrm{SH_2^+}} + [\mathrm{H^+}])$. The effect on the limiting rate constants is shown by plotting log k_0 and log k_∞ against pH, as indicated by the closed circles in Figure 2. The pH profiles at both zero and infinite buffer concentrations, represented by the full and dashed lines respectively, show a downward break reflecting protonation of the substrate. The break in the infinite buffer plot is better characterised because, especially below the break and for the more reactive buffers, extrapolated rate constants at zero buffer concentration are too small for accurate measurement. The non-coincidence of zero and infinite buffer plots at the highest pH values reflects the experimental discrepancy between $k_{\mathrm{max.}}$ determined from hydroxide and buffer measurements.

For trimethylamine and *N*-methylmorpholine buffers the effect of buffer saturation partly obscures the influence of pH on the apparent rate constant for buffer acid catalysis represented by the linear segment of the buffer plots. However this can be seen with the weakly catalytic *N*-methyldiethanolamine buffers, shown in Figure 3b, for which the pK_a of the buffer acid (8.52) is close to that of the substrate.

The pK_a of the substrate was evaluated by combined analysis of the buffer plots for *N*-methylmorpholine and trimethylamine and gave the reasonable value of p$K_{\mathrm{SH_2^+}} = 8.54$. The analysis also yielded an improved value for $k_{\mathrm{max.}}$ of 7.3×10^{-3} l^{-1}, which is closer to the value in sodium hydroxide solutions. Rate constants for buffer acid catalysis $k_{\mathrm{BH^+}}$ were also obtained and are shown with the more directly determined values for *N*-methyldiethanolamine and triethylamine buffers in Table 3. The value of $K_{\mathrm{SH_2^+}}$ may be used to convert these and the corresponding hydroxide rate constants to values of k_2 for attack on the protonated substrate and these are listed in Table 4. The rate constants for hydroxide attack on neutral and protonated substrate differ by a factor of 3 000, and this large reactivity difference suggests why no reaction of the neutral substrate with buffer bases was detected, even in triethylamine buffers of pH >11.

TABLE 4

Rate constants for base attack on the conjugate acid of 9-(dimethylaminomethyl)fluorene [a]

	OH$^-$	Et$_3$N	Me$_3$N [b]	(HOCH$_2$CH$_2$)$_2$-NMe	*N*-Methyl-morpholine [b]
p$K_{\mathrm{BH^+}}$	15.76	10.72	9.76	8.52	7.41
10^2k_2/s^{-1}	4 270.0	55.0	169.0	1.53	2.19
k_{-2}/k_3	0.021 [c]		14.0 [d]		41.2 [e]

[a] Calculated for a substrate pK_a of 8.54. [b] From Table 3, method B. [c] $k_{\mathrm{min.}}/k_{\mathrm{max.}}$ with $k_{\mathrm{max.}}$ 7.3×10^{-3} s^{-1} and $k_{\mathrm{min.}}$ 1.52×10^{-4} s^{-1} [equation (6)]. [d] Method A gives 16. [e] Method A gives 45.

It is clear that the experimental results are indeed consistent with a stepwise reaction *via* a zwitterion, with the fluorenyl anion and *N*-protonated substrate respectively as intermediates at high and low pH values. The change in rate-determining step in both pH regions, effected in one case by increasing hydroxide ion concentration and in the other by increasing buffer concentration, rules out concerted pathways avoiding the zwitterion, such as a or b of Scheme 2. Direct formation of the zwitterion or product by a proton switch or concerted intramolecular elimination, which are kinetically indistinguishable from hydroxide attack on protonated substrate, are unlikely because the hydroxide ion falls squarely on a plot of log k_2 for reaction of the different bases of Table 4 against log k for reaction of the same bases in β-elimination of 9-(chloromethyl)fluorene in 9 : 1 aqueous ethanol, measured by Spencer [26] (Figure 4). For 9-chloromethylfluorene the kinetic dependence on hydroxide ion excludes intramolecular elimination, and had such a mechanism applied in the case of the 9-(dimethylaminomethyl)fluorene a positive deviation from the correlation would have been expected.

Comparisons with Other Systems.—For elimination of the Mannich bases β-piperidino- and β-morpholinopropiophenone Zuman observed kinetics consistent with the lower pH independent path of Figure 2, with downward breaks occurring at the measured pK_a values of the substrates.[5] He interpreted this behaviour in terms of an intramolecular reaction of the neutral substrate with a transition state such as (3), but the present results suggest that a stepwise intermolecular reaction may be more likely. Unfortunately hydration of the vinyl ketone product prevented measurements at high pH, and investigations of catalysis by buffer acids have not been reported. For the morpholine leaving group a rather large rate difference appears to exist between reaction of the protonated Mannich base and of the corresponding methylammonium ion with hydroxide ion,[6,27] but probably this represents a steric effect.[28]

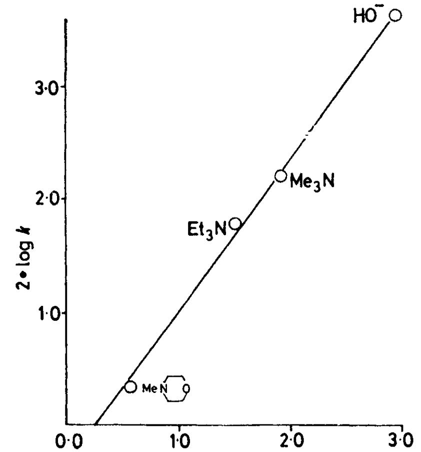
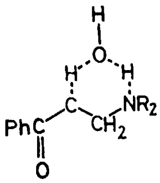
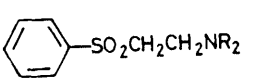


FIGURE 4 A plot of log k for reaction of various bases with the conjugate acid of 9-(dimethylaminomethyl)fluorene against log k for the corresponding reactions with 9-chloromethylfluorene



(3)



(4)

A similar pH dependence was found in elimination of dimethylamine, piperidine, and morpholine from the corresponding phenyl sulphones (4) in 1 : 1 aqueous dioxan.[7] Absence of kinetic salt effects led the authors again to favour reaction of the neutral substrate [7,8] but in this case at pH values below the pK_a of the leaving group rates of elimination of the amino-sulphones are similar to those of the corresponding methylammonium ions. A primary isotope effect (k_H/k_D 3.6) indicates rate-determining hydrogen transfer for the alkylammonium salts [7] and strong pH dependent buffer saturation in ethanolic triethylamine buffers shows that the elimination cannot be $E2$.[29]

Again no increase in rate at higher pH values was reported. However, measurements were extended only to pH 11 and the larger ρ^* for rates of ionisation of 2-X-ethylphenyl sulphones [30] than of 9-(X-methyl)fluorenes [31] (4.9 compared with 2.2) points to a substantially smaller rate of ionisation for the β-hydrogen of the amino substrate relative to its N-protonated conjugate acid in the phenyl sulphone series than in the fluorene. This implies a correspondingly greater range for the pH independent reaction. A surprising result is that in ethanolic sodium ethoxide at concentrations outside the pH range no elimination of dimethylaminoethyl phenyl sulphone is seen.[32]

Comparison with the less closely related carbonyl eliminations also shows similarities. A feature of the carbonyl reactions is that proton transfers between oxygen and nitrogen atoms, notwithstanding their occurrence at the diffusion limit, quite commonly are rate determining.[13] It is satisfactory therefore that the slower proton transfers from carbon implicated in the fluorenyl elimination are also rate determining, at all except the highest pH values. On the other hand, the rate difference between proton and leaving group loss is relatively small, a factor of only 50. The difference is probably greater for leaving groups less basic than dimethylamine, but it suggests that leaving group separation as well as proton transfer may occur less readily in fluorenyl than carbonyl reactions.

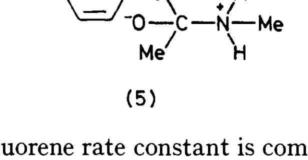
From the rate constant for reaction with hydroxide in Table 4 and other rate and equilibrium data for ionisation of substituted fluorenes,[31,33] a pK_a of *ca.* 15 can be crudely estimated for ionisation of the fluoren-9-yl hydrogen of N-protonated 9-(dimethylaminomethyl)-fluorene. Combination with the p$K_{SH_2^+}$ of 8.54 for N-protonation and $k_3K^{\pm} = k_3K_a/K_{SH_2^+} = 7.3 \times 10^{-3}\ s^{-1}$ (Table 5) gives a rate constant k_3 for expulsion of the dimethylamino group from the fluorenyl zwitterion of *ca.* $10^4\ s^{-1}$. This may be compared with rate constants of *ca.* $4 \times 10^9\ s^{-1}$ for loss of dimethylamine from (5) to form p-methylphenyl acetate [19] and $3.4 \times 10^3\ s^{-1}$ for loss of trimethylamine from (6) to yield formaldehyde.[34]

TABLE 5

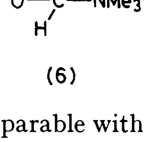
Rate and equilibrium constants for elimination of 9-(dimethylaminomethyl)fluorene

$10^3k_1/s^{-1}$ [a]	$10^3k_3K^{\pm}$	p$K_{SH_2^+}$
16.1	7.3,[b] 10.3 [c]	8.54

[a] Rate constant for hydroxide attack on neutral substrate [from equation (6)]. [b] $k_{max.}$ from buffer saturation measurements; preferred value. [c] $k_{max.}$ from measurements at high hydroxide concentrations.



(5)

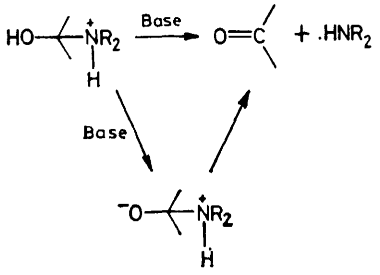


(6)

The fluorene rate constant is comparable with that for formation of the relatively unstable formaldehyde, and since the estimated pK_a for oxygen protonation [34] of (6) is only 9.3, *ca.* 5—6 units less than the likely value for

C-protonation of the fluorenyl anion, the comparison suggests that the intrinsic reactivity of the carbonyl substrate is greater. In the absence of further information, particularly on product stabilities, intrinsic reactivity differences cannot safely be distinguished from thermodynamic or solvation effects, but from a practical standpoint it seems likely that an oxygen anion will expel a β-ammonium leaving group more readily than will a carbanion in most experimental comparisons. A higher estimate of the fluorenyl $\mathrm{p}K_\mathrm{a}$ would give a larger value of k_3 but a larger difference between fluorenyl and oxygen $\mathrm{p}K_\mathrm{a}$ values.

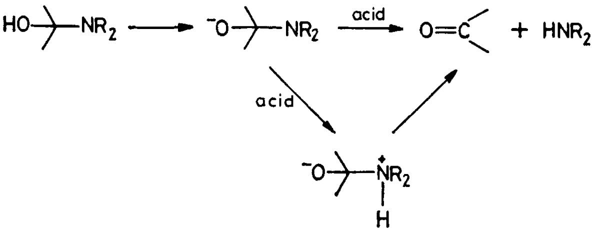
Also consistent with behaviour in carbonyl reactions is the stepwise rather than concerted nature of the fluorenyl reaction. For the lower path of Scheme 3, which operates at more acidic pH values, the corresponding carbonyl reaction (Scheme 4) has been studied in detail in its microscopic reverse direction for additions of amines to substituted benzaldehydes.[21-24] Concerted elimination avoiding the zwitterion intermediate is seen only for very weakly basic leaving groups such as 2-methyl-3-thiosemicarbazide[22] ($\mathrm{p}K_\mathrm{a}$ 1.20) or, marginally, methoxyamine[21] ($\mathrm{p}K_\mathrm{a}$ 4.73). For the strongly basic dimethylamine ($\mathrm{p}K_\mathrm{a}$ 10.77) elimination would be expected to be stepwise, as it is for the fluorenyl substrate.



SCHEME 4

One may predict, however, that in the fluorene series concerted elimination will be seen for more basic leaving groups than in commonly occurring carbonyl reactions. In the latter case the high thermodynamic acidity of the hydroxy group coupled with the intrinsically higher reactivity of non-concerted proton transfers strongly favour a stepwise mechanism. Thus the halogen leaving groups, Cl, Br, and I, despite their lower reactivity than $NHMe_2^+$, eliminate from 9-(halogenomethyl)fluorenes by an *E*2 mechanism.[31,35,36] The strong polarity of the ammonium ion must favour reaction *via* a β-carbanion but a concerted mechanism can presumably be anticipated for amine leaving groups not much more basic than dimethylamine.

For the upper reaction path of Scheme 3, which operates in more basic conditions, and for carbonyl reactions (Scheme 5) which has been called by Schowen[16] the α-mode of elimination (and by Jencks[13] a class *n* reaction), there appears to be no evidence of a concerted mechanism in carbonyl eliminations[14,17-20,23,24] even for so weakly basic an amine as 2-methyl-3-thiosemicarbazone.[23] The analogy between carbonyl and olefin eliminations is here less close than for β-elimination because the rate-determining proton transfer step is normally *to* nitrogen in the carbonyl reaction and *from* carbon, the counterpart of oxygen, in the olefin reaction. In aromatic and vinylic substitutions by amines[10-12] proton transfer to nitrogen can be rate determining in α-elimination and addition modes, but in these cases a β-hydrogen is not present in the reactants and the high barrier to *C*-protonation of the carbanion intermediate precludes involvement of a hydrogen bound to carbon.



SCHEME 5

A point of difference of the fluorenyl from carbonyl reactions is the presence of an anomalously high pH independent rate for the carbonyl reaction, interpreted as an intramolecular proton switch between oxygen and nitrogen.[13,14] The normal value for the pH independent elimination as judged by comparison with the intermolecular elimination of 9-(chloromethyl)fluorenene makes this unlikely for 9-(dimethylaminomethyl)fluorene.

EXPERIMENTAL AND DATA ANALYSIS

9-(Morpholinomethyl)fluorene and 9-(piperidinomethyl)fluorene were synthesised initially following Carpino and Han's procedure, using the tosylate of 9-(hydroxymethyl)fluorene instead of the chloroformate.[37] These amines reacted normally in methanol but gave complex kinetics in aqueous solution, possibly for reasons connected with their poor solubility.[38] 9-(Aminomethyl)fluorene was then prepared by converting fluorene-9-carboxylic acid to its acid chloride and amide and reducing the amide with diborane.[39] This substrate proved too unreactive for study at 25° and 9-(dimethylaminomethyl)fluorene was made by a similar procedure.

Fluorene-9-*NN*-dimethyl carboxamide was prepared by stirring fluorene-9-carbonyl chloride[40] overnight with 30% aqueous dimethylamine. The dimethylamide was filtered off and recrystallised from 20% aqueous ethanol, m.p. 156—158° (lit., 159—160°,[41] 256.5—258[42]), ^{1}H n.m.r. as previously reported.[43] The dimethylamide was heated under reflux for several hours with either (a) 1M-diborane in tetrahydrofuran[44] or (b) lithium aluminium hydride in diethyl ether. The product was acidified with hydrochloric acid and its aqueous extract carefully neutralised with Na_2CO_3 or NaOH and extracted with ether. Precipitation with dry HCl gave 9-(dimethylaminomethyl)fluorene hydrochloride, m.p. 148—149° (ethanol); evaporation of the ether and recrystallisation from a small volume of chloroform–light petroleum gave the *amine*, m.p. 79—81° (Found: C, 86.1; H, 7.6; N, 6.3. $C_{16}H_{17}N$ requires C, 86.05; H, 7.7; N, 6.25%), δ($CDCl_3$) 2.4 (6 H, s), 2.6 (2 H, d, *J* 7 Hz), 4.05 (1 H, t, *J* 7 Hz), 7.1—7.8 (8 H, m).

Kinetic Measurements.—Kinetic measurements were made with a Perkin-Elmer–Hitachi 124 spectrophotometer equipped with a brass cell block thermostatted by water circulation at 25 ± 0.1 °C. Reactions were initiated by injecting a few µl of stock solution of substrate into a buffer or hydroxide solution in a 50 mm cell previously thermostatted in the cell block. The reaction was followed by the increase in the absorption maximum due to dibenzofulvene formation at 255 nm. Solutions of 9-(dimethylaminomethyl)fluorene hydrochloride were stabilised by addition of a small quantity of HCl. All reactions except those in >0.1N-NaOH were carried out at an ionic strength of 0.1 maintained by added sodium chloride.

Buffer Solutions.—*N*-Methylmorphiline, triethylamine, and trimethylamine were purified as their hydrochlorides by 2—3 recrystallisations from ethanol and drying. The hydrochlorides were prepared by precipitation from amine solutions in ether with dry HCl or, for trimethylamine, by adding concentrated HCl to 30% aqueous amine and evaporating. The *N*-methyldiethanolamine was distilled. Buffer solutions were prepared from doubly distilled water protected against carbon dioxide. Measurements of pH were made with a Radiometer PHM 26 pH meter and were consistently 0.2 units higher than calculated without corrections for activity coefficients or the presence of sodium ions at high pH.

Data Analysis.—First-order rate constants were determined by weighted least squares analysis of optical density–time measurements (normally extending over 3—4 reaction half-lives) with the optical density at infinite time OD_∞ obtained by iteration. Periodically OD_∞ was checked by direct measurement.

For measurements in *N*-methyldiethanolamine buffers values of k_0 at constant buffer ratio were obtained by least squares analysis of measured first-order rate constants k_{obs} as a function of buffer acid concentration, $[\mathrm{BH}^+]$, using equation (2). For triethylamine buffers measurements at different buffer ratios were combined, a common value of k was iterated, and values of k_0 for each buffer ratio were calculated by least squares. The iteration was continued until the sum of squares of the differences of observed from calculated rate constants $\Sigma(k_{\mathrm{obs}} - k_{\mathrm{calc}})^2$ was minimised.

In other cases analysis was based on the general equation (13) where y incorporates a parameter determined by

$$yk_{\mathrm{obs}} = k_0 + k[\mathrm{BH}^+] \qquad (13)$$

iteration, and k_0 and k are found by least squares with weighting $1/y^2$. In general weights of $1/k^2_{\mathrm{obs}}$ were also included so that percentage deviations of calculated from observed rate constants were minimised, but commonly this had little influence on the results.

Data for *N*-methylmorpholine and trimethylamine buffers were treated by two methods. In method A data for each buffer ratio were analysed by equation (3), which on rearrangement gives $y = \{1 + (k/k_\infty)[\mathrm{BH}^+]\}$, with k/k_∞ the parameter to be iterated. Values of k_0 and k_∞ are listed in Table 3. Reasonable magnitudes of k_0 were not obtained for buffers of pH <8.0, where k_0 is very small, or for the lower pH trimethylamine buffer. The values of k/k_∞ [$= k_{-2}/k_3$ of equation (12)] should be independent of buffer ratio, and best values of 45 for *N*-methylmorpholine and 16 for trimethylamine were obtained by optimising combined rate constants for all buffer ratios. However values for *N*-methylmorpholine determined for individual buffer ratios, and with and without the $1/k_{\mathrm{obs}}^2$ weighting, varied by ±20%.

The values of k_∞ at different pHs were used to find the limiting rate constant at high buffer concentrations and high pH, $k_{\mathrm{max.}}$ ($= k_3K^\pm$), and the pK_{a} of the substrate, p$K_{\mathrm{SH_2^+}}$. According to equation (4) a plot of $1/k_\infty$ against $[\mathrm{H}^+]$ should have slope and intercept $1/k_{\mathrm{max.}}K_{\mathrm{SH_2^+}}$ and $1/k_{\mathrm{max.}}$ respectively, and weighted least squares analysis gave p$K_{\mathrm{SH_2^+}} = 8.52$ and $k_{\mathrm{max.}} = 6.68 \times 10^{-3}$ s^{-1}. In the analysis calculated values of $[\mathrm{H}^+] = K_{\mathrm{a}}[\mathrm{BH}^+]/[\mathrm{B}]$ were used. These are smaller than measured values because of neglect of the effect of ionic strength upon activity coefficients, but as both buffers and substrate are tertiary amines their relative pK_{a} values should be nearly independent of ionic strength, and the pK_{a} determined should be close to the thermodynamic value. Measured values of $[\mathrm{H}^+]$ gave p$K_{\mathrm{SH^+}} = 8.70$, and this was used in the log$k$–pH profile of Figure 2, in which experimental pH measurements are plotted.

The results also yield rate constants $k_{\mathrm{BH^+}}$ for buffer acid catalysis, from $k_{\mathrm{max.}}/(k/k_\infty)$ ($= K^\pm/k_{-2}$), and these are given in Table 3.

In the alternative method B *N*-methylmorpholine and trimethylamine measurements were combined using equation (13), with k_0 and k replaced by $k_{\mathrm{min.}}$ and $k_{\mathrm{BH^+}}$ and y based upon rearrangement of equation (5), *i.e.* equation (14). Values of $k_{\mathrm{min.}}$ and $k_{\mathrm{BH^+}}$ were calculated for a series of

$$y = \{1 + (k_{\mathrm{BH^+}}/k_{\mathrm{max.}})[\mathrm{BH}^+]\}(1 + {}^{2}\mathrm{H}^+]/K_{\mathrm{SH_2^+}}) \qquad (14)$$

$K_{\mathrm{SH_2^+}}$, and $k_{\mathrm{BH^+}}/k_{\mathrm{max.}}$ was iterated to its optimum value for each buffer. The $K_{\mathrm{SH_2^+}}$ was selected that gave the same $k_{\mathrm{max.}}$ for the two buffers. This was judged more reasonable than, although only 0.04 pK units different from, the value at the rather shallow minimum in the combined residuals $\Sigma\{(k_{\mathrm{obs}} - k_{\mathrm{calc}})/k_{\mathrm{obs}}\}^2$. The weighting $1/k_{\mathrm{obs}}^2$ was included, but its omissions changed $k_{\mathrm{max.}}$ by only 5%. The combination of data is important because the data for *N*-methylmorpholine are effective in evaluating $K_{\mathrm{SH_2^+}}$ and the data for trimethylamine in evaluating $k_{\mathrm{max.}}$, but $k_{\mathrm{max.}}$ and $K_{\mathrm{SH_2^+}}$ cannot be determined independently. Method B is indeed preferred to method A because it appears to offer a more direct treatment of the combined data. However, calculated values of $k_{\mathrm{max.}} = 7.3 \times 10^{-3}$ s^{-1} and the 'thermodynamic' p$K_{\mathrm{SH_2^+}} = 8.54$ are in good agreement with those from method A.

Values of $k_{\mathrm{BH^+}}$ determined by method B are listed in Table 3 and were used to calculate the rate constant-buffer concentration dependences of Figures 3c and d. The value of p$K_{\mathrm{SH_2^+}}$ was used to obtain $k_{\mathrm{BH^+}}$ for *N*-methyldiethanolamine buffers from equation (15). Values of $k_{\mathrm{BH^+}}$ were

$$k_{\mathrm{obs}}(1 + [\mathrm{H}^+]/K_{\mathrm{SH_2^+}}) = k_{\mathrm{min.}} + k_{\mathrm{BH^+}}[\mathrm{BH}^+] \qquad (15)$$

converted to the rate constants k_2 for attack of buffer base upon protonated substrate shown in Table 4, using the relationship $k_{\mathrm{BH^+}} = k_2K_{\mathrm{a}}/K_{\mathrm{SH_2^+}}$.

The rate constant for hydroxide attack on protonated substrate, k'_2, may be derived from $k_{\mathrm{min.}}$, since $k_{\mathrm{min.}} = k_2'K_{\mathrm{w}}/K_{\mathrm{SH_2^+}}$. Values of $k_{\mathrm{min.}}$ together with k_1, the rate constant for hydroxide attack on neutral substrate, and $k_{\mathrm{max.}}$, the limiting rate constant at high hydroxide concentrations, were obtained from kinetic measurements with sodium hydroxide (Table 1) and the extrapolated rate constants at zero buffer concentrations k_0 (Table 3) using equation (16) with expressions (17)—(19) for y, a, and b

based on rearrangement of equation (6). $K_{\mathrm{SH_2^+}}$ was taken as its measured value (Table 5), $k_1/k_{\mathrm{max.}}$ was

$$y = a + b[\mathrm{OH^-}] \tag{16}$$

$$y = k_{\mathrm{obs}}\frac{([\mathrm{H^+}] + K_{\mathrm{SH_2^+}})}{K_{\mathrm{SH_2^+}}}\{1 + (k_1/k_{\mathrm{max.}})[\mathrm{OH^-}]\} \tag{17}$$

$$a = k_{\mathrm{min.}} + \frac{k_1K_{\mathrm{w}}}{K_{\mathrm{SH_2^+}}} \cong k_{\mathrm{min.}} \tag{18}$$

$$b = (1 + k_{\mathrm{min.}}/k_{\mathrm{max.}})k_1 \tag{19}$$

iterated, and a and b were determined as usual by least squares. The derived value of k_2' is shown in Table 4, as also is $k_{\mathrm{min.}}/k_{\mathrm{max.}}$, which corresponds to k'_{-2}/k_3 of equation (9) with k'_{-2} the rate constant for protonation of the zwitterion by water. Values of k_{-2}/k_3 for trimethylamine and *N*-methylmorpholine are also given in Table 4.

The rate constants k_1 and $k_{\mathrm{max.}}$ are shown in Table 5 together with $k_{\mathrm{max.}}$ from buffer saturation measurements. The discrepancy between the two $k_{\mathrm{max.}}$ values has been discussed. The values were used, together with $k_{\mathrm{min.}}$ 1.52×10^{-4} s^{-1} and p$K_{\mathrm{SH_2^+}}$ 8.70, to calculate the log$k$–pH dependences at zero and infinite buffer concentrations, based on equations (6) and (4), shown respectively as the full and dotted lines in Figure 2.

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