A mechanistic study of the reactions of formaldehyde with aniline in the presence of sulfite

John H. Atherton,[a] Kathryn H. Brown[b] and Michael R. Crampton *[b]

[a] *Avecia, PO Box 521, Leeds Road, Huddersfield, Yorkshire, UK HD2 1GA*
[b] *Chemistry Department, Durham University, Durham, UK DH1 3LE*

^{1}H NMR results are reported for the reactions of hydroxymethanesulfonate, **1**, with aniline and its derivatives to produce anilinomethanesulfonates, **3**. The mechanism of the reaction involves dissociation of **1** to produce formaldehyde, as a steady state intermediate, which reacts with aniline to give a carbinolamine;† subsequent dehydration and reaction with sulfite produces the product. The kinetics of individual steps have been investigated. The release of sulfite from **1**, measured by reaction with iodine, is shown to involve the ionised, dianionic form when pH > 3. Rate constants, k_2, and equilibrium constants, K_2, are reported for carbinolamine formation; the values of k_2, but not K_2, are affected significantly by substituents in the aniline. It is deduced that the rate-limiting step in the overall formation of products **3** changes in the pH range 6–8 from carbinolamine formation to carbinolamine dehydration.

Condensation reactions of the type shown in eqn. (1) are widely

$$RNH_2 + CH_2O + HZ \longrightarrow RNHCH_2Z + H_2O \quad (1)$$
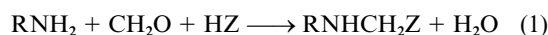
used in synthesis. A well known example is the Mannich reaction[1] where HZ is a methylene compound with an acidic hydrogen. In the Strecker synthesis[2] of amino acids the first stage is the formation of an α-aminonitrile by reaction of a carbonyl compound with ammonia and cyanide. There is strong evidence for the intermediacy of imines or iminium ions in these reactions.[3–8] However the lifetimes of these species are expected to be very small in aqueous solution.[9–11]

Here we report a mechanistic study of reactions of the type shown in eqn. (1) where RNH_2 is aniline, or a substituted aniline, and HZ is hydrogen sulfite. It has been known for some time that sulfite, an excellent nucleophile for carbon,[12] may participate in such reactions to yield *N*-methylsulfonates. However the only previous mechanistic study is a brief report[13] of the kinetics of the reactions using ammonia as the amine.

Results and discussion

It was convenient to use the sodium salt of hydroxymethanesulfonate, **1**, which is a crystalline material, as the source of formaldehyde. ^{1}H NMR measurements were made in deuterium oxide. Spectra obtained with **1** and aniline, **2**, in a 1:1 molar ratio showed the gradual disappearance of bands due to reactants and the appearance of new bands attributed to the adduct **3**, as shown in eqn. (2). The change, which took several
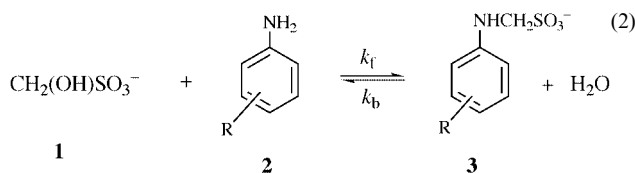
hours, went to virtual completion. Bands due to the adduct, **3**, were close to, but distinct from, those of the reactants. Chemical shifts for reactions with aniline (**2**, R = H) and

† The IUPAC name for carbinolamine is aminomethanol.

Table 1 NMR and UV data for formation of aniline *N*-methylsulfonates, **3**, in water

| | δ | | | |
	CH$_2$	Ring[a]	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}
1	4.24	—	—	—
2, R = H	—	6.70, 6.72, 7.09	230 / 280	7800 / 1400
3, R = H	4.28	6.80, 6.72, 7.16	241 / 287	13 100 / 800
2, R = 4-Me[b]	—	6.64, 6.95	232 / 287	8900 / 1600
3, R = 4-Me[b]	4.22	6.68, 6.97	241 / 291	12 400 / 1700

[a] Spin coupling, $J = 8$ Hz, is observed between adjacent hydrogens. [b] A band due to the CH$_3$ group is observed at δ 2.10. There is little change in position on adduct formation.

4-methylaniline (**2**, R = 4-Me) are in Table 1. It was interesting that spectra obtained in the presence of a two-fold excess of either reagent, **1** or **2**, showed bands only for **3** and for the excess component. Thus there is no evidence for further reaction to produce di-adducts such as **5**, analogous to those
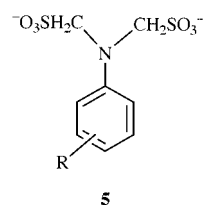
reported[13] in reactions involving ammonia as the amine. The lower basicity of aniline compared with ammonia may be the important factor here. The formation of aniline *N*-methylsulfonates, **3**, was also observable by UV spectroscopy. The absorptions due to aniline were shifted to longer wavelengths with increased extinction coefficient by reaction with **1**. Data are in Table 1. This change in absorption was used to make kinetic measurements. With the concentration of **1** in large excess of the concentration of **2** first order kinetics were

Table 2 Kinetic results for reaction of aniline,[a] **2** R = H, and **1** in water at 25 °C

Item	[CH$_2$(OH)SO$_3$Na]/ mol dm^{-3}	[Added Sulfite]$_{stoich}$/ mol dm^{-3}	pH[b]	k_{obs}[c]/ 10^{-5} s^{-1}	Abs[d] (241 nm)	K[e]/ dm^3 mol^{-1}
1	0	—	—	—	0.30	—
2	0.002	—	—	2.45	0.89	840
3	0.004	—	—	4.40	1.02	820
4	0.007	—	—	6.44	1.10	820
5	0.010	—	—	8.89	1.13	750
6	0.020	—	—	16.6	1.19	—
7	0.050	—	—	40.0	1.20	—
8	0.10	—	—	79	1.23	—
9	0.10	0.003	—	25	—	—
10	0.10	0.007	—	11	—	—
11	0.007	—	6.0	6.68	—	—
12	0.007	—	7.1	6.94	—	—
13	0.007	—	8.2	6.20	—	—
14	0.020	—	6.0	18.8	—	—
15	0.020	—	7.1	19.0	—	—
16	0.020	—	8.2	17.0	—	—
17	0.10	0.003	6.1	40	—	—
18	0.10	0.003	7.0	32	—	—
19	0.10	0.003	8.1	22	—	—

[a] The aniline concentration is 1 × 10^{-4} mol dm^{-3}. A repeat of item 8 using an aniline concentration of 5 × 10^{-5} mol dm^{-3} gave a value for k_{obs} of 83 × 10^{-5} s^{-1}. [b] Phosphate buffers [KH$_2$PO$_4$]$_{stoich}$ = 0.033 mol dm^{-3}. Where no pH is quoted, solutions were unbuffered. [c] Measured at 245 nm. [d] At completion of reaction. [e] Calculated as (Abs − 0.30)/(1.24 − Abs) [CH$_2$(OH)SO$_3$Na].

Table 3 Kinetic results for reaction of 4-methylaniline,[a] **2**, R = 4-Me, and **1** in water at 25 °C

Item	[CH$_2$(OH)SO$_3$Na]/ mol dm^{-3}	[Sulfite]$_{stoich}$[b]/ mol dm^{-3}	pH[c]	k_{obs}/10^{-4} s^{-1}	k_{obs}·[Sulfite]$_{stoich}$/ 10^{-6} mol dm^{-3} s^{-1}
1	0.002	—	5.8	2.12	—
2	0.004	—	5.8	3.22	—
3	0.008	—	5.8	5.15	—
4	0.010	—	5.8	6.13	—
5	0.10	—	5.8	50.4	—
6	0.10	0.0022	5.8	23	5.1
7	0.10	0.0040	5.8	18	7.2
8	0.10	0.0070	5.8	12	8.4
9	0.10	0.010	5.8	9.3	9.3
10	0.10	—	7.9	37	—
11	0.10	0.0020	7.9	16	3.2
12	0.10	0.0044	7.9	8.2	3.6
13	0.10	0.0070	7.9	6.3	4.4
14	0.10	0.010	7.9	2.9	2.9

[a] Concentration is 1 × 10^{-4} mol dm^{-3}. [b] Stoichiometric concentration of added sulfite. [c] Phoshate buffers.

observed. Data for **2**, R = H are in Table 2. Items 2 to 8 show that k_{obs} increases with increasing concentration of **1**. From eqn. (2) we may write eqn. (3), so that from the slope and

$$k_{obs} = k_f \cdot [\mathbf{1}] + k_b \qquad (3)$$

intercept of a linear plot values of k_f (7.8 ± 0.2) × 10^{-3} dm^3 mol^{-1} s^{-1} and k_b (1.0 ± 0.2) × 10^{-5} s^{-1} are obtained. Combination of these values using eqn. (4) gives a value for the

$$K = \frac{k_f}{k_b} \qquad (4)$$

equilibrium constant K of 780 dm^3 mol^{-1} which is in reasonable agreement with that obtained from absorbance values using eqn. (5).

$$K = \frac{[\mathbf{3}]}{[\mathbf{1}][\mathbf{2}]} \qquad (5)$$

Items 8–10 show that k_{obs} decreases in the presence of added sodium sulfite. Items 11–19 indicate that values of k_{obs} are insensitive to the pH over the range studied. It is worth noting that the pK_a value[14] of the anilinium ion is 4.60, and that **1** and **3** will exist, as shown, largely in their monoanionic forms

in the pH range 5–10. Hence the overall equilibrium shown in eqn. (2) is not expected to be sensitive to pH in the quoted range.

Kinetic results for reaction of 4-methylaniline with **1** are in Table 3. Measurements were made either at pH 5.8 or 7.9. Items 1–5 show that in the absence of added sulfite values of k_{obs} increase with the concentration of **1**. A linear plot had slope (5.0 ± 0.5) × 10^{-2} dm^3 mol^{-1} s^{-1} and intercept (1.1 ± 0.1) × 10^{-4} s^{-1}. Since these data were obtained at pH 5.8, and the pK_a value[14] for the 4-methylanilinium ion is 5.08, a small correction is necessary to allow for the reduction in concentration of the free amine by protonation (eqn. (6)). The presence of the

$$[\mathbf{2}] = [\mathbf{2}]_{stoich} \cdot \frac{K_a}{K_a + [H^+]} \qquad (6)$$

CH$_2$SO$_3^-$ substituent in **3** is expected to reduce the basicity of the nitrogen atom by 2–3 pK_a units.[15,16] Hence **3** will remain unprotonated at pH 5.8. After application of the correction we obtain values for k_f, 6 × 10^{-2} dm^3 mol^{-1} s^{-1} and k_b, 1.1 × 10^{-4} s^{-1}. Combination of these values gives K, 550 dm^3 mol^{-1}.

The effect of the 4-methyl substituent in **2** is to increase values of both k_f and k_b, while the value of the equilibrium constant K is little changed.

**Table 4** Kinetic results for reaction of 4-(dimethylamino)aniline[a] **2**, R = 4NMe$_2$, and **1** in water at 25 °C

[CH$_2$(OH)SO$_3$Na]/ mol dm^{-3}	[Sulfite]$_{stoich}$[b]/ mol dm^{-3}	pH[c]	$k_{obs}/10^{-4}$ s^{-1}	$k_{obs}\cdot$[Sulfite]$_{stoich}$/ 10^{-6} mol dm^{-3} s^{-1}
0.10	0	5.9	35	—
0.10	0.002	5.9	13	2.6
0.10	0.004	5.9	6.4	2.6
0.10	0.007	5.9	4.4	3.1
0.10	0.010	5.9	2.8	2.8
0.10	0	8.0	75	—
0.10	0.002	8.0	21	4.2
0.10	0.004	8.0	12	4.8
0.10	0.007	8.0	7.5	5.3
0.10	0.010	8.0	5.1	5.1

[a] Concentration is 1×10^{-4} mol dm^{-3}. The solvent contains 2% acetonitrile (v/v) to aid solubility. [b] Stoichiometric concentration of added sulfite. [c] Phosphate buffers.

Items 5–9 and 10–14 in Table 3 show that there is an inverse dependence of k_{obs} on the sulfite concentration so that values of $k_{obs}\cdot$[sulfite]$_{stoich}$ are approximately constant. Values of this latter term show only a small variation with pH.

Results for reaction of **1** with 4-(dimethylamino)aniline, **2**, R = 4-NMe$_2$, in Table 4, similarly indicate an inverse dependence of k_{obs} on the concentration of added sulfite.

The dependence on sulfite concentration of the rate constant for reaction indicates that the mechanism of formation of **3** is more complicated than bimolecular reaction between **1** and **2**. Previous work on related systems[3–8,13] provides evidence for the intermediacy of formaldehyde, hence we propose the mechanism outlined in Scheme 1. This involves: i) the formation of
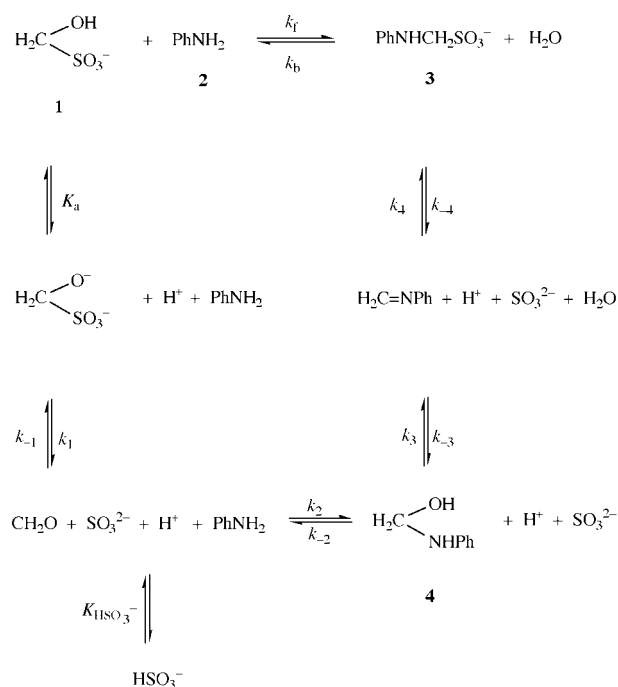
Scheme 1

formaldehyde from hydroxymethanesulfonate, ii) its reaction with amine to yield a carbinolamine, iii) dehydration of the carbinolamine to yield an imine and iv) reaction of the imine, probably through the iminium cation, with sulfite. The scheme is written for reaction with aniline, **2**, R = H but will apply also to substituted derivatives.

Before discussing our results in the light of this Scheme, we report results relevant to the first two steps.

Formation of formaldehyde from hydroxymethanesulfonate

The high affinity of sulfite for aldehydes is well known,[17–19] and

there have previously been kinetic and equilibrium studies of the formaldehyde–sulfite system. However these reports[17,18] relate to solutions with pH values in the range 9–12, or in the range 0–3. Our measurements cover the pH range 1–8. The fast and irreversible reaction of iodine with sulfite and/or hydrogen sulfite ions[20] has been previously used to examine the decomposition of aldehyde–sulfite adducts,[21,22] and we have used this method to measure rate constants for dissociation of hydroxymethanesulfonate.

Our results are interpreted by Scheme 2, in which sulfite
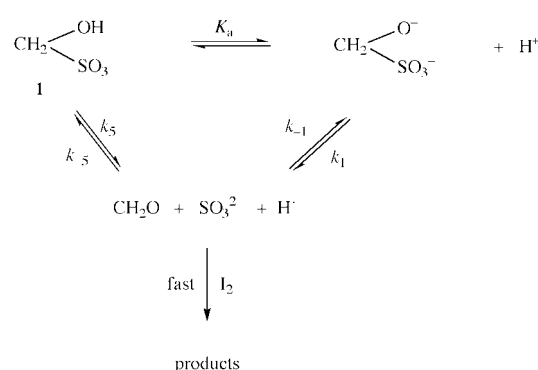
Scheme 2

may be released from hydroxymethanesulfonate **1**, or from the dianion. The pK_a value for acid dissociation of **1** is reported[17] to be 11.7. Hence in the pH range 1–8 the dianion will be a low concentration intermediate. The disappearance of iodine, measured spectrophotometrically at 350 nm, was found to follow a zero order rate law as shown in eqn. (7). According to

$$\frac{-d[I_2]}{dt} = k_{obs} \quad (7)$$

Scheme 2 the relationship between k_{obs} and [**1**] is given by eqn. (8). In agreement with this, values of k_{obs} increased linearly

$$k_{obs} = k_5[\mathbf{1}] + \frac{k_1 K_a[\mathbf{1}]}{[H^+]} \quad (8)$$

with the concentration of **1**; representative data are in Table 5. A plot, in logarithmic form, according to eqn. (9) is shown in

$$k'_{obs} = \frac{k_{obs}}{[\mathbf{1}]} = k_5 + \frac{k_1 K_a}{[H^+]} \quad (9)$$

Fig. 1. The pH independent part of the plot corresponds to decomposition of **1** with a value for k_5 of 2.3×10^{-8} s^{-1}. The pH dependent part results from decomposition of the dianion.

Table 5 Zero order rate constants[a] for the reaction of hydroxymethanesulfonate, **1**, with iodine in water at 25 °C

[**1**]/ mol dm⁻³	k_{obs}[b]/mol dm⁻³ s⁻¹		
	pH 3.1	pH 5.0	pH 7.9
0.005	—	2.13×10^{-8}	1.66×10^{-5}
0.010	9.7×10^{-10}	5.08×10^{-8}	3.62×10^{-5}
0.015	1.14×10^{-9}	8.06×10^{-8}	5.68×10^{-5}
0.020	1.39×10^{-9}	1.14×10^{-7}	7.65×10^{-5}
0.025	1.68×10^{-9}	1.45×10^{-7}	9.37×10^{-5}
0.030	2.00×10^{-9}	1.79×10^{-7}	1.16×10^{-4}

[a] Measured at 350 nm, either by conventional or stopped-flow spectrophotometry. [b] pH values were maintained using phthalate, acetate, or phosphate buffers with a stoichiometric concentration of 0.10 mol dm⁻³.
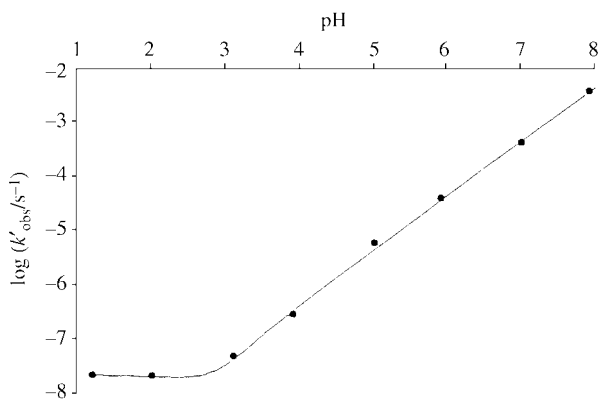

Fig. 1 Logarithmic plot, according to eqn. (9), for the release of sulfite from **1**.

The knowledge[17] that the value for K_a is 2×10^{-12} mol dm⁻³ allows the calculation of a value for k_1 of 25 s⁻¹. Thus expulsion of sulfite from the dianion is nine orders of magnitude faster than from **1**. Further, it is known[15] that the value of the equilibrium constant K_1 is 4.6×10^{-6} mol dm⁻³. Hence we may calculate a value for k_{-1} $(= k_1/K_1)$ of 6×10^6 dm³ mol⁻¹ s⁻¹.

Carbinolamine formation

The initial products of reaction of formaldehyde with aniline, or substituted anilines, are carbinolamines.[23] There is evidence[24] that, in the absence of nucleophiles, cyclic trimers, **6**, may eventually be formed; imines are likely intermediates.


6
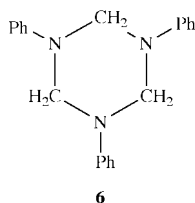
Abrams and Kallen[23] have measured equilibrium constants, K_{carb}, for the formation of carbinolamines, **4**, from anilines and hydrated formaldehyde. Values were ca. 20 dm³ mol⁻¹ and were insensitive to the nature of ring substituents. Kinetic measurements were also reported[23] for reactions of anilines de-activated by strongly electron-withdrawing groups; acid–base catalysis was interpreted in terms of a stepwise pre-association, or spectator, mechanism. We have made kinetic measurements of the reaction of formaldehyde with aniline, and substituted derivatives, in aqueous buffers. Carbinolamine formation was accompanied by a shift to longer wavelength of the UV absorption of aniline together with an increase in extinction coefficient. Hence measurements were conveniently made using

Table 6 Kinetic results for reaction of aniline, 1×10^{-4} mol dm⁻³, with formaldehyde in water[a] at 25 °C

[CH₂(OH)₂]/ mol dm⁻³	k_{obs}[b]/s⁻¹		
	pH = 5.8	pH = 6.9	pH = 7.9
0.0053	2.6	3.1	3.0
0.011	2.8	3.5	3.4
0.021	3.5	4.3	4.4
0.035	4.2	5.3	5.4
0.053	5.2	6.6	6.8

[a] Solutions are in phosphate buffers, $[KH_2PO_4]_{stoich} = 0.05$ mol dm⁻³, with ionic strength maintained at 1 mol dm⁻³ with KCl. [b] Measured by stopped-flow as an increase in absorbance at 245 nm. Values are precise to ±5%.

stopped-flow spectrophotometry. With the formaldehyde concentration in large excess of aniline first order kinetics were obtained. Typical results are in Table 6 and show that values of k_{obs} increase with formaldehyde concentration. The data are interpreted by Scheme 3. Thus linear plots according to eqn.
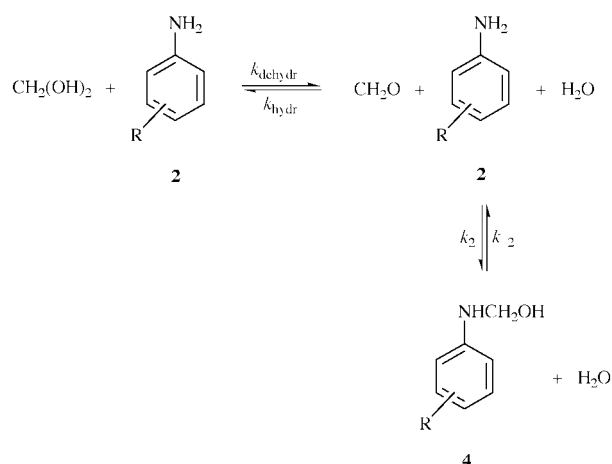
Scheme 3

(13) gave values for k_2', in terms of the hydrated formaldehyde concentration, and k_{-2}. The knowledge[25] that the value for K_{dehydr} is 5×10^{-4}, as shown in eqn. (11), allowed the calculation of values of k_2. Little variation with acidity was found in these values in the pH range 5.8 to 7.9. However in agreement with previous work[23] values were found to increase with the concentration of phosphate buffer.

$$K_{carb} = \frac{[\mathbf{4}]}{[\mathbf{2}][CH_2(OH)_2]} \quad (10)$$

$$K_{dehydr} = \frac{k_{dehydr}}{k_{hydr}} = 5 \times 10^{-4} \quad (11)$$

$$K_2 = \frac{[\mathbf{4}]}{[\mathbf{2}][CH_2O]} = \frac{K_{carb}}{K_{dehydr}} \quad (12)$$

$$k_{obs} = k_2'[CH_2(OH)_2] + k_{-2} \quad (13)$$

$$k_{obs} = k_2 K_{dehydr}[CH_2(OH)_2] + k_{-2} \quad (14)$$

In order to examine substituent effects, measurements for a series of aniline derivatives were made at pH 6.9 with a relatively low concentration of phosphate buffer. The results in Table 7 show that values of the equilibrium constant K_2 are insensitive to the nature of the substituent. This may be due to the similarity in polar properties of hydrogen and the hydroxymethyl group[26] which have σ^* values of 0.49 and 0.56

Table 7 Rate and equilibrium data[a] for formation of carbinolamines, **4**, in water at 25 °C

Aniline, **2**	pK_a[b]	k_2[c]/dm^3 mol^{-1} s^{-1}	k_{-2}/s^{-1}	K_2[c]/dm^3 mol^{-1}
R = H	4.60	1.5×10^5	2.7	5.5×10^4
R = 4-Me	5.08	2.4×10^5	3.3	7.3×10^4
R = 4-Cl	4.15	8.9×10^4	1.5	5.9×10^4
R = 3-Cl	3.46	4.3×10^4	0.80	5.4×10^4
R = 3-CN	2.75	1.5×10^4	0.28	5.4×10^4
R = 3-NO$_2$	2.47	8.0×10^3	0.13	6.2×10^4
N-Methylaniline	4.85	2.2×10^5	6.6	3.3×10^4

[a] Values were obtained at pH 6.9 in the presence of phosphate buffer, $[KH_2PO_4]_{stoich} = 0.05$ mol dm^{-3}. The ionic strength was maintained at 1 mol dm^{-3} with KCl. [b] From ref. 14. [c] These values were obtained using the value for K_{dehydr} given in eqn. (11).

respectively. Hammett plots of the values of both k_2 and k_{-2} gave slopes, ρ, of -1.8.

The results in this section allow estimates to be made for the values of k_2 and k_{-2} expected in these systems. However it should be noted that these values will depend to some extent on the buffer concentration.

It is known that in some reactions[23,25] formaldehyde dehydration may be rate-limiting. The evidence that this is not the case here is that: i) excellent first order kinetics are observed, and ii) rate constants (Table 7) depend on the nature of the amine. If dehydration were rate-limiting, zero order kinetics would be expected and there should be no dependence on the nature of the amine.

In fact it is possible to calculate a value for k_{dehydr} of 0.0175 s^{-1} in the present system (phosphate buffer, 0.05 mol dm^{-3}, at pH 6.9). This calculation uses the following literature values[27,28] for catalytic coefficients: k_W 0.004 s^{-1}, k_{OH^-} 0.0021 dm^3 mol^{-1} s^{-1}, $k_{HPO_4^{2-}}$ 0.39 dm^3 mol^{-1} s^{-1} and $k_{H_2PO_4^-}$ 0.088 dm^3 mol^{-1} s^{-1}. Use of eqn. (11) gives a value for k_{hydr} of 35 s^{-1}.

With an amine concentration of 1×10^{-4} mol dm^{-3}, the value of k_2[**2**] is 15 s^{-1}. Hence the condition $k_{hydr} > k_2$[**2**] is obeyed, so that the free formaldehyde may be treated as a steady state intermediate. This analysis indicates that with amines much more basic than aniline formaldehyde dehydration is likely to become partially rate-limiting.

Mechanism of formation of anilinomethanesulfonates

It is of interest to consider the nature of the rate-determining step in Scheme 1. It should be noted that the bulk of the data in Tables 2–4 was obtained with relatively high concentrations of hydroxymethanesulfonate so that the forward rate term in eqn. (3) was dominant. Hence our discussion will centre on the forward reaction. The values obtained show little dependence on acidity, in the pH range 6–8, but show an inverse dependence on sulfite concentration. The pH independence is not compatible with rate-determining formation of formaldehyde, the k_1 step, since the concentration of the intermediate, $CH_2(O^-)SO_3^-$, should increase with increasing pH in the measured range. The inverse dependence on sulfite concentration rules out the final product forming step, k_4. Hence it is likely that carbinolamine formation, k_2, or dehydration, k_3, is rate-limiting.

The velocity of carbinolamine formation is given in eqn. (15).

$$\text{vel} = k_2[CH_2O][PhNH_2] \quad (15)$$

Allowing for the pre-equilibria of formaldehyde and also for the hydrogen sulfite–sulfite equilibrium,[29] $K_{HSO_3^-}$ 8×10^{-8} mol dm^{-3}, eqn. (16) may be derived. Experimentally, reactions are found

$$\text{vel} = \frac{k_2 K_1 K_a}{[sulfite]_{stoich}} \cdot [\mathbf{1}] \cdot \left(\frac{[H^+] + K_{HSO_3^-}}{[H^+] \cdot K_{HSO_3^-}} \right) [PhNH_2] \quad (16)$$

to be first order in aniline yielding eqn. (17) which is written in terms of the easily measurable product $k_{obs} \cdot [sulfite]_{stoich}$.

Table 8 Comparison of experimental and calculated values of $k_{obs} \cdot [sulfite]_{stoich}$, assuming carbinolamine formation is rate-limiting

Amine	pH	$k_{obs} \cdot [sulfite]_{stoich}$/mol dm^{-3} s^{-1}	
		Experimental[a]	Calculated[b]
Aniline	6.1	1.2×10^{-6}	1.9×10^{-6}
	7.0	1.0×10^{-6}	3.1×10^{-6}
	8.1	0.66×10^{-6}	1.9×10^{-5}
4-Methylaniline	5.8	7×10^{-6}	3×10^{-6}
	7.9	4×10^{-6}	2×10^{-5}

[a] Values from Tables 2 and 3. [b] Calculated from eqn. (17) with k_2 values from Table 7, K_1 4.6×10^{-6} mol dm^{-3}, K_a 2×10^{-12} mol dm^{-3}, $K_{HSO_3^-}$ 8×10^{-8} mol dm^{-3} and [**1**] 0.1 mol dm^{-3}.

$$k_{obs} \cdot [sulfite]_{stoich} = k_2 K_1 K_a \left(\frac{[H^+] + K_{HSO_3^-}}{[H^+] \cdot K_{HSO_3^-}} \right) [\mathbf{1}] \quad (17)$$

The data in Table 8 show that at pH 6 there is reasonable agreement between experimental values of $k_{obs} \cdot [sulfite]_{stoich}$ and those calculated using eqn. (17). The agreement is acceptable since values of quantities in eqn. (17) may be expected to show some variation with buffer concentration and salt concentration.

Nevertheless at pH 7 and particularly pH 8, the calculated values are considerably higher than the experimental ones. This suggests that at these pH values carbinolamine dehydration may become rate-limiting. There is considerable evidence that such dehydration will be acid catalysed.[30–32] Hence the velocity of reaction may be written as eqn. (18). Allowance for the pre-equilibria in the formation of the carbinolamine, **4**, yields eqn. (19). Since reactions are first order in amine we obtain eqn. (20) for the experimental term $k_{obs} \cdot [sulfite]_{stoich}$.

$$\text{vel} = k_3[\mathbf{4}][H^+] \quad (18)$$

$$\text{vel} = \frac{k_3 K_1 K_a K_2[\mathbf{1}][PhNH_2]}{[sulfite]_{stoich}} \left(\frac{[H^+] + K_{HSO_3^-}}{K_{HSO_3^-}} \right) \quad (19)$$

$$k_{obs} \cdot [sulfite] = k_3 K_1 K_a K_2[\mathbf{1}] \left(\frac{[H^+] + K_{HSO_3^-}}{K_{HSO_3^-}} \right) \quad (20)$$

It is worth noting that eqn. (20) predicts that when pH > $pK_{HSO_3^-}$, at *ca.* pH 7, the term $k_{obs}[sulfite]_{stoich}$ should become independent of acidity. This reflects the opposite dependencies on pH of the pre-equilibria and the k_3 step.

Using the experimental values at pH 7.0 and 8.1 for reaction with aniline, and the known values of equilibrium constants, values for k_3 of 0.9×10^7 dm^3 mol^{-1} s^{-1} and 1.2×10^7 dm^3 mol^{-1} s^{-1} respectively are found. A similar calculation using the result for 4-methylaniline at pH 7.9 gives a value for k_3 of 5×10^7 dm^3 mol^{-1} s^{-1}. If proton catalysis is dominant over catalysis by other acidic species present then these values will correspond to the catalytic coefficients for protons. The values obtained are reasonable in view of the value of 1.4×10^8 dm^3 mol^{-1} s^{-1}

found previously[32] for the proton catalysed reaction of the carbinolamine from formaldehyde and cysteine.

The pK_a value of the iminium ion $H_2C=NHPh^+$ will be lower[15,16] than that of the anilinium ion ($pK_a = 4.60$). Hence at the pH values used in this study the unprotonated imine will be dominant. Thus we write Scheme 1 in terms of the imine. Nevertheless it is likely that the product forming step, k_4, will involve reaction of sulfite, SO_3^{2-}, with the iminium ion. The inverse dependence of measured ratio constants on sulfite concentration indicates that this step is not kinetically significant.

The results presented here cover a fairly narrow pH range, and we have not extensively investigated buffer catalysis. However we are able to draw some definite conclusions regarding the mechanism of the overall reaction. The rate-limiting step is likely to change from carbinolamine formation to carbinolamine dehydration over the pH range 6–8. Substituent effects on the overall reaction were limited to the 4-methyl and 4-N,N-dimethyl derivatives which reacted more rapidly than aniline. Derivatives less basic than aniline were found to react inconveniently slowly for kinetic measurements. The general dependence on the basicity of the aniline derivatives is consistent with that expected for rate-limiting carbinolamine formation as shown by k_2 values in Table 7. Rate constants for acid catalysed carbinolamine dehydration, k_3 in Scheme 1, are also expected to increase with increasing electron donation from ring substituents.

In Scheme 1, unhydrated formaldehyde, CH_2O, is written as an intermediate. Previously in this paper we have calculated approximate values for the rate constants for hydration, k_{hydr} 35 s^{-1}, and for reaction with aniline, $k_2[2]$ 15 s^{-1}. It has also been shown that the value for k_{-1} is ca. 10^7 dm^3 mol^{-1} s^{-1}. Hence when $[SO_3^{2-}] \geq 10^{-5}$ dm^3 mol^{-1} the reactions of formaldehyde with water or amine cannot compete with the sulfite reaction. Thus the formaldehyde is effectively a steady state intermediate in equilibrium with its sulfite adduct.

Experimental

Sodium sulfite, sodium hydroxymethanesulfonate, aniline and substituted anilines were the purest available commercial specimens. Solutions of formaldehyde, ca. 0.1 mol dm^{-3}, in water were prepared by diluting purchased 37% (w/w) solutions. They were allowed to stand at 25 °C for several hours to ensure depolymerisation.

^{1}H NMR measurements were made in D_2O with a Varian Mercury 200 MHz spectrometer with reagent concentrations ca. 0.1 mol dm^{-3}. For solubility reasons 95% D_2O–5% CD_3OD (v/v) was used as solvent for reactions with 4-methylaniline. The pH values of buffers were determined using a Jenway 3020 pH meter.

UV spectra and kinetic measurements were made with Perkin-Elmer Lambda 2 or Shimadzu UV-2101 PC instruments; for rapid reactions, an Applied Photophysics SX-17 MV spectrometer was used. The release of sulfite from aqueous solutions of hydroxymethanesulfonate, 1, at six concentrations ranging from 0.005 to 0.03 mol dm^{-3} was measured by reaction with aqueous iodine, 2×10^{-4} mol dm^{-3}, in the pH range 1.2 to 7.9. Plots of absorbance, 350 nm, against time were linear indicating zero order kinetics, and rate constants k_{obs} were determined by dividing the gradients by the extinction coefficient

of iodine, 1.34×10^4 dm^3 mol^{-1} cm^{-1}. Rate constants for this reaction, and for the first order reactions producing carbinolamines, or anilinomethanesulfonate were reproducible to ±5%.

References

1 M. Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791; M. Tramontini, *Synthesis*, 1973, 703; G. A. Gevorgyan, A. G. Agababyan and O. L. Mndzhoyan, *Russ. Chem. Rev.*, 1984, **53**, 561; H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, New York, 1972, 2nd edn.; E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, 1949, **71**, 4014.
2 A. Strecker, *Liebigs Ann. Chem.*, 1850, **75**, 27; R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, New York, 1989.
3 T. D. Stewart and C. Li, *J. Am. Chem. Soc.*, 1938, **60**, 2782.
4 Y. Ogata and A. Kawasaki, *J. Chem. Soc. (B)*, 1971, 325.
5 J. W. Stanley, J. G. Beasley and I. W. Mathison, *J. Org. Chem.*, 1972, **37**, 3746.
6 J. Taillades and A. Commeyras, *Tetrahedron*, 1974, **30**, 2493.
7 J. Taillades and A. Commeyras, *Tetrahedron*, 1974, **30**, 3407.
8 G. Moutou, J. Taillades, S. Bénefice-Malouet, A. Commeyras, G. Messina and R. Mansani, *J. Phys. Org. Chem.*, 1995, **8**, 721.
9 S. Eldin and W. P. Jencks, *J. Am. Chem. Soc.*, 1995, **117**, 4851.
10 S. Eldin, J. A. Digits, S.-T. Huang and W. P. Jencks, *J. Am. Chem. Soc.*, 1995, **117**, 6631.
11 A. Vigroux, A. J. Kresge and J. C. Fishbein, *J. Am. Chem. Soc.*, 1995, **117**, 4433.
12 R. G. Pearson, H. Sobel and J. Songstad, *J. Am. Chem. Soc.*, 1968, **90**, 319.
13 P. Le Henaff, *Compt. Rend. Acad. Sci.*, 1963, **256**, 3090.
14 D. D. Perrin, *Dissociation constants of organic bases*, Butterworths, London, 1965 and 1972 (supplement).
15 P. G. Kallen, R. O. Viole and C. K. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 576.
16 F. E. Condon, *J. Am. Chem. Soc.*, 1965, **87**, 4481, 4485.
17 P. E. Sørensen and V. S. Andersen, *Acta Chem. Scand.*, 1970, **24**, 1301.
18 S. D. Boyce and M. R. Hoffmann, *J. Phys. Chem.*, 1984, **88**, 4740.
19 G. L. Kok, S. N. Gitlin and A. L. Lazarus, *J. Geophys. Res.*, 1986, **91**, 2801.
20 B. S. Yiin and D. W. Margerum, *Inorg. Chem.*, 1990, **29**, 1559.
21 T. D. Stewart and L. H. Donnally, *J. Am. Chem. Soc.*, 1932, **54**, 2333, 3555, 3559.
22 D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, 1958, 2720.
23 W. R. Abrams and R. G. Kallen, *J. Am. Chem. Soc.*, 1976, **98**, 7778.
24 J. Miller and E. Wagner, *J. Am. Chem. Soc.*, 1932, **54**, 3698; E. Smolin and L. Rapoport, *The chemistry of heterocyclic compounds, s-triazines and derivatives*, Interscience, New York, 1959, 476.
25 R. P. Bell, *Adv. Phys. Org. Chem.*, 1996, **4**, 1.
26 J. Hine and R. D. Weimar, *J. Am. Chem. Soc.*, 1965, **87**, 3387.
27 L. H. Funderburk, L. Aldwin and W. P. Jencks, *J. Am. Chem. Soc.*, 1978, **100**, 5444.
28 R. P. Bell and P. G. Evans, *Proc. R. Soc.*, *London, Ser. A*, 1966, **291**, 297.
29 E. Hayon, A. Treinin and J. Wilf, *J. Am. Chem. Soc.*, 1972, **94**, 47; H. V. Tartar and H. H. Garretson, *J. Am. Chem. Soc.*, 1941, **63**, 808.
30 W. P. Jencks, *Prog. Phys. Org. Chem.*, 1964, **2**, 63.
31 S. Rosenberg, S. M. Silver, J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7986.
32 R. G. Kallen, *J. Am. Chem. Soc.*, 1971, **93**, 6236.