mulate highly viscous, well-retained gels, other highly viscous polymer sols or gels were poorly retained in the rabbit eye and did not produce extended miosis duration. The carbomer data suggest that the increased duration was a result of the increased viscosity of the gels as expressed by a yield value above a certain value corresponding to 2.7–3.0% carbomer. As a consequence, it was not rapidly squeezed out of the eye and a significantly longer duration was achieved.

The viscosities measured with the single-point rotational viscometer did not correlate with miosis duration (Table I). This result illustrates the necessity for constructing a rheogram and identifying specific rheological characteristics that may correlate to the observed phenomenon and perhaps suggest an explanation for the results.

Insight into the mechanism of drug release for ethylene maleic anhydride and carbomer preparations can be speculated upon by analyzing the results of Fig. 2. It is reasoned that the time to peak, t_p, as well as peak miosis intensities, I_{max}, for each preparation are related to the corneal absorption rate; the latter can be altered depending on the degree of control of drug release exerted by the gel systems. The large improvement in eye retention observed for ethylene maleic anhydride and carbomer when compared to a solution dosage form would increase bioavailability, but the effect on t_p and I_{max} would depend on the release characteristics of the gel system.

In general, an improvement in retention followed by an increase in bioavailability could result in: (*a*) a large increase in I_{max} with no change in t_p if drug release from the gel preparations is rapid and uncontrolled, or (*b*) a decrease in I_{max} with a delay in t_p if release from the gel systems is controlled.

The extent of the decrease in I_{max} as well as the delay in t_p depends upon the degree to which the release rate is controlled. It is possible, of course, to decrease significantly or even eliminate the response intensities if the release rate is reduced such that biophasic concentrations are insufficient to invoke a response. This is not of concern here, however.

The miosis intensities observed in Fig. 2 for the gel preparations show a reduced I_{max} and a delayed t_p in comparison to either the solution or petrolatum dosage forms. Consequently, some degree of control of the release rate can be attributed to ethylene maleic anhydride and carbomer. Within the gel, release could be controlled by diffusion and/or slow erosion of the gel surface with time. However, further work is necessary to describe more fully the nature of drug release as well as to estimate the physiological constraints of the precorneal area on the response duration.

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Reaction of Sodium Hydroxymethanesulfonate with Substituted Anilines

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Abstract □ The reactions of substituted anilines with sodium hydroxymethanesulfonate to form the anilinomethanesulfonates were studied in 50% ethanol–water at 0–50°. The Arrhenius rate constants were $5.4 \times 10^{10} \exp(-16{,}400/RT)\ M^{-1}\ min^{-1}$ for aniline, $4.8 \times 10^{11} \exp(-17{,}100/RT)\ M^{-1}\ min^{-1}$ for *p*-anisidine, $7.1 \times 10^{9} \exp(-14{,}500/RT)\ M^{-1}\ min^{-1}$ for *p*-toluidine, $1.5 \times 10^{13} \exp(-21{,}100/RT)\ M^{-1}\ min^{-1}$ for *p*-chloroaniline, and $1.1 \times 10^{12} \exp(-19{,}800/RT)\ M^{-1}\ min^{-1}$ for *p*-bromoaniline. Some equilibrium constants and hydrolysis rate constants of the products also were calculated. Hydrolysis rate constants were temperature independent. These reactions had a ρ value of −3.40 in the Hammett equation. The solvent concentrations used proved to be very convenient for obtaining high yields of the aminomethanesulfonates.

Keyphrases □ Anilines, various substituted—kinetics of reaction with sodium hydroxymethanesulfonate, equilibrium and hydrolysis rate constants calculated □ Sodium hydroxymethanesulfonate—kinetics of reaction with various substituted anilines, equilibrium and hydrolysis rate constants calculated □ Kinetics—reaction of various substituted anilines with sodium hydroxymethanesulfonate, equilibrium and hydrolysis rate constants calculated

The sodium salts of substituted methanesulfonic acids are of interest as both synthesis intermediates and pharmacological agents. Sodium *p*-phenetidinomethanesulfonate has been used as an antipyretic, and several other sodium α-aminoalkanesulfonates have antiviral and anticarcinogenic activities (1–3). Industrially, some primary aromatic amines such as aniline and α-naphthylamine have been transformed into their respective sodium methanesulfonates to avoid formation of the diazoamino group (N=NNH) during coupling in the formation of the azo dyes (4, 5). Hydrolysis of those compounds to obtain the desired azo dyes is then performed in appropriate media.

Numerous syntheses of this type of compound were reported (6, 7), but little research has been done on the formation kinetics of these products. Ikeda *et al.* (8) studied the formation of various substituted sodium anilinomethanesulfonates in water but calculated only overall rate constants. The same investigators (9–13) also studied the amine release from different substituted anilinomethanesulfonates in water and its pH dependence. This paper presents the results of research concerning the formation kinetics of anilinomethanesulfonates in mixed ethanol–water solvents at conditions where the syntheses of these compounds are favored.

EXPERIMENTAL

Materials and Apparatus—All reagents were proanalysis grade and were used without further purification except where indicated. The amines proved to be free of any interfering impurities when analyzed by GLC. Toluene did present an impurity peak with a retention time similar to that of aniline, but this impurity was easily removed by distillation.

The formaldehyde content of the mixture was analyzed by the Romijn method, and the metabisulfite content of the initial solutions was determined by iodometric titration.

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Table I—Kinetic and Thermodynamic Data for Substituted Anilinomethanesulfonates

Amine	Temperature	Aminomethanesulfonate Solubility, mole/liter	k_f, M^{-1} min^{-1}	K	k_h, min^{-1}
Aniline	1.5°	—	4.1×10^{-3}	(6.1)	7.4×10^{-4}
	9°	0.50	9.6	20	4.8
	15°	0.55	17	35	4.9
	25°	0.73	50	75	6.6
	31.5°	0.89	67	120	5.5
p-Toluidine	1°	0.10	1.3×10^{-2}	(1.7)	(7.5×10^{-3})
	10°	0.19	2.6	18	1.5
	15°	0.23	4.8	25	1.9
	20°	0.27	7.8	40	1.9
	25°	—	9.0	65	1.4
p-Anisidine	10°	0.32	5.6×10^{-2}	(220)	(3.0×10^{-4})
	15°	0.31	5.7	76	7.0
	20°	0.32	10	240	4.0
	25°	0.36	20	2300	0.9
p-Chloroaniline	30°	0.23	1.1×10^{-2}	14	8.0×10^{-4}
	35°	0.35	1.5	90	2.0
	40°	0.39	3.1	520	0.6
	50°	0.46	10.7	3000	0.4
p-Bromoaniline	30°	0.24	0.7×10^{-2}	n.d.[a]	n.d.
	35°	0.21	1.1	n.d.	n.d.
	40°	0.30	2.2	n.d.	n.d.
	50°	0.40	5.2	n.d.	n.d.

[a] n.d. = not determined.

An ultrathermostat and a thermostatic bath were used[1], both assuring temperature accuracy better than 0.2°. GLC was performed on a gas chromatograph[2] using a flame-ionization detector. A 1.5-m long × 3.1-mm o.d. Chromosorb 103 column was used at 180° for aniline and toluidine and at 220° for the other amines.

Procedure—The anilinomethanesulfonates were prepared in the usual way by mixing solutions containing stoichiometric amounts of hydroxymethanesulfonate and the amine (14). The hydroxymethanesulfonate solution was prepared by dissolving the required amount of sodium metabisulfite in a minimal amount of water and adding to it a solution of formol with agitation at room temperature, the total amount of added formaldehyde being equimolar to that of metabisulfite. After diluting and thermostating, the solution was mixed with the same volume of an equimolar solution of the amine in ethanol to obtain the required 50% ethanol–water solvent.

Samples of 2 ml were withdrawn from the reaction vessel at different times, whereupon amine analyses were performed as follows. The sample volume was extracted four times with 5 ml of toluene. The toluene, besides extracting the amine from the aminomethanesulfonate, also stopped the reaction by phase separating the aniline from the hydroxymethanesulfonate. In the analyses of samples where the aminomethanesulfonates had already precipitated, a rapid filtration was performed before extraction. The amine solution in toluene thus obtained was diluted and analyzed by GLC with an internal standard.

RESULTS

The reactions between sodium hydroxymethanesulfonate and various substituted anilines (Scheme I) were studied in 50% ethanol–water.

$$RNH_2 + HOCH_2SO_3^- \rightarrow RNHCH_2SO_3^- + H_2O$$

Scheme I

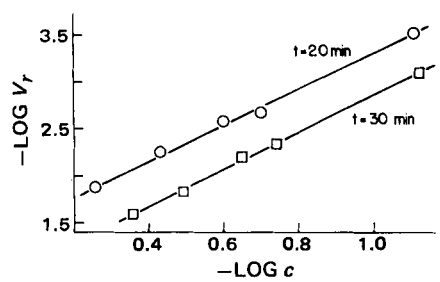


Figure 1—*Reaction order plot for aniline plus hydroxymethanesulfonate at 25° (t_{30} values are displaced in the scale).*

That solvent was chosen for several reasons:

1. The hydroxymethanesulfonate formation reaction is displaced toward its total conversion, avoiding the decomposition (Scheme II) that occurs to some extent in pure water (15).

$$HOCH_2SO_3^- \overset{K_2}{\rightleftharpoons} H_2CO + SO_3^{2-} + H^+$$

Scheme II

In water, the K_2 for aliphatic aldehydes is about 10^{-3}–10^{-4} (16), but it should be less in ethanol–water mixtures because of the higher solvation energy of the ionic products in pure water compared to ethanol–water mixtures.

2. The anilinomethanesulfonates precipitate, keeping the homogeneous phase concentration low enough to neglect their hydrolyses, and are able to reach high conversions without affecting the formation rate.

A second-order reaction rate in aniline plus hydroxymethanesulfonate was found in all cases, although slight deviations from the second-order graph were found occasionally near and after the anilinomethanesulfonate solubility concentrations[3]. This order was also confirmed for the system of aniline plus hydroxymethanesulfonate by performing several runs at 25° and different initial concentrations. Reaction rates, V_r, at 20 and 30 min are shown in Fig. 1. From this graph, a second order can be easily deduced in agreement with results of the individual experiments.

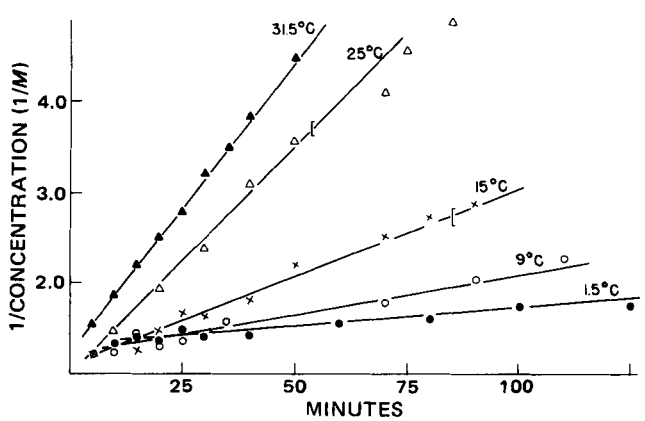


Figure 2—*Second-order plot for the reaction of hydroxymethanesulfonate with aniline at various temperatures; ([) indicates precipitation of the anilinomethanesulfonate.*

[1] ASCA and Sargent model 84805, respectively.
[2] Varian model 2800.
[3] As suggested by the reviewer, these deviations may be due to the constancy of the hydrolysis rate after precipitation of the anilinomethanesulfonate.

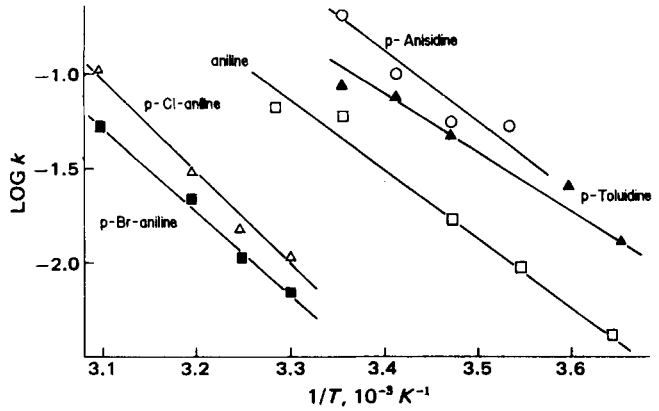


Figure 3—*Arrhenius plot for the reaction of anilines with hydroxymethanesulfonate.*

Figure 2 shows the second-order graph for the reaction of aniline with hydroxymethanesulfonate. Similar graphs were obtained for the other anilines. In Table I, the overall reaction rate constants for these reactions are shown together with the solubilities of the anilinomethanesulfonates, some equilibrium constants, and the hydrolysis reaction rate constants. The equilibrium constants were obtained from the amines limiting concentration and the solubility data using:

$$K = \frac{[RNHCH_2SO_3^-]_\infty}{[RNH_2]_\infty[HOCH_2SO_3^-]_\infty} = \frac{\text{solubility}}{([RNH_2]_\infty)^2} = \frac{k_f}{k_h} \quad \text{(Eq. 1)}$$

Overall hydrolysis reaction rate constants also were obtained using Eq. 1 together with the overall formation reaction rate constants.

Activation energies were obtained for the reactions of the five anilines. Arrhenius plots are shown in Fig. 3. The pH values during the reaction were measured continuously in some runs, and no change could be detected throughout the reaction time. Although these "pH" values cannot be related directly to the conventional acidity of the solutions because the solvents were different from pure water, their invariability should correspond to a constancy of the proton concentration. The measured pH values in 50% ethanol–water mixtures (~7.0) corresponded to proton concentrations higher than those in equivalent true pH's (17).

DISCUSSION

Although it has been postulated that the mechanism for this type of reaction in aliphatic series goes through an immonium ion, $RN^+H_2{=}CH_2$ (18, 19), the results obtained in this work suggest an alternative or collateral pathway for aromatic series under the experimental conditions. The overall kinetic order two is hardly compatible with the Schiff-base mechanism, because in that case the rate-determining step must be the dehydration of the alkylammoniumcarbinol (Scheme III) or the reaction of the immonium ion with sulfite (Scheme IV).

$$RN^+H_2CH_2OH \rightarrow H_2O + RN^+H{=}CH_2$$
Scheme III

$$RN^+H{=}CH_2 + SO_3^{2-} \rightarrow RNHCH_2SO_3^-$$
Scheme IV

Furthermore, in neutral media and nonaqueous solvents, as used here, the dissociation of hydroxymethanesulfonate is greatly reduced compared with the value found in aqueous solutions containing aliphatic amines (19) (pH > 9). Therefore, the concentration of free formaldehyde is largely reduced, allowing a competition between the Schiff-base mechanism with other mechanisms.

It is proposed that the rate-determining step of this alternative mechanism is an S_N2 reaction between the protonated hydroxymethanesulfonate free aniline (Scheme V), followed by deprotonation of the anilinomethanesulfonate through an intermediate involving simultaneous protonation of hydroxymethanesulfonate (Scheme VI).

$$RNH_2 + H_2O^+CH_2SO_3^- \rightarrow RN^+H_2CH_2SO_3^- + H_2O$$
Scheme V

$$RN^+H_2CH_2SO_3^- + HOCH_2SO_3^- \rightarrow RNHCH_2SO_3^- + H_2O^+CH_2SO_3^-$$
Scheme VI

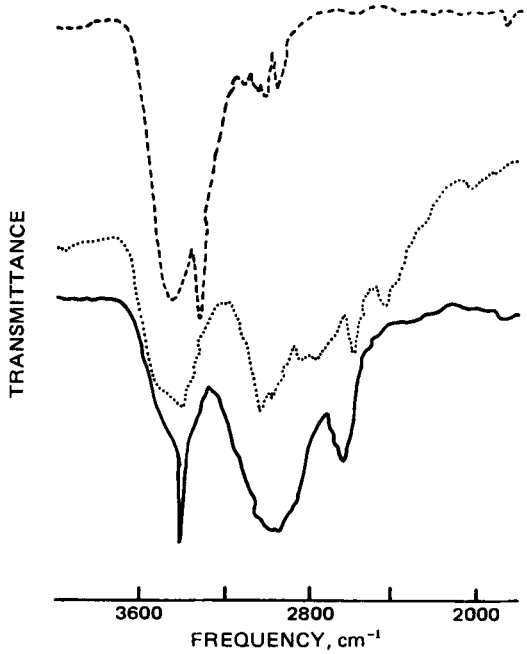


Figure 4—*IR spectra of anilinomethanesulfonate (- - -), the anilinimmethanesulfonate zwitterion (···), and the reaction intermediate (—).*

The anilinimmethanesulfonate deprotonation to the sulfonic group on the hydroxymethanesulfonate ion (Scheme VII) is also possible.

$$RN^+H_2CH_2SO_3^- + HOCH_2SO_3^- \rightarrow RNHCH_2SO_3^- + HOCH_2SO_3H$$
Scheme VII

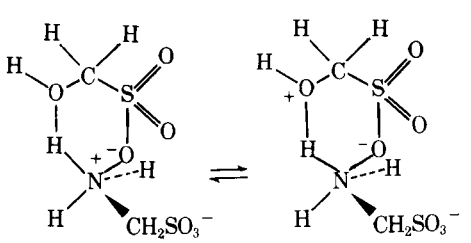
However, since both acid constants K_a ($HOCH_2SO_3H$) and K_a ($H_2O^+CH_2SO_3^-$) (20) must be similar (~10^{-2} M^{-1}), a rapid equilibrium between both protonated species is established (Scheme VIII) with no effect on the overall kinetics.

$$HOCH_2SO_3H \rightarrow H_2O^+CH_2SO_3^-$$
Scheme VIII

The reaction in Scheme VI can be obtained through a six-membered ring ion-pair such as that shown in Scheme IX.

The existence of this type of ion-pairs was postulated in the hydrolysis of sulfamates (21). In the present case, it can also be inferred from the existence of a similar intermediate found in the reaction of formation of anilinomethanesulfonate when reacting hydroxymethanesulfonate with aniline in an acid medium. In the initial stages of that reaction, a solid precipitates. Upon heating or further addition of hydroxymethanesulfonate, this solid redissolves. When separated, the product presents an IR spectrum with bands corresponding to secondary amine and quaternized nitrogen at ~3400 and 2950 cm^{-1}, respectively.

A similar spectrum was obtained from the reaction of the anilinomethanesulfonate with anilinium chloride;* thus, an ion-pair ($C_6H_5NHCH_2SO_3^-$)($N^+H_3C_6H_5$) does occur during the reaction, that adduct having a spatial configuration similar to I (Scheme IX). The existence of this adduct is further confirmed by the fact that its spectrum is very different from that of anilinimmethanesulfonate hydrochloride (Cl^-)($C_6H_5N^+H_2CH_2SO_3^-$) or the anilinomethanesulfonate ion,



I

Scheme IX

Table II—Maximum Conversion Data for Formation of Anilinomethanesulfonates in 50% Ethanol–Water

Temperature	Anilinomethanesulfonate Maximum Conversion, %	Anilinomethanesulfonate $t_{1/2}$, min	*p*-Toluidinomethanesulfonate Maximum Conversion, %	*p*-Toluidinomethanesulfonate $t_{1/2}$, min	*p*-Anisidinomethanesulfonate Maximum Conversion, %	*p*-Anisidinomethanesulfonate $t_{1/2}$, min
9° (10)	84	100	80	75	96	18
15°	87	60	81	40	94	18
20°	—	—	84	13	96	10
25°	90	20	93	11	99	5
31.5°	92	15	—	—	—	—

$C_6H_5NHCH_2SO_3^-$; its bands are generally displaced with respect to the sum of the latter (Fig. 4).

The mechanism accounting for hydrolysis involves a different pathway with direct anilinomethanesulfonate protonation (Scheme X), as suggested by Kurono *et al.* (13), followed by a direct S_N2 process in which water, acting as a nucleophilic agent, attacks the partially positive methylenic carbon atom (Scheme XI).

$$RNHCH_2SO_3^- + H^+ \rightarrow RN^+H_2CH_2SO_3^-$$

Scheme X

$$RN^+H_2CH_2SO_3^- + H_2O \rightarrow H_2O^+CH_2SO_3^- + RNH_2$$

Scheme XI

The data in Table I for the hydrolysis reactions show that these processes are not temperature dependent or only slightly so. Previous work done on similar systems, but in different solvents, seems to be consistent with these results. The overall hydrolysis rate constants compare rather well with the values found (13) for the reaction in water at pH 7: 2×10^{-3} for the aniline derivative, 6×10^{-3} for the *p*-toluidine derivative, and 1.5×10^{-4} min^{-1} for the *p*-chloroaniline derivative.

The results obtained were also used to set up a linear free energy relationship using the Hammett equation; the corresponding graph is shown in Fig. 5. A ρ value of −3.40 was obtained. This value compares well with that found for the same reaction in water at 37° (13), $\rho = -3.0$. Furthermore, that value also confirms the proposed mechanism and the rate-determining step. Scheme V corresponds to a reaction similar to nucleophilic attack by a base, *i.e.*, aniline in this case. For the ionization equilibrium of substituted anilines in 30% ethanol–water at 25°, a ρ value of −3.44 was reported (22), which also agrees well with the present mechanistic assumption.

Syntheses of Anilinomethanesulfonates—From the data in Table II, the maximum yields under the experimental conditions can be calculated to be always larger than 80% when working at room or higher temperatures for the anilino-, *p*-toluidino-, and *p*-anisidinomethanesulfonates. The time necessary to attain 50% conversion when starting with 1 *M* reagent concentrations also is presented.

The hydrolysis rate was practically temperature independent, which may have been due to the low hydrolysis power of the solvent (50% ethanol–water) and the low solubility of the products in this medium. Therefore, this solvent is recommended for these syntheses in view of the low hydrolysis rate of the anilinomethanesulfonates in comparison with the rather high rate found in pure water (8). When the temperature was increased to about 60°, conversions reached their maximum values in less than 5 min.

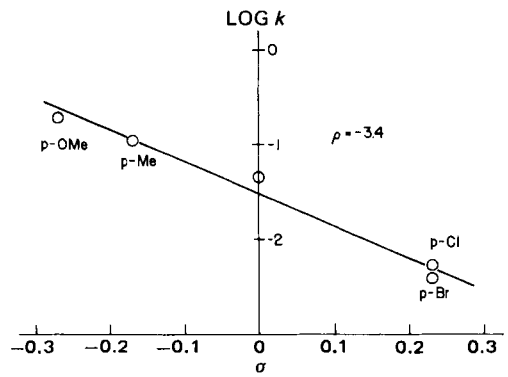


Figure 5—*Hammett plot for the reaction of substituted anilines with hydroxymethanesulfonate.*

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