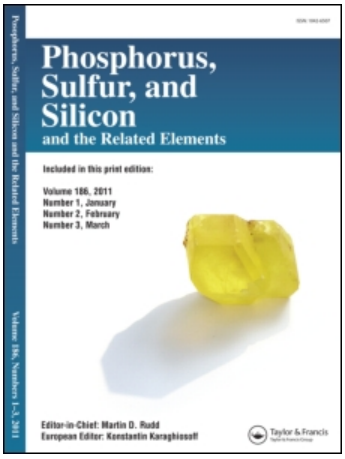

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MECHANISM OF AMINOMETHANESULFONATE FORMATION AND HYDROLYSIS REACTIONS

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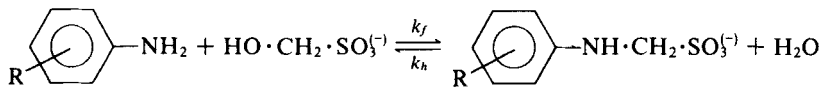
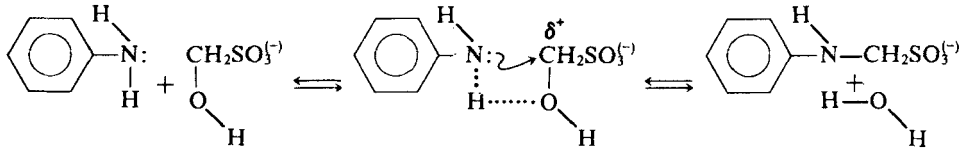
Based on kinetic, structural and synthetic evidence, a mechanism is proposed for the synthesis of aminomethanesulfonates ($R \cdot NH \cdot CHR' \cdot SO_3^{(-)}$). The mechanism involves the initial protonation of the amine, proton transfer to the hydroxymethanesulfonate *via* a six-membered cyclic intermediate followed by a nucleophilic attack of the free amine on the carbon atom. The transition state is assumed to correspond to a structure with practically all the positive charge on the nitrogen atom. For the hydrolysis reaction, the initial protonation of the aminomethanesulfonate is followed by the nucleophilic attack of a water molecule. This mechanism is in agreement with the experimentally determined Hammett reaction constants ρ, *i.e.* -3.5 for the formation reaction and -2.3 for the hydrolysis.

During the last years, we have carried out extensive studies on the characteristics and properties of aminomethanesulfonate compounds.[1-6] Very few studies have been made regarding the kinetics of formation and hydrolysis of these compounds aiming to elucidate their reaction mechanisms. Steward and Bradley[7] discussed the formation of iminium intermediates (Schiff bases) during the formation and hydrolysis of substituted aliphatic aminomethanesulfonates in acid solutions. A similar mechanism, also involving transient Schiff bases, was proposed by McMillan and Pattison[8] for the mechanism of formation of *n*-butylaminomethanesulfonate. The intermediate carbinolamine, when in neutral or basic solutions, formed the expected[9] cyclic trimer 1,3,5-*n*-butylhexahydro-s-triazine. Ikeda *et al.* studied the kinetics of formation and hydrolysis of methanesulfonated aromatic amines[10-12] and sulfonamides[13] in water. The formation reactions were found to follow an overall second order when starting with equimolar amounts of aniline and sodium hydroxymethanesulfonate, HMS.



HMS

The hydrolysis reactions were found to be first order and acid catalyzed at lower pHs.[12] For both processes, formation and hydrolysis, Ikeda *et al.*[11] proposed a common 4-membered cyclic intermediate.



Based on the confirmation of the second order kinetics for the formation of the AMS compounds in water and ethanol-water solutions,[1] and the Hammett reaction constants of $\rho = -3.5$ for the formation reaction and -2.3 for the hydrolysis, a mechanism is proposed which involves a rate-determining nucleophilic substitution.

EXPERIMENTAL

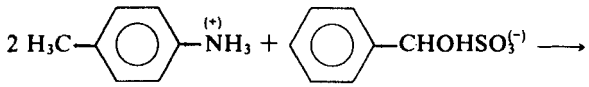
Syntheses of Substituted Anilinomethanesulfonates

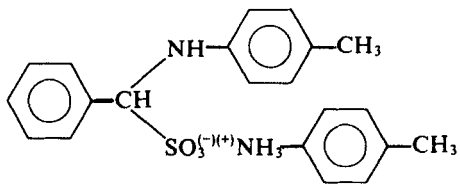
These compounds were prepared by the standard method, already described,[1] of mixing equimolar amounts of hydroxymethanesulfonate with the substituted aniline in 50% water-ethanol mixture.

$$R \cdot C_6H_4 \cdot NH_2 + HO \cdot CH_2 \cdot SO_3^{(-)} \longrightarrow R \cdot C_6H_4 \cdot NH \cdot CH_2 \cdot SO_3^{(-)} + H_2O$$

Syntheses of C-substituted Anilinomethanesulfonate Anilinium Salts

These compounds were synthesized by mixing solutions of the corresponding α-hydroxymethanesulfonate with anilinium chloride in molar proportions of 1:2, at room temperature. Typically, *p*-toluidinium *p*-toluidine-phenylmethanesulfonate, **1**, was obtained by adding a solution of 0.02 moles of *p*-toluidinium chloride in 20 ml of water to a solution of 0.01 moles of sodium α-hydroxyphenylmethanesulfonate in 20 ml of water. On addition a precipitate is formed which is filtered and washed with ethanol.



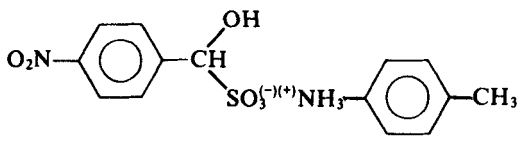


1

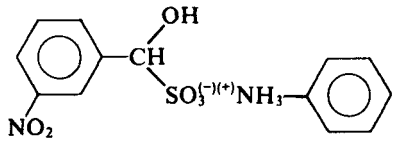
Analysis: Calculated for $C_{21}H_{24}O_3N_2S$: C, 65.60; H, 6.29; N, 7.28; S, 8.34.
Found: C, 65.67; H, 6.28; N, 7.01; S, 8.30.

For the other compounds of this series, similar results were obtained, except for the nitro-substituted α-hydroxycompounds.

Using the same method described above, for the latter compounds only the α-hydroxy(nitrophenyl) methanesulfonate anilinium salts were obtained: compound **2** by the mixture of *p*-toluidinium chloride with sodium α-hydroxy(*p*-nitrophenyl)methanesulfonate and compound **3** by mixing anilinium chloride with sodium α-hydroxy(*m*-nitrophenyl)methanesulfonate.



2



3

Analysis of Compound **2**. Calculated for $C_{14}H_{16}O_6N_2S$: C, 49.90; H, 4.74; N, 8.23.
Found: C, 49.97; H, 4.70; N, 8.20.
Analysis of Compound **3**. Calculated for $C_{13}H_{14}O_6N_2S$: C, 47.85; H, 4.32; N, 8.59.
Found: C, 47.97; H, 4.39; N, 8.36.

Reaction Kinetics

The kinetics for the formation reaction in water, at neutral pH and various temperatures, were followed by monitoring the amount of free aniline in the reaction mixture. Small amounts of the reaction mixture were extracted with 1,2-dichloroethane and the aniline concentration in the organic phase was measured through its absorption in the ultraviolet region.

The value of the formation rate constant, k_f, was calculated using

$$\frac{x_e}{a^2 - x_e^2} \ln \frac{x_e(a^2 - x_e \cdot x)}{a^2(x_e - x)} = k_f \cdot t$$

where a is the initial concentration of aniline or sodium hydroxymethanesulfonate; x, the concentration of aniline at time t; and x_e, the concentration of aniline at equilibrium.

The results for the formation rate constants and equilibrium constants for the various substituted anilinomethanesulfonates are shown in Table I.

The rate constants for the hydrolysis reaction shown in Table II, k_h, were calculated from the ratio between the equilibrium constant K, and the formation rate constant k_f

$$k_h = k_f/K$$

TABLE I

Experimental results for formation rate constants and equilibrium constants for reaction (1)

Substituent / temperature (°C)	*p*-OCH_3	*p*-CH_3	*m*-CH_3	H	*p*-Cl	*m*-Cl
	Formation rate constants ($M^{-1} \cdot min^{-1}$)					
5	0.78					
15	2.02					
25	6.09	1.82	0.54	0.59	0.09	0.03
35	10.7	4.46	1.07	0.96	0.19	0.06
45		6.81	2.26	2.00	0.41	0.14
55		11.46	3.68	2.53	0.84	0.31
Activation energy† kcal/mol	15.3	11.6	12.7	10.0	14.5	15.8
	Equilibrium constants (M^{-1})					
5	1841					
15	1502					
25	1086	2285	1257	1307	1002	188
35	872	1832	651	833	658	176
45		1018	474	710	339	167
55		592	354	532	284	160
Reaction enthalpy† kcal/mol	−4.4	−9.0	−8.0	−5.6	−8.7	−1.0

† ±1.5 kcal/mol

TABLE II

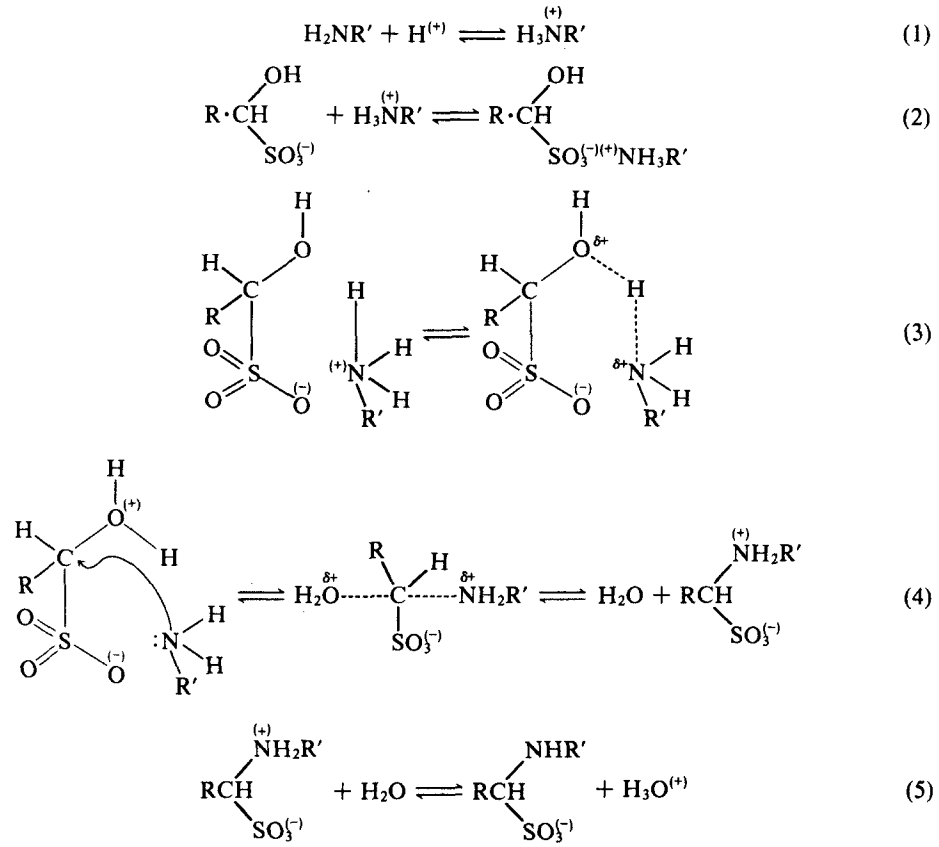
Hydrolysis rate constants at 25°C and activation energies for substituted anilinomethanesulfonates

Compound	Rate Constant (min^{-1})	Activation energy (kcal/mol)
p-methoxyanilinomethanesulfonate	5.72×10^{-3}	18.7
p-methylanilinomethanesulfonate	9.43×10^{-4}	20.6
m-methylanilinomethanesulfonate	5.67×10^{-4}	20.7
anilinomethanesulfonate	5.39×10^{-4}	15.6
p-chloroanilinomethanesulfonate	1.06×10^{-4}	23.2
m-chloroanilinomethanesulfonate	1.56×10^{-4}	16.8

The Hammett ρ constant for the formation reaction has been found to be -3.5, in good agreement with the value found for the same reaction in water-ethanol mixtures.[1] For the hydrolysis reaction a ρ-value of -2.3 has been calculated.

DISCUSSION

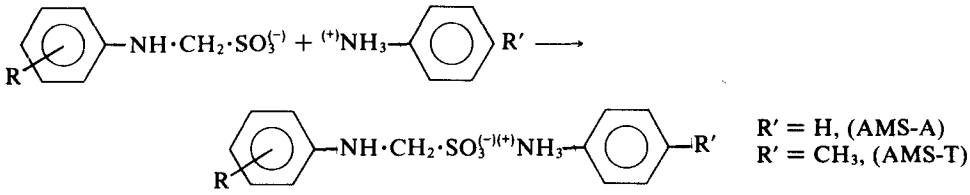
The mechanism shown in Scheme I should be valid for the formation and hydrolysis reactions of most aminomethanesulfonates in neutral solutions.



SCHEME I

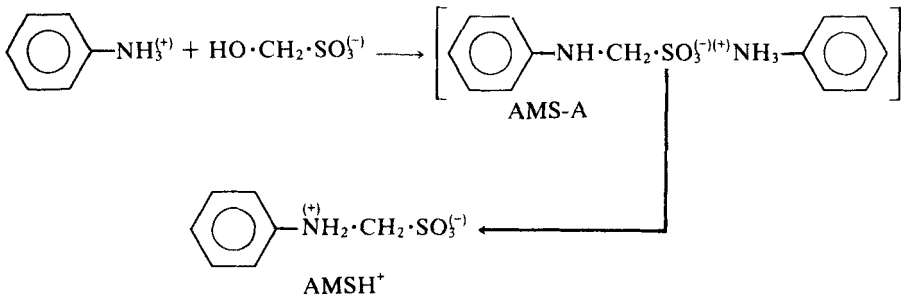
Equilibrium 2

A large affinity exists between the $SO_3^{(-)}$ and $^{(+)}NH_3$ groups. This affinity is exemplified by the use of *p*-toluidine and benzidine salts for quantitative precipitation of sulfonates.[14,15] Furthermore, the use of *p*-toluidinium and anilinium salts of anilinomethanesulfonates as characteristic derivative of the AMS recently has been proposed.[2,5]



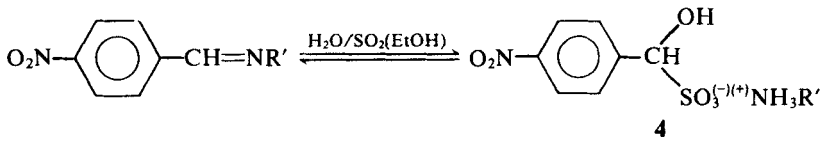
R′ = H, (AMS-A)
R′ = CH_3, (AMS-T)

On the other hand, when hydroxymethanesulfonate reacts with a solution of aniline hydrochloride, a precipitate is observed initially, which upon continuation of the reaction redissolves forming $AMSH^+$. That precipitate, when isolated and analyzed, proved to be AMS-A.[16]

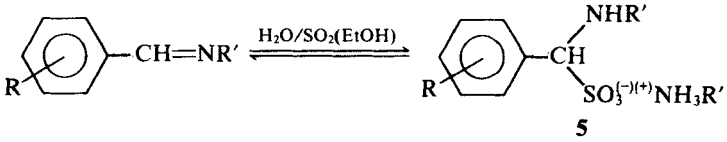


Equilibrium 3

This proton-transfer equilibrium seems to depend more on the donor ability of the hydroxyl group than on the basicity of the amines. This can be proved by analyzing the results of Clark and Miles[17] regarding the synthesis of aminomethanesulfonates starting with the corresponding Schiff bases and $HSO_3^{(-)}$ in alcoholic solutions: for Schiff bases originated from aromatic aldehydes substituted with strong electron-withdrawing groups, only the ammonium salts of the α-hydroxymethanesulfonates (**4**) were obtained; whereas for other Schiff bases, the C-substituted aminomethanesulfonate ammonium salts (**5**) were formed.



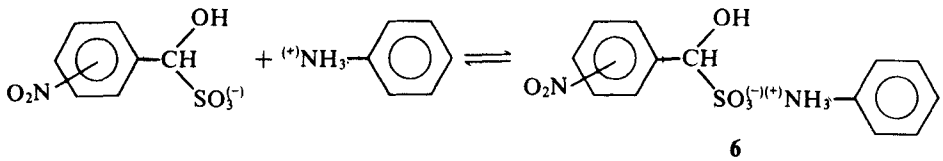
4



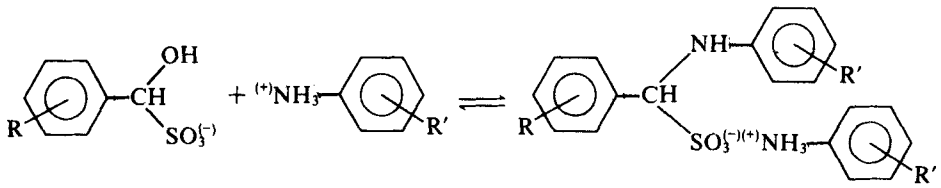
5

Additionally, various attempts to synthesize the *p*- and *m*-nitrophenyl derivatives of structure **5** by the usual method of mixing the corresponding α-hydroxymethanesulfonate with aniline hydrochloride failed,[18] and the only product found was the anilinium salt of a α-hydroxycompound (**6**). The same reaction, when performed with all the other α-hydroxymethanesulfonates, produced the C-substituted compounds (**7**)

These results can be explained by the large electron-withdrawing effect of the nitro group attached to the aromatic ring which significantly diminishes the electron donating power of the hydroxyl group, thus avoiding the formation of the new



6



7

R = H, *p*-Cl, *m*-Cl, *m*-CH_3, *p*-CH_3, *p*-OCH_3
R′ = H, *p*-CH_3, *m*-NO_2, *p*-NO_2

hydrogen bond $^{(+)}O\cdots H$. This transmission of electronic effects across a CH_2 group also can be detected for the ionization equilibria of the phenylacetic acids.[19]

Reaction 4

It is well known that the nucleophilicity of aromatic and aliphatic amines is not sufficient to displace a hydroxyl group.[20] This problem is avoided in the proposed mechanism by assuming the formation of a six-membered cyclic intermediate which allows a rapid proton exchange, possibly concerted with the attack of the neutral amine on the carbon atom. In this nucleophilic process, which is assumed to be rate determining, the hydroxyl group leaves as a water molecule.

Formation Mechanism

The kinetics of the formation reaction of anilinomethanesulfonates, according to the mechanism shown in Scheme I and assuming step 4 to be rate determining, should be second order and the observed rate constant, k_{obs},

$$k_{obs} = k_4 \cdot K_3 \cdot K_2 \cdot K_1$$

The total substitution effect constant $\rho_{obs} = \rho_4 + \rho_3 + \rho_2 + \rho_1$ is found experimentally to be -3.5. This value is very close to that for formation of anilinium ions in water-ethanol mixtures[21] ($\rho = -3.44$). Thus, in the equation above, as the substitution effects for equilibria 1 and 3 will be similar and of different sign, and as equilibrium 2 will not depend on substituents, for all practical purposes the observed ρ-value will correspond to reaction 4. This means that for the nucleophilic substitution the transition state will correspond to a structure with a large proportion of the positive charge already on the nitrogen atom.

Hydrolysis Mechanism

The overall ρ value of -2.3 found for the hydrolysis of the anilinomethanesulfonates may be explained by the mechanism shown in Scheme I, but starting from the

end products. The rather high negative ρ value is ascribed to the protonation reaction of the anilinomethanesulfonic compound (reaction 5). This equilibrium, which should have a ρ value similar to that for substituted anilines[22] ($\rho \cong -3.0$), is followed by an SN2 attack of a water molecule on the $AMSH^+$ (reaction 4). In this case the position of the activated complex should be the same as in the formation reaction, *i.e.* the charge should be practically all on the nitrogen atom, which means that the influence of the substituents will be small and positive for this step. Then, as $k_{obs} = K_{(-5)} \cdot k_{(-4)}$, the overall ρ value must be $\rho_{(-5)} + \rho_{(-4)} < |-3|$, which agrees with the experimental value.

In addition, data on activation energies and reaction enthalpies show that the hydrolysis activation energies are some 5–10 kcal/mol higher than the overall formation activation energies. These values are in accord with what may be expected thermodynamically for similar reactions.[23]

ACKNOWLEDGMENT

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