β-Aminoethylsulfuric Acid, an Irregular Ampholyte[1]

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Although an enormous amount of work[3] has been done on amphoteric substances, and the compounds studied have been of many varieties,[4] the literature contains no mention of β-aminoethylsulfuric acid as an ampholyte other than the assignment to it of an inner salt structure by its discoverer,[5] who found that neither acids nor alkalies formed salts with it.

Incidental to work along other lines, we had occasion to investigate some of the properties of β-aminoethylsulfuric acid and were impressed by its desirability as a subject for study by those interested in ampholytes. The compound is very stable and easily purified by recrystallization from dilute ethanol. In common with the aliphatic amino acids,[6] it has an absence of a true melting point, insolubility in ethanol, great solubility in water, a definite end-point by the formol titration and an anomalous end-point by direct titration with alkali, but it differs from them by the presence of an ester linkage and a sulfate group in the molecule. Although its composition is very similar to that of taurine, it differs from it in having an ester linked sulfate group instead of the sulfonic group. By its faintly acid reaction with litmus it shows a closer similarity to the aliphatic amino acids than to taurine.

Since other demands prevent our continuing the study of this compound, we desire to bring it to the attention of investigators in the field of ampholytes, and offer our findings, together with our simple method for obtaining theoretical yields of β-aminoethylsulfuric acid, an improvement over the method which superseded Gabriel's.[7,8]

Experimental

Reagents.—Monoethanolamine, 99.4% purity, from the Carbon and Carbide Chemicals Corporation; sulfuric acid, C. P. grade, 88.3%.

β-**Aminoethylsulfuric Acid Preparation, Preferred Method.**—To 8.9 g. (0.8 mole) of acid cooled in a freezing mixture and stirred vigorously by a motor, there was added dropwise, in the course of ten minutes or more, 4.9 g. (0.8 mole) of cooled monoethanolamine. Too rapid addition, or addition of the reactants in the reverse order, produced a violent reaction. After all the amine had been added there was put into the mixture 0.9 g. (0.08 mole) of acid, the entire mixture was heated in an oil-bath to 130°, and while being stirred was held at this temperature for one hour. At the end of this time the mixture was cooled and 40 ml. of absolute ethanol added with stirring. The precipitate was collected on an asbestos or fritted glass filter and washed with four 5 ml. portions of absolute ethanol; yield 9.9 g. Evaporation of the acid filtrate, preferably under reduced pressure, and the addition of two volumes of absolute ethanol to the cooled residue gave an additional 1.5 g., total yield 11.4 g. or 100%.

Alternate Method.—An equimolal mixture of acid and amine was prepared as above, 2.4 g. (0.27 mole) of acid was added, and the mixture allowed to stand at room temperature for seventy-two hours. Treatment of the reaction mixture with absolute ethanol, as in the preferred method, gave a total yield of 11.6 g. of coarse crystalline aggregates containing some occluded acid.

Purification.—The crude product was recrystallized by solution in hot water (15 g. in 30 ml.), the cooled solution poured into 90 ml. of absolute ethanol, and the mixture cooled to 0°; recovery 94.5%. In a melting point tube this purified material started to sinter at 230° and decomposed at 255° with incomplete fusion. Analyses of the crude and the purified product are given in Table I. All nitrogen determinations were semi-micro Dumas and sulfur was determined by both wet and dry oxidation. After three additional recrystallizations, using five volumes of absolute ethanol per volume of aqueous solution, the refined product began to sinter at 275° and became brown at 280° without melting. Its aqueous solution showed only a faintly acid reaction to litmus; and gave not the slightest turbidity with barium chloride even after standing for ten hours at room temperature. Neither acids, alkalies, nor salts precipitated the compound from even its concentrated aqueous solutions. Microscopic examination of the refined product revealed but one crystalline form, identical with that described by Gabriel.[5] The purified compound did not give insoluble derivatives with any of the reagents used for the detection of amino groups.

(1) Original manuscript received October 4, 1937.

(2) Present address: 3105 Cross Street, Madison, Wisconsin.

(3) See "Symposium on the Dielectric Properties of Matter," *Chem. Rev.*, **19**, 163 (1936), especially the papers by Wyman and by Cohn, for excellent bibliographies on the subject.

(4) Bjerrum, *Z. physik. Chem.*, **104**, 147 (1923), gives a good review of the substances studied.

(5) Gabriel, *Ber.*, **21**, 2667 (1888).

(6) Sidgwick, "Organic Chemistry of Nitrogen," new edition, revised and rewritten by J. W. T. Taylor and Wilson Baker, Oxford University Press, New York, 1937, Chap. IV, pp. 105 *et seq.*

(7) Gabriel, *Ber.*, **21**, 1056 (1888).

(8) Frankel and Cornelius, *ibid.*, **51**, 1666 (1918).

TABLE I

ANALYSIS OF CRUDE AND PURIFIED PRODUCTS

Material	Crude		Purified		Calcd.
	I	II	I	II	$C_2H_6NO_4S$
Sample, g.	0.07025	0.07753	0.07117	0.07054	
Nitrogen, %	9.96	9.94	10.13	10.05	9.93
Sample, g.	0.2710	0.2652	0.2745	0.2714	
Sulfur. %					22.68
Wet			22.40	22.48	
Dry	22.34	22.37			

Determination of the Molecular Weight.—Direct titration with alkali, phenolphthalein indicator, gave two end-points: the first, which persisted upon the addition of more base until the second was reached, being a faint pink and giving large and irregular values for the molecular weight; the second end-point, much deeper in color, gave values agreeing closely with the theoretical. In order to secure concordant results with the formol titration it was necessary to add at least one equivalent or more (a large excess caused no change in the final results) of the aldehyde, prior to the addition of any alkali. Under these conditions the observed and the theoretical values were in good agreement. The calculated and the observed molecular weights as determined by titration were corroborated by cryoscopic measurements of aqueous solutions of the compound. These molecular weight data have been assembled in Table II.

TABLE II

DETERMINATIONS OF THE MOLECULAR WEIGHT OF β-AMINOETHYLSULFURIC ACID

Method		I	II
Titration { First end-point		620	588
direct alkali { Second end-point		141.3	142.0
Titration, "formol"		141.2	142.5
Cryoscopic, water solution		140.5	141.5
Theoretical		141	

Hydrolysis.—An aqueous solution of the refined substance treated with barium chloride and set aside for ten hours at room temperature did not form enough barium sulfate to produce even a slight turbidity. Heating this mixture on a steam-bath for fifteen hours produced a precipitate of barium sulfate which was far below the theoretical amount. When the solution was made strongly acid, methyl orange indicator, with hydrochloric acid, treatment with barium chloride and heating for fifteen hours on the steam-bath produced so little barium sulfate as to cause only a slight turbidity. The solutions of the refined material remaining after direct alkali titration, when made acid to phenolphthalein with hydrochloric acid, showed only a slight turbidity after the addition of barium chloride. Hydrolysis with stoichiometric amounts of barium hydroxide produced very little barium sulfate at room temperature, and the reaction was not completed even after digestion for several days on a steam-bath.

The quantitative experiments reported in Table III were made as follows: the sample (0.27 to 0.29 g.) was dissolved in 10 ml. of water, the reagent solution added, and the mixture refluxed on the steam-bath. The extent of the hydrolysis was calculated from the weight of barium sulfate obtained. In the experiments with barium chloride the hydrolyzed solutions were diluted with hot water, made acid to methyl orange with hydrochloric acid, and digested overnight on the steam-bath. The weight of barium sulfate was determined in the usual manner. In the experiments with potassium hydroxide the addition of 10 ml. of ethanol was necessary to prevent frothing during hydrolysis. After hydrolysis the solutions were distilled with steam to remove the ethanol and the volatile amines. To the steam distillation residue, diluted with hot water and made acid to methyl orange with hydrochloric acid, two moles of barium chloride were added and the amount of

barium sulfate was determined by the method described above.

TABLE III

HYDROLYSIS OF β-AMINOETHYLSULFURIC ACID

Name	Concn., %	Reagents Moles in excess	Hours refluxed	% Hydrolyzed Crude	Refined
BaCl₂	10	1	5.0	0.035	0.067
BaCl₂	10	1	15.0	.039	.070
KOH	25	21	3.5	...	75.56
KOH	25	54	5.0	...	75.27

Discussion

Although β-aminoethylsulfuric acid possesses the characteristic properties of a "zwitterion," and our determinations of its neutralization and cryoscopic values indicate that in aqueous solution the compound exists in the simplest possible state of molecular aggregation, the acid reaction with litmus points to actual ionization, even though so slight as not to appear in the cryoscopic measurements. From the above it might be assumed that the compound is an acyclic ampholyte, the irregularities being caused by the activating effect of the sulfate group,[9] and one might expect the compound to have a large electric moment. By the same reasoning, the two strong polar groups of the compound, by preventing ionization at the ester linkage[9] (pp. 166–167, 262–265) might be the cause of the latter's great resistance to hydrolysis demonstrated both in our work and elsewhere.[10] Dielectric constant and X-ray studies might help to decide these questions.[11]

On the other hand, the absence of insoluble derivatives with amino group reagents, the great resistance of the ester linkage to hydrolysis, the slight acid reaction in solution, together with the occurrence of but one crystalline form, might be considered evidence of ring–chain isomerism, with the cyclic form predominant, an opinion favored by the long molecule (a six atom chain) and in agreement with some of the current views on amino acids.[12]

It would be interesting to see further work done upon β-aminoethylsulfuric acid in order to obtain a better knowledge of its structure.

(9) Waters–Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1936, Chap. VIII, pp. 159–194.

(10) Wenker, THIS JOURNAL, **57**, 2328 (1935).

(11) Wyman and McMeekin, ibid., **55**, 908 (1933).

(12) Sidgwick,⁴ p. 106; Wyman and McMeekin, ibid., **55**, 912 (1933).

Summary

1. We have improved the Frankel and Cornelius method for preparing β-aminoethylsulfuric acid from monoethanolamine and sulfuric acid so that the theoretical yields may be obtained readily.

2. The crude product is purified easily, since water is the only other reaction product.

3. Although copiously soluble in water, the compound is not precipitated, even from its concentrated solutions, by acids, alkalies, or salts.

4. In aqueous solution the compound exists in the simplest possible state of molecular aggregation.

5. The compound displays many of the properties common to the aliphatic amino acids.

6. The ester linkage of the compound is very resistant to hydrolysis, thus allowing it to be used in solution with substances that catalyze hydrolytic reactions.

7. The compound is worthy of further study as an ampholyte.

Complex Formation between Carboxylic Acids and Divalent Metal Cations

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This paper contains a comparison of the hydrogen electrode titration curves of a number of mono- and dicarboxylic acids in 0.2 M potassium chloride and in various KCl–MCl_2 solutions of the same ionic strength. M represents Mg, Ca, Sr, Ba or Zn. The work was instigated by recent observations of Greenwald[1] on the effect of calcium chloride on the pH of a variety of carboxylic acid buffer solutions. Its immediate purpose was to provide information as to the relative activity coefficients of certain salts of physiological importance but observations were extended to a number of related cations and acids. The ionic strength at which observations were made is comparable to that of mammalian body fluids.

The results indicate the existence of notable specific effects which are consistently related not only to the nature of the cation but to the molecular structure of the acid. These effects have been reduced to mass action constants for the formation of binary compounds between the carboxylate anions and each cation. Within the range of concentrations studied, and within the plausible errors of the method, we find that the formation of binary compounds suffices for a fairly satisfactory quantitative description of the observations. Were association to more complex compounds to occur to any important extent, we should expect the specific effects which have been observed to be a function of the total concentration of organic acid. We have found no

clear indication of this for concentrations of acid ranging from 0.002 to 0.05 M (Tables III and VII).

In our use of the law of mass action to describe the effects observed, we are committed to no particular views as to the nature of the forces involved. It is generally acknowledged that mass action constants may be expected to describe, with fair precision, certain specific electrostatic effects, whose existence is ignored in the approximations which are involved in the working equations of interionic attraction theory. Where electrostatic forces of ions are involved the definition of what constitutes a reversibly dissociable compound is difficult. The mass action constants are submitted merely as convenient descriptions of relative activity coefficients.

We appreciate the fact that the use of the hydrogen electrode introduces indeterminate errors due to the presence of a liquid junction (L. J.) potential. The observations comprise two types of hydrogen electrode potentials: (a) those of the organic acid buffer in KCl–MCl_2 solutions; and (b) those of dilute solutions of hydrochloric acid in corresponding KCl–MCl_2 solutions. The latter were employed to calculate γ_{H^+} for the corresponding solutions containing the carboxylic acid. Into both of these potential measurements L. J. potentials enter as a source of error. In the majority of the calculations, however, γ_{H^+} appears only as a small correction term. Its precise value is unimportant. In the few systems in which it is an important term (those of rather low

(1) I. Greenwald, J. Biol. Chem., 124, 437 (1938).