[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Base Strengths of N,N′-Dialkylguanidines

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Contrary to an earlier report by Davis and Elderfield, N,N′-dimethylguanidine and N,N′-diethylguanidine are shown by potentiometric titrations to be strong bases, comparable in strength with sodium and potassium hydroxides. The guanidines studied in this investigation have been identified by synthesis, by elementary analysis, and by quantitative hydrolysis to ammonia and primary amine. Although the supposed N,N′-dialkylguanidinium salts of Davis and Elderfield cannot now be definitely identified, it is probable that these substances were primary ammonium salts.

Davis and Elderfield[1] have reported that guanidine and all of its N-alkyl, N,N-dialkyl and N,N′,-N″-trialkyl derivatives which they examined are strong bases, comparable in strength with potassium hydroxide; but that N,N′-dimethylguanidine, N,N′-diethylguanidine and N,N′-di-*n*-amylguanidine are relatively weak bases with ionization constants K_b equal to about 2×10^{-4}. These authors proposed no explanation for the unexpected weakness of the N,N′-dialkylguanidines but, somewhat later, Pauling[2] did so. Pauling's explanation, however, appears to be unsatisfactory since, if extended to simple amines, it leads to the incorrect conclusion that alkyl groups, when directly linked to the nitrogen atoms in these latter substances, should in general decrease the base strengths. For this reason it seemed desirable to re-examine the experimental data.

In the studies which form the subject of this paper, dilute aqueous solutions of the following salts were potentiometrically titrated with sodium hydroxide: guanidinium, N,N′-dimethylguanidinium, N,N′-diethylguanidinium, ammonium, methylammonium, ethylammonium, diethylammonium, sodium, and potassium picrates; guanidinium, N,N′-dimethylguanidinium, ammonium, methylammonium and sodium nitrates. The several picrate salts listed were employed because some of them proved to be more easily prepared and purified than the corresponding salts of inorganic acids. Since picric acid behaves as a strong acid in aqueous solution, the use of the picrates should introduce no complication; in any event, no difference in the behaviors of the picrates and of the corresponding nitrates was observed. The ammonium and substituted ammonium salts were studied in order that the method used might be checked with bases which not only are of known strengths but also are of about the same strengths as those reported by Davis and Elderfield[1] for the N,N′-dialkylguanidines. Finally, blanks were run, in which the "salts" that were titrated consisted simply of distilled water.

Results

The results obtained in a typical series of runs are shown in Fig. 1, in which the measured values of *p*H are plotted against the volumes of standard sodium hydroxide added. It is at once seen that these curves do not confirm the conclusion of Davis and Elderfield,[1] since they show that, within the accuracy of the measurements, the salts of N,N′-dimethylguanidine and of N,N′-diethylguanidine are potentiometrically indistinguishable from those of either guanidine or potassium hydroxide, or from distilled water. It is especially to be noted that the curves for the salts of any bases with the strengths reported by Davis and Elderfield for the N,N′-dialkylguanidines would have to lie between the ones for the ammonium and the monoalkylammonium salts.

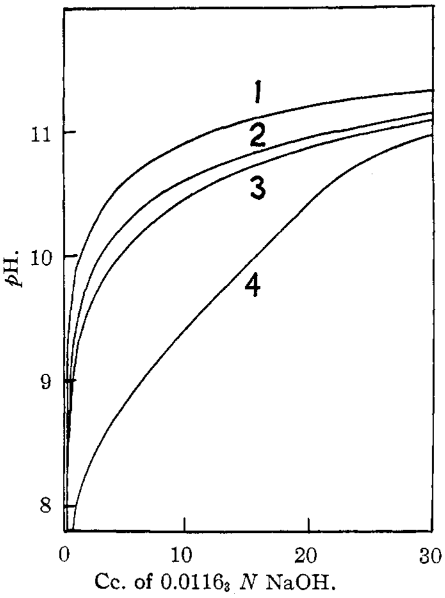

Fig. 1.—Titrations of 100-cc. portions of 0.002 *N* solutions of guanidinium and other salts: 1, N,N′-dimethylguanidinium picrate, N,N′-diethylguanidinium picrate, guanidinium picrate, potassium picrate and distilled water; 2, diethylammonium picrate; 3, methylammonium picrate and ethylammonium picrate; 4, ammonium picrate.

In a number of other runs, which need not here be further described, the concentrations of the solutions were as much as 10 times as great as in the ones summarized in Fig. 1. In some of these additional measurements, the curves for the various guanidinium salts were no longer exactly identical either with each other or with the ones for the corresponding sodium and potassium salts. The differences were, however, never greater than about ±0.2 *p*H unit and so were not out of line with the variations often found, at comparable concentrations, in the titrations of other neutral salts composed of different ions. Moreover, the differences in question are in such directions that, if they were accepted as significant, the conclusion would follow

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(1) T. L. Davis and R. C. Elderfield, THIS JOURNAL, **54**, 1499 (1932)

(2) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1st edition, 1939, pp. 198 ff.; 2nd edition, 1941, pp. 213 ff.

TABLE I

ANALYSES OF GUANIDINIUM SALTS

Salt[a]	Carbon, % Calcd.	Carbon, % TSM[b]	Carbon, % WS[c]	Hydrogen, % Calcd.	Hydrogen, % TSM[b]	Hydrogen, % WS[c]	Nitrogen, % Calcd.	Nitrogen, % TSM[b]	Nitrogen, % WS[c]	Nitrogen, % BN[d]
DMP	34.18	34.68	34.32	3.83	3.71	3.87	26.58	25.49	26.27	26.93
		33.93	34.32		3.80	3.86		25.35	26.60	
			34.55						26.49	
DMN	24.00	24.36	...	6.71	6.19	..	37.32	35.23	36.1	37.39
								35.89	36.2	37.37
									36.3	
DEP	38.37	35.56	38.27	4.68	4.79	4.61	24.41	23.80	24.23	24.41
			38.53			4.61			24.38	
									24.34	

[a] DMP = N,N′-dimethylguanidinium picrate; DMN = N,N′-dimethylguanidinium nitrate; DEP = N,N′-diethylguanidinium picrate. [b] Analyses performed by T. S. Ma. [c] Analyses performed by William Saschek. [d] Analyses performed by B. Neivelt.

that the two dialkylguanidines are actually *stronger* bases than sodium hydroxide. In any event, therefore, it appears that, contrary to the conclusions of Davis and Elderfield,[1] N,N′-dimethylguanidine and N,N′-diethylguanidine (and presumably also all other N,N′-dialkylguanidines) are strong bases.

On the other hand, diethylamine, ethylamine, methylamine and ammonia are seen from Fig. 1 to be definitely weak bases, in agreement with the experience of innumerable earlier workers. The values of pK_b, calculated from the midpoints of the titration curves (addition of 8.6 cc. of sodium hydroxide) and corrected for hydrolysis but not for ionic-strength effects, were 3.10 for diethylamine, 3.33 for ethylamine, 3.35 for methylamine and 4.77 for ammonia; the values given by Hall and Sprinkle[3] are, respectively, 3.02, 3.33, 3.36, and 4.73. The agreement is probably as good as could be expected since we made no effort to achieve great precision. Moreover, in the experiments at higher concentrations, mentioned above, values in equally satisfactory agreement with those of Hall and Sprinkle were obtained.

Discussion

The only reasonable explanation for the discrepancy between our results and those of Davis and Elderfield[1] is that either we or Davis and Elderfield (or both) did not have the N,N′-dialkylguanidines assumed. It was therefore essential that the substances studied be identified with more than usual care.

Davis and Elderfield prepared their N,N′-dialkylguanidines by the method of Kaess and Gruszkiewicz,[4] according to which the guanidinium chloride is formed from the appropriate primary amine and cyanogen chloride in cold anhydrous ether. Many years before Kaess and Gruszkiewicz published their method, however, Clöez and his co-workers[5–8] had studied this same reaction and had reported that the solid which separates from the ethereal solution is not the guanidinium chloride but is instead the hydrochloride of the monoalkylamine used. This same conclusion was reached also by Hofmann,[9] and is in complete agreement with our own observations described below in the experimental part. Moreover, Kaess and Gruszkiewicz found that their supposed guanidinium salts were *di*hydrochlorides whereas all other investigators, including Davis and Elderfield, have found that guanidines behave as *mono*acid bases.[10] There is, therefore, considerable reason to question the preparative method employed by Davis and Elderfield. Our own syntheses were carried out by the method of Schenck[11] which, unlike that of Kaess and Gruszkiewicz, has not been challenged by other workers. Moreover, the diethylguanidinium salts were prepared also by the method of Noah.[12] The samples obtained in the two ways were found to be identical.

The quantitative elementary analyses reported by Davis and Elderfield for their compounds were uniformly in good agreement with the belief that these substances were indeed the assumed guanidinium salts. Our own analyses, which were carried out by three independent analysts over a period of four or five years, show rather large variations among themselves but on the whole appear to be satisfactory. The values obtained are listed in Table I. It will be seen that the values for nitrogen are rather less satisfactory and less consistent than are those for carbon and hydrogen. As is well known, however, the analysis of a guanidine for nitrogen is quite difficult; low values are frequently obtained, especially if the sample is not very finely ground. The reported analyses by one of us (B.N.) were the last of a much larger number of determinations, during the course of which the technique was perfected. The analyses by Dr. T. S. Ma were performed by standard techniques and without special precautions. Those by Mr. William Saschek are doubtless the most reliable, since Mr. Saschek had had much previous experience with the analyses of guanidines. It is therefore gratifying that these last determinations are in excellent agreement with the calculated values, except for dimethylguanidinium nitrate, which possibly was not quite pure.

The melting points found for the various salts by Davis and Elderfield and by us are in agreement

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(3) N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

(4) L. Kaess and J. Gruszkiewicz, *Ber.*, **35**, 3598 (1902).

(5) Clöez and Cannizzaro, *Ann.*, **78**, 228 (1851).

(6) Clöez and Cannizzaro, *Compt. rend.*, **32**, 62 (1851).

(7) Cahours and Clöez, *Ann.*, **90**, 91 (1854).

(8) Cahours and Clöez, *Compt. rend.*, **38**, 354 (1854).

(9) A. W. Hofmann, *Ber.*, **3**, 264 (1870).

(10) *Cf.*, however, V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, who on page 103 quotes the original incorrect statement of Kaess and Gruszkiewicz that N,N′-dimethylguanidine forms a dihydrochloride.

(11) M. Schenck, *Arch. Pharm.*, **247**, 490 (1909).

(12) G. Noah, *Ber.*, **23**, 2195 (1890).

with each other and with the literature values in all those cases in which the melting points have previously been reported. In one case, however, in which no independent literature value is available, our melting point and that of Davis and Elderfield do not agree (see the experimental section, below). Moreover, for N,N'-dimethylguanidinium sulfate, Davis and Elderfield reported the melting point of 264–265°. Although no independent value for this substance has been recorded, we have observed that methylammonium sulfate melts at 240–260° with decomposition.

In view of the above conflicting evidence, it was necessary to carry out still further experiments in order rigorously to identify the various salts. We accordingly hydrolyzed both the dimethylguanidinium picrate and the diethylguanidinium picrate in basic solution, and quantitatively determined the amounts of ammonia and of amine produced. A somewhat indirect method of analysis was, however, required by the fact that, in the basic media used, ammonia was formed not only from the dialkylguanidinium ions but also, and in non-stoichiometric amount, from the picrate ion.[13] The procedure adopted was the following. First, picrate-free solutions of the two guanidinium sulfates were prepared by treating the picrates with dilute aqueous sulfuric acid and then extracting the aqueous solutions with ether. Although the concentrations of these resulting solutions were not precisely known, the molar ratios of amine to ammonia in the hydrolysates obtained from them could be determined[14] without interference from picrate ion. This ratio was found to be 2:1. Finally, the actual amounts of amine produced in the hydrolysis of weighed amounts of the picrates themselves were determined. Each mole of guanidine was in this way found to give two moles of amine and hence also, from the previously determined ratio, one mole of ammonia. That the amines obtained in the hydrolyses were primary was established by quantitative Van Slyke determinations, in which the observed amounts of nitrogen evolved were within 10% of those calculated. That the amines from dimethylguanidinium picrate and from diethylguanidinium picrate were, respectively, methylamine and ethylamine was established by isolation and identification (by melting point and mixed melting point) of methylammonium picrate and ethylammonium picrate.

From all the evidence cited above, it seems impossible to doubt that the salts which we studied were indeed the N,N'-dialkylguanidinium compounds assumed. It remains to consider the identities of the salts studied by Davis and Elderfield.[1] Since these were clearly salts of weak bases and since they were prepared by a reaction which, according to several different authors,[5–9] gives the salts of monoalkylamines, it is natural to suppose that Davis and Elderfield had primary ammonium, rather than N,N'-dialkylguanidinium, salts. An obvious objection which may be made to this explanation is that, from the published titration curves,[1] the equivalent weights of the bases studied by Davis and Elderfield appear to be those expected for the guanidines, and hence to be widely different from those of the amines. However, in view of the particular way in which the titrations were performed, this objection is easily seen to be not valid. Thus, Davis and Elderfield described their procedure as follows: To "an exactly 0.05 normal solution of the sulfate . . . was added 0.1 normal barium hydroxide in quantity exactly sufficient to precipitate all the sulfate and thus give a solution of the free base. The latter was then titrated with 0.1 normal hydrochloric acid . . . ." Presumably, the concentration of the original salt solution and the required amount of barium hydroxide were both calculated on the assumption that the sulfate was a guanidinium salt. Consequently, even if the sulfate had actually been an ammonium salt, its equivalent weight would have appeared to be that of the corresponding guanidinium salt, since the volume of hydrochloric acid required for neutralization was determined solely by the amount of barium hydroxide which had been added.

More positive evidence supporting the suggestion that the supposed N,N'-dialkylguanidinium salts of Davis and Elderfield were really *primary ammonium* salts is that the ionization constants which these authors ascribed to the guanidines are fairly close to the accepted values for the corresponding amines. Moreover, as was pointed out by Professor Elderfield in a personal communication, the differences are in the direction, and are of at least approximately the magnitudes, that would be expected. For, if the salts were derived from primary amines rather than from guanidines, the fractions of the bases which had been neutralized at the midpoints of the titrations would have been much greater than one-half since, when the titrations were begun, the solutions would have contained large amounts of unprecipitated sulfate. If the ionization constants of Davis and Elderfield are "corrected" on this basis, they are multiplied by a factor of approximately 2, and are thereby brought into materially closer agreement with the values for the corresponding amines.

In spite, however, of the arguments just advanced, there remains the more serious difficulty that the analyses and melting points reported by Davis and Elderfield[1] appear to exclude the possibility that the salts in question were those of primary amines. A reasonable explanation for these discrepancies, which Professor Elderfield suggested in a personal communication but which he now after 20 years can neither definitely confirm nor refute, is that the analyses and melting points refer, not to the salts which were prepared by the method of Kaess and Gruszkiewicz[4] and were used in the determinations of base strengths, but rather to some salts which were prepared by the method of Wheeler and Jamieson[15] (essentially the same as that of Noah[12]) in connection with a different problem.[16] This confusion could easily have arisen from a misunderstanding, since the late Provessor Davis wrote the two papers[1,16] while he was in Europe on sabbatical leave and hence out of contact with his coauthor. In view, therefore, of all the evidence

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[13] E. Wedekind and J. Haeussermann, *Ber.*, **35**, 1133 (1902).

[14] M. François, *Compt. rend.*, **144**, 563, 857 (1907).

[15] H. L. Wheeler and G. S. Jamieson, *J. Biol. Chem.*, **4**, 111 (1908).

[16] T. L. Davis and R. C. Elderfield, THIS JOURNAL, **55**, 731 (1933).

which is now available, it appears most probable that the weak bases studied by Davis and Elderfield were monoalkylamines instead of N,N′-dialkylguanidines.

Experimental

Preparation of Dialkylguanidines.—N,N′-Dimethylguanidinium iodide was prepared by the method of Schenck[11] from methylamine and cyanogen iodide. The corresponding nitrate was formed by the action of silver nitrate on the purified iodide, and the picrate was formed by the action of picric acid on the nitrate. The melting point of the nitrate, after repeated crystallizations from water and from ethyl alcohol, was 101–101.5°; that reported by Davis and Elderfield[1] was 68°. (For methylammonium nitrate, Beilstein lists the two melting points of 99–100° and 70°.) The melting point of the picrate, crystallized from water, was 177.5°; that reported by Schenck and by Davis and Elderfield was 178°. (Methylammonium picrate melts at 215°.) In another preparation, the cyanogen iodide of Schenck's original procedure was replaced by cyanogen bromide, and the picrate was formed directly from the resulting dimethylguanidinium bromide. The product thus obtained melted at 177–177.5°, and its melting point was not altered by admixture with the previous sample.

N,N′-Diethylguanidinium iodide was prepared by the method of Schenck[11] from ethylamine and cyanogen iodide. The product did not crystallize, but was transformed directly into the picrate by treatment with aqueous picric acid. The picrate, after crystallization from water, melted at 143–144°. The melting point reported by Noah[12] and by Davis and Elderfield[1] was 141°. This same salt was prepared also by the method of Noah.[12] One sample thus obtained melted at 141–142°; a second sample, from an independent preparation, melted at 143–143.5°. The melting point of neither sample was depressed on admixture with the picrate prepared by the method of Schenck.

An attempt was made to prepare the N,N′-dimethylguanidinium chloride by the method of Kaess and Gruszkiewicz[4] (the method used by Davis and Elderfield[1]). The white precipitate, which was formed as the reaction progressed, was separated by filtration, recrystallized from 95% ethyl alcohol, and dried over concentrated sulfuric acid, m.p. 226–228°; m.p. of methylamine hydrochloride purified in the same way, 225–228°; m.p. of a mixture of the two, 225–228°. *Anal.* Calcd. for CH_6ClN: N, 20.75. Found: N, 20.66. The ethereal filtrate remaining after separation of the methylamine hydrochloride was evaporated to dryness, and the flesh-colored residue was crystallized from 95% ethyl alcohol and dried over concentrated sulfuric acid. The resulting white powder softened at 115–118° and melted at 176–178°. It was presumably 1,3,5-trimethylisomelamine, for which Beilstein lists the two melting points, 123–124° (air-dried material, rapidly heated) and 179° (anhydrous material). *Anal.* Calcd. for $C_6H_{12}N_6$: N, 49.99. Found: N, 49.64, 49.00.

Potentiometric Titrations.—In the titrations, the values of *p*H were measured with a glass electrode. In some of the measurements (B. N.), the apparatus was the one previously described[17]; in others (D. H. S.), a Beckman *p*H meter, Model G, was used. The electrodes were standardized and checked against potassium acid phthalate buffers in the former runs, and against a *p*H 7.00 ± 0.01 standard buffer (National Technical Laboratories) in the latter. Since precise measurements were not required, the titrations were carried out at "room temperature," which may be taken as 22–26°.

Hydrolysis of Guanidines.—(a) A weighed amount (about 1.5 millimoles) of the picrate was treated with about 50 cc. of 2 *N* aqueous sulfuric acid, and the resulting solution was extracted with ether until the ethereal extracts were no longer colored. On evaporation of the combined extracts, an almost quantitative yield of picric acid, melting at 120–121°, was obtained. The aqueous solution, containing the guanidinium sulfate, was then treated with 25% aqueous potassium hydroxide and distilled into standard acid. The hydrolysis of the guanidine was rather slow; about 800 cc. of distillate had to be collected before all of the volatile base that was formed had come over. The total amount of base was determined by back titration of the resulting solution (standard acid plus distillate) to the methyl red end-point. The amounts of ammonia and of amine were separately determined by the method of François.[14] Since some guanidine was unavoidably lost in the removal of the picric acid, the amounts of total base found were somewhat lower than the values calculated from the weights of picrate used; except in one case, however, the recoveries of amine and of ammonia were better than 90%. The significant results of these hydrolyses were, therefore, the molar ratios of amine to ammonia, which should theoretically be exactly 2 for any N,N′-dialkylguanidinium salt. The values found were 2.07 and 1.98 for N,N′-dimethylguanidinium picrate, and 2.17 and 2.16 for N,N′-diethylguanidinium picrate.

(b) A weighed amount (about 1.5 millimoles) of the guanidinium picrate was hydrolyzed with 20% aqueous potassium hydroxide, and the amounts of total base, of amine and of ammonia were determined as before. For each salt, the calculated amount of amine is exactly 2 equivalents per mole of salt. The values found were 2.01 and 1.96 for N,N′-dimethylguanidinium picrate, and 1.88 and 1.97 for N,N′-diethylguanidinium picrate. As explained above, the corresponding amounts of ammonia, which were found to be 1.6–2.0, are not significant.

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[17] G. W. Wheland, R. M. Brownell and E. C. Mayo, THIS JOURNAL, **70**, 2492 (1948).