49. *Complexes Formed by α-Hydroxy-amidines with Transition-metal Ions. Part I. Acid Dissociation Constants of the Ligands.*

By R. O. Gould and R. F. Jameson.

The rate of decomposition of some α-hydroxy-amidinium ions in basic solution at 25° has been measured by means of a glass electrode and shown to have a first-order rate dependence on hydroxyl-ion concentration. The results have been used to calculate acid dissociation constants for the α-hydroxy-amidinium ions. The weakly acidic nature of the hydroxyl-hydrogen has been established and the role of the hydroxyl group in the formation of stable complexes with transition-metal ions by these compounds is discussed. Methods for the treatment of pH data to yield acid dissociation constants for weak dibasic acids are also discussed.

Although considerable interest has been shown in recent years in the pharmacological properties of amidines,[1] their properties as metal-complexing agents have received little attention, such studies generally being concerned with complex polymers of *N*-substituted amidines.[2] In the case of the α-hydroxy-amidines, there is the possibility of a simple *ON*-chelate ring involving the hydroxyl-oxygen and one of the amidine-nitrogen atoms.

The amidines chosen for study were homologous α-substituted hydroxyphenylacetamidines, $(\pm)\text{-HO}\cdot\text{CPhR}\cdot\text{C}(\text{:NH})\cdot\text{NH}_2$, where R = H (mandelamidine, abbreviated to mdH), Me (atrolactamidine, alH), and Et (α-hydroxy-α-phenylbutyramidine, hbH). As has been reported previously,[3] amidines of this type form stable complexes with transition-metal ions in strongly basic solutions. The importance of the hydroxyl group in the α-position has been established by the failure of phenylacetamidine and of β-hydroxy-amidines [4] to form such complexes, and the fact that the α-hydroxy-amidines are soluble

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[1] See especially Craver, Cameron, and Barrett, *J. Pharmacol.*, 1950, **99**, 353.

[2] Bradley and Wright, *J.*, 1956, 640.

[3] Gould, Jameson, and Neilson, *Proc. Chem. Soc.*, 1960, 314.

[4] Price and Zomlefer, *J. Org. Chem.*, 1949, **14**, 210.

in 10M-sodium hydroxide[5] suggests that the hydrogen of the hydroxyl group is weakly acidic and may ionise to leave an anion which forms the complex. (An analogous case has been reported by Hall and Dean.[6])

Although Shriner and Neumann[7] state that acetamidine and benzamidine are stronger bases than ammonia (pK_a for NH_4^+ = 9·26 at 25°), no quantitative measurements appear to have been made previously of the acid strength of the amidinium ions. Since the hydroxyl group would be expected to be an even weaker acid than the amidinium group, it was necessary to work in fairly strongly basic solutions in order to measure acid dissociation constants. The amidines, however, are unstable in basic solution, although the amidinium ions appear to be stable indefinitely in acid solution, and so it was necessary to study this decomposition further before accurate dissociation constants could be obtained.

RESULTS

Solutions varying between 0·008M and 0·04M in amidinium chloride were prepared and measured quantities of sodium hydroxide added. The ionic strength of all solutions was maintained at 0·1 with potassium chloride, and the pH measured at 25° over a period of about 40 min. from the time of mixing. It was not possible to work with solutions containing a molar ratio of base to amidinium ion greater than one, as the resulting pH values were too high to be measured accurately with a glass electrode. The results are summarised in Fig. 1, from which it can be seen that the decomposition is of the first order with respect to hydroxyl-ion concentration. Table 1 gives the first-order rate constants.

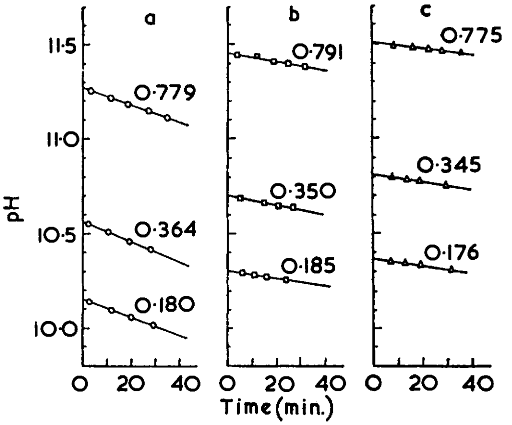

FIG. 1. Rates of decomposition of the α-hydroxyamidines; illustrative results for various degrees of neutralisation, *g*, given on each plot. a, mdH_2^+; b, alH_2^+; c, hbH_2^+.

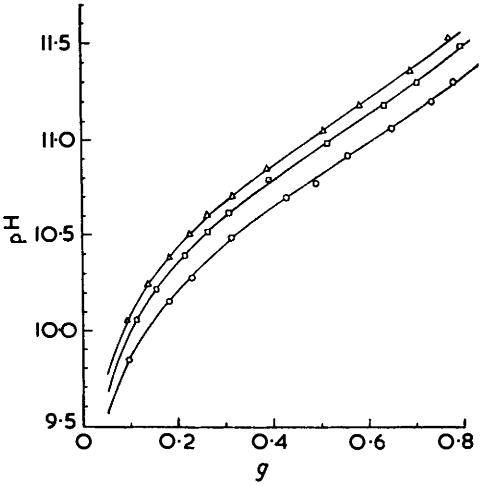

FIG. 2. pH titrations of α-hydroxy-amidinium chlorides. Theoretical curves, calculated for pK values in Table 2, and experimental points: ○ = mdH_2Cl; □ = alH_2Cl; △ = hbH_2Cl.

The extrapolation of the kinetic data to zero time gave the necessary pH data for the calculation of dissociation constants. The average number of protons abstracted from each amidinium ion, *g*, was calculated (this is thus analogous to the $\bar{n}$ of Bjerrum[8]) and the pH titration curves were plotted. In the case either of a monobasic acid or of a dibasic acid for which the two dissociation constants are fairly far apart, such a curve would be symmetrical

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[5] Roger and Neilson, *J.*, 1959, 688.

[6] Hall and Dean, *J. Amer. Chem. Soc.*, 1958, **80**, 4183.

[7] Shriner and Neumann, *Chem. Rev.*, 1944, **35**, 351.

[8] Bjerrum, " Metal Ammine Formation in Aqueous Solution," P. Maase and Son, Copenhagen, 1941.

about $g = 0{\cdot}5$ and asymptotic to $g = 1$. The results, illustrated in Fig. 2, show clearly that these conditions are not fulfilled and the existence of two dissociation constants, rather close together, is confirmed by fitting the appropriate theoretical curves to the experimental results. Table 2 gives the values of pK_1 and pK_2 (for the amidinium group and the α-hydroxy-group, respectively) for each amidine.

TABLE 1.

Decomposition of α-hydroxy-amidines; first-order rate constants with respect to hydroxyl-ion concentration at 25°.

Amidinium ion	mdH_2^+	alH_2^+	hbH_2^+
10^5k (sec.$^{-1}$)	18·0	8·4	8·1

TABLE 2.

Acid dissociation constants for some α-hydroxy-amidines, measured at 25° and at an ionic strength of 0·1.

Amidinium ion	pK_1	pK_2
mdH_2^+	10·82 ± 0·01	12·52 ± 0·05
alH_2^+	10·96 ± 0·01	12·72 ± 0·05
hbH_2^+	11·06 ± 0·01	12·86 ± 0·05

DISCUSSION

The Hydrolysis of the Amidinium Ions.—The much greater speed at which the mandelamidinium ion is hydrolysed (Table 1, Fig. 1) is in agreement with Cason and Wolfhagen's findings concerning the steric effects of α- and β-substituents on the hydrolysis of acid amides.[9]

An explanation of this first-order dependence on hydroxyl-ion concentration is that the attack involves displacement of ammonia from the cation:

$$OH^- + R{\cdot}C(NH_2){:}NH_2^+ \longrightarrow NH_3 + R{\cdot}CO{\cdot}NH_2$$

and this hypothesis is supported by the fact that the amidines being studied are relatively stable in extremely concentrated alkaline solutions. De Roo and Bruylants [10] have shown that acid amides are further decomposed in basic solution to give the anion of the free acid and ammonia, the reaction having a first-order dependence on both amide and hydroxyl concentration.

The Dissociation of the α-Hydroxy-amidinium Ions.—Two methods of calculating pK_1 and pK_2 from the pH data were tried. A method analogous to that of Ackermann and Schwartzenbach was tried first.[11] For this method, possible values for K_1 and K_2 are calculated for several points on the titration curve. If K_1 is then plotted against K_1K_2, the result is a family of lines intersecting at a point giving K_1 and K_1K_2 for the acid. Although pK_1 was readily obtainable by this method, difficulty was experienced in obtaining a good value for pK_2 as the lines intersected over a fairly large area. Better precision could have been obtained had it been possible to take pH readings for solutions having g greater than one. With such measurements precluded by the weakness of the acid, the method is inflexible and is badly impaired by slight experimental variation.

The curve-fitting method of Rossotti, Rossotti, and Sillén [12] was found much more suitable, and was used to calculate the results in Table 2. The experimental points were fitted by the " strip " technique.[13] This method is particularly valuable because it is

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[9] Cason and Wolfhagen, *J. Org. Chem.*, 1949, **14**, 155.

[10] de Roo and Bruylants, *Bull. Soc. chim. belges*, 1954, **63**, 140.

[11] Ackermann and Schwartzenbach, *Helv. Chim. Acta*, 1949, **32**, 1547.

[12] Rossotti and Rossotti, *Acta Chem. Scand.*, 1955, **9**, 1166.

[13] Rossotti, Rossotti, and Sillén, *Acta Chem. Scand.*, 1956, **10**, 203.

most sensitive, over the range of *g* to which one is limited, for dibasic acids whose two pK values are close to one another. The range of curves which give a good fit is readily estimated, giving the tolerances also listed in Table 2.

The results show the expected weakening of acid strength with lengthening side chain; pK_2, the hydroxyl ionisation constant, changes the more rapidly. The behaviour of α-hydroxy-acid amidines contrasts markedly with that of ethanolamine in which the hydroxyl-hydrogen does not ionise. Likewise, ethanolamine forms no pink complex with bivalent nickel ions, whereas even glycollamidine does.[14] This does not imply, of course, that the hydroxyl-hydrogens of the amidines studied are invariably ionised in metal complexes.

EXPERIMENTAL

Apparatus.—pH measurements were made on a Doran precision pH meter, reading to 0·001 pH unit, and were reproducible to ±0·003 pH unit. As nearly all readings had to be taken above pH 10, lithium-glass electrodes were employed with a saturated calomel electrode having a ground-glass junction. The reaction vessels were kept at 25° ± 0·1°. An oil-filled thermostat bath was found necessary to prevent undue fluctuation of the pH-meter readings. All leads were shielded, and the solution was stirred by a stream of nitrogen. The meter was restandardised after every reading with 0·025M-borax as a secondary standard [15] (pH found: 9·173 against 0·05M-potassium hydrogen phthalate.)

Preparation of Materials.—(±)-Mandelamidinium chloride,[16] (±)-atrolactamidinium chloride,[5] and ± α-hydroxy-α-phenylbutyramidinium chloride [17] were synthesised according to the instructions of Beyer and of Roger and Neilson. The products were recrystallised three times from 8M-hydrochloric acid, dried for 2 hr. at 80°, and analysed as chlorides. It was found that the yields of acetophenone cyanohydrin and propiophenone cyanohydrin could generally be improved and the reaction time greatly shortened by cooling the reaction vessel in acetone–solid carbon dioxide during addition of hydrochloric acid. Stock 0·100M-solutions were made up directly.

Carbonate-free 0·25M-sodium hydroxide was prepared by diluting an appropriate volume of 10M-sodium hydroxide (to which a sufficient quantity of barium chloride had been added to give complete precipitation of barium carbonate) with freshly boiled deionised water cooled in a stream of nitrogen. It was standardised against solid potassium hydrogen phthalate, and was protected from carbon dioxide.

In order to justify the adjustment of ionic strength with alkali-metal chlorides, series of measurements were made with sodium hydroxide and tetramethylammonium hydroxide in the absence of added potassium chloride. There was no noticeable discrepancy in the results thus obtained.

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[*Received, June* 30*th*, 1961.]

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[14] Gould and Jameson, unpublished work.

[15] Bates, " Electrometric pH Determinations," John Wiley and Sons, Inc., New York and London, 1954.

[16] Beyer, *J. prakt. Chem.*, 1884, **31**, 387.

[17] Roger and Neilson, *J.*, 1961, 3181.