[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VILLANOVA COLLEGE]

THE ELECTRONIC STRUCTURE OF 4-HYDROXYPHENACYLAMINES AND THE STABILITY OF α-AMINOKETONES[1]

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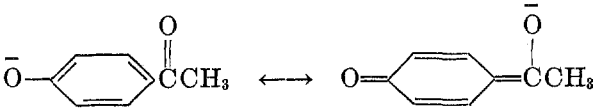
As a rule, primary and secondary α-aminoketones are stable as salts only; the free bases undergo dimolecular condensation to substituted dihydropyrazines and pyrroles, respectively. The literature on these condensations is too extensive to be quoted in full: aminoacetone (1), phenacylamine (2), and N-methylphenacylamine (3) may serve as representative examples.

Exceptions to the above rule are N-acyl-α-aminoketones such as α,α′-bis-(acetylamino)acetone (4) and N-aryl-α-aminoketones such as phenacylaniline (5). They are stable also without an extra proton attached to the N. So are phenacylamines with a phenolic hydroxyl group, provided this group is in the *para* position to the side chain. In the *ortho* or *meta* position it does not protect the side chain from a dimolecular condensation.

The present paper contains a report on studies carried out on several such phenacylamines and certain related compounds in the hope of throwing some light on the structural reasons why these particular aminoketones, as well as N-aryl- and N-acyl-α-aminoketones and α-ammonium ketones are stable when ordinary α-aminoketones are not.

As a preliminary step, the acidity of *p*-hydroxyacetophenone was determined. This compound possesses the complete structure of the 4-hydroxyphenacylamines in question, except their amino group. Its K_A was found to be 3.7×10^{-9}, more than 20 times the acidity of phenol. This greatly increased acidity must certainly be attributed to the resonance stabilization of the anion in which the



negative charge on the ketonic oxygen is increased by electrons from the phenolic oxygen. This increase in charge is certainly operative also in 4-hydroxyphenacylamines and suggests a hydrogen bond between the nitrogen and the carbonyl oxygen. Hydrogen bonds in five membered chelate rings are ordinarily weak, but this may well be different in the present case where the O carries a negative charge and thus will be better able to attract a proton from the amino group.

In 3-hydroxyphenacylamines no resonance is possible which would transfer electrons from the hydroxyl to the carbonyl oxygen, and if there is a hydrogen bond, it must be weak. In 2-hydroxyphenacylamines, in line with currently accepted views (6), the hydrogen bond goes from the carbonyl oxygen to the phen-

[1] Part of this investigation was presented before the 116th meeting of the American Chemical Society at Atlantic City, September 1949.

olic oxygen rather than to the amino group. It must therefore be the hydrogen bond which stabilizes the 4-hydroxyphenacylamines.

Just as a negative charge on the carbonyl oxygen favors a relatively strong O—H—N hydrogen bond so, also, will a positive charge on the nitrogen. This case is realized in the ammonium-, acylamino-, and arylamino-ketones, all of which have positive N, either by ionization or by resonance. Since these classes of compounds as well as 4-hydroxyphenacylamines are stable, the conclusion appears warranted that in each case an O—H—N hydrogen bond forming a five-membered ring is the stabilizing factor.

Because the hydrogen bond pulls a proton closer to the O and away from the N, thus in effect transferring some of the negative charge from the O to the N, it must increase the basicity of those amino ketones where it operates. Therefore the basicities of several 4-hydroxy- and 3,4-dihydroxy-phenacylamines were determined in the hope of obtaining further information. The results of these measurements are shown in Table I.

TABLE I

BASICITY OF PHENACYLAMINES

R	4-HYDROXYPHENACYLAMINES[a] $K_B \times 10^7$	3,4-DIHYDROXYPHENACYLAMINES[b] $K_B \times 10^7$
H	11.1	5.5
CH_3	5.0	4.0
C_2H_5	5.9	2.3
n-C_3H_7	7.9	6.3
n-C_4H_9	35.4	3.3
iso-C_4H_9	5.5	3.0
tert-C_4H_9	7.9	3.2

[a] Formula: $HOC_6H_4COCH_2NHR$ [b] Formula: $(HO)_2C_6H_3COCH_2NHR$

There appears to be no correlation between these K_B values and the known relative electron-donor properties of the several alkyl groups. In particular it is at first sight quite inexplicable why in both series the primary amine is more basic than all but one of the alkylamines, and why the *n*-butylamine is outstandingly basic in one series but not in the other.

If, however, three-dimensional scale models of these molecules are constructed, a remarkable steric phenomenon emerges which provides a full explanation of the basicities recorded in the table. The models which were used for this purpose consisted of aluminum spheres ground to represent the known diameters of various atoms (7) on the scale $17\frac{1}{2}$ mm. to 1Å. The spheres could be connected by pegs and holes at the correct bond angles so that both the actual interatomic distances and free rotation around single bonds were realized in the models.

Since the K_B values were calculated from the K_A of the corresponding conjugate acids, the models were constructed with an ammonium rather than an amino group. Measurements on them showed that in the aminoketones the O—N distance varies between 2.65 Å and 3.76 Å as the parts of the side chain rotate

around its C—C bond. Perhaps more pertinent is the information that when O and N are in closest approach the distance between the O and the closest proton of the amino group is 2.13 Å; when O and N are farthest from each other, the corresponding O—H distance is 4.15 Å. Obviously no hydrogen bond can exist when the O and N are at their most distal position, not only because of the great distance involved but also because in this case the entire side chain is found between the O and the proton of the amino group. On the other hand, at their closest approach a hydrogen bond appears entirely reasonable; the O—N distance of 2.65 Å is less than corresponding distances in compounds in which hydrogen bonding is generally accepted such as water (8) or formic acid (9).

If one of the protons attached to the nitrogen is replaced by a methyl group, the model shows that the protons of the methyl group may actually touch the carbonyl oxygen. This is a phenomenon quite analogous to the one discussed by Dippy (10) for *n*-butyric acid. It should result in a partial dissipation of the

TABLE II

O—N AND O—H DISTANCES IN THE GROUP —$COCH_2NHR$ WHEN THE PROTONS OF THE TERMINAL CARBON ATOM OF R ARE IN CONTACT WITH THE OXYGEN OF THE CARBONYL GROUP

R	O—N (Å°)	O—H (Å°)
CH_3	2.75	3.69
C_2H_5 or *tert*-C_4H_9	2.77	2.90
n-C_3H_7 or iso-C_4H_9	2.94	2.64
n-C_4H_9	2.65	2.13

negative charge on the oxygen; more important, in order to permit the protons of the methyl group to touch the carbonyl oxygen the nitrogen must move slightly away from it—to a distance of 2.75 Å—and turn around so that the distance from the oxygen to the protons attached to the nitrogen is increased to 3.69 Å. Either way, the presence of the N-methyl group must result in a weakening of the hydrogen bond and in a corresponding decrease of basicity.

In similar fashion the O—N and O—H distances were measured on models of the other N-alkylated α-aminoketones with the terminal protons of the N-alkyl groups in contact with the ketonic oxygen. The results are shown in Table II. They show that in the *n*-butylamine (and only in it) the O—H—C bond actually strengthens the O—H—N bond by rigidly holding the amino group in the position most favorable for hydrogen bonding (O—N and O—H in maximum approach). Hence the maximum basicity of N-*n*-butyl-4-hydroxyphenacylamine.

If, as Table I shows, the N-*n*-butyl group has no such effect in the 3,4-dihydroxyphenacylamine series, the necessary conclusion is that the *meta*-hydroxyl counteracts the basicity-increasing effect of the carbonyl group. This it could do by competing with the carbonyl oxygen for the terminal protons of the butyl group. In fact, the model shows that these protons can strainlessly touch also the oxygen of the *meta*-hydroxyl in which case the nitrogen is at 3.46 Å and its protons at 3.58 Å from the carbonyl oxygen—distances quite unfavorable for hydrogen bonding.

It must be emphasized that it is not implied that the attraction between the oxygen and the protons of an alkyl group can destroy the N—H—O hydrogen bond. Certainly the N—H bond is more polar, hence a better proton-donor, than the C—H bond, and the N—H—O hydrogen bond must always be the most important effect, otherwise 4-hydroxyphenacylamines would not be stable; but the "Dippy effect" just discussed will interfere in a way which may be derived from scale models and is fully borne out by the measured basicities.

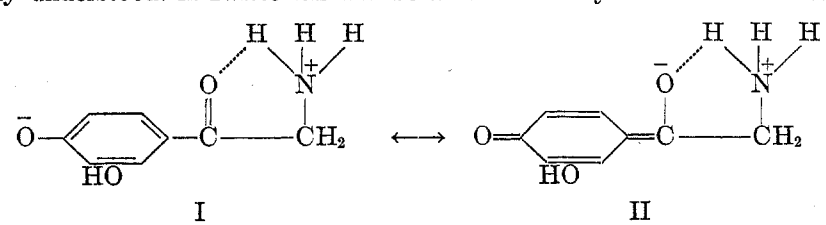
From the results reported so far the evidence appears to be strong in favor of the phenolic hydroxyl of 4-hydroxyphenacylamines being unusually acidic and their amino group being unusually basic. The question then arises quite naturally: should we not go one step further and assume reaction between the acidic hydroxyl and the basic amino group, resulting in a zwitterion, much as we do in amino acids?

It is not easy to give a decisive answer to this question but there are several points which may be interpreted in favor of a zwitterion structure.

To begin with, we have seen that if our interpretation of the steric effects shown by the models is correct (and its close correspondence with the results of the K_B measurements seems to indicate that it is) then the striking difference in basicity between N-*n*-butyl-4-hydroxyphenacylamine and N-*n*-butyl-3,4-dihydroxyphenacylamine is due to the mutual attraction of the terminal protons of the butyl group and the oxygen of the *meta*-hydroxyl group. But it is difficult to see how a phenolic oxygen could compete for these terminal protons with a ketonic oxygen of more than ordinary negativity. Therefore, our interpretation requires a structure in which the oxygen of the *meta*-hydroxyl is at least qualitatively of the same character as that of the CO group in the side chain.

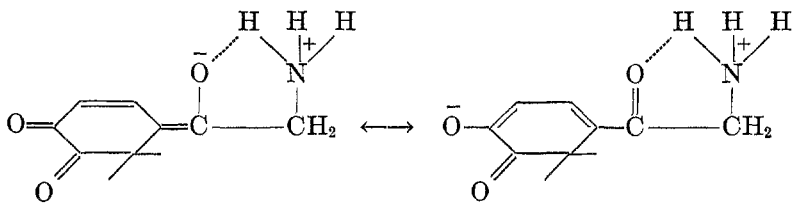
In this connection it is important that the 4-hydroxyphenacylamines are colorless, but the 3,4-dihydroxyphenacylamines are yellow. This color cannot be attributed to oxidative *o*-quinone formation because it disappears on adding acid: the salts of such bases are colorless. Also, epinine and epinephrine, compounds differing from N-methyl-3,4-dihydroxyphenacylamine (adrenalone) only in having a methylene and carbinol group, respectively, instead of the carbonyl group, are colorless bases although they are much more easily oxidized than adrenalone. The yellow color is thus characteristic of the 3,4-dihydroxyphenacylamine bases and has nothing to do with the easy oxidation of catechol derivatives. (It is noteworthy that all 4-hydroxyphenacylamines, and even *p*-hydroxyacetophenone, turn yellow in alkaline solution; on acidifying the color disappears).

The assumption of zwitterionic structure for the 4-hydroxyphenacylamine may perhaps provide an explanation for both phenomena which are otherwise not easily understood. A zwitterion will be a resonance hybrid of two structures:



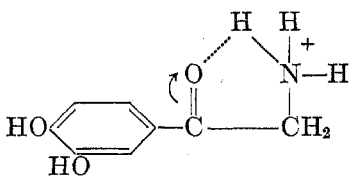
I II

of which I is favored by the aromaticity of the ring, II by lesser charge separation. We may therefore assume that the contribution of II is at least not negligible. The high acidity of *p*-hydroxyacetophenone, reported initially, shows that such resonance is important; it must be more so with support from a positive nitrogen which favors a strong negative charge on the ketonic oxygen. In this structure, however, the *meta*-hydroxyl is enolic, not phenolic, and the reduced aromaticity of the molecule will favor rearrangement to a ketonic structure. The resonance hybrid (I, II) may therefore be considered in tautomeric equilibrium with the resonance hybrid (III, IV):



III IV

Both III and IV show in the *meta* position a keto group whose oxygen, unlike a phenolic oxygen, is definitely negative as postulated above; and both structures show a system of four conjugated double bonds, accounting for the yellow color of the 3,4-dihydroxyphenacylamine bases. Addition of a proton will greatly favor structure I because it will tend to immobilize the electron pair of the *para*-hydroxyl whose resonance shift is responsible for the other structures. Hence the conjugate acid of the yellow bases is rather completely represented by the structure



which does not have the chromophoric arrangement of four non-aromatic conjugated double bonds.

A further piece of evidence in favor of zwitterions may perhaps be provided by a rather strange behavior on titration characteristic of the 4-hydroxyphenacylamines.

The *p*H curves obtained on titration are similar to the customary *p*H titration pattern whenever the dilution and the solubility of the aminoketones are great enough to permit the titrations to proceed entirely in a homogeneous solution. However, most such bases are rather insoluble in water, and these follow the usual pattern only when the bases are titrated with acid. On backtitrating the hydrochloride solutions with alkali, it was found that the *p*H curve coincides with the one obtained on titration with *HCl* on the acid side of neutralization but on further addition of alkali, the *p*H curve rises high above the acid-titration curve

(sometimes as much as two pH units higher) and stays up as long as supersaturation keeps the base dissolved. As soon as the base begins to precipitate, there is a discontinuity in the pH curve which drops sharply to a value close to the acid-titration curve, and during the remainder of the titration the two curves coincide rather well. The break in the alkali-titration curve on appearance of the precipitate is in sharp contrast with the acid titration where the pH curve continues smoothly downward at the point where the base goes completely into solution (Figure 1).

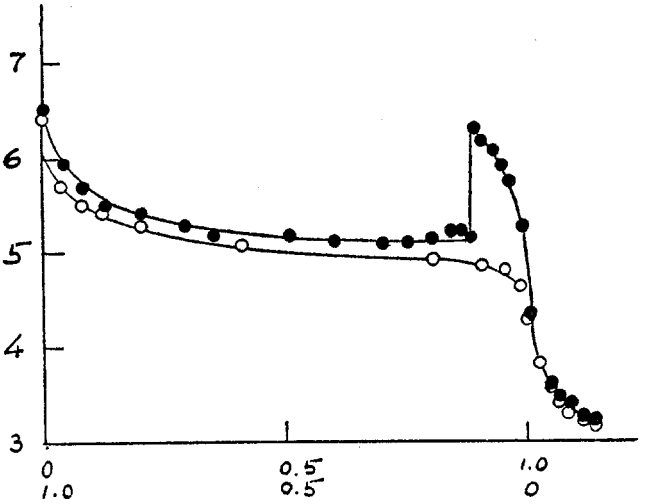


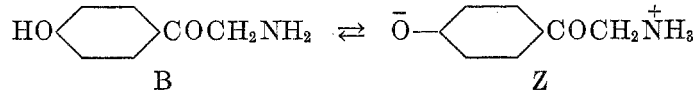
FIG. 1. ADRENALONE, MOLARITY 1/100. Titration of the base with HCl (○) and back titration with NaOH (●). pH units are shown along the y axis; along the x axis the upper row of figures indicates equivalents of HCl per mole of base, the lower row equivalents of NaOH per mole of hydrochloride. Crystallization of the base always coincides with the break in the titration curve.

It is easy to explain this behavior as a consequence of supersaturation: the equilibrium $BH^+ + H_2O \rightleftarrows B + H_3O^+$ is disturbed when supersaturation breaks and much of the base (B) precipitates out of the solution, therefore the reaction proceeds from left to right and $[H_3O^+]$ increases.

The question is whether this is the complete explanation. Supersaturation is not unusual and if no such behavior on pH titration was observed before it might perhaps be peculiar to the 4-hydroxyphenacylamines. In fact, epinine—which lacks the ketone group in the side chain but tends just as much to supersaturation as the 4-hydroxyphenacylamines—shows no break in the pH curve when titrated at the same concentration as adrenalone in Fig. 1; at a concentration twenty times as great there is a barely perceptible break which cannot be compared at all to the large pH drop in the aminoketones. Thus the ketone group appears to make an essential difference, and the following hypothesis might provide an additional explanation of the pH curve:

Solutions of p-hydroxyphenacylamines contain a tautomeric equilibrium mix-

ture of the base B and the zwitterion Z:



B Z

This equilibrium mixture is obtained at first when addition of alkali takes a proton from the phenol-ammonium cation (BH^+). However, solid *p*-hydroxyphenacylamines are assumed to be wholly zwitterionic because the close and orderly spatial arrangement of the elongated molecules brings the phenolic and amino groups close together and favors the transition of a proton. (The high melting points of these compounds are in excellent agreement with the assumption of zwitterions). Hence when solid—zwitterionic—base appears, the transition $Z_{aq} \rightarrow Z_s$ disturbs the equilibrium $B_{aq} \rightleftarrows Z_{aq}$, decreasing the concentration of Z_{aq} and forcing enough B_{aq} to change into Z_{aq} to maintain equilibrium.[2] This change is accompanied by a drop in *p*H since the ammonium group of Z is surely a stronger acid than the phenolic OH group of B. From then on throughout the buffering region titration with alkali occurs in the heterogeneous equilibrium $BH^+_{aq} \rightleftarrows B_{aq} \rightleftarrows Z_{aq} \rightleftarrows Z_s$, with only slowly rising *p*H.

The same equilibrium mixture obtains throughout the buffering region in the titration with acid and hence here, too, the solid phase, consisting of essentially acidic zwitterion, holds the *p*H down until dissolution occurs at the neutralization point where the *p*H, as usual drops steeply to even lower values.

It is remarkable that while epinine hardly shows any break in the titration curve, epinephrine—the alcohol to which N-methyl-3,4-dihydroxyphenacylamine can be reduced—shows it as strongly as the ketones themselves. If therefore our hypothesis on the O—H—N hydrogen bond and the zwitterionic structure of solid 4-hydroxyphenacylamines is correct, the break in the titration curve of epinephrine would mean that this compound, too, is zwitterionic and has an O—H—N hydrogen bond, caused not—as in the ketones—by a negative resonance charge on the oxygen, but only by its greater electronegativity supported perhaps by the inductive effect of the electron-rich ring. If there were other indications of an O—H—N hydrogen bond in epinephrine or other 2-aminoalcohols, this would provide additional evidence in favor of the views expressed above.

EXPERIMENTAL

p-Hydroxyacetophenone was prepared by recrystallizing the technical product (Dow Chemical Co.) repeatedly from water with charcoal until a constant melting point (109–110° uncorr.) was attained.

3,4-Dihydroxyphenacylamine and *adrenalone* were synthesized essentially following Stolz' method (12). Because of the insolubility of the bases, the hydrochlorides were recrystallized from dilute ethanol until the melting point was constant at 259° for 3,4-dihydroxyphenacylamine hydrochloride and 248° for adrenalone hydrochloride (both uncorr.);

[2] This is entirely analogous to what happens in the equilibrium mixture of α- and β-lactose in a supersaturated solution when crystallization begins, as reported by Hudson (11). The author wishes to express his thanks to Dr. Hudson for bringing this paper to his attention.

then the bases were obtained by adding a slight excess of ammonia to the aqueous solutions of the hydrochlorides.

All other aminoketone hydrochlorides were kindly supplied by Dr. B. L. Zenitz of the Sterling-Winthrop Research Institute, Rensselaer, N. Y., for which the author wishes to express his appreciation. He likewise wishes to thank Dr. D. S. Searle of Burroughs-Wellcome & Co., Tuckahoe, N. Y., for having helped with a supply of epinine.

Epinephrine was prepared by catalytic hydrogenation of adrenalone hydrochloride dissolved in water, with palladium-charcoal catalyst. When the absorption of hydrogen had stopped, the solution was filtered and the epinephrine precipitated by adding a slight excess of ammonia. It was then filtered, washed thoroughly with water and alcohol, and dried in the dark in a vacuum-desiccator.

The K_A of *p*-hydroxyacetophenone was calculated from the *p*H of a 0.50% solution in water, the K_B's of the aminoketones from the *p*H's of $M/100$ solutions of their hydrochlorides in water. This procedure was chosen because of the insolubility of many of the aminoketones. It yielded the K_A values of the conjugate acids of the several bases, from which $K_B = K_W/K_A$ was calculated.

All *p*H measurements were carried out with a Beckman Model G *p*H-meter with glass and calomel electrodes.

In the *p*H titrations a total volume of 200–500 ml. was used and titrated with 2 *N* HCl and NaOH. Thus even at the highest concentrations ($M/5$) the titration changed the initial volume of the solution only 10% one way or another, a difference which has no appreciable influence on the results.

Conductivity water was used throughout.

SUMMARY

1. The acidity of *p*-hydroxyacetophenone was measured and found to be more than twenty times as great as that of phenol. From this it is concluded that in this and related compounds a resonance form is important in which the ketonic oxygen carries an unusually strong negative charge.

2. If the α-position of the side chain of *p*-hydroxyacetophenone carries a primary or secondary amino group a hydrogen bond is assumed between this amino group and the highly negative ketonic oxygen. Such a hydrogen bond is called upon to explain the paradoxical stability of 4-hydroxyphenacylamines (other primary and secondary α-aminoketones are unstable) and the general stability of α-aminoketone derivatives, all of which have positive nitrogen.

3. The K_B's of a number of 4-hydroxyphenacylamines were measured and found at variance with the known electron-donor properties of the several alkyl groups but in agreement with expected steric influences on the hypothetical hydrogen bond.

4. The possibility of a zwitterion structure of 4-hydroxyphenacylamines is considered and support for it is found in certain of the K_B values, in the yellow color of the 3,4-dihydroxyphenacylamines, and in the behavior of 4-hydroxyphenacylamines on *p*H titration.

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