from alcohol on cooling and was therefore more easily purified. It was a yellow solid soluble in benzene, acetone, or chloroform, insoluble in sodium hydroxide and sparingly soluble in cold alcohol. Formula, C_6H_5—CO—$C_6H_4N:CH$—C_6H_4OH.

Found: N, 4.84. Calculated, 4.65.

β-Naphthol-α-methylol-para-aminobenzohydrol.—Equivalent quantities of para-aminobenzohydrol and β-naphthol aldehyde were dissolved in a small quantity of 95 per cent. alcohol and boiled for one hour. On cooling, a yellow crystallin substance separated out which was readily soluble in alcohol, acetone, alkalis, or hot benzene, but crystallized from the latter on cooling in a fair state of purity. Its melting point was found to be 167.5°. Formula, C_6H_5—CHOH—$C_6H_4N:CH$—$C_{10}H_6OH$.

Found: N, 3.98. Calculated, 3.98.

The corresponding ketone, prepared in a similar way with para-aminobenzophenone, was a fine yellow crystallin substance melting at 152°. It was insoluble in alkalies, in this respect differing from the hydrol derivative.

It was easily purified by crystallizing from hot methyl alcohol. Formula, C_6H_5CO—$C_6H_4N = CH$—$C_{10}H_6OH$.

Found: N, 3.90. Calculated, 3.99.

The insolubility of this last compound in alkalies would be expected as it fulfils both the conditions found necessary[1] to produce this phenomenon in other cases—the free hydroxyl group is ortho to a large side chain, and another substituting group is present on the benzene ring to which the hydroxyl is attached—in this case the C_4H_4 of naphthalene which has been found to be specially effective; but the addition compound of salicylaldehyde and para-aminobenzophenone does not conform to the second of these conditions and its insolubility in alkalies is therefore not in harmony with the general rule. Only two or three other exceptions to the above rule have been found. This substance therefore will be studied further in this laboratory.

[Contribution from the Research Laboratory, Roosevelt Hospital, New York.]

PHENOLPHTHALEIN AND ITS COLORLESS SALTS.

(Potassium Salt of Phenolphthalic Acid.)

By P. A. Kober and J. Theodore Marshall.

Received November 17, 1910.

Contents.—(1) Introduction. (2) The Study of Speed of Reaction: (*a*) Colorimetrically; (*b*) Electrolytically. (3) The Study of Concentrations at Equilib-

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[1] Torrey and Kipper, This Journal, **30**, 841 (1908).

rium. (4) The Isolation and Analysis of the Colorless Salt (Tripotassium Phenolphthalate). (5) Discussion of Results. (6) Summary. (7) Addendum.

(1) Introduction.

While studying different chemical tests for blood, we found that certain substances inhibited[1] the reactions. A futher investigation of this phenomenon, using phenolphthalein as suggested by Kastle,[2] showed that the color of a standard solution of phenolphthalein faded, even after the possible action of carbon dioxide had been excluded. This fact, noted by McCoy,[3] Acree,[4] Kastle, and others, had not been thoroughly investigated from a quantitative point of view, so it was with the object of determining the exact reaction and extent of the fading under various conditions, that these experiments were undertaken.

Believing that the colorless salts existed in the presence of free alkali only, and consequently could not be isolated, we attempted to solve the problem by studying the rate of reaction, and the concentrations at equilibrium. When our experiments were almost completed, we read the excellent review of the phenolphthalein question, given by Curtiss,[5] in his article on the theory of color in organic compounds. Finding our results to be in harmony with the ideas expressed in his article, we intended publishing our work, both as a confirmation of previous results, and also to show the effect of fading on blood tests.

Attempts had been made, both here and abroad, to isolate the heretofore hypothetical colorless salt, but without success. Since we have been able to obtain a precipitate of the salt, in an alkaline solution and have developed a method of purification which yields an abundance of beautiful colorless crystals of this salt, we believe the publication of all our experiments is perfectly justifiable, although our results are in part repetitions of previous experimentation. It may be mentioned, had we known the field to have received so much attention and disputation, we should not have entered it, but considering it our duty to do so now, we do not hesitate to submit the following results.

(2) The Study of Speed of Reaction.

In order to study the rate of fading with the Duboscq colorimeter we found it necessary to establish a permanent standard for comparison

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[1] Kober, Lyle, and Marshall, *J. Biol. Chem.*, July, 1910. Since the publication of this note on the inhibitive action of tannic and gallic acids, on blood tests, we found that nearly all the polyhydric phenols and polyhydroxymonocarboxylic phenols, as pyrocatechol, resorcinol, hydroquinone, pyrogallol, phloroglucinol; protocatechuic, 2,4-dioxybenzoic, gentisinic, gallic and tannic acids; and other substances, like indole and skatole, as well as uric acid, inhibit the reactions. The phenomenon is being studied in this laboratory with the view of eventually obtaining a satisfactory blood reagent.

[2] Kastle, Pub. Health and Marine Hosp. Service, *Bull.* 59.

[3] McCoy, *Am. Chem. J.*, 31, 503 (1904).

[4] Acree, *Ibid.*, 42, 122.

[5] Curtiss, THIS JOURNAL, 32, 795.

as the color of the standard phenolphthalein solution varied with the slightest change of alkalinity. A set of Lovibond tints[1] fulfilled this requirement.

Our first experiment was to follow the change in a determinable amount of color, after an excess of alkali had been added. For this purpose 2.000×10^{-6} gram-molecules (0.00064 g.) phenolphthalein was dissolved in 100 cc. of water after 1.093×10^{-2} gram-molecules of alkali had been added. At various intervals the amount of color was determined, and plotted against time. The points obtained indicated that the fading followed a regular curve resembling that of an irreversible monomolecular reaction. The constants of the equation, however, as shown below, were not good. The color never faded entirely, but seemed to come to an equilibrium. When the values were substituted in a formula for an opposing unimolecular reaction; $1/t \log E/E - X = K_1 + K_2$, a fairly good constant was obtained, although no effort was made to keep the temperature constant.

TABLE I.

Time.	X.	Irreversible. K.	Balanced reaction. $K_1 + K_2$.
0	0	....	....
1	4.5	0.0341	0.0334
3	19.0	0.0340	0.0370
6	34.0	0.0330	0.0358
10	50.0	0.0328	0.0366
15	66.5	0.0316	0.0362
20	76.4	0.0314	0.0371
30	86.5	0.0290	0.0380
40	90.0	0.0260	0.0366
45	91.0	0.0232	0.0365

At equilibrium $X = 93.2$ $1 - X = 6.8$ $K_1/K_2 = 93.2/6.8$

According to this formula the constant of the direct reaction is 0.0341, and that of the reverse reaction 0.00238. (The above values hold for this amount of alkali and dilution only.)

That alkali actually takes part in the fading as a chemical reaction was demonstrated by studying the change in conductivity. A slight change of alkali cannot be very accurately determined as the conductivity of the alkaline solution is very high. Notwithstanding this, by carefully regulating the temperature of the solution, a curve of conductivity values was obtained which approximated that of a dimolecular reversible reaction.

After isolating the tribasic salt, we attempted to study the reverse action alone, by neutralizing the alkali as rapidly as formed, but here encountered a new difficulty: *i. e.*, on the addition of a weak acid (acetic) to an aqueous solution of the tribasic salt, the acid was neutralized with extreme rapidity until two gram-molecules of acid had been added. After

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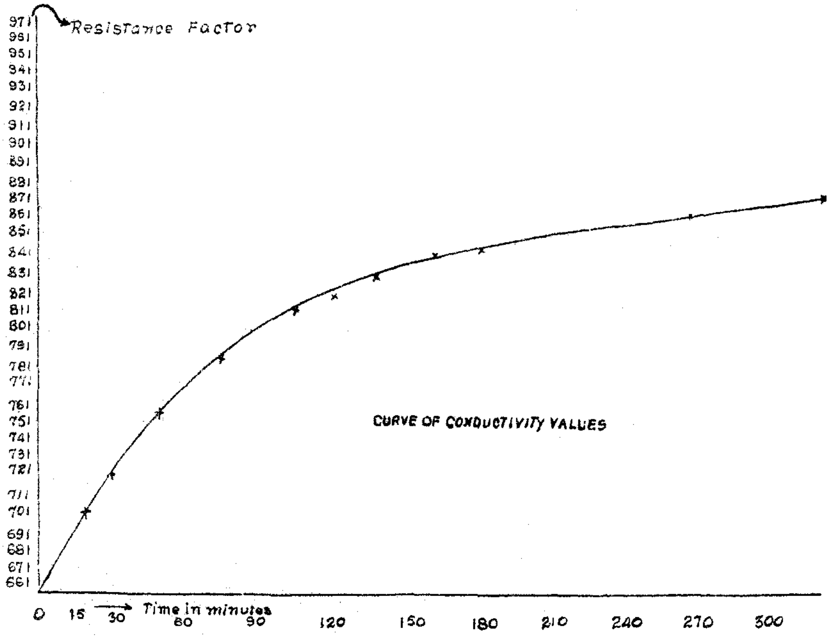
[1] Eimer & Amend, *Lovibond Tints*, 50 (1180 and Z 3.1 (200)).

this point an apparently new reaction began, and the monobasic colorless salt of phenolphthalic acid decomposed very slowly.

As the number of molecules that enter into a reaction can be more definitly determined from conditions at equilibrium than from the study of the speed of reaction, a series of equilibrium experiments was made in which the concentrations of the constituents were varied.



(3) The Study of Concentrations at Equilibrium.

0.001258 g. phenolphthalein was dissolved in varying amounts of 0.450 *N* KOH and made up to 100 cc. At room temperature we found:

TABLE II.

Color, per cent. (*a*).	Cc. KOH (*b*).	Colorless, per cent. (*c*).	Constant = *a* × *b*/*c*.
41.7	3	58.3	21.8
37.1	4	62.9	23.6
30.6	5	69.4	22.1
25.1	7	74.9	23.5
19.6	10	80.4	24.4
13.2	15	86.8	22.8
8.85	20	91.1	19.6
7.06	25	92.9	19.0
4.70	35	95.3	17.3.

The slight decrease of the constant in the first part of the series may be attributed to the absorption of carbon dioxide during the measurements, and to hydrolysis of the dibasic salt. The lowering of the constant at the end of the series is as yet unexplained. Two hypotheses may be brought forward, but definit proof of their correctness is lacking (see Discussion).

When the water concentrations were changed, the amount of alkali and of phenolphthalein being kept constant, the following values were obtained:

TABLE III.

Water conc. (d).	$a \times b/c \times d = K$.	Water conc. (d).	$a \times b/c \times d = K$.
1	6.35	1	6.37
2	6.65	2	6.24
1	6.45	4	5.18
2	5.87		

The great difficulty encountered here was the measurement of faintly colored solutions.

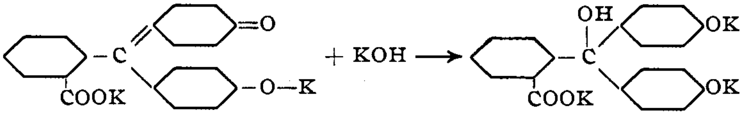
Assuming that it is not a dissociation phenomenon, these equilibrium studies prove that water takes part in the reaction, and consequently water should be included in the equation. Our experiments show unmistakably that one molecule of colored salt combines with another molecule of alkali to form a colorless compound; and that one molecule of water enters into the reverse reaction. As the colored salt, isolated by Meyer and Spengler, was found by them to be dibasic, the colorless salt must then be, as suggested by Green and Perkin, the tribasic salt of phenolphthalic acid. We also prepared the red salt in two different ways and found it to be essentially dibasic.

A definit amount of standard alkali was treated with a weighed portion of phenolphthalein. After standing, the undissolved portion was filtered, dried and weighed. From these weights the following data were obtained:

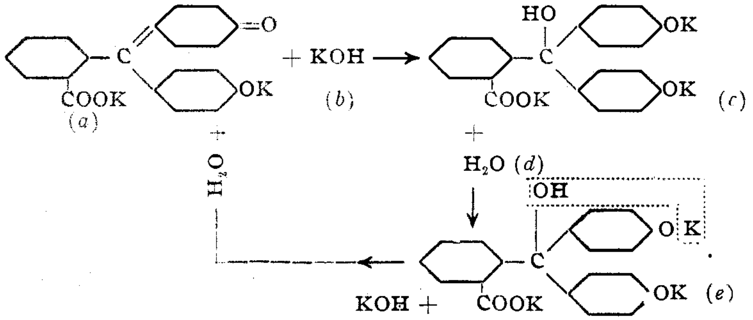
Phenolphthalein.	Alkali.	Residue.	Theoretical (for dibasic).
1.0057 g.	13.80 cc. $N/10$	0.784 g.	0.786 g.
2.0005	34.50 cc. $N/10$	1.444	1.450
1.380	43.40 cc. $N/10$	0.675	0.695

The discrepancy between the theoretical and the actual amounts is due no doubt to hydrolysis and to the solubility of free phenolphthalein in the water used for washing the residues.

From the above data it may be readily seen that the tribasic salt of phenolphthalic acid is formed from the red compound by the addition of one molecule of alkali, as shown structurally below:



This equation does not indicate the way in which water enters the reverse reaction. As will be discussed in the summary, this phenomenon may be due to dissociation, and therefore may not require a chemical explanation. The balanced reaction, written to include water, appears to us as follows:



In order that this equation may fit the formulas and data given elsewhere in this paper, compound "*e*" is assumed to split up into "*a*" very rapidly. This assumption is warranted by the fact that phenolphthalic acid cannot be readily isolated by neutralizing its potassium salt in aqueous solution, even at —10°.

The following studies corroborate our series No. 3. Varying amounts of phenolphthalein were dissolved in 4.50 *N*/10 KOH and made up to 100 cc. At room temperature the following values were found:

Phenolphthalein.	Colored salt (*a*).	Cc. KOH (*b*).	Colorless salt (*c*).	Water (*d*).	K = *a.b/c.d.*
0.229 g.	25.4 per cent.	24.50	74.6 per cent.	100	83
0.307	32.1 per cent.	18.00	67.9 per cent.	100	84
0.395	43.0 per cent.	11.95	57.0 per cent.	100	90
		.....			
0.229	0.0060 gram	18.00	0.2230 gram	10	48
0.229	0.0148 gram	18.25	0.2142 gram	25	50
0.229	0.0530 gram	19.55	0.1760 gram	100	54
0.229	0.0289 gram	18.75	0.2000 gram	50	59
0.229	0.0907 gram	20.85	0.1383 gram	250	55

In these experiments the amount of alkali was calculated as the amount which remained after allowing for that portion in combination with dibasic and tribasic phenolphthalein. The temperature was subject to the usual variations of room temperature.

The equation above, which may also be written in the ionic form, permits the use at equilibrium of $a.b/c.d = K$ when the reverse reactions are assumed to be very slow or nil, and the action almost exclusively cyclic.

(4) The Isolation and Analysis of the Colorless Salt (Tripotassium Phenolphthalate).

A priori, a salt containing several atoms of potassium replacing the hydrogen of the phenol group would have properties similar to those of an alkali. It would be readily soluble in water, returning in part to the colored salt, soluble in alcohol with the splitting off of alkali to form alkaline alcoholates and the colored compound, but insoluble in ether and benzene, etc. In short, we believed the colorless salt would decompose into the colored as soon as excess alkali was removed; and for this reason we did not make any systematic attempt to isolate it.

Accidentally,[1] however, we found certain conditions under which a copious microcrystallin precipitate of the salt could be obtained. Upon microscopic examination, the crystals are revealed as colorless rhomboidal plates, which rapidly assume small, discrete, superficial areas of color, giving the mass, when viewed macroscopically, a pinkish tinge. On careful heating they lose water and their crystallin form, taking on an intense opaque purple color (the dibasic salt; see salt of Mayer[2] and Spengler) with a bronze iridescence, simulating in luster crystals of potassium permanganate. They retain their purple shade on cooling in the absence of moisture, but on exposure to air fade, by passing through various tones of red, to lighter colors, after which they deliquesce. Under ordinary conditions, the almost colorless salt is fairly stable, showing a slight pink tinge only. The crystals are insoluble in ether, benzene or acetone, slightly soluble in amyl alcohol, but in water or ethyl alcohol, they dissolve rapidly, and with the production of very little color, especially if the temperature be kept at 0°. Upon long standing or boiling, however, the aqueous solution develops intense color.

After several purifications, the salt was subjected to different methods of analysis, the results being consistent with the formula $C_{20}H_{12}O_4K_3(OH) + 5H_2O$.

Found: C, 44.40; H, 4.37; K (six determinations), 21.77.
Calculated: C, 44.38; H, 4.28; K, 21.73.

Although the average of the determinations of potassium was in close agreement with the theoretical, the individual values varied considerably, as illustrated by the determinations enumerated below.

As a confirmation of our work, we obtained the theoretical amount of phenolphthalein ($C_{20}H_{14}O_4$) from our colorless salt both by precipitation, and by comparing the amount of color with that of a freshly prepared standard solution of phenolphthalein. In both cases the results showed that the salt, on long standing in acid solution or on heating in an acid solution, yielded the theoretical amount of phenolphthalein.

0.1445 gram salt lost, upon heating at 150° C. in air oven, 0.014 gram = 9.7 per cent.[3] Titrated with 0.1 *N* acid: required 7.6 cc. = 0.0297 gram of potassium,

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[1] It is our intention to publish the details of the isolation and purification of the salt, together with other items on this subject, in a future paper.

[2] Meyer and Spengler, *Ber.*, **38**, 1318; 41, 2446.

[3] This amount of water represents about three molecules of water of crystallization only, the remaining two being probably in combination with alkali, as potassium hydrate.

= 20.6 per cent.[1] The solution was boiled, rendered alkaline, and diluted to 250 cc.; and the amount of color compared with a solution of standard color. This gave a molecular weight of 548, the theoretical being 540.

1.103 grams of the salt; dissolved in water; titrated with 0.1 N hydrochloric acid and heated to split off all the alkali. Total amount of acid required: 61.6 cc.; equivalent to 22.07 per cent. of potassium. The precipitate of phenolphthalein was collected on a Gooch crucible and weighed. The filtrate was evaporated and weighed as potassium chloride.

	Found.	Theoretical.
Phenolphthalein, 0.6427 gram	58.3	58.8
Potassium, as KCl, 0.4679 gram	22.2	21.7
Hydroxyl and water (by difference)	19.5	19.5

The preceding results leave no doubt in our minds but that our compound is the tribasic salt of phenolphthalic acid. The isolation of *phenolphthalic acid*, or any of its salts, except the tribasic, presents great difficulties, but we believe that we have developed a method of preparing the monobasic salt. This method has not, as yet, however, been successful as to the process of purification.

(5) Discussion of Results.

Baeyer[2] showed that phenolphthalein has a lactone structure, and it was assumed that sodium hydroxide split the lactone ring and neutralized the resulting acid group. In 1893, Friedlander[3] assumed that the red salt was dibasic, but not until 1905 was it actually demonstrated[4] that it contained two atoms of alkali. Since then, nearly all investigators have agreed that the alkali combines with phenolphthalein with the resulting formation of a quinoid group. This latter is assumed to be the chromophore,[5] or at least a part of it. Meyer and Marx[6] demonstrated that the production of color was incident to a molecular rearrangement with the formation of this group.

According to the preceding explanation, the disappearance of color, upon the addition of an excess of alkali, was assumed to be caused by the destruction of the quinoid ring. As this was believed to occur in strong alkali only, most investigators considered the fading of the colored salt, in dilute alkaline solution, to be due solely to hydrolysis. *Our figures, however, show that hydration begins with the smallest amount of alkali.*

Baeyer, K. Meyer, and A. Hantzsch[7] believed that the colorless salt was formed by the addition of another molecule of alkali. Our experi-

[1] This titration is low, because it was not until later that we realized that it required longer than a few hours for the last traces of tribasic salt to be decomposed.

[2] Baeyer, *Ann.*, **202** (1880).

[3] Friedlander, *Ber.*, **26**, 172.

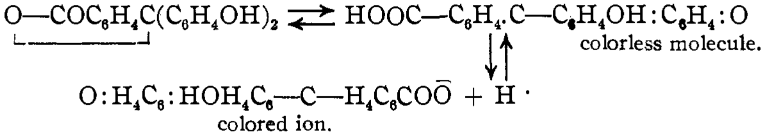
[4] Meyer and Spengler, *Ibid.*, **38**, 1318; **41**, 2446.

[5] Stieglitz and Acree, *Am. Chem. J.*, **39**, 543, 650 and 651.

[6] Meyer and Marx, *Ber.*, **40**, 3603.

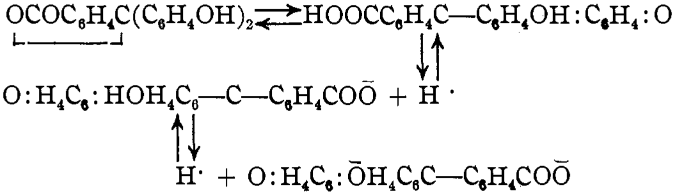
[7] A. Hantzsch, *Ber.*, **40**, 3481 (1907).

ments and analysis of this new compound point unmistakably to this view. In fact all investigators of the subject, except Ostwald and a few others, who believe it to be a dissociation phenomenon, agree that the colorless modification is due to the addition of alkali. Rohland holds, however, that the ions are colored and the associated molecules colorless; Acree on the other hand does not believe it to be dissociation because the fading requires time. We can conceive of dissociation not occurring instantaneously, hence the time factor would not, of necessity, be a proof against dissociation. The fact that the color fades to an equilibrium, and that the fading is a function of the amount of alkali, would point to the ionization theory. According to the supporters of the ionization hypothesis, the reaction or dissociation is as follows:



$$\underbrace{O{-}COC_6H_4}C(C_6H_4OH)_2 \rightleftharpoons HOOC{-}C_6H_4.C{-}C_6H_4OH:C_6H_4:O \quad \text{colorless molecule.}$$
$$\downarrow\uparrow$$
$$\underset{\text{colored ion.}}{O:H_4C_6:HOH_4C_6{-}C{-}H_4C_6CO\bar{O}} + H^{\cdot}$$

According to the work of Nietzki[1] and Burckhardt, Nietzki[2] and Schroeter, Green,[3] and King,[3] Bistrzyckis,[4] and others, the color can not be ascribed to the ion, but to the quinoid character of the compound. Stieglitz, and also Meyer and Spengler, pointed out that the dry dibasic salt is highly colored. We have prepared this colored compound from absolute alcohol and sodium ethylate and found it to have intense color and metallic luster. According to Stieglitz, McCoy, and Hildebrand the indicator functionates as monobasic acid, but Wegscheider[5] employed the following equation (dibasic acid) in determining the dissociation of phenolphthalein



$$\underbrace{OCOC_6H_4}C(C_6H_4OH)_2 \rightleftharpoons HOOCC_6H_4C{-}C_6H_4OH:C_6H_4:O$$
$$\downarrow\uparrow$$
$$O:H_4C_6:HOH_4C_6{-}C{-}C_6H_4CO\bar{O} + H^{\cdot}$$
$$\uparrow\downarrow$$
$$H^{\cdot} + O:H_4C_6:\bar{O}H_4C_6C{-}C_6H_4CO\bar{O}$$

We believe that the conflicting results obtained by previous workers[6] in determining, colorimetrically, the dissociation of phenolphthalein are due, in a large measure, to the neglect of hydration. The amount of color appears, therefore, to depend on two factors, *i. e.*, dissociation or hydrolysis of the colored salt, and hydration. If we consider the hy-

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[1] Nietzki and Burckhardt, *Ber.*, 30, 172–178.

[2] Nietzki and Schroeter, *Ibid.*, 28, 48.

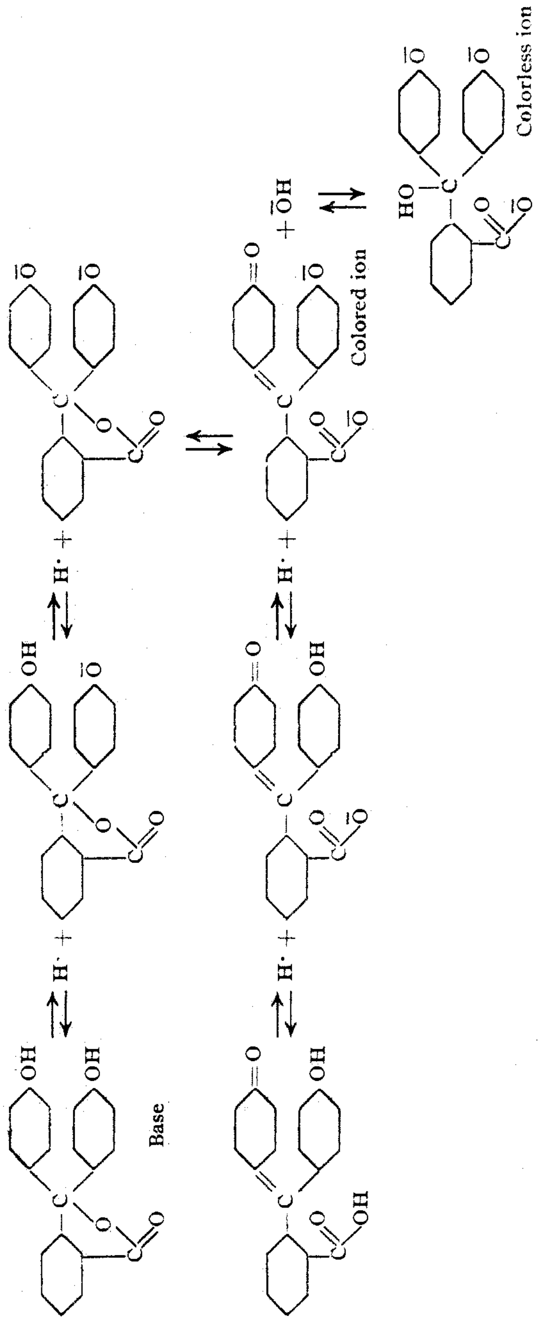
[3] Green and King, *Ibid.*, 40, 3724.

[4] Bistrzyckis, *Ber.*, 36, 3558.

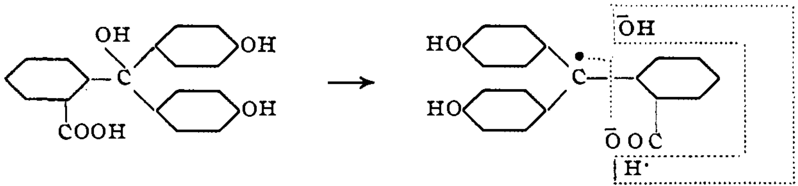
[5] Wegscheider, *Z. Elektrochem.*, 14, 510 (1904).

[6] Quoted by A. A. Noyes, This Journal, 32, 816.

dration from the ionic view-point, phenolphthalein on solution in alkali may be represented as passing through the following stages:



According to this method of writing the equation, phenolphthalic acid has a strongly alkaline group which, when dissociated, neutralizes the acid group to form the lactone, thus:



(6) Summary.

We have shown that beside *the fading, due to hydrolysis of the dibasic phenolphthalein, there is also that produced by hydration* (with the formation of alkaline phenolphthalates) and that therefore phenolphthalein is not an accurate colorimetric standard.

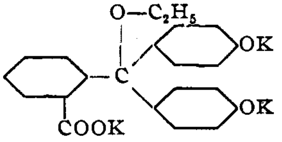
We have isolated and described, for the first time, a salt of phenolphthalic acid.

In conclusion we wish to express our thanks to Dr. H. C. Fleming and to Dr. W. G. Lyle, for their interest and encouragement in this work.

(7) Addendum.

We have also prepared the corresponding sodium salt, which crystallizes in cubes, and is considerably more soluble than the potassium derivative, but otherwise very similar. In order to see that the physiological action of our salts were different from other phenolphthalein derivatives, we submitted to Professor Abel, of Johns Hopkins University, some of our potassium compound. Professor Abel, who has most kindly studied its behavior when injected subcutaneously in dogs, found that there was little evidence of local pain or swelling at the point of injection, contrary to the action of the other salts of phenolphthalein and that it produced purgation. For these reasons, we are hopeful that it will fill the need that exists for a hypodermic purgative.

Our attention has been called to the German Patent 223,968, granted to Farbenfabriken v. Baeyer and Co., August 7, 1910, for *weakly colored, alkaline salts of phenolphthalein*, having useful pharmacological properties. Surmising only from the preparation from alkali alcoholates and the evolution of alcohol upon heating, these compounds are not simple salts of phenolphthalic acid, but ethyl derivatives as



It is obvious from the analysis of our salt that it was not prepared from alcoholates, but from aqueous solutions. Furthermore, we obtained large amounts of *perfectly colorless crystals*, which have remained unchanged for several months.

THE BASIC PROPERTIES OF OXYGEN: COMPOUNDS OF THE HALOGEN ACIDS WITH BENZENE DERIVATIVES CONTAINING OXYGEN

By O. Maass and D. McIntosh.

Received October 24, 1910.

In a paper on the basic properties of oxygen[1] von Baeyer and Villiger say: "While the substitution of positive groups, such as the alkyls, for the hydrogen in water makes the oxygen basic this is not the case with negative groups like phenyl. Phenyl, benzophenone, etc., do not give salts with acids. This is in full agreement with the behavior of ammonia derivatives, etc."

This generalization is not justifiable, for we shall show in this paper that benzophenone and other oxygen substances containing the phenyl group form complexes almost as readily as do ether, ketone,[2] etc.

Archibald[3] has made an extended study of the electrical conductance of organic compounds dissolved in the halogen hydrides, and in our effort to produce additive compounds we have been largely guided by his results; for it appears almost certain that conduction of organic substances in liquefied hydrobromic or hydrochloric acid is brought about by their union with the acid and the subsequent ionization of the compound. High conducting power in general means the formation of a large amount of the compound, and under proper conditions these addition products may be separated and analyzed.

Experiments with Hydrogen Bromide.—Nitrobenzene, phenol, anisol, phthalic acid, hydroquinone, and pyrogallol are only slightly soluble in liquefied hydrobromic acid, and under the conditions of experiment give no compounds. Benzoin, the cresols, thymol, salicylic acid, naphthol and benzyl alcohol are soluble and probably form compounds in solution, which, however, could not be separated, Resorcinol, benzophenone and benzoic acid give compounds which crystallize readily. They are all colorless substances with sharp melting points well above that of hydrobromic acid (— 86°) and they form supersaturated solutions.

Resorcinol compound, melts —71°; analyses—sample I, 77.8 and 76.8 per cent. acid; sample II, 75.6 and 77.4 per cent. acid. $C_6H_4(OH)_2$ 4HBr contains 74.6 per cent. acid.

Benzoic acid compound, melts —44°, 56.7, 59.0, 56.4 per cent. acid was found. $C_7H_6O_{22}HBr$ contains 57.2 per cent.

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[1] *Ber.*, 33, 1438 (1900).

[2] Walker, McIntosh and Archibald, *J. Chem. Soc.*, 85, 1098 (1904). Vorländer, *Ann.*, 341, 1 (1905).

[3] This Journal, 29, 665, 1416 (1907).