where C is concentration in weight per cent. of $Li_2Cr_2O_7\cdot 2H_2O$, with an average error of 0.0006 in the density. These data are in substantial agreement with those of Heydweiller,[4] which cover the range up to 23%, when the temperature difference is taken into consideration.

Solubility in Water.—This was determined by agitating about 2 liters of solution with an excess of the solid phase in a covered container at a constant temperature provided by an immersion heater and a vapor-mercury sensitive element. After reaching equilibrium (about six hours) a sample of the clear solution was removed by means of a sintered glass funnel and analyzed. The results given are the average of duplicate analyses for chromate on each of two samples, which checked with an average error of 0.04%. The value for 0.8° was obtained by surrounding the solution container with crushed ice, and represents an average of temperatures varying from 0.6 to 1.0°. The following data were obtained:

Temp., °C.	Soly., % by weight $Li_2Cr_2O_7\cdot 2H_2O$	Temp., °C.	Soly., % by weight $Li_2Cr_2O_7\cdot 2H_2O$
0.8	62.36	70.0	69.49
30.0	65.11[a]	80.0	70.76
40.0	66.08	90.0	72.26
50.0	67.28	100.0	73.55
60.0	68.39		

[a] Schreinemakers' data[3] at 30° give 65.4% $Li_2Cr_2O_7\cdot 2H_2O$ for the solubility.

These data, when plotted, deviate an average of 0.06% from the empirical equation: $S = 62.18 + 0.0890t + 0.000243t^2$, where S is solubility in weight per cent. and t is temperature in degrees C. The maximum deviation is 0.12%.

Freezing Point of Solutions.—Five hundred milliliter portions of analyzed solutions were cooled in an insulated container by means of solid carbon dioxide and alcohol. Time-temperature heating and cooling curves were employed to determine the ice-point for each solution, and these data further checked by observation of the appearance and disappearance of ice-crystals. The following data were obtained:

% $Li_2Cr_2O_7\cdot 2H_2O$ by weight	Ice point, °C.	% $Li_2Cr_2O_7\cdot 2H_2O$ by weight	Ice point, °C.
0.0	0.0	41.10	−24.0
20.14	− 6.2	47.39	−35.4
29.97	−12.0	52.32	−49.8
34.82	−17.2	57.53	No crystallization at −60

A smooth curve may be drawn through these points with an average deviation of 0.4°.

Eutectic Point.—Facilities did not permit investigation of the system below −60°. Graphical analysis indicates the eutectic composition to be close to 56.5% $Li_2Cr_2O_7\cdot 2H_2O$ and the eutectic temperature below −70°.

Solubility in Organic Liquids.—Lithium dichromate dihydrate is insoluble in ether, carbon tetrachloride and hydrocarbon solvents. It dissolves in ethyl alcohol to the extent of about 20 g. per 100 ml. of solvent at room temperature. No exact measurement is possible because of the rapid oxidation of the alcohol and reduction of the dichromate. In acetone solution occurs at first, then the dichromate decomposes with precipitation of yellow lithium chromate.

Summary

1. Lithium dichromate dihydrate has been prepared and shown to consist of red-orange crystalline plates when pure.
2. Its density, solubility and behavior on heating have been described.
3. Data have also been presented giving the density and freezing point of aqueous solutions, and the eutectic composition and temperature estimated.
4. The solubility in common organic liquids has been qualitatively examined.

BALTIMORE, MARYLAND RECEIVED SEPTEMBER 25, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Colorimetric Determination of Iron with 4-Hydroxybiphenyl-3-carboxylic Acid[1]

BY JOHN H. YOE AND AUBREY E. HARVEY, JR.[2]

As early as 1834,[3,4,5] the color reactions between ferric ions and phenolic derivatives were observed and used as a qualitative test for the aromatic hydroxyl group. Salicylic acid was the first phenol to be used for the detection of ferric ions,[6,7,8,9] and for its quantitative determination.[10–16] Derivatives of salicylic acid which have been used as quantitative colorimetric reagents for iron are: sulfosalicylic acid,[17,18,19] salicylaldoxime,[20] and β-resorcylic acid.[21]

This paper introduces 4-hydroxybiphenyl-3-carboxylic acid as a new colorimetric reagent for ferric iron. The reagent is very sensitive and is

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(1) Abstracted from the Ph.D. thesis of Aubrey E. Harvey, Jr., University of Virginia, 1946.

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practically specific, its only other color reaction being with the uranyl ion. The latter reaction will be studied in more detail. The colorless solution of the reagent in ethanol appears to be stable indefinitely. The iron complex is soluble in slightly acid 40% ethanol solution; its intense violet color is stable for at least fourteen hours. Iron may be determined without difficulty in the presence of titanium, and there is remarkably little interference from other cations. Anions such as phosphate, fluoride, oxalate, phthalate, and tartrate which form complexes with the ferric ion, either reduce the sensitivity of the reaction or prevent color formation altogether. The procedure for the determination of iron is simple and may be applied to a wide variety of materials with highly satisfactory results.

Apparatus and Solutions

Instruments.—Spectrophotometric measurements were made with a Beckman quartz spectrophotometer, Model D, using 10.0 mm. Corex glass transmission cells, at a spectral band width of 5 mμ.

Visual color matching was made in 50-ml. Nessler cylinders (220 mm.); also with a color comparator[22] using 100-ml. tubes (160 mm.).

Reagent Solution.—4-Hydroxybiphenyl-3-carboxylic acid, mol. wt. 214, was furnished by courtesy of E. I. du Pont de Nemours and Company. The compound is only slightly soluble in water, but is highly soluble in 70% ethanol. The melting point is 214–215° (cor.) as compared with 212–213° reported in the literature.[23] Solutions containing 0.1916 and 1.0000 g. of solute, respectively, in 100 ml. of 95% ethanol were used. One milliliter of the more dilute solution added to 50 ml. of a solution containing 10 p. p. m. iron furnished 1 mole of reagent to 1 gram-ion of ferric ions. Reagent solutions appear to be stable indefinitely.

Standard Iron Solution.—7.0224 g. of ferrous ammonium sulfate hexahydrate was dissolved in 100 ml. of distilled water, 5 ml. of concentrated sulfuric acid and 1 ml. of bromine were added, and the solution boiled to oxidize the iron and expel the excess bromine. The solution was diluted to 1 liter and the iron determined gravimetrically. The solution should contain 1.00 mg. of iron per ml. More dilute solutions may be prepared from this stock solution as needed.

Solutions of Diverse Ions.—Solutions of salts were prepared from reagent grade, iron-free chemicals, and contained 0.5 mg. of the desired ion per ml.

Spectrophotometric Study of the Color Reaction

Spectrophotometric measurements were made to determine the effect of reagent concentration on the color intensity in an effort to establish the empirical formula for the violet complex formed in 40% ethanol solution.[24] Two series of solutions were prepared in which the molar ratio of reagent to iron varied from 0.2:1 to 10:1. The pH of one series was adjusted to 2.8 and of the other to 3.0. All solutions contained 10 p. p. m. of iron and 40% ethanol. The absorbancy ($-\log T$) was measured for each solution at 575 mμ, the wave length of maximum absorption for the complex. The results are plotted in Fig. 1.

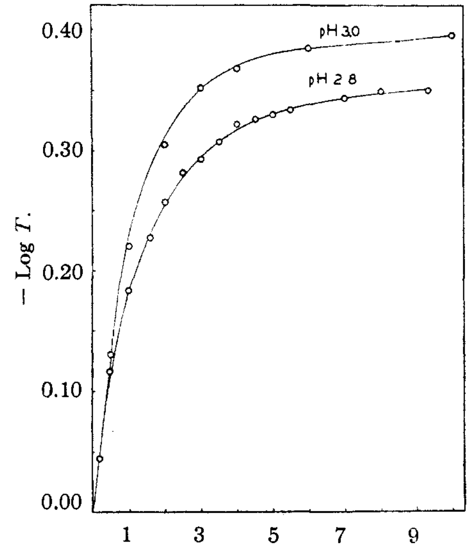

Fig. 1.—Effect of reagent concentration: 10 p. p. m. Fe; λ575 mμ.

These curves show no sharp break or leveling off to a constant maximum absorbancy. The absorbancy is still increasing slightly at a reagent–iron ratio of 10:1, indicating that the complex is appreciably dissociated in solution. The curves show, moreover, that a large excess of reagent (at least a 10:1 molar ratio) is necessary to insure full color development.

The method of "continuous variation" first proposed by Job[25] and extended by Vosburgh and co-workers[26,27] was applied to the determination of the ratio of reagent to iron in the complex studied in this investigation. A 1.79×10^{-4} M solution of ferric ions (10 p. p. m.) and a reagent solution of the same molarity were prepared in 40% ethanol. The pH of these solutions was adjusted to 3.0. Twelve solutions of the colored complex were obtained by mixing x ml. of the reagent solution and $(20 - x)$ ml. of the iron solution. The pH of each solution after mixing was checked with a glass electrode and found to be 3.0. The values of x were chosen so that the molar ratio varied from 0.25 to 9 moles of reagent for each mole of iron. In one experiment, ammonium sulfate was added to the reagent solution so that the concentration of sulfate ion remained constant in the whole series. This precaution did not affect the results in any way. The absorbancy was determined at 550, 575 and 600 mμ, respectively. In Fig. 2 the absorbancy values at 575 mμ are plotted against the volume of reagent solution [expressed x liters added to $(1-x)$ liters of iron solution].

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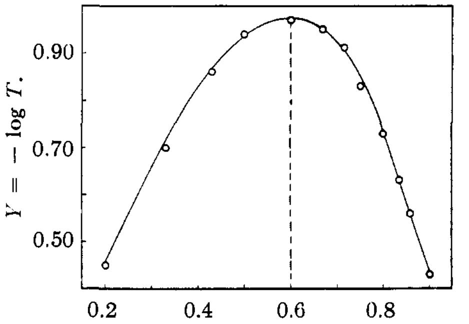


Fig. 2.—X liters of 1.79×10^{-4} M reagent solution added to $(1 - X)$ liters of 1.79×10^{-4} M Fe^{+++} solution: λ, 575 mμ, pH 3.0.

A Y function, first introduced by Job[25], may be defined as the difference between the observed absorbancy and the calculated absorbancy, assuming no reaction between the components of the colored complex.

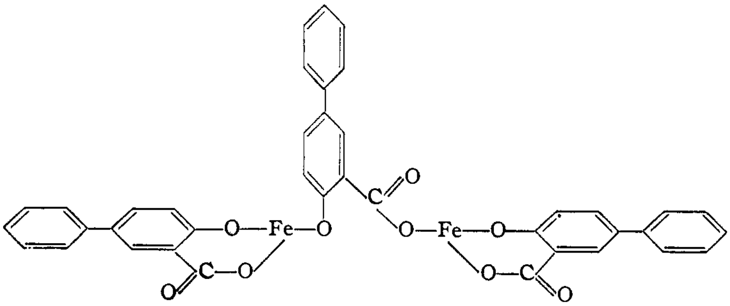
$$Y = E_{\text{obs.}} - d[\epsilon_1 M(1 - x) + \epsilon_2 Mx]$$

The symbols ϵ_1 and ϵ_2 represent, for a given wave length, the molecular extinction coefficients of ferric ion and the reagent, respectively; M the molarity of the solutions used; d the thickness of the ransmission cell; $(1 - x)$ and x the volumes in liters of the solutions mixed.

The new iron reagent is colorless and therefore ϵ_2 is zero at any wave length in the visible range. The term $\epsilon_1 M(1 - x)$ may be neglected because ferric ions show no appreciable absorption at the concentration used in this procedure. The Y function for this particular case is then simply the observed absorbancy ($-\log T$). It has been shown[26] that if Y is plotted against x, the value of x for which the curve passes through a maximum or a minimum will give the value of n in the formula FeR_n by the relationship $n = x/(1 - x)$. The maximum in Fig. 2 indicates a formula of $FeR_{1.5}$ or Fe_2R_3 for the complex. The curve has a rather broad maximum which is to be expected when there is appreciable dissociation.

Vosburgh and Cooper[26] point out that for solutions in which only one complex is formed, the maximum or minimum in Y will occur at the same value of x for any wave length at which measurements are made. The absorbancy values at 10 mμ intervals from 520 to 620 mμ were determined for solutions containing 10 p. p. m. of iron with the following molar ratios of reagent to iron: 0.2:1, 0.5:1, 1:1, 2:1, 3:1 and 9:1. Plotting log E against wave length gave curves which were identical in shape and could be superimposed by adding a suitable constant to the ordinates of each curve. This shows that in the color system under consideration the reagent forms only one complex with ferric iron.

Various attempts have been made to establish the structures of complexes formed by the reaction between ferric ions and phenolic derivatives.[28,29,30,31,32,33,34] Wesp and Brode[35] found that the absorption curves for the water-soluble complexes of ferric ions with 44 phenols and 10 naphthols, as well as the curves for the ferric–salicylic acid color in 28 different solvents were identical in shape, though the wave length of maximum absorption depended on the particular phenolic derivative used and varied also with the solvent. The characteristic shape of these absorption curves is duplicated by that of the ferric thiocyanate complex. This similarity indicates that all the complexes have the same or very similar structures. Bent and French,[36] and also Edmonds and Birnbaum[37] independently, have reported that the color of the thiocyanate complex is due to the $Fe[CNS]^{+2}$ ion. Gould and Vosburgh[27] confirmed the presence of the $Fe[CNS]^{+2}$ ion using the method of continuous variation. Hence it would seem that the water-soluble iron complexes with phenolic derivatives have the formula FeR^{+2} in solution. Weinland and Binder[33] have assigned the formula $[Fe(OC_6H_4\text{-}OCH_3)_4]$ H to the violet complex formed by ferric ions and guaicol in alcoholic solution. Wesp and Brode[35] point out that the structure of the guaicol compound may well differ from that of the other phenolic complexes of iron because the compound is insoluble in water. The same reasoning would apply in the present case since the complex under investigation is insoluble in water and the color is formed in ethanol solution. It is probable that a molecule rather than an ion is responsible for the color. Since the reagent has two replaceable hydrogens, it is reasonable to assume that the structure of the complex may be represented as



A Spectrophotometric Study of the Effect of pH on the Color Reaction.—Attempts to form the colored complex of ferric ions with 4-hydroxy-

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biphenyl-3-carboxylic acid in aqueous solution were unsuccessful. The reagent precipitates immediately from solutions as dilute as 0.15 mg. per ml. if the *p*H is 3.3 or below. In higher concentrations the reagent precipitates at any *p*H below 4.4. At this latter *p*H the precipitation of ferric hydroxide from aqueous solution interferes with the color reaction.

The intensity of the color in 40% ethanol is extremely sensitive to changes in hydrogen-ion concentration. Visual observations indicated that maximum absorption is reached at a *p*H of about 3. In more acid solutions, the absorption is markedly diminished. Decreasing the acidity not only causes a decrease in color intensity, but also a change in hue from violet to reddish-violet at *p*H 4. This change in hue is thought to be due to the formation of colloidal, hydrated ferric oxide. Solutions containing 10 p. p. m. iron in 40% ethanol developed a red color without addition of the reagent when the *p*H was adjusted to 4.0 or above. Ferric hydroxide precipitated from these solutions on standing overnight.

Spectrophotometric measurements were made on a series of solutions containing 10 p. p. m. iron and varying in *p*H from 2.1 to 3.6. All solutions contained 4 moles of reagent to each mole of iron. Absorbancy measurements were made at 10 mμ intervals from 400 to 700 mμ. The absorbancy *vs.* wave length curves are shown in Fig. 3. The solutions of *p*H 2.1, 2.4 and 2.8 are deep violet in color and have absorption maxima at 575 mμ, the absorbancy being greatest at *p*H 2.8. The curve at *p*H 3.6 shows a slight shift of the maximum toward the shorter wave lengths, and increased absorption from 400 to 500 mμ. These variations are increasingly pronounced from *p*H 3.8 to 4.3 and correspond with a change in hue to reddish-violet. The increased absorption between 400 and 500 mμ could be explained by the formation of colloidal ferric oxide, which absorbs in this range. On standing twenty-four hours, the reddish-violet solutions of *p*H 3.6 and above became turbid, the color faded and a reddish-brown precipitate gradually settled out.

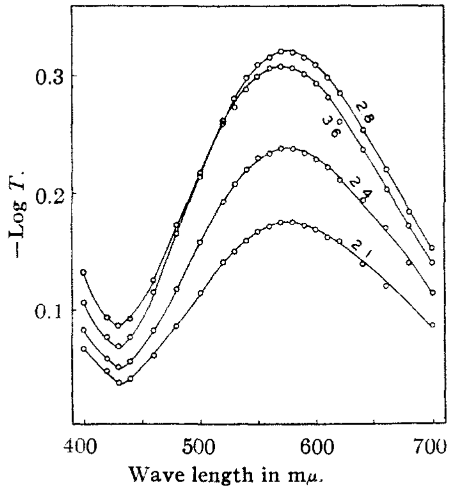

Fig. 3.—Effect of *p*H on extinction: moles reagent: moles Fe = 4:1; 10 p. p. m. Fe.

In order to determine more closely the optimum *p*H range, three solutions were used having *p*H values of 2.8, 3.0 and 3.2. These solutions differed from the first series in that each contained a 10:1 molar ratio of reagent to iron. Their extinction is plotted against wave length in Fig. 4. The upper curve of Fig. 3 is reproduced in Fig. 4. The curves for *p*H 3.0 and 3.2 coincide at all wave lengths. The difference in intensity of these solutions and of that at *p*H 2.8 cannot be detected visually. The optimum *p*H range may therefore be set at 2.8–3.2.

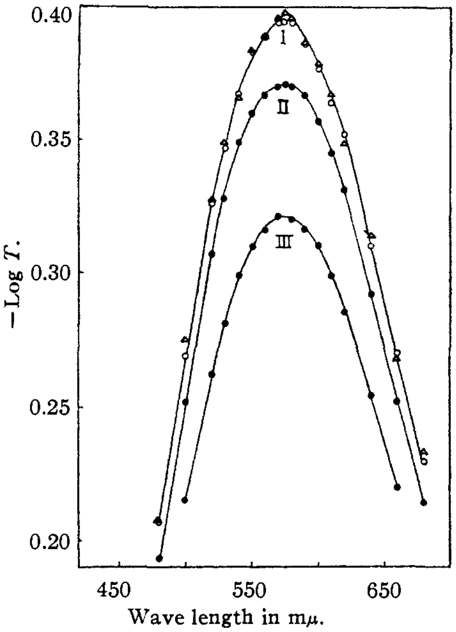

Fig. 4.—Effect of *p*H on extinction: moles reagent: moles Fe; I and II 10:1, III 4:1; △, *p*H 3.2, ○, *p*H 3.0, ●, *p*H 2.8.

It was found that the *p*H can be adjusted closely enough by adding 1 *N* sodium hydroxide until the solution is alkaline to congo red paper, and then 0.1 *N* hydrochloric acid until a drop of the solution turns the paper light blue. The use of a buffer was dispensed with in order not to decrease the sensitivity of the reaction.

Conformity to Beer's Law

The new iron complex was found to conform to Beer's law up to an iron concentration of 10 p. p. m. Solutions containing 15 and 20 p. p. m. iron showed increasing deviation from Beer's law, and on standing a short while gave a mixed blue-white precipitate of complex and reagent. Spectrophotometric measurements were made over a wave length range from 520 to 620 mμ.

Stability of the Colored Complex.—Solutions of the colored complex in the optimum *p*H range, containing a large enough excess of reagent for full color development, are stable from fourteen to sixteen hours in the diffuse light of the laboratory. A precipitate of reagent and complex separates from solutions containing 10 p. p. m. iron after thirty-six hours, and from solutions with 1 p. p. m. after a week. It is recommended that fresh standards be prepared daily.

Sensitivity of the Reaction.—The limit of sensitivity of the violet iron complex is 1 part of iron in 40 million parts of solution when observations are made either in 50-ml. tall-form Nessler cylinders or in a color comparator.[22] Solutions having a *p*H of 3.0 and containing 1 part of iron in 10, 20, 30, 40 and 50 million parts of solution, respectively, with 1 ml. of 1% reagent and 40 ml. of 95% ethanol per 100 ml. of solution were transferred to comparator tubes or Nessler cylinders. Three independent observers were able to arrange the four more concentrated solutions in the proper order and to distinguish from a reagent blank, the solution containing 1 part of iron in 40 million.

The optimum concentration range for comparison in the Nessler cylinders is 0.2 to 1 p. p. m. of iron. Over this range, increments of 1 part of iron in 30 million parts of solution may be detected. Solutions containing 5 p. p. m. of iron are too dark for comparison in Nessler cylinders, though solutions of this concentration differing by 1 part of iron in 20 million parts of solution may be distinguished in the color comparator.

The spot-plate sensitivity was determined by transferring 0.05 ml. (one drop) of iron solutions of varying concentrations to depressions of a white porcelain spot-plate and adding 0.05 ml. of a 1% reagent solution of *p*H 3. Two-tenths of a microgram of iron could thus be detected.

Effect of Diverse Ions

Reactions with Various Ions.—Spot-plate tests were made by adding a drop of 1% reagent solution to a drop of the solution containing 1 mg. per ml. of the respective ions. Tests were made in acid, neutral and alkaline media when the character of the ion permitted. No color or precipitate formation was observed with the following ions: Al^{+3}, Ag^{+1}, As^{+3}, AsO_4^{-3}, $AuCl_4^{-1}$, $B_4O_7^{-2}$, Ba^{+2}, Be^{+2}, Bi^{+3}, Br^{-1}, CO_3^{-2}, Ca^{+2}, CbO_4^{-3}, Cd^{+2}, Ce^{+3}, Cl^{-1}, Co^{+2}, Cr^{+3}, Cs^{+1}, Dy^{+3}, Er^{+3}, Eu^{+3}, F^{-1}, Fe^{+2}, Ga^{+3}, Gd^{+3}, Ge^{+4}, HfO^{+2}, Hg^{+1}, Hg^{+2}, I^{-1}, In^{+3}, Ir^{+4}, K^{+1}, La^{+3}, Li^{+1}, Mg^{+2}, Mn^{+2}, MoO_4^{-2}, NO_2^{-1}, NO_3^{-1}, Na^{+1}, Nd^{+3}, Ni^{+2}, OsO_5^{-2}, HPO_4^{-2}, Pb^{+2}, Pd^{+2}, Pr^{+3}, $PtCl_6^{-2}$, Rb^{+1}, ReO_4^{-1}, Rh^{+3}, Ru^{+3}, S^{-2}, SO_4^{-2}, Sb^{+3}, Sc^{+3}, SeO_3^{-2}, SiO_3^{-2}, Sm^{+3}, Sn^{+2}, Sn^{+4}, Sr^{+2}, TaO_4^{-3}, TeO_4^{-2}, Th^{+4}, Ti^{+4}, Tl^{+3}, Tm^{+3}, VO^{+2} WO_4^{-2}, Y^{+3}, Yb^{+3}, Zn^{+2}, ZrO^{+2}.

TABLE I

EFFECT OF DIVERSE IONS

Ion	Added as	Amount present p. p. m.	Results
Al^{+3}	$Al(NO_3)_3$	100	M
Ca^{+2}	$Ca(NO_3)_2$	100	M
Co^{+2}	$Co(NO_3)_2$	100	X (reddish)
		50	M
Cr^{+3}	$Cr(NO_3)_3$	25	NM
		10	M+
		5	M
$Cr_2O_7^{-2}$	$K_2Cr_2O_7$	5	X (gray)
		1	M+
Cu^{+2}	$Cu(NO_3)_2$	25	NM
		10	M+
		5	M+
		1	M
F^{-1}	KF	5	NM, D
		1	M
Fe^{+2}	$Fe(NH_4)_2(SO_4)_2$	1	NM (oxidizes)
K^{+1}	KCl	100	M
Mg^{+2}	$MgSO_4$	100	NM (slight reddish tint)
		50	M
Mn^{+2}	$MnCl_2$	100	M
Na^{+1}	NaCl	100	M
NH_4^{+1}	NH_4Cl	100	NM (reddish tint)
		50	M (slight reddish tint)
Ni^{+2}	$Ni(NO_3)_2$	25	NM
		10	M+
		5	M+
		1	M
PO_4^{-3}	Na_3PO_4	100	B
		1	NM
SiO_3^{-2}	Na_2SiO_3	100	NM (color develops slowly)
		50	M−
		25	M (after five minutes)
Sn^{+2}	$SnCl_2$	1	NM, D
Sn^{+4}	$SnCl_4$	5	NM, D
		1	M
Ti^{+4}	$TiCl_4$	1	NM (gray solution)
		Concn. in millimoles per liter	
Acetate	Acetic acid	500	NM
		350	M
Borate	Sodium tetraborate	20	NM
		10	M
Citrate	Citric acid	1	B
Malate	Malic acid	50	NM
		10	M
Oxalate	Oxalic acid	1	B
Phthalate	Potassium hydrogen phthalate	10	NM
		5	M
Succinate	Succinic acid	50	NM
		10	M
Tartrate	Tartaric acid	1	B

Key to symbols: M = matches 1 p. p. m., M+ = 1.05 p. p. m., M− = matches 0.95 p. p. m., NM = no match or matches 1.10 or 0.90 p. p. m., X = off-tint, D = intensity greatly decreased, B = color bleached.

Ferric ions produced a violet color and a blue precipitate; UO_2^{+2} an orange color. These are the only ions reacting with the reagent in acid solution; in ammoniacal solution, the cupric ion gives a green color.

Determination of Iron in the Presence of Other Ions.—In determining the interference of diverse ions, a measured volume of a standard solution of the diverse ion and 20 ml. of 95% ethanol were added to 5.0 ml. of standard iron solution (0.01 mg. per ml.) in a 50-ml. tall-form Nessler cylinder; the volume was made up to 45 ml. with distilled water and the *p*H adjusted to about 3 with congo red paper; 1 ml. of 1% reagent solution was added; the tube was filled to the mark and the solution mixed. These solutions containing 1 p. p. m. of iron with the diverse ion were compared with color standards containing 0.90, 0.95, 1.00, 1.05 and 1.10 p. p. m. of iron, respectively. The diverse ion was judged not to interfere if the solution was not off-tint, and the intensity could be matched with that of the 1 p. p. m. standard. If the solution matched the 0.95 or 1.05 p. p. m. standard, it is so indicated. If the color corresponded to the 1.10 or 0.90 p. p. m. standard, "no match" is reported. No concentration of diverse ions greater than 100 p. p. m. or less than 1 p. p. m. was used. The results of these tests are shown in Table I.

These data show that the most serious interference is encountered with anions such as fluoride, phosphate, and the anions of organic acids which are common constituents of buffer solutions. Fortunately, the acidity may be satisfactorily adjusted with the aid of congo red paper. Fluoride must be removed if its concentration is greater than that of the iron. Phosphate interferes at a concentration equal to that of the iron.

Of the metallic ions which interfere, only Cu^{+2} and Ti^{+4} are likely to exceed the limiting concentration in materials to which colorimetric methods for iron are commonly applied. Copper is easily separated from iron by precipitation as copper sulfide. An investigation showed that the interference of titanium is due to hydrolysis and that this can be avoided by decreasing the *p*H of the solution. A gray color results when the reagent is added to solutions containing 1 p. p. m. each of iron and titanium. These solutions give a brownish precipitate on standing a few hours. A similar precipitate was observed in 40% ethanol solution of *p*H 3.0 containing 1 p. p. m. of these metals without the reagent. If the *p*H of the solution and color standards is adjusted to 2.5, the solution containing titanium shows no off-tint, and a match may be made without difficulty.

Recommended Procedure

A procedure for the colorimetric determination of iron with 4-hydroxybiphenyl-3-carboxylic acid has been based on the foregoing study of the properties of the reagent. The color must be developed in 35–40% ethanol solution because of the small solubility of the reagent in water. A 10:1 molar ratio of reagent to iron is sufficient for full color development at the optimum *p*H of 3. If titanium is present adjust the *p*H to 2.5.

Weigh out a sample containing 1 mg. of iron or less. Dissolve the sample by alkali fusion, mineral acid treatment, or both as may be necessary. If interfering ions are present in excess of the limiting concentrations shown in Table I, remove them by standard methods. Dilute the solution in a volumetric flask to 100 ml. with distilled water. After thorough mixing, transfer 5 ml. (or an aliquot part that will give an iron concentration of 0.1 to 1 p. p. m. when diluted to 50 ml.) to a Nessler cylinder. Add 20 ml. of 95% ethanol and dilute to 40–45 ml. with distilled water. Add 1 *N* sodium hydroxide dropwise until a drop of the solution on a stirring rod does not change the color of congo red paper. Then add 0.1 *N* hydrochloric acid until the indicator paper just turns blue when tested with a drop of the solution. If the acid concentration in the aliquot is excessively high, the solution should be partially neutralized with a stronger solution of base before the 1 *N* sodium hydroxide is added. After the *p*H has been adjusted, add 1 ml. of 1% reagent solution, dilute to the mark with distilled water, mix thoroughly, and compare the color with a series of standard solutions similarly prepared.

If the sample contains titanium, the solution will develop a gray color on addition of the reagent. In this case, add 0. 1 *N* hydrochloric acid dropwise until the color becomes violet. Add the same amount of acid to the standards, before matching. The *p*H of standards and sample should be checked with the *p*H meter after matching and should agree within 0.1 of a *p*H unit. If the titanium is known to be present in high enough concentration to interfere, the *p*H may be adjusted to 2.5 before the reagent is added.

Determination of Iron in Various Materials.—The applicability of the reagent to the colorimetric determination of iron in various materials

TABLE II

DATA ON IRON DETERMINATIONS

Materials N. B. S.	Fe$_2$O$_3$ N. B. S. value, %	Fe$_2$O$_3$ found, %	Diff., %
Feldspar 70	0.03	0.05	+0.02
		.04	+ .01
Glass sand 81	.073^a	.072	− .001
		.072	− .001
Dolomite 88	.084	.086	+ .002
		.086	+ .002
Silica brick 102	.66^b	.67	+ .01
		.66	.00
Soda lime glass 128	.039	.039	.000
		.036	− .003
	%Fe	%Fe	
Sheet brass 37b	.21	.22^c	+ .01
		.23^c	+ .02

[a] Sample contained 0.095% TiO$_2$. Matched at *p*H 2.5.
[b] Sample contained 0.16% TiO$_2$. Matched at *p*H 2.5.
[c] Copper removed as CuS.

was established by analyzing a representative group of samples issued by the National Bureau of Standards. The results are recorded in Table II.

Discussion of Results

The data in Table II show that the reagent may be used successfully for the determination of small amounts of iron in various materials. All values determined with the new reagent are well within the range of values reported by the Bureau. The precision between individual analyses is excellent. Feldspar 70, dolomite 88, silica brick 102 and soda lime glass 128 contained, respectively, 0.012, 0.003, 0.025 and 0.01% of P_2O_5. No interference from phosphate was encountered with any of these samples. When no interfering ions are present, a sodium carbonate fusion of the sample may be taken up in dilute hydrochloric acid, filtered directly into a 100-ml. volumetric flask, diluted to the mark and mixed. An aliquot part of the solution is taken for analysis. Dehydration of the silica before filtration is not necessary.

Summary

A new, sensitive and practically specific reagent for the colorimetric determination of iron is presented. The nature of the reaction and the optimum conditions for color formation have been determined spectrophotometrically. The colored complex obeys Beer's law over the useful range of iron concentration.

The reagent is sensitive to 1 part of iron in 40 million parts of solution when observations are made in Nessler cylinders (50-ml. tall-form). An analytical procedure based on visual methods of color matching has been applied to a variety of materials with good accuracy. The number of interfering cations is small. Iron may be determined in the presence of titanium without interference.

CHARLOTTESVILLE, VA. RECEIVED JULY 31, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The Effect of Fluorine Substitution on Chemotherapeutic Agents. I. Synthesis of Some Fluorine-Containing Medicinals[1]

BY H. LEON BRADLOW[2] AND CALVIN A. VANDERWERF

Because of the increasing interest in organic compounds containing fluorine we have undertaken a program involving the synthesis of a variety of fluorine substituted compounds, with the ultimate aim of determining the effect on the pharmacological properties of various medicinals produced by the substitution of fluorine atoms for other groups in the molecule. The present paper describes the synthesis of sample compounds of a number of types, the pharmacological and germicidal testing of which it is hoped will provide leads for future work. Previous investigations of this nature have been concerned mainly with the substitution of fluorine for other halogen atoms[3]; in view of the fact that a number of isosteres of important medicinal agents have proved to be as effective or better than the original drugs,[4] however, emphasis in the present work has been placed upon the substitution of fluorine atoms for the isosteric amino and hydroxy groups.[5] Representative fluorine-containing compounds related to medicinals of the following general types were prepared: (1) antimalarials, (2) arsenicals, (3) diphenylsulfones, (4) antiseptics derived from resorcinol and (5) sulfonanilides.

Experimental[6,7]

p-Nitrofluorobenzene.—Direct nitration of fluorobenzene by dropwise addition, with vigorous stirring, of 3 moles to 600 cc. of a 2:1 (by volume) mixture of concentrated sulfuric acid and yellow fuming nitric acid (sp. g. 1.5) at −10°, followed by addition of ice, ether extraction and careful fractionation through a packed column of the residue after removal of the ether, gave 338 g. (80%) of *p*-nitrofluorobenzene, b. p. 109–109.5° at 36 mm., f. p. from cooling curve 26.0°, together with 40.0 g. (7.2%) of 2,4-dinitrofluorobenzene, b. p. 129–130° at 2.7 mm. In an alternate method *p*-nitrofluorobenzene was obtained from *p*-nitroaniline in 65% yield by diazotization followed by decomposition at 40° in anhydrous hydrogen fluoride.

p-Fluoroaniline.—Reduction of *p*-nitrofluorobenzene in absolute alcohol using Raney nickel catalyst with a small amount of platinum tetrachloride as promoter repeatedly gave 92–95% yields of *p*-fluoroaniline, b. p. 98–99° at 33 mm. With Adams catalyst the reduction in either absolute alcohol or acetic acid gave only 65–70% yields of the amine together with 5% of *p*-fluoroacetanilide, m. p. 150.6–151.1°, when the latter solvent was used; this

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(1) Presented before the Organic Division of the American Chemical Society at the Atlantic City meeting in April, 1947.

(2) H. P. Cady Fellow, 1946.

(3) See, for example: (a) Dunker and Starkey, THIS JOURNAL, **61**, 3005 (1939); (b) Suter and Weston, *ibid.*, **61**, 2317 (1939); (c) **62**, 604 (1940); (d) Suter, Lawson and Smith, *ibid.*, **61**, 161 (1939); (e) English, Mead and Niemann, *ibid.*, **62**, 350 (1940).

(4) Compare the bactericidal action of sulfathiazole and of sulfadiazine with that of sulfapyridine, the analeptic activity of the N,N-diethylamide of thiazole-5-carboxylic acid with that of the corresponding derivative of pyridine and the hypnotic properties of dialkyl derivatives of 2,4-dioxothiazolidine with those of the analogous barbiturates.

(5) Relatively few studies of this type have been made; see: (a) Schiemann and Winkelmüller, *Ber.*, **65B** 1435 (1932); (b) Hansen, THIS JOURNAL, **59**, 280 (1937); (c) Fosdick and Campaigne, *ibid.*, **63**, 974 (1941).

(6) All melting points corrected; boiling points uncorrected.

(7) All analyses by Oakwood Laboratories, Alexandria, Virginia.