[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

STUDIES ON THE DIRECTIVE INFLUENCE OF SUBSTITUENTS IN THE BENZENE RING. I. A CHEMICAL METHOD FOR ESTIMATING THE META ISOMER IN SOME DISUBSTITUTED DERIVATIVES OF BENZENE[1,2]

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Mixtures of isomeric derivatives of benzene are analyzed commonly by physical methods such as freezing curves,[3] solubility[4] and density.[5] These are subject to considerable error with small amounts of impurities, and require isolation of the mixture, and some degree of purification, which may cause loss or change in the relative amount of the isomers. In most cases, considerable preliminary research is required.

Some chemical methods, such as selective displacement of groups,[6] or sulfonation,[7] have been employed, but these are limited in application.

Ditz[8] has given a method for the estimation of *m*-cresol in mixtures with *o*- and *p*-cresols, which depends upon the substitution of three bromine atoms in the former case, and only two in the latter two isomers.

In this investigation, a chemical method has been developed for distinguishing the *meta* isomer, quantitatively, from the *ortho* and *para* isomers in practically all cases in which one of the substituent groups is NH_2, OH or NO_2. This covers a majority of disubstituted benzene derivatives which are of practical importance. The method does not distinguish between *ortho* and *para* compounds but, in conjunction with other methods, may greatly improve analyses of ternary mixtures in that respect. It is also satisfactory for the direct quantitative determination of any single isomer.

The method depends upon the fact that the directive influences of hydroxyl and amino groups are so great in comparison with those of other groups that, in aqueous solution, when one of the former is present, all avail-

[1] This paper is constructed from Part I of a dissertation presented by Alfred W. Francis to the Faculty of the Graduate School of Yale University, 1924, in candidacy for the degree of Doctor of Philosophy.

[2] Presented in part at the Sixty-seventh Meeting of the American Chemical Society, Washington, D. C., April, 1924.

[3] Holleman and others, *Rec. trav. chim.*, **28**, 411 (1909); **30**, 55, 365 (1911); **31**, 244 (1912); **33**, 1 (1914); *Ber.*, **44**, 704 (1911).

[4] Holleman and others, *Rec. trav. chim.*, **18**, 267 (1899); **19**, 89, 367 (1900); *Z. physik. Chem.*, **31**, 79 (1899).

[5] (a) Lunge, *Chem. Ind.*, **8**, 74 (1885). Compare (b) Allen's "Commercial Organic Analysis" Blakiston, **1914**, vol. VI, p. 70.

[6] Holleman and others, *Rec. trav. chim.*, **23**, 253 (1904); **24**, 143 (1905); **35**, 1 (1916); **37**, 195 (1918); **39**, 435, 736 (1920); **40**, 67 (1921). Wagner, *Ber.*, **7**, 76 (1874).

[7] Levinstein, *J. Soc. Chem. Ind.*, **3**, 77 (1884).

[8] Ditz, *Z. angew. Chem.*, **37**, 873 (1899); **38**, 897 (1899); **42**, 1050 (1900).

able *ortho* and *para* positions are substituted quantitatively with bromine. Aniline and phenol, as is well known, are converted into 2,4,6-tribromoaniline and 2,4,6-tribromophenol, respectively. All *m*-amino and phenolic compounds are likewise *tri*brominated in the 2, 4 and 6 positions. *Ortho* and *para* compounds, on the other hand, have one of these positions already filled, and are therefore *di*brominated in 4,6 and 2,6, respectively. The actual amount of bromine consumed is therefore a measure of the amount of *meta* isomer present. Thus: 2.70 and 2.44 moles of bromine signify, respectively, 70% and 44% of *meta* isomer.

In the case of nitro compounds, the method involves[9] a preliminary quantitative reduction to the corresponding amino compounds by means of titanous chloride.[10] (X is any other substituent.)

$$C_6H_4XNO_2 + 6TiCl_3 + 6HCl \longrightarrow C_6H_4XNH_2 + 6TiCl_4 + 2H_2O \quad (1)$$

Without separating the amino compounds from solution, they are titrated with the bromine solution in the same way as before.

Instead of a free aqueous bromine solution, which is somewhat unstable, it is best to use a solution of potassium bromide and potassium bromate, which on acidification gives free bromine.

$$KBrO_3 + 5KBr + 6HCl \longrightarrow 6\ KCl + 3Br_2 + 3H_2O \quad (2)$$

Since substitution reactions with bromine produce hydrobromic acid, which can replace some of the potassium bromide in this reaction, two equivalents of the latter substance are sufficient, as shown in the following equation for a *m*-amino compound.

$$C_6H_4XNH_2 + KBrO_3 + 2KBr + 3HCl \longrightarrow C_6HBr_3XNH_2 + 3KCl + 3H_2O \quad (3)$$

A solution made up with this smaller amount of potassium bromide proved satisfactory for analytical work involving substitution, but obviously not for addition reactions, such as the bromination of cinnamic acid.

The excess of titanous chloride used in the reduction of nitro compounds also reacts with the bromine solution.

$$KBrO_3 + 6TiCl_3 + 6HCl \longrightarrow 6TiCl_4 + KBr + 3H_2O \quad (4)$$

From Equations 1, 3 and 4 it is evident that a *m*-nitro compound consumes equivalent amounts of titanous chloride and potassium bromate, and therefore does not change the results from those of a blank relation between the solutions. The method is more strictly, therefore, a determination of combined *ortho* and *para* isomers, which take less bromate than they do titanous chloride. Thus, if the titanous chloride and the bromate solution were equivalent, and 42 cc. of the former were the reduction requirement, and 50 cc. or an excess of 8 cc. were used, a *meta* compound would take 50 cc. of the bromate solution as in the relation; and an *ortho* or *para* compound would take $8 + (2/3 \times 42)$ or 36 cc., which is 14 cc.

[9] Hill and Francis, preliminary paper, New Haven Meeting of the American Chemical Society, April, 1923.

[10] Knecht and Hibbert, *Ber.*, **36**, 166, 1554 (1903); **40**, 3819 (1907).

less. A mixture containing 50% of *meta* would take 43 cc.; 48 cc. would indicate (48−36)/14 = 85.7% of *meta*, etc.

The best procedure is not the same for all compounds coming under the scope of this method for reasons that will be shown in the following discussion, but the three isomers of any one system can be titrated in the same way.

Bromine titration of aniline is extremely accurate, because tribromo-aniline is precipitated promptly and quantitatively as a crystalline solid, thus permitting no over-bromination or adsorption, and because mono- and dibromo-aniline are soluble in acid solution, and therefore do not precipitate, causing under-bromination. Since these conditions are not met as well in the derivatives of aniline or phenol, certain modifications must be introduced in some cases. There are three classes of difficulties, namely: (1) oxidation and destruction of the molecule; (2) precipitation of partially brominated products; (3) displacement of certain groups, namely, COOH, SO_3H, CHO.

In the first class are *o*- and *m*-toluidines, the phenylenediamines, *o*- and *p*-aminophenols, *p*-phenetidine and pyrocatechol. The titration may be either high or low, but in general a dark color results and the end-point is obscured. When the mixture is cooled below 0° by means of ice in the solution, this difficulty is avoided in the case of the toluidines, *p*-phenylenediamine and *p*-aminophenol.

The second kind of difficulty may cause low results. It is easily avoided, however, by using a sufficient quantity of a solvent, preferably alcohol, and by acidifying *after* the addition of bromide-bromate solution. *Para* compounds are most likely to cause trouble in this respect, especially *p*-nitro-aniline and *p*-iodo-aniline.

The third type of difficulty may cause high results. The remedy is the same as for the first, and is successful in every case, though extreme care must be taken with the hydroxybenzoic acids. Table I shows approximately the temperature, T_1, below which the group is not displaced, and the temperature, T_2, above which displacement is quantitative.

TABLE I

DISPLACEMENT OF GROUPS BY BROMINE

Compound	T_1 °C.	T_2 °C.
o- and *p*-Hydroxybenzoic acids	−5	20
o- and *p*-Aminobenzoic acids	0	40
o- and *p*-Hydroxybenzaldehydes	10	40
o- and *p*-Aminobenzaldehydes	15	45
Sulfanilic acid	0	20

When sufficient alcohol is added to prevent precipitation of the dibromo compounds, displacement of the group is quantitative at 20° in every case, the end product being identified as tribromophenol, or tribromo-aniline.

The mechanism of the displacement of the sulfonic and carboxylic groups has been demonstrated, at least to the extent that the former is eliminated as sulfuric acid and the latter as carbon dioxide. After filtering out the tribromo-aniline from a sulfanilic acid titration, a quantitative yield of barium sulfate was obtained by adding barium chloride to the filtrate. Allen[11] has shown that carbon dioxide is evolved from salicylic acid on bromination. The displacement of the sulfonic group from sulfanilic acid by bromine at high temperatures in glacial acetic acid was observed by Fuchs.[12] The mechanism of displacement of the aldehyde group is less evident. That it is not preceded by oxidation to carboxyl, is shown by the fact that when four moles of bromine were added to salicyl aldehyde, one was titrated back quantitatively with thiosulfate, after addition of potassium iodide, while oxidation and subsequent tribromination would have required four moles. Furthermore, yields of over 94% of tribromo compounds were obtained with each of the four aldehydes mentioned in Table I, although only three equivalents of bromine had been consumed. Tests for formic acid by heating the solution with mercuric chloride, or by reduction with zinc and application of Schiff's reagent were negative. The only remaining possibility seemed to be that carbon monoxide was evolved. This was identified in the case of salicyl aldehyde by means of tubes of "Hoolamite."[13] Air was bubbled through the reaction mixture, through sodium hydroxide solution to remove bromine, through soda lime and charcoal to remove organic material, and finally through the Hoolamite tube giving the characteristic green and brownish-black color. A blank failed to give a color change. In applying this test it was necessary to use sufficient alcohol in the reaction solution to prevent precipitation of dibromosalicyl aldehyde, which in solid form is not attacked readily by an excess of bromine. A possible mechanism for the displacement is that the hypothetical formyl bromide, HCOBr, is first formed but decomposes into carbon monoxide and hydrobromic acid.

That all the displaceable groups mentioned are *meta* controlling, lends support to Flürscheim's hypothesis that these groups are weakly linked to the benzene nucleus. The nitro group is a conspicuous exception, however, since attempts to displace it from *p*-nitro-aniline and *p*-nitrophenol failed, even at 60–5°, the resulting precipitate giving in each case a theoretical titration with titanous chloride for the dibromonitro compounds. Dhar[14] has, however, displaced the nitro group by bromine at high temperatures.

Since *m*-hydroxybenzoic acid and metanilic acid give no precipitate

[11] Ref. 5b, vol. III, p. 480.

[12] Fuchs, *Monatsh.*, **36**, 113 (1915).

[13] Hoover, *J. Ind. Eng. Chem.*, **13**, 770 (1921). The tubes used were furnished kindly by Prof. C. R. Hoover of Wesleyan University.

[14] Dhar, *J. Chem. Soc.*, **117**, 993 (1920).

when tribrominated, an alternative gravimetric method of analysis is afforded for mixtures of these compounds with their isomers. An excess of bromine for trisubstitution is added at room temperature, and the precipitate of tribromophenol or tribromo-aniline is weighed and calculated as *ortho* and *para* acids. This is preferable to the volumetric method with the hydroxybenzoic acids, because of the difficulty in quantitative dibromination. Either method is satisfactory with sulfanilic acid.

If a compound has two hydroxyl or two amino groups, or one of each, *meta* compounds should be tribrominated as before, because the influences of the two groups are in coöperation; but in *ortho* and *para* compounds the influences are opposed, with the result that no bromine should be consumed. This is the case with hydroquinone even at room temperature, and with pyrocatechol, *p*-phenylenediamine, and *p*-aminophenol when cooled to 0° to prevent oxidation. The other two *ortho* compounds are oxidized.

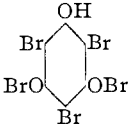
Although resorcinol is brominated readily and quantitatively, mixtures with hydroquinone always give low results unless an excess of at least one, and preferably two equivalents of bromine is added. It seems probable that, while hydroquinone shows no net consumption of bromine, it is temporarily oxidized to quinone, which is later reduced quantitatively to hydroquinone again by the hydriodic acid.

On bromination, *m*-phenylenediamine decomposes invariably, even at 0° when about two-thirds of the bromine is added, giving a black precipitate. When mixed with an equal amount of resorcinol, however, both compounds are tribrominated quantitatively at room temperature, with no decomposition. A reasonable explanation is that *m*-phenylenediamine first forms a compound, $C_6H_4(NBr_2)_2$, having four bromine atoms. Since only three positions in the nucleus can be substituted, the fourth bromine atom is free to oxidize the molecule. Resorcinol acts as a receptor for this fourth bromine atom, thus protecting the diamine. Other phenolic and amino compounds exercise a similar protective effect. *m*-Aminophenol, which is somewhat analogous to *m*-phenylenediamine, is tribrominated at room temperature without decomposition, probably because its intermediate compound, $BrOC_6H_4NBr_2$, has only three bromine atoms, all of which can be accommodated in the nucleus.

The analytical method might be applied also to certain trisubstituted derivatives, of which one type should be tribrominated, three dibrominated and two monobrominated. A few example reactions have been tried.

Thymol is dibrominated quantitatively according to the theory. *m*-Xylidine is easily oxidized, and its titration is a little high for monobromination. Vanillin gives a good titration for monobromination, when it is kept at zero. At room temperature, or a little above, like its parent, *p*-hydroxybenzaldehyde, it loses its aldehyde group, but it is difficult to make this reaction quite quantitative.

Phloroglucinol is tribrominated quantitatively according to the theory, giving a heavy colorless precipitate. Two additional moles of bromine, however, cause the precipitate to redissolve. A sixth mole produces a slight oily precipitate and no odor of excess of bromine is observed until more than six moles are added. Back titrations with thiosulfate solution after addition of potassium iodide show a net consumption of three moles of bromine and cause reprecipitation of tribromo-phloroglucinol. It is reasonable to suppose that the following compounds are formed,



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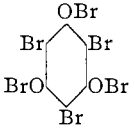

II

the former being soluble and the latter an oil. Aniline is not brominated to any extent by the former. This explanation is consistent with that offered for the behavior of *m*-phenylenediamine. Further evidence for preliminary substitution in the directing group will be offered in a later paper.

Details of the analytical method are as follows.

(*a*) **For Amino and Phenolic Compounds.**—One millimole of the sample is dissolved in 10 to 25 cc. of water or dil. sulfuric acid or alcohol, and a slight excess, 2 to 5 cc. over the calculated amount, of 0.13 *N* solution of potassium bromide and potassium bromate is added. The solution is acidified with about 7 cc. of 50% sulfuric acid. This gives the pale yellow color of an excess of bromine, the odor of bromine and usually a precipitate. A few drops of saturated potassium iodide solution are added, thereby liberating iodine, which is titrated back with 0.1 *N* sodium thiosulfate solution using starch as an indicator.

(*b*) **For Nitro Compounds.**—One and two-thirds millimoles of the sample are dissolved in 25 cc. of water or alcohol in a 500cc. Erlenmeyer flask with the aid of a little acid or alkali if necessary. The solution is made strongly acid with 25 cc. of 50% sulfuric acid and heated to boiling, the flask being swept out with carbon dioxide for five minutes to displace the air, which would oxidize titanous chloride. Fifty cc. of 0.25 *N* titanous chloride solution is added through a hole in the stopper of the flask. The solution is boiled for five minutes and cooled to room temperature, or in certain cases to 0° by means of ice, while the carbon dioxide stream is still continued. The flow of gas is stopped and a slight excess of the bromide-bromate solution, as shown by the color, odor or a spot test on potassium iodide starch paper, is added. Potassium iodide solution is added and the iodine is titrated with sodium thiosulfate solution.

In the case of the nitrotoluenes and the nitrochlorobenzenes, the solution cannot be boiled at first because of loss by volatilization. The flask is swept out with carbon dioxide, which is then stopped, the sample is introduced in alcoholic solution, titanous chloride is added in the cold and the solution is heated over a small flame, requiring 15 minutes to bring it to boiling. The analysis is completed as in the other cases.

Preparation and Standardization of Solutions

0.25 *N* Titanous Chloride.—A mixture of 160 cc. of "20% titanium chloride" and 400 cc. of concd. hydrochloric acid per liter of solution is preserved under an atmosphere of hydrogen both in the supply bottle and in the buret, the top of which is connected

to the supply bottle. It decreases in strength on standing, about 4% the first month and 0.5% per month thereafter, and should be standardized accordingly.

It is standardized by reduction of some pure nitro compound, preferably *p*-nitroaniline. The reduction is carried out as in (*b*) above, but instead of cooling the solution, the excess of titanous chloride is titrated hot with 0.1 *N* ferric alum solution using 2 cc. of methylene blue as an indicator. The end-point is green.

0.1 *N* Ferric Alum.—Fifty g. of crystallized ferric ammonium sulfate, $FeNH_4(SO_4)_2.12H_2O$, per liter of solution is dissolved, a little sulfuric acid is added, the solution is filtered if necessary and diluted. It is standardized by a "relation" with titanous chloride, following the procedure described above, but without a sample.

Methylene Blue.—A solution of 0.5 g. of the dye in 500 cc. of water is filtered, decolorized with titanous chloride and preserved under carbon dioxide.

0.13 *N* Potassium Bromide-Potassium Bromate Solution.—Three and one-half g. of potassium bromate and 13 g. of potassium bromide are dissolved for each liter of solution. When the solution is to be used for analyses involving substitution only, 5.5 g. of potassium bromide per liter is sufficient. The solution is standardized by titration against a sample of pure aniline.

0.1 *N* Sodium Thiosulfate Solution.—Twenty-five g. of crystallized sodium thiosulfate is dissolved for each liter of solution. The resulting solution is standardized by titrating the iodine liberated when a definite volume of the bromide-bromate solution is acidified and potassium iodide added.

TABLE II

BROMINE TITRATION

Compound	Bromine solution Cc.	Milli-equivalents Found	Milli-equivalents Calcd.	Error[a] %	Remarks
Toluidines					
o	32.74	2.002	2.000	0.2	
o	32.58	1.993	2.000	.7	
m	48.90	2.991	3.000	.9	Acidified before addition of bromine Ice in solution
m	48.95	2.994	3.000	.6	
p	32.68	1.999	2.000	.1	
p	32.75	2.003	2.000	.3	
1/3 each (*o*, *m*, *p*)	38.36	2.346	2.333	1.3	
2/3 *o*, 1/3 *m*	38.02	2.325	2.333	0.8	
Nitrochlorobenzenes					
o	71.67	1.997[b]	2.000	0.3	
o	71.82	2.002	2.000	.2	
m	98.82	2.994	3.000	.6	
m	99.04	3.002	3.000	.2	
p	71.65	1.996	2.000	.4	Room temperature
p	71.76	2.002	2.000	.2	
p	71.72	1.999	2.000	.1	
1/3 each (*o*, *m*, *p*)	80.87	2.334	2.333	.1	
1/3 *m*, 2/3 *p*	80.54	2.324	2.333	.9	

[a] Error in per cent. as *meta* isomer.

[b] For nitro compounds, 1 2/3 millimoles were used in each case; 50 cc. of $TiCl_3$ was used in reduction, which is equivalent to 98.98 cc. of bromine solution. The excess of $TiCl_3$ requires 17.23 cc. of bromine solution. "Milli-equivalents found" is obtained by subtracting this 17.23 cc. from the titration, and dividing by 27.25 cc. (one milli-equivalent).

In Table II is given a tabulation of the experimental results obtained with *o*-, *m*- and *p*-toluidines and nitrochlorobenzenes, singly and mixed.

Similar results for other amino, phenolic and nitro compounds are summarized in Table III. These include all three isomers of each system, except where otherwise stated, and also various mixtures.

TABLE III

BROMINE TITRATION

Compounds	Titrations	Mean error %	Temp. °C.	Remarks
Aminobenzoic acids	6	0.7	−4	Acidified before bromine
Aminosulfonic acids (*m*, *p*)	8	.3	−4	Acidified before bromine
Bromo-anilines	6	.1	20	Acidified before bromine
Nitro-anilines	7	.5	20	25 cc. of alcohol
Aminophenols (*m*, *p*)	5	.8	−4	Acidified before bromine
Cresols	9	.6	20	25 cc. of alcohol
Dihydroxybenzenes	6	.8	−4	
Hydroxybenzaldehydes (*o*, *p*)	7	.3	10	15 cc. of alcohol
Hydroxybenzoic acids	6	1.1	−4	
Nitrophenols	6	0.7	20	25 cc. of alcohol
Nitrobenzaldehydes	8	.4	15	
Nitrobenzoic acids	15	.6	−4	
Nitrotoluenes (*o*, *m*)	5	.4	0	

Summary

A rapid and accurate method of analysis for the *meta* isomer of amino, phenolic and nitro derivatives of benzene has been developed. It depends upon the fact that in aqueous solution *m*-amino and phenolic compounds are substituted quantitatively by three atoms of bromine while *ortho* and *para* compounds receive only two.

The *meta* isomer can be determined with an accuracy of about 0.5%. The method has the following advantages over others.

1. It is more general than any except that employing freezing curves.
2. It is more rapid, requiring only 10 minutes for amino and phenolic compounds and 30 minutes for nitro compounds.
3. It can be applied to new cases with only a few preliminary experiments.
4. The compounds need not be of high purity.
5. Samples of 0.1 to 0.2 g. are sufficient for analysis.

The carboxyl, sulfonic acid and aldehyde groups have been shown to be displaced by bromine quantitatively at ordinary temperatures from *o*- and *p*-amino and phenolic compounds in aqueous solution.

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