The Free Radicals of the Type of Wurster's Salts

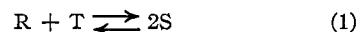BY L. MICHAELIS, M. P. SCHUBERT AND S. GRANICK

The univalent oxidation products of the aromatic p-diamines, or Wurster's salts,[1] are free radicals which may polymerize in a sufficiently concentrated solution and at low temperature or in the solid state.[2] This paper is concerned with their properties, especially their stability and color, in dilute solution where they appear only as free radicals. They are in general much more stable than the corresponding quinone diimines although the latter are not radicals. The absorption spectra of these radicals show a very distinct pattern of bands in the visible range of wave lengths varying according to substitutions of the hydrogen atoms either at the amino groups or at the ring. The influence of substitutions at the amino groups has been described by Piccard. This study will be extended here, and a study of the effect of substitutions at the ring will be added.

1. Stability.—The study of stability in the dissolved state is complicated by the fact that it is impossible to obtain any pure solution of these radicals at all. They exist only in equilibrium with one molecular species at a lower level of oxidation, the diamine, and another at a higher level of oxidation, the diimine. Since the latter are very unstable compounds, liable to undergo irreversible changes, such a system may undergo irreversible changes, which are not directly due to any lability of the radical itself. For this reason the criteria for stability or lability of the radical should be discussed first. Stability in general may be conceived as the reluctance to undergo chemical reactions. One is faced with an obvious ambiguity with respect to the definition and measurement of stability, because the tendency to enter into a chemical reaction depends also on the nature of the substance with which the substance in question is to react. This is true for all reactions except those which are strictly monomolecular such as radioactive decompositions. Among the various chemical reactions which a radical is inclined to undergo there are three types which might be chosen as criteria for stability.

If we designate, as previously, the three levels of oxidation–reduction by R, S, and T (the diamine, the semiquinone radical, and the diimine), and the dimerized radical as D, the stability of the radical may be measured either by the equilibrium constant of the reversible reaction

$$R + T \rightleftarrows 2S \qquad (1)$$

or by the equilibrium constant of the reversible reaction

$$2S \rightleftarrows D \qquad (2)$$

or (3) by the rate at which the free radical undergoes any irreversible reaction. The kind and rate of such a reaction depends on the solvent and on the nature of the substance with which the radical is to react.

The study of each such reaction will lead to a different notion of the stability of the radical. If we choose the equilibrium constant of reaction (1) as criterion for stability and compare the stabilities of various radicals of the homologous series, not only S is varied but also R and T. If we choose the constant of reaction (2), not only S is varied but also D. So the best comparison available of stabilities of the radicals among themselves seems to be a reaction of the type (3) as standard method, chosen in such a way that only the radical is varied, and the substance with which it reacts is always the same, namely, nothing else but a properly chosen solvent. Thus it seems to be the fairest and most natural method for measuring the stability of the radical just to measure its lifetime in a properly chosen solvent. This criterion of stability is preferable furthermore because the equilibrium constant of reaction (1) cannot be measured (except for diamino-durene) on account of the lability of the quinone diimine, and the process (2) from left to right does not take place to any measurable degree in dilute solution.

The criterion for stability, then, will be the lifetime of the radical in a properly chosen solvent. There is only one difficulty involved in this procedure which must be first overcome. It is characteristic of the systems to be investigated in this paper that the free radicals (the S forms, Wurster's salts in the present case) are much more resistant to irreversible changes when exposed to a solvent, than are the T forms, the quinone-di-

(1) R. Willstätter and J. Piccard, *Ber.*, **41**, 1458 (1908); J. Piccard, *ibid.*, **46**, 1843 (1913); E. Weitz, *Z. Elektrochem.*, **34**, 538 (1928); L. Michaelis, THIS JOURNAL, **53**, 2953 (1931); L. Michaelis and E. S. Hill, *ibid.*, **55**, 1487 (1933).

(2) J. Piccard, *Ann.*, **381**, 351 (1911); *Ber.*, **59**, 1438 (1926).

imines, though the latter are not free radicals. It is known that quinone diimines in all solvents not entirely water free, are very unstable; whereas some of the free radicals such as Wurster's blue, are very stable compounds even in an aqueous solution. Consequently, if in some particular case a radical in a certain solution has only a short lifetime, it cannot be decided directly whether the irreversible disappearance of the radical is due to its own lability, or to the lability of the diimine with which it is in equilibrium. How much of the labile diimine is present in equilibrium with the radical depends on the thermodynamical constant of the equilibrium $R + T \rightleftarrows 2S$. This constant need not show any simple relation to the tendency of the radical to undergo irreversible reactions. Hence we have to find a method to distinguish what may be designated as the *direct*, and the apparent or *indirect*, lability of the radical. The aim is to measure the direct lability of the radical. The lifetime of the radical in a properly chosen solvent will be taken as a measure of its stability provided the lability of the radical under the experimental conditions is a direct one, and not an indirect one. In order to show how this idea can be used in practice we shall describe four typical cases.

First Case.—If a solution of tetramethyl-*p*-phenylenediamine bihydrochloride, about 0.01 M, in an aqueous acetate buffer, *p*H 4.6, is oxidized with a very small amount of bromine, say not more than 1 atom of bromine to 50 or 100 molecules of the diamine, the intense blue color of the radical developed is stable for practically any length of time. It is known that the quaternary diimonium compound derived from this diamine is a compound extremely unstable in water. According to Willstätter even in the solid state it readily decomposes with production of formaldehyde. This experiment shows that the amount of the diimonium compound formed under the conditions chosen in equilibrium with the blue radical is vanishingly small, and the radical itself is very stable.

Second Case.—When the same experiment is performed with *p*-phenylenediamine instead of its tetramethylated derivative, the result is quite different. When aqueous acetate buffer is chosen as a solvent, the yellow color of this radical primarily formed on addition of bromine, turns pink in a few minutes. The rate at which this irreversible reaction takes place greatly depends on the

initial concentration of the diamine. When this is varied, keeping constant the amount of bromine used for the oxidation, the rate of the irreversible reaction is greatly diminished as the concentration of the diamine is increased. According to reaction (1) the amount of diimine formed is decreased as the concentration of the diamine is increased. This experiment shows that the irreversible reaction is caused essentially by the irreversible changes of the diimine present and that the free radical is much more stable in this solvent than is the diimine. The diimines which have been prepared by Willstätter[3] are all extremely unstable in organic solvents not perfectly water free. When methanol—even containing as much as 20% water—is chosen as a solvent, the life-time of the radical is much longer, but also here the lifetime of the radical is increased as the initial concentration of the diamine is increased. The concentrations of the diamine and of bromine being properly chosen, the lifetime of the radical may be extended to more than a whole day. By extrapolation we may infer that the direct lifetime of this radical is very long, and its apparent lability for the greatest part is due to the fact that the equilibrium constant of the reaction (1) is such as to cause the two steps of oxidation greatly to overlap. This is a case where the direct lifetime proper of the radical can be proven to be quite long, although at first glance the radical may have the appearance of being very labile.

Third Case.—When the same experiment is performed with the diamine (formula A) the radical has a half lifetime of about ten minutes in an aqueous acetate buffer. In this case the lifetime is not influenced at all by varying the initial concentration of the diamine. This radical itself has a restricted lifetime and its breakdown is not caused indirectly by the diimine which may be in equilibrium with it. The direct disappearance of the radical is so fast that the rate of the indirect breakdown, if there be any, plays no role.
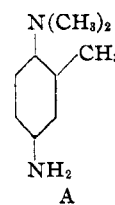
Fourth Case.—When the same experiment is performed with symmetrical dimethyldiaminodurene, no radical is formed under any conditions. In this case the corresponding diiminium compound, although not perfectly stable for any

(3) R. Willstätter and E. Mayer, *Ber.*, **37**, 1494 (1904); R. Willstätter and A. Pfannenstiehl. *ibid.*, **37**, 4605 (1904); R. Willstätter and H. Kubli, *ibid.*, **42**, 4135 (1909).
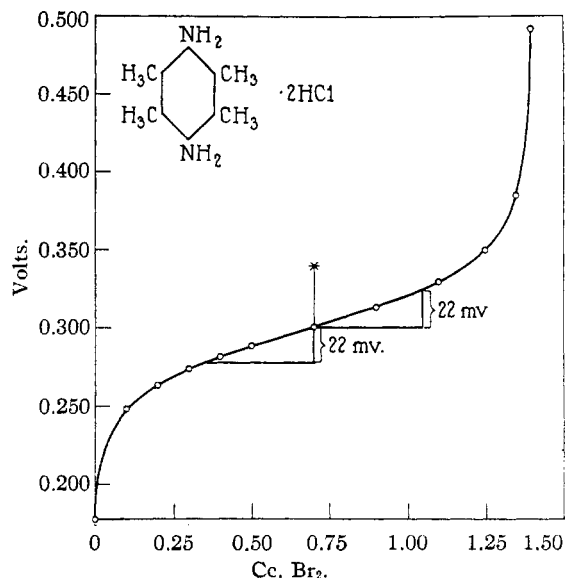
Fig. 1.—Durene diamine bihydrochloride, 50 cc. of 0.001 M in a solvent consisting of 8 volumes of methanol + 2 volumes of aqueous acetate buffer of pH 4.62 (apparent pH of the mixture is 6.21) is titrated with aqueous bromine. Potentials are constant throughout the titration. The titration curve indicates a two-step oxidation with the formation of an intermediate radical (which is yellow). The curve is symmetric, the index potential 22 mv. Hence, the semiquinone formation constant $k = 1.0$; maximum ratio of semiquinone to total substance is 0.33. In this case both the radical and the diimine are stable, at any rate within the period necessary for titration. The initial solution is colorless; it turns yellow during the titration and fades out again at the end-point of titration.

length of time, is yet stable enough to allow a satisfactory potentiometric titration in 80% methanol. The shape of the titration curve confirms that there is no intermediate radical formed at all. Here it is meaningless to speak of the lifetime of the radical. The fact that it is never formed to any measurable extent is itself an expression of its utmost instability, although it must be conceded that here the term "instability" has not precisely the same meaning as in the other cases.

These four examples cover all cases which may be actually encountered. Using critically such tests for stability, the results obtained may be summarized as follows:

The radical derived from p-phenylenediamine may be considered as the parent substance. Considering its stability proper according to the above criterion, it is a rather stable compound. Its well-known instability in aqueous solution is essentially an indirect one. Its direct stability can be

modified by substitutions. These may be either at the amino groups or at the ring. Considering first compounds with the amino groups unsubstituted, it can be generally stated that substitution of the H atoms in the ring by methyl groups has no influence on the stability exceeding the limits of error of the method. Comparing the compounds not methylated at the ring but methylated at the amino groups, methyl groups appear to increase the stability. The tetramethylamino compound is the most stable of the series. There is, however, no cogent proof that these differences may not be due to differences of the indirect labilities. When both the amino groups and the H atoms of the ring are substituted, the effect largely depends on the particular structure. A methyl group at the ring in ortho position to an unmethylated amino group has sometimes very little effect, sometimes more, and, if any at all, a destabilizing effect. However, if a methyl group is in ortho position to a methylated amino group, it always has a distinct destabilizing effect; two
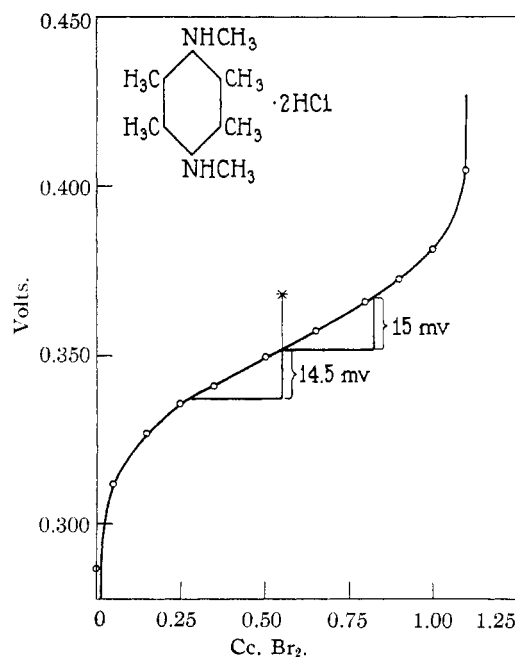

Fig. 2.—Symmetrical dimethyldurene diamine bihydrochloride. Conditions of titration the same as in Fig. 1. Here also a full titration curve is obtained. The index potential is between 14 and 15 mv., indicating that no intermediate radical is formed, in agreement with the fact that no trace of any intermediate colored compound is visible during the titration. The point * in this and all the other curves marks the end of the first step, where 1 atom of bromine per molecule of the diamine has been added.
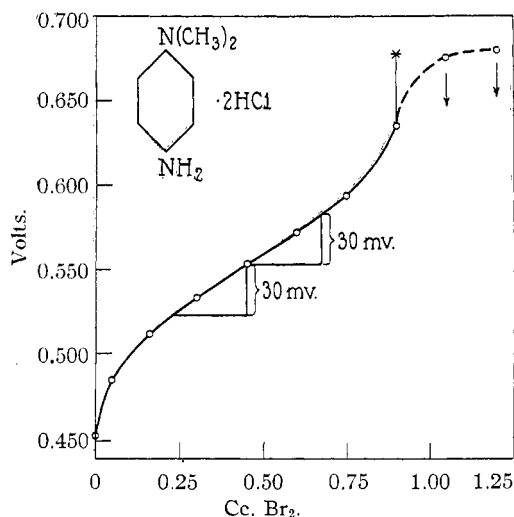
Fig. 3.—Unsymmetrical dimethyl-p-phenylenediamine bihydrochloride, 50 cc. of 0.001 M solution in a mixture of 8 volumes of methanol and 2 volumes of 0.05 M aqueous acetic acid (apparent pH of mixture is 3.1) are titrated with aqueous bromine. Potentials are nearly steady only to the end of the first step which is marked with a star (*). During the second step, potentials show considerable drift, as indicated by arrows. Since there is a slight jump at the end of the first step this first step can be treated approximately as a univalent step with no overlapping. The index potential of this univalent step should be 28.6 mv. It is found to be 30 mv., which is in sufficiently good agreement considering the limits of accuracy under the conditions prevailing. Hence, the curve suggests two successive univalent steps of oxidation with no, or very little, overlapping; the first step is reversible; the second step is irreversible due to the spontaneous breakdown of the diimonium compound.

methyl groups, especially if both are ortho to a methylated amino group, decrease the stability to an enormous extent. It may be added that the lifetime of any of these compounds is not affected by diffuse daylight.

To give some examples, the radical derived from 1 (Wurster's red) is a very stable one; 2 is
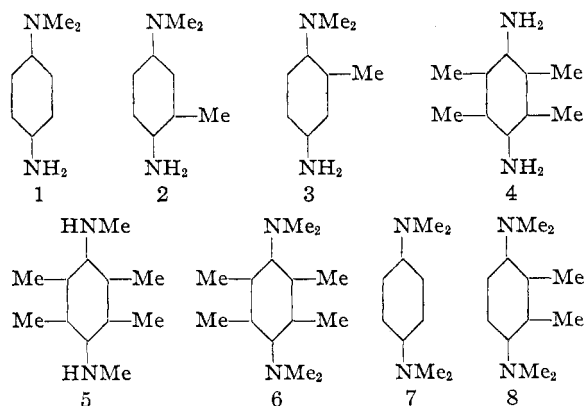
almost as stable; but 3 has a half-lifetime only of less than five minutes in an aqueous solution; the radical derived from 4 is very stable; 5 and 6 do not establish any radicals at all; 7 gives a very stable radical, perhaps the most stable of all; whereas the radical derived from 8 fades out in an aqueous solution within a few minutes.

Substitutions of one single H atom at the ring other than by methyl such as by OCH_3, Cl, SO_3H, all have a distinct destabilizing effect.
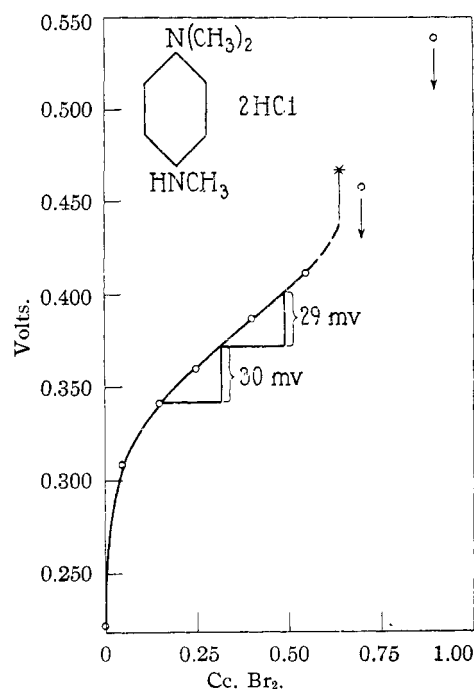

Fig. 4.—Trimethyl-p-phenylenediamine dihydrochloride. Conditions of titration similar to those of Fig. 3. Potentials are fairly stable during the first step of oxidation; the index potential corresponds practically to a univalent oxidation (theoretically, 28.6 mv.) and no overlapping with the second step. During the second step of oxidation potentials drift rapidly, showing the instability of the diimine.

The decay of the radical can be observed most easily from the change of its color. In some cases the color simply fades out, in others a new dyestuff may be formed due to condensations. In addition, potentiometric measurements give some indications as to the stability of the radical. If both the radical and the diimine are stable, a potentiometric titration of the diamine with bromine gives a full reproducible potentiometric titration curve up to the end-point of titration. Diaminodurene is the only example of this kind among the
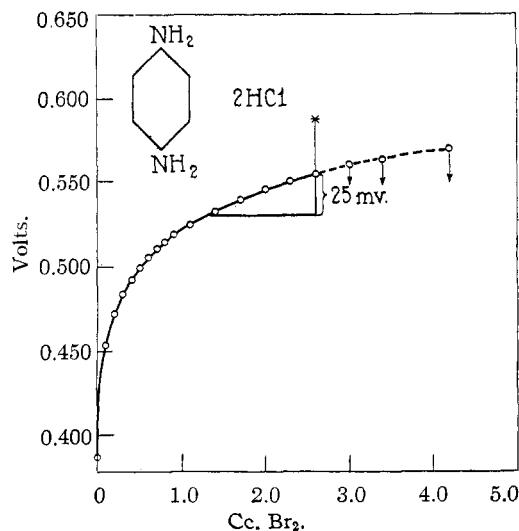
Fig. 5.—p-Phenylenediamine dihydrochloride. Conditions of titration similar to those of Fig. 3. The potentials are almost, although not perfectly, steady in the first part of the titration and then begin to drift rapidly.

compounds investigated.[4] If the radical is stable and the diimine is unstable, steady potentials are obtained only in the first stages of the titration as long as there is no appreciable overlapping of the two steps of oxidation. If the radical itself is unstable, the potentials will not be steady even in the first stages of the titration. Many examples of these types of titration curves were obtained, and some are reproduced graphically in the experimental part. Thus a critical discussion of the potentiometric titration curves gives an indication as to the comparative stability of various radicals. The results of the two methods never showed any discrepancy. The limiting case of instability of a radical is the case where no radical is formed at all. If in such a case the diimine happens to be a relatively stable compound, the titration curve should have the shape of a reversible bivalent titration without any intermediate step. Such a case is realized for symmetric dimethyldiaminodurene. If a radical is not formed, and the corresponding diimine compound is not stable either, no steady potentials can be obtained at all during the titration. Such a case is realized in tetramethyldiaminodurene.

2. Absorption Spectra.—The absorption bands for the radicals of the diamines substituted in the amino group, but not in the ring, have been

(4) Another example of this kind is symmetrical diphenyl-p-phenylenediamine [Michaelis and Hill, THIS JOURNAL, **55**, 1481 (1933)]. Aromatic substituents are not included in the present paper.
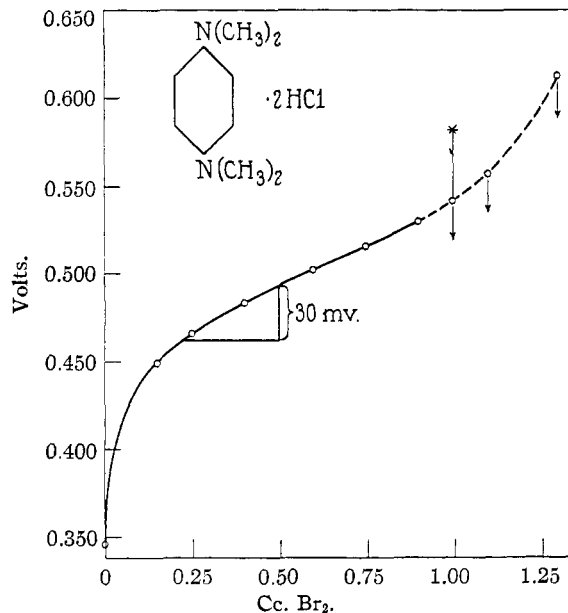

Fig. 6.—Symmetrical tetramethyl-p-phenylenediamine dihydrochloride under the same conditions as in Fig. 3. This curve is similar to that of Fig. 3 except that the potentials begin to drift a little earlier.

described by Piccard. There are two distinct bands and, if the amino groups are in part or all methylated, a third less conspicuous one toward the shorter wave lengths. Each methyl group substituted in the amino group has a bathochromic effect, displacing the bands toward longer wave lengths. The molar absorption is distinctly greater for the tri- and tetramethyl compounds than for the others. There is scarcely any dif-
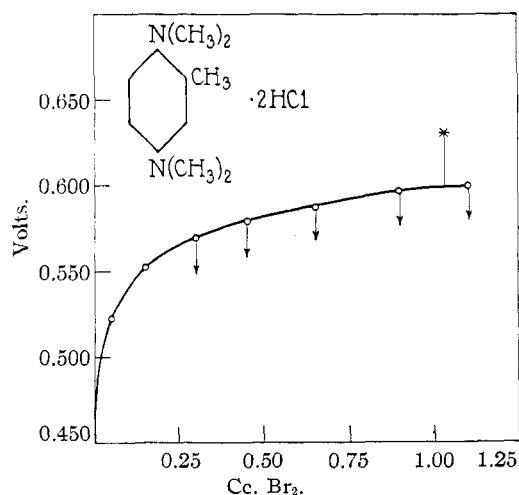

Fig. 7.—Symmetrical tetramethyldiaminotoluene dihydrochloride. Same conditions as in Fig. 3. This curve is one example for a much more unstable radical than Figs. 5 or 6. Potentials drift even in the first stages of titration.

ference in the effect of methyl and ethyl; however, carboxymethyl (CH_2COOH) has a stronger bathochromic effect.

Comparing compounds not methylated at the amino groups, the effect of gradually attaching methyl groups at the ring is no bathochromic effect at all, but consists in changing the pattern of the bands as follows (Fig. 8). Without any methyl in the ring the first peak (the one toward the shorter wave lengths) is higher than the second; with one methyl, the two peaks are blurred into one; with two and more methyls, the first peak is decreased in height, the second increased; this effect is greatest in the durene compound.

Comparing the effect of substitutions at the ring in compounds with one or more methyls at the amino groups, the effect of one methyl in the ring consists usually in blurring the pattern; the two bands overlap to a greater extent (Figs. 10, 11, 13). Two methyl groups in the ring make the absorption pattern rather diffuse, (Figs. 9, 13) showing a
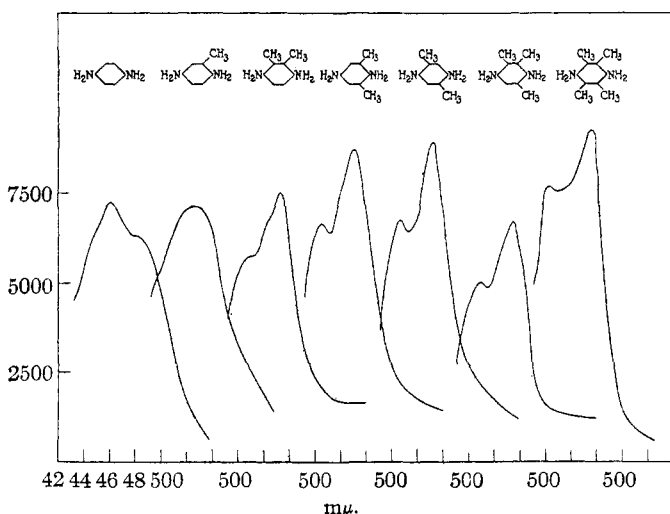

Fig. 8.—Molar absorption plotted against wave lengths for radicals of diamines methylated at the ring, but not at the amino groups. In reality all the curves overlap. All curves should be imagined as displaced horizontally to the left so that the points marked "500 mμ" coincide.

weak, broad, blurred band. As the bands are blurred the total molar absorption is diminished.

3. Interpretation.—The fact that such radicals are capable of existence at all can be attributed to a particular symmetry of structure resulting in resonance. The molecule has an odd number of electrons; the electrons may be paired in various ways, leaving always one unpaired electron. The odd electron has no fixed place, but

there is resonance among various limiting states. Each of them may be considered as contributing a share to the resonating or mesomeric state but none of them can exist as a separate, tautomeric structure for any conceivable length of time. Those two limiting states which may be considered as the main contributors to the resonating state may be symbolized[5] by 9 and 10. There are more configurations of which 11 and 12 are examples.
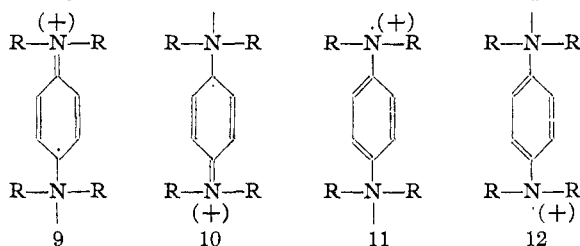
Resonance among these various structures can take place only if the six carbon atoms of the ring, the two nitrogen atoms and the four atoms attached to the two nitrogen atoms, all are located in one plane. Structures such as 9 or 10 resemble a quinone structure with an odd electron at a carbon atom, while structure 11 or 12 represents a benzenoid structure with an odd electron at a nitrogen atom. Radicals of this type may be designated as semiquinones. The ambiguity as to the benzenoid and the quinonoid structure, or the meriquinoid character which is responsible for the color, lies within a single ring,[6] in contrast to ordinary organic dyestuffs, such as indophenols or triphenylmethane dyes, which are not radicals, and in which this ambiguity is distributed over two (or three) rings. It is the aim of this paper to show that all those radicals showing little stability possess a structure which counteracts a coplanar arrangement such as would be necessary for resonance.

Although not all, yet some of the effects of substitution may be accessible to a rational interpretation at the present time. It is very remarkable that methyl groups in the ring have such a strong destabilizing effect on the radical if the amino groups also are methylated. This effect can be accounted for as follows. In the resonating state, the bond between N and C is

(5) In these formulas letters are atomic kernels, dashes are pairs of electrons, which represent a chemical bond only if they connect two kernels, and the dot is a single electron.

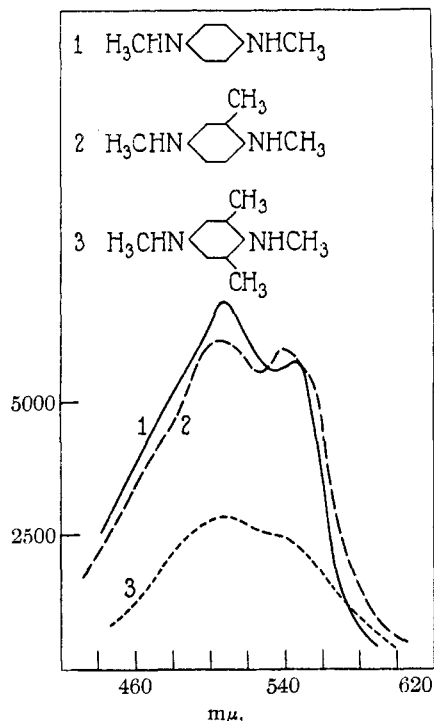(6) G. Schwarzenbach and L. Michaelis, THIS JOURNAL, **60**, 1667 (1938).

Fig. 9.—Molar absorption plotted against wave lengths for radicals of three symmetrical dimethyl diamines differing by substitution at the ring.

something intermediate between a single and a double bond. The properties of such a quasi double bond will approach those of a double bond and restrict the free rotability of the amino group around this bond as the axis. The two atoms linked by the double bond and the four atoms attached to them must lie in one plane. This plane must be also the plane of the benzene ring. If such a coplanar arrangement requisite for resonance is hampered, stability is diminished.[7]

Some Additional Remarks on the Solvent and on pH.—The stability of all of these radicals depends on pH. Even the most stable radicals are stable only within a certain pH range, which in aqueous solution is usually from pH 3.5 to 6. Outside this range all of these radicals become unstable. This is easily accounted for by taking into consideration that among the three possible states of ionization of the radical only formula 2 can exhibit the resonance necessary for the stability. This state, or rather the resonance system of which formula 2 is one of the limiting states, secures whatever stability may be inherent in such an unsaturated compound. A pH very suitable

(7) Compare: L. Pauling and G. W. Wheland, J. Chem. Phys., 1, 362 (1933); E. Hückel, Z. Physik, 83, 632 (1933); Z. Elektrochem., 43, 752 and 827 (1937).
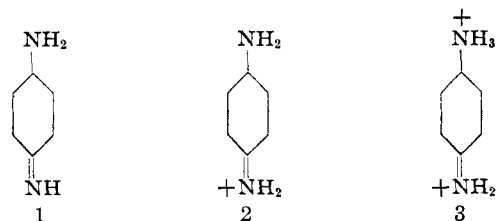
for stability in most compounds in aqueous solution is 4.6; in 80% methanol it is about pH 3 for most of the compounds, and about pH 6 for the durene compounds. One easily understandable exception is the radical derived from tetracarboxymethyl-p-phenylenediamine, which has its best stability in aqueous solution at pH 7. At a lower pH, not all of the four carboxyl groups are ionized. If there be any asymmetry with respect to the free electrical charges at these carboxyl groups, resonance will be counteracted.

Fig. 10.—Another example of the influence of substitution at the ring upon the pattern of the absorption spectrum.

It has been pointed out before that the radical of p-phenylenediamine is very much more stable in methanol than in water. As the amino groups are progressively methylated, the difference of the stability in aqueous and in alcoholic solutions becomes much smaller, and in the tetramethyldiamino compound the radical is perfectly stable both in water and in alcohol. This is quite different from the behavior of the diimines which are all quite unstable in water, and even in alcohol if not
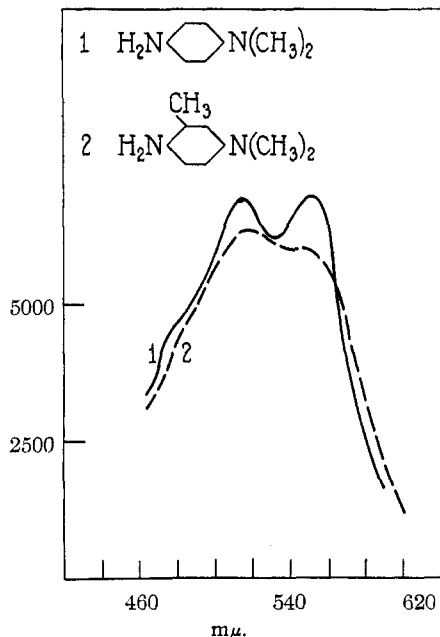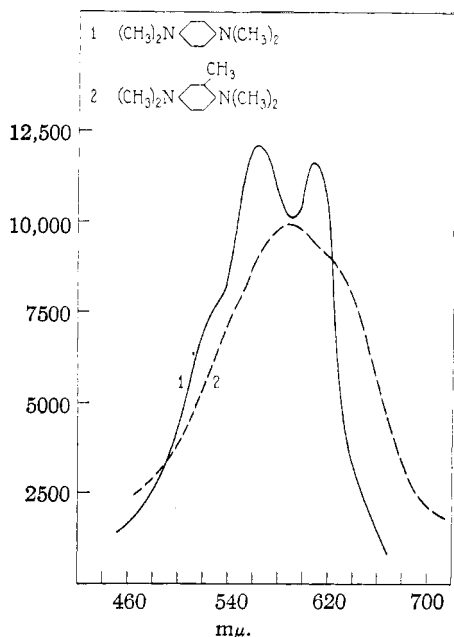
Fig. 11.—A further example of the influence of substitution at the ring upon the pattern of the absorption spectrum.

quite water free; whereas the stability of the radicals in methanol is scarcely diminished even if the
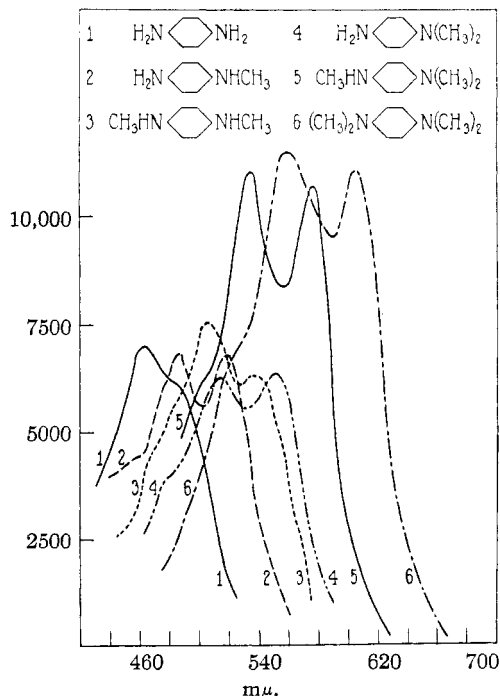

Fig. 12.—Molar absorption plotted against wave lengths for radicals derived from diamines substituted at the amino group but not at the ring. The tetracarboxymethyl derivative is not included in this graph. It is shown in Fig. 13, the last curve, dotted line.

alcohol contains 20% of water. The only diimines which in such a solvent have a sufficient stability to allow reproducible potentiometric titration curves throughout both steps of oxidation are the diimine compounds derived from diaminodurene and symmetrical dimethyldiaminodurene.
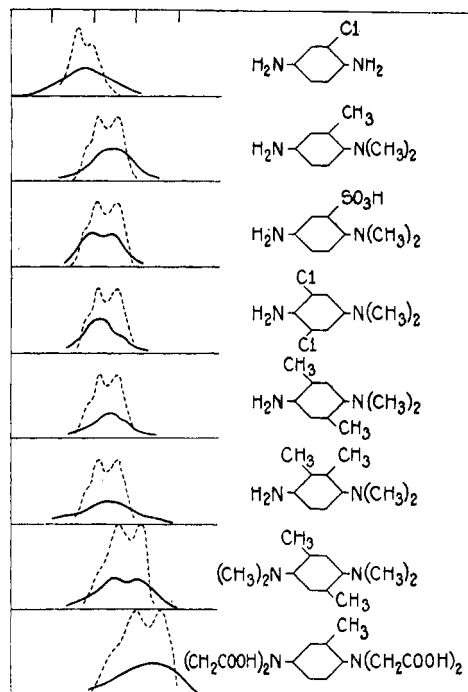
Fig. 13.—Rough sketches of absorption spectra of some compounds substituted at the benzene ring which are not stable enough for accurate measurements of the absorption (drawn out curves). They are obtained by comparing in the hand spectroscope the freshly prepared solutions with those obtained by the homologous, more stable compound with no substitution at the ring. The latter is always plotted in the dashed curve, reproduced from the accurate measurements with the spectrophotometer.

The authors are greatly indebted to Professor Linus Pauling for comments and advice with respect to some of the theoretical discussions.[8]

Experimental

1. Preparation of the Compounds.—All of the *p*-diamines used in this work were prepared as the dihydrochlorides. 1,4-Diaminobenzene, 1,4-diamino-2-methylbenzene and 1-amino-4-dimethylaminobenzene were obtained as commercial preparations and purified by dis-

(8) Professor L. Pauling has drawn our attention to the following analogous case of steric hindrance on resonance: Birtles and Hampson [*J. Chem. Soc.*, 10 (1937)] show that the magnitude of the electric dipole moment of nitrobenzene can be accounted for by resonance due to coplanar arrangement of the NO₂ group and the benzene ring. In nitrodurene this effect of the NO₂ group is strongly diminished.

solving in boiling methanol or boiling methanol containing 10% of water. The solution is decolorized with Darco G. 60 and the hydrochlorides reprecipitated by addition of 5 to 10 volumes of acetone and about 5% volume of concentrated hydrochloric acid.

The symmetrical N,N'-dimethyl derivatives, 1,4-di-(methylamino)-benzene, 1,4-di-(methylamino)-2-methyl-benzene, 1-4-di-(methylamino)-2,6-dimethylbenzene and 1,4-di-(methylamino)-2,3,5,6-tetramethylbenzene were all prepared similarly. For example, 12 g. of 1,4-diamino-benzene dihydrochloride in 50 cc. of dry pyridine is heated with 26 g. of toluenesulfonyl chloride at 100° for one and one-half hours. The product is precipitated by pouring the mixture into water and is recrystallized by dissolving in dilute sodium hydroxide solution and adding acetic acid. This ditosyl derivative is methylated in aqueous alkali by the use of excess dimethyl sulfate and the crystalline product is filtered off and washed with dilute alkali. The tosyl groups are removed by warming this product at 90° in a mixture of 30 cc. of acetic acid and 60 cc. of concentrated sulfuric acid until a clear solution results and then for about two hours more. The mixture is diluted with water, made alkaline and extracted with ether. The base is dissolved in 300 cc. of acetone and the dihydrochloride precipitated by the addition of 6 cc. of concentrated hydrochloric acid. It is recrystallized by dissolving in hot methanol and adding 5% volume of concentrated hydrochloric acid and 5 volumes of acetone.

1-Amino-4-methylaminobenzene was prepared from methylacetanilide (55 g.) by nitration in a cold solution of 55 cc. of acetic acid and 110 cc. of sulfuric acid with 19 cc. of fuming nitric acid (d. 1.5); reduction of this nitro compound with stannous chloride in concentrated hydrochloric acid and hydrolysis of the resulting product by heating in this acid mixture under reflux for five hours. The base is separated and the dihydrochloride precipitated from acetone as above.

1-Methylamino-4-dimethylaminobenzene was prepared from 1-amino-4-dimethylaminobenzene by tosylating, methylating and hydrolyzing as for the N,N'-dimethyl derivatives.

A number of the desired compounds were prepared by coupling the appropriate amino compound with diazotized sulfanilic acid, recrystallizing the resulting azo compound and reducing it in boiling water containing a trace of acid by means of zinc dust.[9] By this method there were prepared 1-amino-4-dimethylamino-3-methylbenzene, 1-amino-4-dimethylamino-2-methylbenzene, 1,4-diamino-2,5-dimethylbenzene, 1-amino-4-dimethylamino-2,5-dimethylbenzene, 1,4-diamino-2,6-dimethylbenzene, 1,4-diamino-2,3-dimethylbenzene and 1-amino-4-dimethylamino-2,3-dimethylbenzene.

Pseudocumene was prepared in pure form from a technical product by the method of Jacobsen.[10] The pseudocumene sulfonic acid was recrystallized twice by dissolving in water and adding an equal volume of concentrated hydrochloric acid. The pseudocumene, b. p. 166–167°, obtained from this sulfonic acid was nitrated by the method of Schultz[11] and reduced to pseudocumidine.

The subsequent transformation to 1,4-diamino-2,3,5-trimethylbenzene followed the method of Smith.[12]

Most of the N,N'-tetramethyl compounds were prepared either from 1,4-diamino or 1-amino-4-dimethylamino dihydrochlorides by heating with approximately a 50 to 100% excess of methanol in a sealed tube at 150° for eight hours. The free bases were separated in ether or chloroform and distilled at about 1 mm. pressure. In most cases no attempt was made to crystallize the resulting oily bases but these were converted directly in acetone to their dihydrochlorides.

Methylation of diaminodurene with methanol at 150° led, however, to the symmetrical N,N'-dimethyl derivative (m. p. of the base 93°) identical with that obtained by the method described above for preparing N,N'-dimethyl derivatives. This N,N'-dimethyldiaminodurene with nitrous acid in aqueous acid solution gives a dinitroso derivative quite smoothly (m. p. 212°). However, by refluxing diaminodurene in a methanol–water mixture with methyl iodide and sodium carbonate, tetramethyldiaminodurene can be obtained directly (m. p. of the base 67°).

1,4-Tetraethyldiaminobenzene and 1-dimethylamino-4-diethylaminobenzene were prepared from 1,4-diaminobenzene and 1-dimethylamino-4-aminobenzene, respectively, by heating 8 g. of the hydrochlorides in sealed tubes with 15 cc. of absolute ethanol, 1 g. of calcium chloride, 1 g. of cuprous chloride and 1 g. of sodium bromide. The bases are distilled and the hydrochlorides recrystallized from acetone as usual.

2,5-Diaminobenzenesulfonic acid monohydrochloride was prepared by reduction of 2-amino-5-nitrobenzenesulfonic acid with stannous chloride and recrystallization of the product by dissolving in boiling water and precipitating with an equal volume of concentrated hydrochloric acid.

2-Dimethylamino-5-aminobenzenesulfonic acid monohydrochloride was prepared by heating 1-chloro-5-nitrobenzenesulfonic acid with dimethylamine at 100° for two hours and reducing the resulting product with stannous chloride. The tin is removed with hydrogen sulfide and the hydrochloride is recovered by evaporation. It is recrystallized by dissolving in a methanol–water mixture and precipitated with acetone.

The tetracarboxymethyl compounds were prepared as described previously.[13]

2. Compounds not Methylated at the Amino Groups.—The properties of the radicals derived from p-phenylenediamine and its homologs substituted at the ring but not substituted at the amino groups are summarized in Table I.

These compounds are more difficult to judge than the others, because they show a greater overlapping of the two steps of oxidation. If the diimine is relatively stable (as in no. 7), the radical is perfectly stable also. If the diimine is very unstable (as in no. 1), it is always obvious that the radical is at least very much more stable than the diimine. The apparent instability of the radical is either in part or entirely an indirect one as can be proved for all these compounds with the "concentration test" described above. Using a higher concentration of the diamine, but

(9) E. Noelting and G. Thesmar, *Ber.*, **35**, 628 (1902).

(10) O. Jacobsen, *Ann.*, **184**, 199 (1877).

(11) G. Schultz, *Ber.*, **42**, 3606 (1909).

(12) L. I. Smith, THIS JOURNAL, **56**, 472 (1934).

(13) L. Michaelis and M. Schubert, *J. Biol. Chem.*, **106**, 331 (1934).

TABLE I

The first column gives the diamine from which the radical is derived by partial oxidation with bromine. All compounds were prepared as bihydrochlorides, except for the two last ones. All compounds mentioned in the table gave satisfactory analyses for N and Cl.

		Color	Lifetime	$m\mu$		Type	Potential behavior in Br₂ titration in solvent indicated[h]
			p-Phenylenediamines				
1	Unsubstituted diamine (1,4)	Yellow (turning blue)	4–8 hrs.	462	479	Sharp	Steady to 75% of 1st step
2	2-Methyl-	Yellow (turning brown)	4–8 hrs.		466	Broad	Steady to 75% of 1st step
3	2,5-Dimethyl-	Yellow (fading out)	2–3 days	452	480	Sharp	Steady to 75% of 1st step
4	2,6-Dimethyl-	Yellow	12 hrs.	452	480	Sharp	
5	2,3-Dimethyl-	Yellow	12 hrs.	452	480	Sharp	
6	2,3,6-Trimethyl-[a]	Yellow	2–3 days	452	480	Sharp	Steady to 70% second step
7	2,3,5,6-Tetramethyl-[a]	Yellow	2–3 days!	452	480	Sharp	Steady throughout both steps
8	2-Methoxy-	Yellow	15 min.	475		Broad	Unsteady
9	2-Sulfonic acid-[b]	Yellow-pink	2–3 sec.	. . .	. . . .		Unsteady
10	2-Chloro-	Pink-yellow	2–3 min.	475		Broad	Unsteady
11	2,6-Dichloro-	Yellow	2–3 sec.	. . .		Diffuse	Unsteady
		Monomethyl-*p*-phenylenediamine					
12	Unsubstituted	Orange-pink	1 day	483	516	Sharp	Steady to 100% of 1st step
		Symmetrical Dimethyl-*p*-phenylenediamines					
13	Unsubstituted	Pink	1 day	508	540	Sharp	Steady to 100% of 1st step
14	2-Methyl-	Pink	1 day	505	540	Sharp	Steady to 100% of 1st step
15	2,6-Dimethyl-	Pink	2 hrs.	505	540	. . . .	. . . .
16	2,3,5,6-Tetramethyl-[a]	Colorless	No radical	. . .	. . .	. . . .	Steady[c]
		Unsymmetrical Dimethyl-*p*-phenylenediamines (1-Dimethylamino-4-aminobenzene)					
17	Unsubstituted	Red	>7 days[d]	515	550	Sharp	Steady to 100% of 1st step[e]
18	2-Methyl-	Violet-red	5 min.	520		Broad	Unsteady
19	3-Methyl-	Red	2 days!	515	550	. . . .	Steady to 100% of 1st step
20	2,5-Dimethyl-	Violet-pink	1 min.	490	600	Broad	Unsteady
21	2,3-Dimethyl-	Violet-pink	20 sec.	470	510	Broad	Unsteady
22	2-Sulfonic acid	Pink	2 min.	495	530	. . . .	Unsteady
		Trimethyl-*p*-phenylenediamine					
23	Unsubstituted	Purple-red	>7 days	536	578	Sharp	Steady to 90% of 1st step
		Symmetrical Tetramethyl-*p*-phenylenediamines					
24	Unsubstituted	Blue	Weeks!	560	606	Sharp	Steady to 100% of 1st step
25	2-Methyl-	Blue	1 day	590		Broad	Steady to 30% of 1st step
26	2,5-Dimethyl-	Blue	2–3 hrs.	540	560	Diffuse	Unsteady
27	2,3-Dimethyl-	Blue	1 min.	Diffuse		Broad	Unsteady
28	2,3,6-Trimethyl-	No radical formed		. . .	. . .	. . . .	Unsteady
29	2,3,5,6-Tetramethyl-	No radical formed		. . .	. . .	. . . .	Unsteady
		Miscellaneous *p*-Phenylenediamines					
30	*unsym.*-Dimethyl-diethyl-[f]	Blue	14 days	560	606	Sharp	Steady to 100% of 1st step
31	Tetraethyl-	Blue	14 days	560	606	Sharp	Steady to 100% of 1st step
32	Tetracarboxymethyl-[g]	Blue	14 days	596	645	Sharp	Steady to 80% of 1st step
33	Salt of 2-methyl-tetra-(carboxymethyl)-	Blue	5 min.	Very diffuse spectrum			Unsteady

[a] Dissolved in 8 volumes of methanol + 2 volumes aqueous acetate buffer, *p*H 4.6. [b] Dissolved in aqueous acetate buffer, *p*H 4.6. In all other cases, where no letter is indicated, the solvent is 8 volumes of methanol + 2 volumes of 0.005 *N* aqueous solution of acetic acid. [c] Curve for a simple bivalent oxidation without intermediate step. [d] In absence of O₂, color and intensity change relatively slowly. After five days, the intensity had diminished appreciably, while the intensity of Wurster's blue and the trimethyldiamine had not changed under the same conditions. In aqueous acetate buffer (*p*H 4.6) even in the absence of oxygen, the solution turns to a dirty violet color in one day, the original bands being just visible. [e] Potential jumps to second step, and becomes unstable. [f] Indistinguishable from the tetramethyl compound. [g] Aqueous phosphate buffer at *p*H 7.26. [h] The potentials are, of course, never steady in the strictest sense of the word. There is also a certain arbitrariness in the stage of oxidation where a potential begins to show a distinct drift. The indications in this column can, however, be used for comparative purposes.

the same amount of bromine, the life-time is considerably longer than given in the table.

As the yellow color of these radicals disappears in time it either may be replaced by a different color due to condensation (e. g. in no. 1), or simply fade out if such condensations are inhibited owing to substitutions at the benzene ring (as in no. 3 or 7). If a condensation to a colored substance (pink or violet, according to the particular compound) takes place, the lifetime of the radical may be greatly underestimated since its yellow color is superseded by the deeper color of the secondary reaction product. The duration of the yellow color is greatest in pure methanol. However, in order to make possible a variation in pH so as to find out its optimum condition, and also in order to make possible the maintenance of a given pH during the corresponding potentiometric titration experiment as shown in the last column, the experiments as tabulated were performed in a solvent consisting of 80% methanol and 20% of an aqueous buffer. The latter was chosen so as to give the greatest stability. It was 0.05 M aqueous solution of acetic acid, producing in the mixture an apparent pH of about 3, for the compounds nos. 1 to 5; it was acetate buffer (pH 4.6) producing an apparent pH about 6 for compounds nos. 6 and 7.

In order to demonstrate how much the two steps of oxidation overlap in these compounds, the potentiometric titration curve for no. 7 (Fig. 1) may be chosen, which shows steady potentials throughout both steps of oxidation. From this curve it can be derived[14] that the semiquinone formation constant is equal to 1.0. Hence, in the midpoint of titration, where the concentration of the radical is maximum, not more than 33% of the substance exists as radical. When only 0.1 atom of bromine is added to 1 molecule of the diamine, 8% of the substance is present as radical, and still almost 1% as diimine: there is always appreciable overlapping. In aqueous solution the overlapping seems to be even greater, although definite figures cannot be given on account of the instability of the potentials.

So it is evident that the direct stability of the radicals nos. 1 and 7 is much greater than the lifetime in column III seems to indicate. Whether the differences of lifetime within this group are real differences in direct stability or indirectly caused by differences in the stabilities of the diimines, is difficult to decide. There is no doubt that the diimines, although all of them are unstable, differ greatly in stability among themselves according to the number and positions of the methyl groups at the ring which influence the ease and possibility of secondary reactions. For instance, the diimine no. 7 should be, and really is, much more stable than no. 1. It is not certain whether this difference is reflected also in the corresponding radicals.

In contrast, in the compounds 8 to 11, the lifetime of the radical is so short under any condition that the radical itself must be considered as unstable.

3. Compounds Methylated at the Amino Groups (Table I, from no. 12 to the end). (a) **Benzene Derivatives.**— The common feature of these compounds is the fact that the difference between the stability in aqueous and in al-

coholic solution is much less conspicuous. This difference becomes smaller as the number of methyl groups at the nitrogen is increased. In the extreme case, for the tetramethylamino compound, the difference between water and alcohol as a solvent vanishes entirely. The fact that these radicals are much more stable in an aqueous solution than the unmethylated ones, may be attributed essentially to the fact that the overlapping of the two steps of oxidation is smaller. As a consequence the indirect lability of the whole system due to the hydrolysis of the diimine in aqueous solution is almost eliminated. Although full potentiometric titration curves cannot be obtained because of the lability of the diimines, such a curve as Figs. 3 and 4 indicates that in spite of the rapid drift of the potentials in the negative direction during the second half of titration, there appears a transient potential jump in the mid-point of titration. This is possible only when the semiquinone formation constant is essentially larger than 16, whereas in the unmethylated diaminodurene mentioned before this constant is 1.0.

The most suitable solvent to combine a sufficient stability of the potentials with a sufficient buffer capacity in order to maintain a constant pH during the titration is 8 volumes of methanol and 2 volumes of 0.05 M aqueous acetic acid (apparent pH of the mixture, 3.1) but the stability is quite satisfactory also in an aqueous acetate buffer pH 4.6. Under proper conditions, all of these radicals are stable at least for several days. In the tri- and tetramethylamino compounds the radical does not fade out even over a period of many days; on the contrary, the color increases somewhat, in part due to further oxidation by exposure to the air, and to a slight extent even in the strict absence of oxygen, due to secondary dismutation of the traces of the diimine present. The nature of this peculiar decomposition of the diimine is of no interest for the present purpose.[15] At any rate, all of these radicals are very stable compounds in great contrast to their corresponding diimines.

(b) **Compounds Substituted both at the Ring and at the Amino Groups.**—A single methyl group at the ring has no, or at least no conspicuous, effect on the stability of the radical, if it is ortho to an unmethylated amino group; however, it has a very decided destabilizing effect when it is ortho to a methylated amino group. This effect is a direct one and is not caused indirectly by the interference of the diimine, as can be shown by the test described before. In the ψ-cumene and durene compounds, no radical is established at all if the amino groups are methylated. This is true whether the corresponding di-

(14) Regarding the method of calculation see Michaelis and Schubert, *Chem. Rev.*, **22**, 437 (1938).

(15) For the understanding of this peculiar process it will suffice to describe the following observations. When a solution of dimethyl-p-phenylenediamine in acetate buffer is titrated very rapidly with just enough bromine to cause the red color of the radical to disappear again, and when the colorless solution is allowed to stand, the color of the radical reappears in a short time. The same is true for tri- and for tetramethyl-p-phenylenediamines. In the tetra compound there is a remarkable difference insofar as the radical which is secondarily reëstablished is, according to its spectrum, that of the tri, instead of the tetra compound. This again is in conformity with Willstätter's observation that the tetramethyldiimonium compound, even in the solid state, easily loses one methyl group in the form of formaldehyde. The radical itself of the tetramethyl compound (Wurster's blue), has not the slightest tendency to lose a methyl group. This shows once more how much more stable is the radical than the diimonium compound.

imine is stable or labile. In the symmetrical dimethyl-diaminodurene, the diimine is rather stable in 80% methanol; in tetramethyldiiminodurene it is extremely labile, yet, in both cases, no radical is formed at all.

Of the many details presented in this table one item is worth special attention. No. 18 is considerably more labile than 17; correspondingly no. 26 is more labile than 25, but no. 26 is much more stable than 18. While in unsymmetrical dimethyldiaminobenzene the introduction of one CH₃ group in the ring ortho to the methylated amino group has a strong destabilizing effect, this effect is smaller for a corresponding substitution in tetramethyldiaminobenzene. In the latter case, the introduction of two methyl groups in the ring is necessary to exert a really strong destabilizing effect. Compare also the difference of this effect according to the position of the two methyl groups (nos. 27 and 28).

4. Absorption Spectra.—Ten cc. of a 0.01 M solution of the dihydrochloride in the same solvent as indicated in the tabulation, was mixed with 1 cc. of 0.001 N aqueous solution of bromine. The concentration of the radical was calculated according to the amount of bromine added, neglecting the overlapping of the two steps, which causes no appreciable error if the excess of unoxidized diamine is as large as in these experiments. A König–Marten's spectrophotometer was used for the readings.

Summary

The radicals derived from aromatic p-diamines as modified by substitutions at the amino groups and at the benzene ring, by univalent oxidation, are compared with each other with regard to stability and color. The stability is measured approximately in terms of the lifetime in a properly chosen solvent. A distinction has to be made as to whether the disintegration is due to the direct breakdown of the radical ensuing from interaction with the solvent, or is caused indirectly by the lability of the diimine with which it always is in equilibrium. The indirect lability is most obvious in compounds not methylated at the amino groups. It may make the radicals appear to be much more labile than they really are. The direct spontaneous lability of the radicals is increased whenever there is a steric hindrance preventing the coplanar arrangement of the molecule necessary for resonance. This is the case when one or two methyl groups substituted in the benzene ring are in ortho position to a methylated amino group. Direct observations of changes in color are supported by potentiometric oxidative titrations of the diamines. The absorption spectra are recorded. It is especially noteworthy that diamino durene forms a very stable radical, but that any methylation of its amino groups entirely prevents the formation of a radical, due to the steric hindrance preventing coplanar arrangement of the molecule.

Studies on the Wolff–Kishner Reduction of Steroid Ketones[1]

BY JAMES D. DUTCHER AND O. WINTERSTEINER

In connection with a problem related to the steroid compounds of the adrenal cortex we had occasion, in a practice experiment, to reduce the semicarbazone of cholestanone by the method of Wolff and Kishner. However, the usual agent, sodium ethylate, as well as the benzylate modification described by Ruzicka and Goldberg,[2] yielded not the expected hydrocarbon, cholestane, but α- and β-cholestanol as the sole reaction products. This unusual result prompted us to study the behavior of other ketonic steroids in the Wolff–Kishner reduction, in order to learn whether constitutional or experimental factors were primarily involved.

A search of the literature revealed only two cases in which a similar atypical course of the Wolff–Kishner reduction had been observed. According to Eisenlohr and Polenske,[3] β-decalone semicarbazone yielded, besides the hydrocarbon, 33% of β-decalol. When the experiment was repeated under strictly anhydrous conditions, the yield of alcohol was but little lower, 25%. A complete failure to obtain the normal product had been reported by Reindel and Niederländer,[4] who after treating the semicarbazone of acetyl-nor-lithocholyl methyl ketone with sodium ethylate at 200° were able to isolate only the corresponding carbinol. The formation of secondary alcohols from cyclic steroid ketones

(2) Ruzicka and Goldberg, *Helv. Chim. Acta*, **18**, 668 (1935).
(3) Eisenlohr and Polenske, *Ber.*, **57**, 1639 (1924).
(4) Reindel and Niederländer, *Ann.*, **522**, 218 (1936).