lead for equilibrium. Taking the lower limit of 12.1%, we calculate that $a_2 = 0.1458$, which is now less than the value $a_2(s) = 0.1487$. Assuming Raoult's law to be obeyed in the dilute β-solid solutions, as has been shown to be true for lead–bismuth solid solutions,[1] we calculate for the solid solubility of lead in antimony at the eutectic temperature, $N_\beta = 0.1458/0.1487 = 0.973$, which corresponds to a solubility of 4.51% of lead. In a similar manner, the composition of the α-solid solution at the eutectic can be determined. The activity of solid lead, relative to liquid, from equation (2) is 0.8694, and a_1 for the 12.1% solution is 0.8132, which gives for the solid solubility $N_\alpha = 0.936$, corresponding to a solubility of 3.86% of antimony.

Summary

1. The activities and relative heat contents of lead and antimony in their liquid alloys have been determined.

2. The eutectic temperature for the system has been shown to be 250° and the eutectic composition 12.1% antimony. The eutectic solids have been calculated to have the compositions 3.86% antimony for the α-phase and 4.51% lead for the β-phase.

PITTSBURGH, PENNA. RECEIVED JULY 10, 1939

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

Proof of the Steric Nature of the Ortho Effect in the Hydrogen Exchange Reactions of Aromatic Tertiary Amines

BY WELDON G. BROWN, ALEX H. WIDIGER AND NICHOLAS J. LETANG

It has been postulated previously[1] that the acid catalyzed hydrogen exchange reactions of dimethylaniline and its derivatives take place through a direct addition of deuterons at the ortho or para positions, giving rise to tautomeric forms of the amine salt with a quinoid type of structure. In view of the requirement in classical structural theory that the dialkylamino group should be coplanar with the quinonoid ring in these forms, it was possible to interpret the inhibiting effect of an ortho nitro group, which had been observed in a study of the exchange reactions of the nitrodimethylanilines in deuteroalcohol, as a steric effect having to do with the obstruction offered by the nitro group to the attainment of a coplanar configuration. Several further examples of inhibition of the hydrogen exchange reaction by ortho substituents have since been discovered and it is now obvious that the ortho effect is as characteristic for this reaction as it is for numerous other reactions of aromatic tertiary amines.[2]

In an effort to test experimentally the validity of this theory of the ortho effect in hydrogen exchange reactions, two independent lines of approach were explored. One obvious method of attack was to vary the size of the ortho substituent in the expectation that as the size of the group becomes small the inhibiting effect should diminish or eventually vanish. The series selected for this purpose was that of the bromo, chloro and fluoro derivatives of dimethylaniline (*cf.* Fig. 1). The second line of attack was based on the argument that if the amino nitrogen were to be linked to the ortho carbon atom in such a way as to form a five-membered ring, as in N-methylindoline (I), which would necessarily be coplanar with the benzene ring, there should be no ortho effect. A similar result was predicted for

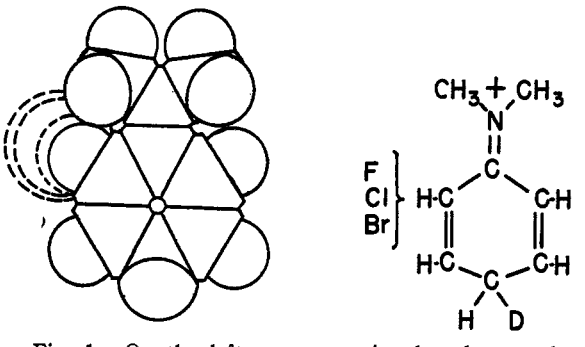
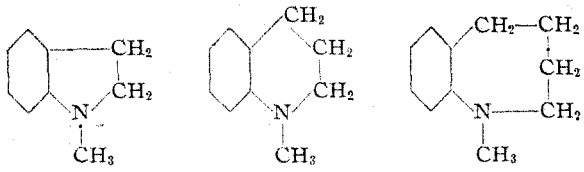


Fig. 1.—On the left, representation based on scale atomic models of the structures indicated on the right. The dotted lines show approximately the relative dimensions of F, Cl and Br.

(1) Brown, Kharasch and Sprowls, *J. Org. Chem.*, in press.

(2) The literature on the subject of ortho effects in the reactions of aromatic tertiary amines, particularly with regard to the reactions with methyl iodide, nitrous acid, diazo compounds, and formaldehyde, is too extensive to be cited here in detail, but the very extensive work of the late Julius von Braun in this field deserves special mention. For a review on the subject of ortho effects in general, see Ludwig Anschütz, *Z. angew. Chem.*, **41**, 691 (1928).

an analogous compound with a six-membered ring, N-methyltetrahydroquinoline (II), though perhaps with less certainty because of the probable slight strain in the coplanar configuration. With a highly puckered seven-membered ring, on the other hand, as in N-methyl-*homo*-tetrahydroquinoline (III), the opportunity for a steric effect of the type under consideration definitely arises and this compound should exhibit the characteristic inhibition of the normal lability of the para and unsubstituted ortho hydrogen atoms.



The experimental results are entirely in accordance with the predictions. We find a pronounced ortho effect in the failure of *o*-bromodimethylaniline and of *o*-chlorodimethylaniline to undergo hydrogen exchange to any appreciable extent under experimental conditions such that the exchange reactions of the corresponding meta and para isomers are substantially complete. The effect is very much less conspicuous, although not entirely absent, in *o*-fluorodimethylaniline which undergoes hydrogen exchange at an intermediate rate. In the series of cyclic bases, it is observed that N-methylindoline and N-methyltetrahydroquinoline exhibit a very high degree of reactivity in the exchange reaction, the former being more reactive but both exceeding dimethylaniline, whereas N-methyl-*homo*-tetrahydroquinoline exchanges hydrogen at a relatively slow rate. These results provide rather convincing evidence that the key to the situation really lies in the ability of the dialkylamino group to come into the plane of the benzene ring.

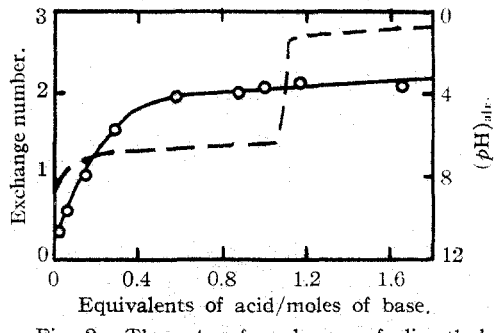


Fig. 2.—The rate of exchange of dimethylaniline in deuteroalcohol with varying amounts of sulfuric acid. The dotted line indicates the estimated $(p\mathrm{H})_{alc.}$

In the meantime further evidence in support of the mechanism of direct deuteron addition at the site of the exchange (ortho and para carbon atoms) was forthcoming in a study of the effect of acid concentration on the rate of exchange of dimethylaniline in deuteroalcohol solution. As Ingold, Raisin, and Wilson[3] first pointed out, and verified experimentally with reference to the exchange of dimethylaniline in dilute hydrochloric acid, it is a consequence of this mechanism that on increasing the amount of acid the rate of exchange should reach a maximum value which would represent a compromise between the increasing concentration of acid catalyst and the decreasing concentration of free base. Our results on the sulfuric acid catalyzed exchange reaction of dimethylaniline in deuteroalcohol are similar to those obtained by Ingold, Raisin, and Wilson in showing that beyond a certain point the rate of exchange does indeed fail to keep pace with the increasing concentration of acid (*cf.* Fig. 2).

It is characteristic of the ortho effect in the reactions of aromatic tertiary amines that it does not always appear as a completely dominant effect. It is rather an effect of limited magnitude which may be partially or wholly obscured by opposing influences. In the hydrogen exchange reaction the effect is known to be of limited magnitude not only in the case of *o*-fluorodimethylaniline, in which the inhibition of reactivity is only slight, but also in the case of *o*-chlorodimethylaniline which does not exchange hydrogen readily at 110° but does so at 180°. It is therefore of interest in connection with the interpretation of the behavior of more complicated molecules to know the extent to which the ortho effect can be overcome by suitably oriented activating groups. An effect in this direction can be seen in the fact that dimethyl-*p*-xylidine exchanges hydrogen, albeit slowly, while under similar conditions N-dimethyl-*o*-toluidine and 2-dimethylamino-*m*-xylene exhibit no appreciable exchange. In this example the deactivating steric effect of an ortho methyl group is to some

(3) Ingold, Raisin, and Wilson, *J. Chem. Soc.*, 1639 (1936). The fundamental difference between the mechanism proposed by these authors and our mechanism is that they apparently believe the hydrogen exchange to be effected in a single step involving simultaneous proton and deuteron transfers and nothing is indicated with regard to a possible quinonoid structure for the intermediate complex. In our view the formation of a quinoid form of the cation by deuteron transfer is followed by a proton transfer in which the acceptor will not necessarily be the anion derived from the catalyzing acid.

TABLE I

EXCHANGE REACTIONS OF TERTIARY AROMATIC AMINES IN DEUTEROALCOHOL

In all experiments the amount of substance used was 0.0130 mole, the amount of alcohol 0.0850 mole.

Substance	H_2SO_4, cc.	Time, hours	Temp.	Initial % D_2O	Final % D_2O	Exchange number
o-Chlorodimethylaniline	0.02	65	115	2.60	2.60	0
o-Chlorodimethylaniline	.02	140	115	2.60	2.58	0.05
o-Chlorodimethylaniline	.02	72	185	2.60	2.29	.89
o-Chlorodimethylaniline	.02	159	185	2.60	2.20	1.24
m-Chlorodimethylaniline	.02	65	115	2.60	1.90	2.43
p-Chlorodimethylaniline	.02	65	115	2.60	2.06	1.73
o-Bromodimethylaniline	.02	65	115	2.60	2.60	0
o-Bromodimethylaniline	.02	140	115	2.60	2.59	.02
m-Bromodimethylaniline	.02	65	115	2.60	1.88	2.53
p-Bromodimethylaniline	.02	65	115	2.60	2.08	1.7
o-Fluorodimethylaniline	.02	65	115	2.60	2.41	0.52
o-Fluorodimethylaniline	.02	140	115	2.60	2.27	.96
N-Dimethyl-*o*-toluidine	.02	90	115	2.30	2.30	0
N-Dimethyl-*o*-toluidine	.08	70	115	2.25	2.26	0
2-Dimethylamino-*m*-xylene	.02	90	115	2.30	2.30	0
2-Dimethylamino-*m*-xylene	.08	90	115	2.25	2.26	0
N-Dimethyl-*p*-xylidine	.02	70	115	2.30	2.24	0.20
5-Dimethylaminotetralin	.02	74	115	2.29	2.24	.19
α-Dimethylaminonaphthalene	.02	41	115	2.76	2.29	1.36
Dimethylaniline	.01	24	60	2.81	2.75	0.12
N-Methylindoline	.01	24	60	2.80	2.25	1.58
N-Methyltetrahydroquinoline	.01	24	60	2.74	2.42	0.87
N-Methyl-*homo*-tetrahydroquinoline	.01	44	60	2.79	2.78	0
N-Methyl-*homo*-tetrahydroquinoline	.02	70	120	2.77	2.57	0.85

extent alleviated by the normal activating effect of a meta methyl group. A similar case is provided by 5-dimethylaminotetralin, which undergoes hydrogen exchange slowly. These results provide a clue to the behavior of α-dimethylaminonaphthalene, which can be regarded, formally at least, as an ortho substituted amine but which shows a high degree of reactivity in the hydrogen exchange reaction. We suppose that the steric inhibition which might be expected is very nearly compensated by the activating effect of the benzo group. It is to be anticipated that the steric factor in such a molecule could be greatly increased by substituents in the 8-position and experiments are in progress to test this prediction.[4]

It will be obvious, in view of the parallel occurrence of ortho effects in the hydrogen exchange reaction and in coupling, nitrosation, and condensation reactions of aromatic amines, that the elucidation of the nature of the effect for one type of reaction has important implications with regard to the others. There appears to be no obstacle in the way of extending the principles and the experimental approach of the present work to these related reactions, and in fact much of the necessary data is already available in the literature. In subsequent papers an attempt will be made to show how this extension can be carried out.

(4) The α-dialkylaminoanthraquinones present a similar picture in so far as the steric relationships are concerned and it seems possible that this may be the origin of many of the anomalies to be encountered in the chemistry of these substances.

TABLE II

HYDROGEN EXCHANGE OF DIMETHYLANILINE WITH VARYING AMOUNTS OF ACID[a]

H_2SO_4, cc.	Acid/base	Initial % D_2O[b]	Final % D_2O	Exchange number
0	0	2.83	2.81	0
0.005	0.014	2.81	2.68	0.32
.020	.058	2.78	2.56	.57
.050	.14	2.74	2.38	1.01
.100	.29	2.69	2.19	1.56
.200	.58	2.58	2.02	1.97
.300	.88	2.48	1.95	2.01
.342	1.00	2.44	1.91	2.10
.400	1.17	2.39	1.87	2.15
.500	1.46	2.29	1.81	2.09

[a] These experiments were carried out with mixtures containing 0.0130 mole of dimethylaniline, 0.085 mole of alcohol, and the amount of sulfuric acid shown in the table. The reactions were allowed to proceed at 60° for sixty-nine hours. [b] The initial concentrations have been corrected for the dilution of the deuterium by the normal hydrogen of the sulfuric acid.

Experimental

Experimental Procedure.—The procedure for carrying out exchange reactions in deuteroalcohol described by

TABLE III

PHYSICAL CONSTANTS OF THE TERTIARY AMINES AND SOME OF THE INTERMEDIATES

Substance	B. p. °C.	B. p. Mm.	$n^{20}D$	Notes
Dimethylaniline	188	750	1.5582	
o-Chlorodimethylaniline	207.5–208.5	749	1.5524	
m-Chlorodimethylaniline	239–240	747	1.5732	
p-Chlorodimethylaniline	231–232	746	(M. p. 35.5°)	
o-Bromodimethylaniline	107–108	14	1.5750	
m-Bromodimethylaniline	133–134	14	1.5988	
o-Nitrofluorobenzene	188	750		*a*
o-Fluorodimethylaniline	69-70	16	1.5173	
N-Dimethyl-*o*-toluidine	180	750	1.5255	
2-Dimethylamino-*m*-xylene	193–194	748	1.5138	
N-Dimethyl-*p*-xylidine	199	745	1.5223	
5-Aminotetralin	149–152	15	1.6044	
5-Dimethylaminotetralin	134–134.5	16	1.5608	
α-Dimethylaminonaphthalene	129	10	1.6224	
N-Methylindole	123–124	20	1.6060	*b*
N-Methylindoline	102	20	1.5682	
N-Methyltetrahydroquinoline	105–106	8	1.5843	*c*
homo-Tetrahydroquinoline	114–115	10	1.5751	
N-Methyl-*homo*-tetrahydroquinoline	105–106	10	1.5597	*d*

[a] The mixture of the ortho and para derivatives which was obtained on nitrating fluorobenzene, and which contained approximately 13% of the ortho compound, was separated without difficulty by fractional distillation at 50 mm. pressure using a 1-meter column packed with glass helices. [b] This compound was prepared by the method of Koizumi, Kowski, and Titani. *Bull. Jap. Chem. Soc.*, **13**, 645 (1938), and was reduced to N-methylindoline by the method of Wenzing, *Ann.*, **239**, 246 (1887). Other methods for the preparation of the latter which were first tried gave unsatisfactory results. [c] The compound assumes a bright red color when exposed to air and the rate of coloration is enormously accelerated by traces of acid. In the exchange experiments the samples were distilled into reaction tubes under high vacuum without subsequent exposure to air. Under these conditions no color developed in the control experiments and only a slight yellow color in the tubes containing acid. [d] The methylation of *homo*-tetrahydroquinoline was carried out by refluxing equal volumes of the amine, methyl iodide, and methyl alcohol for three hours, resulting in a 65% yield of the tertiary amine as compared with a 20% yield reported by v. Braun and Seemann.[9]

Kharasch, Brown, and McNab,[5] and later modified,[1,6] has been improved as a result of the discovery[7] that significant errors can arise from isotopic fractionation in the distillation of ethyl alcohol at reduced pressure. In order to minimize these errors the distillations are now carried out at atmospheric pressure and care is exercised in collecting the same fraction in each distillation. With these precautions a constant decrease, amounting to 0.8% of the concentration of deuterium, was obtained. Control experiments, in which no catalyst was added, were carried out with each compound and in no case did we find evidence of exchange in the absence of added acid.

Experimental Results.—The experimental results are given in tabular form in Tables I and II. The extent of hydrogen exchange is expressed in terms of the "exchange number," which is used here as a matter of convenience,[8] and which is derived from the data by means of the relation: $n = (a/s)(D_1 - D_2)/D_2$, where a/s is the molar ratio of alcohol to substance, and D_1 and D_2 are the initial and final concentrations of deuterium in the alcohol. Since the unit of deuterium concentration does not enter into the result, it is unnecessary to transform the analytical data from mole % D_2O in the water of combustion, in which form they are obtained and are given in the tables, to mole % C_2H_5OD in the alcohol.

Corrections were applied for the dilution of the deuterium by the normal hydrogen of the sulfuric acid added. In the series of experiments recorded in Table II, this correction becomes quite large with the higher concentrations of acid and there is some uncertainty as to how it should be applied.

Materials.—The tertiary amines required for this work have been described previously and were prepared by the methods given in the literature, the principal exception being the preparation of N-methyl-*homo*-tetrahydroquinoline which was carried out by a less laborious route than the original one of v. Braun and Seemann.[9] Extensive use was made of the acetic anhydride treatment as a method of purifying tertiary amines, and in connection with the possible occurrence of secondary amines as impurities in certain cases it may be mentioned that the amino hydrogen exchanges rapidly in the absence of added catalyst and thus the control experiments served also as a check on the purity of the substances.

The physical constants of the materials used in the exchange experiments, and also of some of the intermediates required in the preparations, are given in Table III.

(5) Kharasch, Brown, and McNab, *J. Org. Chem.*, **2**, 36 (1937).

(6) Brown and Eberly, unpublished work.

(7) Widiger and Brown, THIS JOURNAL, **61**, 2453 (1939).

(8) Since equilibrium data are in most cases not yet available the true degree of completion of the reactions cannot be given. Experience indicates that the limiting value of the "exchange number" in reactions involving C–H hydrogens is less than the actual number of exchanging hydrogen atoms per molecule by 15–20%.

(9) Von Braun and Seemann, *Ber.*, **55**, 3824 (1922).

A careful examination of the problems involved in the synthesis of N-methyl-*homo*-tetrahydroquinoline by the method of v. Braun and Seemann[9] led to the discovery that γ-(*o*-aminophenyl)-butyric acid, one of the later intermediates, could be prepared more conveniently by the Beckmann rearrangement of the *p*-toluenesulfonic ester of α-tetraloneoxime.[10] This method was adopted and the subsequent steps were carried out essentially as described by v. Braun and Bartsch[11] and by v. Braun and Seemann.[9]

α-Tetralone.—The following method was used for the preparation at a reasonable cost of the relatively large quantities of α-tetralone needed for the above-mentioned synthesis. Air is blown gently for a period of one hundred hours through a suspension of finely powdered copper oxide in tetralin maintained at 90°. The suspension is then allowed to settle and the liquid decanted. Upon fractional distillation at reduced pressure 80% of the tetralin is recovered and there is obtained in 20% yield a mixture of α-tetralol and α-tetralone containing 50–75% of the latter. This product is dissolved in an equal volume of acetic acid and treated in the cold with an equal weight of chromic acid dissolved in a small quantity of water. After the addition of chromic acid is complete, the solution is allowed to warm to room temperature and is maintained at room temperature for six hours. The product is then isolated by the usual methods, yield 90% based on tetralin consumed, b. p. 134° (15 mm.).

α-Tetraloneoxime.—The oxime was prepared using a technical grade of neutral hydroxylamine sulfate, recrystallized from 50% alcohol using a little Norite; yield 90%, m. p. 102°.

(10) Schroeter, *Ber.*, **63**, 1323 (1930).

(11) Von Braun and Bartsch, *ibid.*, **45**, 3376 (1912).

Summary

Some further examples of the inhibition of the acid catalyzed hydrogen exchange reactions of dimethylaniline derivatives by ortho substituents are reported.

In support of the theory that the ortho effect is primarily a steric effect having to do with the tendency of an ortho substituent to block the formation of quinonoid structures, it is shown that the inhibition of hydrogen lability caused by an ortho fluorine atom is much less than that caused by an ortho chlorine atom. A more decisive test of the theory is provided by a study of the exchange reactions of the cyclic bases, N-methylindoline, N-methyltetrahydroquinoline, and N-methyl-*homo*-tetrahydroquinoline. The first two of these, having bicyclic structures which are coplanar or nearly so, were observed to exchange hydrogen readily, while the third, in which the heterocyclic ring must be highly puckered, exhibited the inhibition of reactivity which is characteristic of ortho substituted tertiary amines.

CHICAGO, ILLINOIS RECEIVED JUNE 26, 1939

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Inactivation of Tyrosinase in the Oxidation of Catechol

BY B. J. LUDWIG AND J. M. NELSON

When catechol is oxidized by means of an excess of the oxidase, tyrosinase, two atoms of oxygen are consumed per mole of the substrate. If, however, less than a sufficient amount of the enzyme is used, then the enzyme becomes inactivated before the catechol is completely oxidized (curves I and III, Fig. 1).

The inactivation of one unit of catecholase[1] has been found to involve a definite amount of oxygen uptake. In fact the amount of oxygen required for the inactivation may be used as a quantitative measure of the amount of catecholase present in a given preparation of the enzyme, provided the latter has been purified sufficiently. Crude tyrosinase preparations[2] are apt to contain from the plant, serving as the source, catechol or catechol derivatives and phenols which are aerobically oxidized by the enzyme, or tend to form with the latter inactive complexes. For this reason crude tyrosinase preparations often tend to lose activity on standing. These concomitant substances are usually lost when the purification has reached the stage, in the case of tyrosinase from the common mushroom, *Psalliota campestris*, when 1 mg. dry weight is equivalent to 80 or more catecholase units (for definition of units see legend Fig. 1). Sufficiently purified tyrosinase preparations from the last-mentioned source require for complete inactivation an uptake of 100 ± 5 cu. mm. of oxygen per catecholase unit (column 4, Table I).

It has been shown by Parkinson (unpublished) in these laboratories and also by others[3,4] that in

(1) Since tyrosinase catalyzes the oxidation of both catechol and *p*-cresol, the terms catecholase and cresolase have been used for the respective enzymic activities.

(2) M. W. Onslow, "Principles of Plant Biochemistry," University Press, Cambridge, England, 1931, p. 131.

(3) F. Kubowitz, *Biochem. Z.*, **299**, 32 (1938).

(4) D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **B125**, 187 (1938).