that was not used in determining the point for m-nitro in Fig. 1 (which falls reasonably near the line) is the solubility of m-dinitrobenzene in water, there may be an interaction between the basic oxygen atoms of water and the carbon atoms *ortho* and *para* to the nitro groups in m-dinitrobenzene. Such an interaction is somewhat analogous to the reaction that results in a purple solution of m-dinitrobenzene in liquid ammonia,[19] but we are not postulating that the contributions of the right-hand structures above are sufficient to make the geometry of the m-dinitrobenzene significantly dif-

(19) J. D. Farr, C. C. Bard and G. W. Wheland, *J. Am. Chem. Soc.*, **71**, 2013 (1949).

ferent from that in a solvent with which it has no such interaction.

To express our activity coefficients in terms of contributions for various substituent groups in a manner analogous to that used by Derr and co-workers[20] would yield values of 1.0 for the activity-coefficient ratio in eq. 1. Benson and Buss pointed out that if ϕ is a molecular property, then for the disproportionation reaction

$$RNR + SNS \rightleftharpoons 2RNS$$

$\Delta\phi$ approaches zero as the separation between R and S becomes large compared to their dimensions.[21] In our case ϕ is the logarithm of the activity-coefficient ratio. The values of ϕ are small, but in several cases significantly larger than zero, showing that for the N groups (m- and p-phenylene) that we used the interacting substituents are not removed a sufficient distance from each other for ϕ to be a simple additive property of the nature of the groups present. Equation 1 may be thought of as providing the correction for this deviation from simple additivity.

(20) G. J. Pierotti, C. A. Deal and E. L. Derr, *Ind. Eng. Chem.*, **51**, 95 (1959); O. Redlich, E. L. Derr and G. J. Pierotti, *J. Am. Chem. Soc.*, **81**, 2283 (1959); M. N. Papadopoulos and E. L. Derr, *ibid.*, **81**, 2285 (1959); C. H. Deal, E. L. Derr and M. N. Papadopoulos, *Ind. Eng. Chem. Fundamentals*, **1**, 17 (1962).

(21) S. W. Benson and J. H. Buss, *J. Chem. Phys.*, **29**, 546 (1958).

Polar Effects on Rates and Equilibria. VII. Disproportionation and Isomerization of Alkyl- and Halobenzenes[1,2]

BY JACK HINE AND HENRY E. HARRIS

Equilibrium constants have been determined for the simple disproportionation reactions of bromobenzene and ethylbenzene and the mixed disproportionation reactions of bromobenzene with toluene and with fluorobenzene. Equilibrium constants for the formation of m-disubstituted benzene derivatives are correlated satisfactorily by an expression based on the Hammett equation, but equilibrium constants for the formation of p-disubstituted benzenes are correlated very poorly by this expression. When the Hammett substituent constants in the expression are replaced by inductive substituent constants the correlation becomes excellent for both *meta* and *para* compounds. The significance of these results is discussed.

Introduction

It has been pointed out earlier that on the basis of the Hammett equation, or of a less restrictive form of the Hammett equation, in which ρ_{meta} and ρ_{para} need not be equal, an equation may be derived to predict the equilibrium constant for such aromatic disproportionation reactions as[3]

$$C_6H_5X + C_6H_5Y \rightleftharpoons m\text{- or } p\text{-}XC_6H_4Y + C_6H_6$$
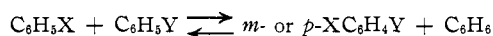
including cases where X and Y are the same. By studying compounds with electrically neutral X's and Y's that are incapable of direct resonance interaction even when *para* to each other, it should be possible to test the disproportionation equation with a minimum of complications due to (1) resonance interactions between groups attached to the aromatic ring, (2) solvation of electrically-charged groups, (3) complications peculiar to rate processes (such as changes in reaction mechanism), and

(1) For paper VI in this series see ref. 18.
(2) Abstracted largely from the Ph.D. thesis of Henry E. Harris, 1962.
(3) J. Hine, *J. Am. Chem. Soc.*, **82**, 4877 (1960).

(if the solvent and substituent groups are carefully chosen) (4) hydrogen bonding. More important, a new test would also be provided for the parent relationship, the Hammett equation, and in this test the effect of the four factors listed above—those most commonly blamed for failure of the Hammett equation—is minimized so that the influence of other factors, such as how near each other the substituent group and the reaction center may be, can be evaluated.

Unfortunately we found in the literature no direct quantitative measurements on aromatic disproportionations of the type needed. The thermochemical data from which equilibrium constants for such reactions could be calculated are not nearly so precise as desired. However, von Dumreicher and subsequent workers showed that halobenzenes disproportionate to benzene and dihalobenzenes in the presence of Friedel–Crafts catalysts,[4,5] and Heise and others showed that similar reactions occur with alkylbenzenes.[6] We therefore

(4) O. von Dumreicher, *Ber.*, **15**, 1866 (1882).
(5) F. Fairbrother and N. Scott, *Chem. Ind.* (London), 998 (1953).

determined the equilibrium constants for the disproportionation of several halobenzenes and alkylbenzenes.

After the conclusion of our experimental work we learned of Kooyman and Louw's study of isomerizations, disproportionations and transbrominations involving bromobenzenes in the presence of aluminum bromide,[7] and the investigations, by Olah and co-workers, of Friedel–Crafts isomerizations of halobenzenes[8] and halotoluenes.[9]

Experimental Results

Reagents.—The benzene, bromobenzene, anisole, toluene, ethylbenzene, o-bromotoluene, fluorobenzene and bromofluorobenzenes used were reagent-grade chemicals that were fractionally distilled to give materials whose boiling points agreed with values in the literature. Each of these materials was shown by gas–liquid chromatography (g.l.c.) to contain less than 0.1% impurity except for the p-bromofluorobenzene, which contained 1.6% of the o-isomer, and the o-bromofluorobenzene, which contained 0.36% of the p-isomer. The m- and p-bromotoluenes and o- and m-dibromobenzenes were obtained similarly; the former could not be separated by g.l.c. but infrared measurements at 12.445 μ showed that the m-isomer could not contain more than 2.1% of the p-isomer in addition to the 0.5% o-isomer found by g.l.c.; measurements at 12.966 showed that the p-isomer contained no more than 2.3% m-isomer, and g.l.c. showed less than 0.1% o-isomer present. The m-dibromobenzene contained less than 0.1% bromobenzene and o-dibromobenzene (g.l.c.) and less than 0.34% p-dibromobenzene (measurements at 12.310 μ), while the o-dibromobenzene contained about 0.8% bromobenzene and 0.1% p-dibromobenzene (g.l.c.). Less than 0.1% of bromobenzene or any other dibromobenzene (g.l.c.) was present in the p-dibromobenzene, which had been recrystallized from methanol. American Petroleum Institute standard samples of the diethylbenzenes containing 0.07 ± 0.04% impurity were used as standards, but a commercial diethylbenzene with a meta–para ratio of 1.18 and a commercial m-diethylbenzene (99.5+% pure by g.l.c.) were used in the disproportionation experiments. The diphenyl ether and xylenes were redistilled reagent grade materials.

Anhydrous aluminum bromide was prepared from aluminum and bromine and sealed in glass ampoules by a method based on that of Nicholson, Winter and Fineberg.[10]

Analyses.—All g.l.c. analyses were carried out on one of two Perkin–Elmer vapor fractometers (model 154-D). One instrument was used for packed columns (all 0.25 in. diameter and 2 meters long) and one for Golay (capillary) columns (all 0.010 in. diameter and 300 ft. long). In the following descriptions of procedures, packed columns are used unless otherwise stated; C columns have dimethyl siloxane polymer as the liquid phase, K polyethylene glycol, O silicone grease, P succinate polyester of diethylene glycol, and R polypropylene glycol, and Q Apiezon "L" grease.

The concentrations of the components of the mixtures analyzed were determined from the corresponding peak heights. A number of standard samples were prepared to contain the various compounds desired in approximately the concentrations present in the equilibrium mixture for the reaction being studied. Each of these standard samples was subjected to g.l.c. under the conditions used for the reaction mixture. From the data on most of these standard samples plots of peak height vs. mole % composition were made. The other standard samples were used as control samples whose compositions calculated from the peak height vs. mole % plots were compared with the known compositions in order to assess the reliability of the analytical method. Samples from the reaction mixture were analyzed in the same way.

All infrared analyses were carried out using a Perkin–Elmer recording spectrophotometer, model 21, and isoöctane as a solvent.

Disproportionation of Bromobenzene.—In a typical experiment an ampoule containing a known quantity of aluminum bromide was broken into a flask containing a known quantity of bromobenzene under dry nitrogen and the flask was stoppered, shaken, and placed in a constant temperature bath. The solution became yellow immediately and later reddish brown, but it remained homogeneous. At various times 3-ml. samples were removed under nitrogen and added to centrifuge tubes each containing about 3 ml. of 5% hydrochloric acid and some crushed

(6) R. Heise, Ber., **24**, 768 (1891).

(7) E. C. Kooyman and R. Louw, Rec. trav. chim., **81**, 365 (1962).

(8) G. A. Olah, W. S. Tolgyesi and R. E. A. Dear, J. Org. Chem., **27**, 3441, 3449, 3455 (1962).

(9) G. A. Olah and M. W. Meyer, ibid., **27**, 3464 (1962).

(10) D. G. Nicholson, P. K. Winter and H. Fineberg, "Inorganic Synthesis," Vol. III, McGraw–Hill Book Co., Inc., New York, N. Y., 1950, p. 33.

ice. The tubes were shaken to destroy the anhydrous aluminum bromide and centrifuged to separate the organic layer, which was removed, dried over about 0.1 g. of anhydrous magnesium sulfate, and analyzed by g.l.c.

In some cases the reactions were carried out in small sealed glass ampoules which were broken into cold hydrochloric acid to stop the reaction. In some cases dibromobenzenes and/or benzene were present in addition to or instead of the bromobenzene; equilibrium was approached from both sides.

Preliminary experiments showed that with bromobenzene as the reactant the ratio $[C_6H_6][p\text{-}C_6H_4Br_2]/[C_6H_5Br]^2$ rapidly approached a value around 0.02 at 25°, whereas the corresponding ratio for m-dibromobenzene increased more slowly (in a typical run the meta ratio was 0.001 when the para ratio was 0.014) and became constant around 0.04.[11] These experiments also showed that changes in the aluminum bromide concentration between 0.5 and 4.0 mole % changed these equilibrium ratios by less than 10% and that essentially the same ratios were obtained when mixtures of benzene and either m- or p-dibromobenzene were used as reactants in experiments where the concentration of benzene present at equilibrium varied from 16 to 72%. These experiments, using columns K and R, which do not give complete separation of m- and p-dibromobenzene, gave K_{d-m} values[12,13] of 0.040 ± 0.003, 0.047 ± 0.004 and 0.056 ± 0.003 at 25°, 53.5° and 99.5° and K_{d-p} values of 0.021 ± 0.002, 0.025 ± 0.002 and 0.029 ± 0.002 at 25°, 53.5° and 99.5°. From these approximate K_d values, ΔH and ΔS values of 1.0 kcal./mole and −3.2 e.u. and 0.9 kcal./mole and −4.7 e.u. may be calculated for the meta and para disproportionation reactions, respectively.

More reliable data were obtained by use of Golay column Q at 175°, whereby almost complete separation of m- and p-dibromobenzene was achieved. The results obtained in a run using 5.0 g. of aluminum bromide and 50 ml. of bromobenzene at 35° are shown in Table I. The mole % figures given are based on the total amount of benzene, bromobenzene and dibromobenzenes present and ignore any polybromobenzenes that may have been present. Although polybromobenzenes were sought in the preliminary runs only 1,2,4-tribromobenzene was found and its concentration never reached 0.2% under the conditions empolyed. The disproportionation constants calculated from the data in Table I and statistically corrected are listed in Table III.

TABLE I
DISPROPORTIONATION OF BROMOBENZENE AT 35.0°

Time, days	C_6H_6	C_6H_5Br	o-	m-	p-
0		100.00			
1[a]	16.25	67.28	0.82	10.35	5.31
2[a]	16.32	67.45	.78	10.23	5.22
3[a]	16.18	67.39	.78	10.40	5.27
4	16.29	67.22	.81	10.40	5.28
Av.[b]	16.26	67.36	.79	10.33	5.26
	±0.17	±0.15	± .04	±0.13	±0.06

Column headers for o-, m-, p- under span "$C_6H_4Br_2$", all under span "Mole per cent".

[a] Average of several values.   [b] Average of 18 values.[12]

Disproportionation of Ethylbenzene.—In a typical experiment hydrogen bromide was bubbled into a mixture of 7.2 ml. of benzene, 40 ml. of ethylbenzene and 0.75 g. of aluminum chloride. This caused the aluminum chloride to dissolve and a viscous dark yellow oil to separate. The material was maintained at 35° and stirred with a magnetic stirrer for 8 days, at the end of which a sample was taken from the top (major) layer of the reaction mixture. Using Golay column Q at 125°, benzene, ethylbenzene, m- and p-diethylbenzene could be determined, but the o-diethylbenzene peak followed so closely after the much larger p-diethylbenzene peak that the analysis for the ortho compound was unsatisfactory. The o-diethylbenzene concentration was therefore determined using column P at 103°. The results from this run

(11) Fairbrother and Scott and also Kooyman and Louw have reported values for the equilibrium constant $[C_6H_6][C_6H_4Br_2]/[C_6H_5Br]^2$, where $[C_6H_5Br_2]$ presumably refers to the total concentration of dibromobenzenes. Fairbrother and Scott's value, 0.040 at 25°, is admittedly approximate, and in view of the statement that the dibromobenzene produced is chiefly para[5] it seems probable that equilibrium had not been reached in the formation of the m-isomer. Kooyman and Louw give a value of 0.05 at 19° in their text and from their Fig. 2 we calculate a value of 0.06, with about twice as much m- as p-dibromobenzene being formed.[6] We regard these observations as being in satisfactory agreement with ours.

In the only cases where Olah and co-workers give enough data to calculate an equilibrium ratio this ratio is considerably larger than ours, but in these experiments they used one mole of aluminum bromide per mole of bromobenzene; their dibromobenzene isomer ratios are about the same as ours.[8]

(12) The ± figures are average deviations rounded upward.

(13) K_d is defined as $[C_6H_6][XC_6H_4Y]/[C_6H_5X][C_6H_5Y]$ or if X and Y are identical, as $[C_6H_6][C_6H_4X_2]/[C_6H_5X]^2$.

TABLE II
DISPROPORTIONATION OF ETHYLBENZENE[12,13]

Starting material	C_6H_6	C_6H_5Et	$C_6H_4Et_2$			10^3K_{d-o}	10^2K_{d-m}	10^1K_{d-p}
			o-	m-	p-			
C_6H_5Et	36.72 ± 0.31	48.28 ± 0.24	0.45	10.15 ± 0.11	4.40 ± 0.03	7.09	160 ± 1	69.3 ± 0.6
$C_6H_4Et_2{}^a$	38.47 ± .14	47.58 ± .01	.48	9.37 ± .12	4.11 ± .04	8.16	159 ± 2	69.8 ± .4
$m\text{-}C_6H_4Et_2$	33.10 ± .06	49.39 ± .03	.54	11.84 ± .04	5.12 ± .01	7.33	161 ± 1	69.7 ± .1
					Av.	7.53 ± 0.43	160^b ± 1	69.3^b ± 0.3

^{a} A mixture of 54% m- and 46% p-diethylbenzene. ^{b} Average of 15 determinations.

are listed in the first line of Table II. In the second line are the results of a similar 3-day equilibration of 16 ml. of benzene and 20 ml. of a 54% m- 46% p-diethylbenzene mixture and in the third line the results of a 6-day equilibration of 4.7 g. of benzene and 5.3 g. of m-diethylbenzene. These results show that the same values are obtained for the equilibruim constants whether the equilibrium is approached from the side of ethylbenzene or from the diethylbenzenes. Points taken earlier in the reaction showed that the *meta–para* equilibrium is established more rapidly than the disproportionation equilibrium.

Reaction of Bromobenzene and Fluorobenzene to Give Bromofluorobenzenes.—The reaction of bromobenzene with fluorobenzene in the presence of aluminum bromide was carried out in a manner analogous to that described for the disproportionation of bromobenzene. The concentrations of bromobenzene and m- and p-bromofluorobenzene were determined using Golay column Q at 125°, and benzene, fluorobenzene, bromobenzene and o-bromofluorobenzene concentrations were determined using column P at 90°. Dibromobenzenes were also formed but no difluorobenzenes were detected (although they were sought). Both the *meta* and *para* equilibria were approached from both sides with less than 2% difference in the values of K_d obtained. At 35.0° average values are 595 ± 4 for 10^4K_{d-m}, 282 ± 3 for 10^4K_{d-p} and 52 ± 1 for 10^4K_{d-o}.[12,13] Points taken early in the reaction showed that equilibrium is attained in the *ortho* and *para* disproportionation reactions faster than in the *meta* reaction.

Reaction of Bromobenzene with Toluene.—Hydrogen bromide was bubbled into a solution of aluminum bromide in a bromobenzene–toluene mixture causing the separation of a dark red oil. The two-phase system was shaken in a constant temperature bath and, at a given time, centrifuged. The upper layer was washed with aqueous hydrochloric acid, dried and analyzed. Use of g.l.c. column P at 102° gave the concentrations of benzene, toluene, bromobenzene and o-bromotoluene. The bromotoluene fraction was separated by use of preparation column O at 145° and analyzed by infrared measurements at 12.445, 12.966 and 13.403 μ. At 35° equilibrium was reached within a few hours. On the basis of the assumption that the m- and p-bromotoluene used are not contaminated with each other, K_{d-m} is 0.515 ± 0.007, K_{d-p} 0.185 ± 0.003 and K_{d-o} 0.419 ± 0.009 at 35°.[12,13] With the assumption that the m- and p-bromotoluene used are each contaminated by the other (see Reagents section) to the extent of 2.1 and 2.3%, respectively, K_{d-m} and K_{d-p} values 5–10% lower would result. Measurements early in the reaction showed that the rate of attainment of the *meta–para* equilibrium is somewhat faster than the rate of attainment of the disproportionation equilibrium.

Attempted Reaction of Bromobenzene with Anisole and Diphenyl Ether.—The addition of 10 ml. of anisole to 10 ml. of a solution of 4.8 g. of aluminum bromide in 40 ml. of bromobenzene caused the red solution to become colorless immediately. After 24 hours the only compound that was detected by g.l.c. (using column C), other than bromobenzene and anisole, was benzene, whose concentration (0.6%) was not significantly higher than it had been after 2 hours (0.5%).

Hydrogen bromide was bubbled into a stirred mixture of 0.90 g. of aluminum chloride and 50 ml. of benzene until the aluminum chloride dissolved and then 5 ml. of this suspension of viscous oil in hydrocarbon was added to 10 ml. of diphenyl ether and 10 ml. of bromobenzene. After an hour at room temperature a sample was withdrawn, washed with water, and found, by analysis with column Q at 300°, to contain benzene, bromobenzene, diphenyl ether and phenol (in a larger amount than the diphenyl ether).

Discussion

Equilibrium Constants for Aromatic Disproportionations.

—If the equilibrium constants for the bromination of aromatic compounds fit the Hammett

$$ArH + Br_2 \rightleftarrows ArBr + HBr \qquad (1)$$
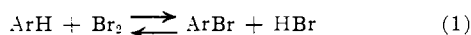
equation,[14] the equilibrium constant for the *para* bromination of the compound phenyl Y should fit the relation

(14) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII.

$$\log (K_{p\text{-}Y}{}^{\text{chem}}/K_0{}^{\text{chem}}) = \rho\sigma_{p\text{-}Y} \qquad (2)$$

where $K_0{}^{\text{chem}}$ is the equilibrium constant for the bromination of benzene, multiplied by a statistical factor to remove complications caused by differences in the number of positions available for bromination, etc.,[15] $K_{p\text{-}Y}{}^{\text{chem}}$ is the statistically corrected equilibrium constant for the *para* bromination of phenyl Y, $\sigma_{p\text{-}Y}$ is the substituent constant for p-Y, and ρ is the reaction constant. It has been shown earlier that ρ is equal to the product of τ_p, a constant whose value depends only on the solvent and temperature, and the difference between the σ-constants for the two substituent groups that are interchanged by the equilibrium in question.[17] In the present case these groups are Br and H so that ρ equals $\tau_p(\sigma_{p\text{-}Br} - \sigma_H)$, or since σ_H is zero, ρ equals $\tau_p\sigma_{p\text{-}Br}$ and therefore

$$\log (K_{p\text{-}Y}{}^{\text{chem}}/K_0{}^{\text{chem}}) = \tau_p\sigma_{p\text{-}Br}\sigma_{p\text{-}Y}$$

From the definition of the K's it may be seen that the ratio $K_0/K_{p\text{-}Y}$ is equal to $[C_6H_6][p\text{-}BrC_6H_4Y]/[C_6H_5Br][C_6H_5Y]$ and is therefore identical with the disproportionation constant, K_d, for the reaction of C_6H_5Br with C_6H_5Y.[13] Thus

$$-\log K_{d\text{-}p}{}^{\text{chem}} = \tau_p\sigma_{p\text{-}Br}\sigma_{p\text{-}Y}$$

or, more generally, for the reaction

$$C_6H_5X + C_6H_5Y \rightleftarrows C_6H_6 + XC_6H_4Y \qquad (3)$$
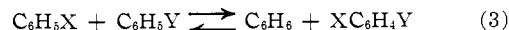
equations of the form

$$-\log K_{d\text{-}p}{}^{\text{chem}} = \tau_p\sigma_{p\text{-}X}\sigma_{p\text{-}Y} \qquad (4)$$

and

$$-\log K_{d\text{-}m}{}^{\text{chem}} = \tau_m\sigma_{m\text{-}X}\sigma_{m\text{-}Y} \qquad (5)$$

may be written.

In Table III are listed $-\log K_d{}^{\text{chem}}$ values for the aromatic disproportionation reactions that we have studied and also for the formation of bromochlorobenzenes and benzene from bromobenzene and chlorobenzene as calculated from the experimental data of Kooyman and Louw.[7]

If eq. 4 and 5 hold, plots of $-\log K_d{}^{\text{chem}}$ vs. $\sigma_X\sigma_Y$ for the *meta* and *para* disproportionations for which data are given in Table III should give straight lines through the origin with slopes of τ_m and τ_p, respectively. In such a plot, shown in Fig. 1, the *meta* points are seen to give fairly satisfactory agreement with eq. 5, the best line through the points (shown on the figure) having a slope (τ_m value) of 4.9. For the *para* points, however, the agreement with eq. 4 is not at all satisfactory, especially when it is considered that we are not free to choose any value we wish for τ_p. Numerical values for τ's have been reported only for

(15) This statistical factor, as Benson has pointed out, is equal to the product of the symmetry numbers of the products divided by the product of the symmetry numbers of the reactants.[16] The factor "6" given for the *para* disproportionation of phenyl X in a previous paper in this series[1] is incorrect. The equilibrium constants for "mixed" *para* disproportionations

$$C_6H_5X + C_6H_5Y \rightleftarrows C_6H_6 + p\text{-}XC_6H_4Y$$
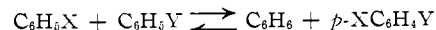
must be multiplied by a statistical factor of "6" to obtain K^{chem} (and the corresponding factor for mixed *ortho* or *meta* disproportionation is "3") but for a "simple" *para* disproportionation of C_6H_5X to C_6H_6 and $p\text{-}C_6H_4X_2$ the factor is "12" (the corresponding *ortho* or *meta* factor is "6").

(16) S. W. Benson, *J. Am. Chem. Soc.*, **80**, 5151 (1958).
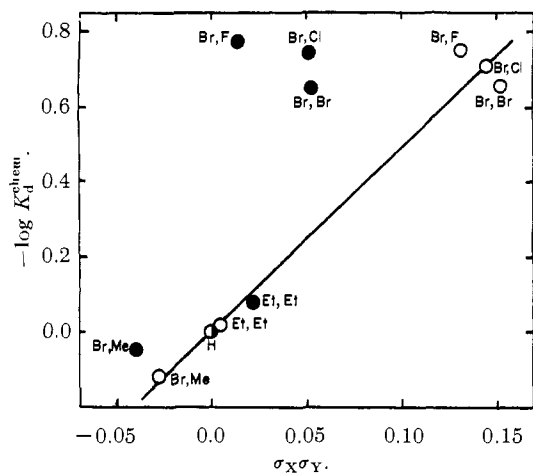
(17) J. Hine, *ibid.*, **81**, 1126 (1959).

Fig. 1.—Plot of eq. 4 and 5 for aromatic disproportionation. Solid circles refer to the formation of p-disubstituted benzenes and open circles to the formation of m-disubstituted benzenes.

aqueous solutions at room temperature.[3,1] However, studies of the activity coefficients of benzene, bromobenzene, nitrobenzene, toluene, m- and p-dibromobenzene, m- and p-dinitrobenzene, and m- and p-xylene show that in decalin τ's are not much larger than they are in water; the disproportionation constants for bromobenzene and toluene do not change by as much as 20% between water and decalin and the disproportionation constants for nitrobenzene change by less than 50%.[18] Therefore the plots in Fig. 1 should yield τ-values not much higher than the range (2.66–3.57) previously reported for aqueous solution.[3,17] The τ_m value 4.9 obtained from Fig. 1 is a little larger than expected, but the best line through the para points in Fig. 1 would give a τ_p value around 10 or 15, in *very* poor agreement with previous values.

TABLE III

STATISTICALLY CORRECTED EQUILIBRIUM CONSTANTS FOR REACTIONS OF THE TYPE $C_6H_5X + C_6H_5Y \rightleftarrows C_6H_6 + XC_6H_4Y$ AT $35°$ [12,13,15]

X	Y	$-\log K_{d-o}{}^{chem}$	$-\log K_{d-m}{}^{chem}$	$-\log K_{d-p}{}^{chem}$
Br	Br	1.770 ± 0.025	0.654 ± 0.006	0.645 ± 0.007
Br	F	$1.807 \pm .010$	$.748 \pm .004$	$.772 \pm .005$
Br	Cl	$1.94 \pm .20^a$	$.71 \pm .07^a$	$.74 \pm .07^a$
Br	CH$_3$	$-0.099 \pm .010$	$-.118 \pm .006$	$-.045 \pm .007$
C$_2$H$_5$	C$_2$H$_5$	$1.345 \pm .025$	$.018 \pm .003$	$.080 \pm .002$

^{a} Calculated from the data of Kooyman and Louw.[7]

A clue as to the reason for the deviations from eq. 4 may be found in the fact that the values of $K_{d-p}{}^{chem}$ in Table III are very near the corresponding values of $K_{d-m}{}^{chem}$; that is, it seems that the substituents present have about the same influence in the *para* position as in the *meta*. Since it is ordinarily considered that both *meta* and *para* substituents have both inductive and resonance effects but differ largely in that the resonance effect is much stronger for *para* substituents, it seems possible that in the present case the substituent effects are inductive to a much greater extent than usual. If the effects are entirely inductive then the same type of reasoning that led to a derivation of eq. 4 and 5 would lead to the relations

$$-\log K_{d-m}{}^{chem} = \tau_m{}^I \sigma_X{}^I \sigma_Y{}^I \qquad (6)$$

and

$$-\log K_{d-p}{}^{chem} = \tau_p{}^I \sigma_X{}^I \sigma_Y{}^I \qquad (7)$$

where the σ^I values are inductive substituent constants and τ^I's refer to the transmittal of inductive effects. The plot, in Fig. 2, of the data of Table III, using

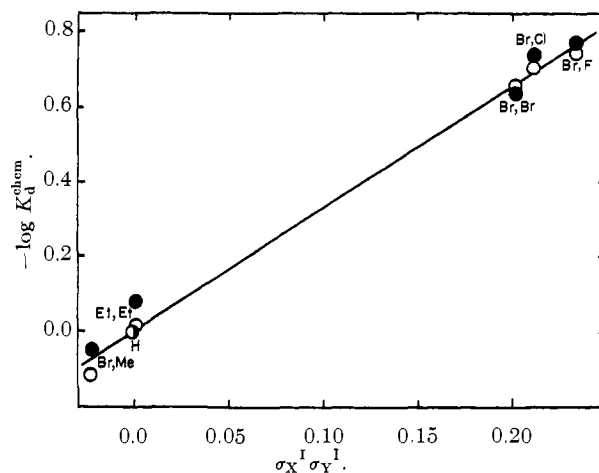(18) J. Hine, H. W. Haworth and O. B. Ramsay, *J. Am. Chem. Soc.*, **85**, 1473 (1963).

Fig. 2.—Plot of eq. 6 and 7 for aromatic disproportionation. Solid circles refer to the formation of p-disubstituted benzenes and open circles to the formation of m-disubstituted benzenes.

Taft's σ^I values,[19,20] shows a definite improvement for the *meta* points but, more important, it is found that the *para* points also fall near a straight line. The best straight line through the origin happens to be essentially the same one for both sets of points. The average deviation of the ten points from this line, whose slope (τ^I) is 3.3, is 0.028, considerably smaller than the 0.071 average deviation noted by Hammett for the first 52 reaction series to which his equation was applied.

The poor agreement between eq. 4 and our experimental results shows that, contrary to the assumption used in deriving eq. 4, the equilibrium constants for reaction 1, aromatic bromination, are not fit satisfactorily by the Hammett equation (eq. 2). It does not seem reasonable that the equilibria we have studied are complicated significantly by solvation effects (including hydrogen bonding) or by direct resonance interactions between substituent groups (although there are probably such complications in the reference reaction, the ionization of benzoic acids). Although our equilibrium constants for aromatic disproportionations are fit satisfactorily by eq. 6 and 7, in which inductive substituent constants are used, we have not studied a wide enough variety of substituents (because of the difficulty in finding aromatic disproportionations in which equilibrium can be established) to assure that such agreement will prove to be general. In fact, the argument given in the next paragraph shows that eq. 6 and 7 are probably not general.

In previous derivations, in which the *energy of polar interaction* of substituents was assumed to be proportional to the product of certain properties of the substituents referred to as their polar substituent constants, it was shown that the Hammett equation may be derived if it is assumed that the polar substituent constants are equal to Hammett substituent constants.[3,21] Analogously, eq. 6 and 7 may be derived if inductive substituent constants are used. The fact that it is necessary to give the polar substituent constants one set of numerical values to derive an equation to fit our equilibrium constants and another set to derive the widely applicable Hammett equation shows that neither set of values can be used generally. It is possible, however, that this is due to the various complications already mentioned (solvation, direct

(19) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

(20) In addition to the published σ^I values, Dr. Taft has informed us of an unpublished σ^I value for the ethyl group (-0.03).

(21) J. Hine, "Physical Organic Chemistry," 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Sec. 4-1.

resonance interactions, etc.) in the case of the reactions to which the Hammett equation has been applied, practically all of which involve ionic species, hydroxylic solvents and/or rate processes.

The inapplicability of Hammett substituent constants to our disproportionation data may stem from the fact that the nature of the atom attached to the aromatic ring is being changed. McDaniel has pointed out that linear plots of σ_m vs. σ_p, which would be expected if the Hammett equation were entirely

general, are usually found when the atom attached to the aromatic ring is held constant, but not otherwise.[22]

We hope to learn more about the proper method of calculating the energy of polar interaction of substituents in subsequent work.

Catalytic Reactions Involving Azomethines. I. The Imidazole Catalysis of the Transamination of Pyridoxal by α-Aminophenylacetic Acid[1a]
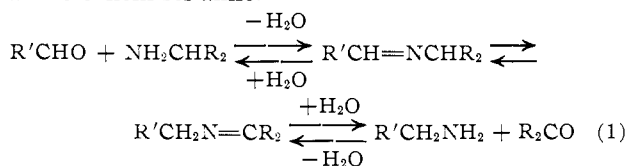
BY THOMAS C. BRUICE AND RICHARD M. TOPPING[1b]

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The transamination of pyridoxal by α-aminophenylacetic acid has been studied in aqueous medium at pH 8.6, 30° and $\mu = 0.05\ M$. The reaction occurred readily in the presence of imidazole buffer and in both product isolation (reactants at $5 \times 10^{-2}\ M$) and spectrophotometric (reactants at $10^{-4}\ M$) studies the catalyzed reactions could be followed up to 95% completion (approach to an equilibrium position) without divergence from apparent first-order kinetics. Spectrophotometrically the reaction was established to occur in two distinct phases. In the first phase equilibrium is established between the initial reactants and ketimine with aldimine at a low steady state (*i.e.*, pyridoxal + amino acid ⇌ aldimine ⇌ ketimine), while in the final phase equilibrium is established between all reactants, products and intermediates (*i.e.*, pyridoxal + amino acid ⇌ aldimine ⇌ ketimine ⇌ α-keto-acid + pyridoxamine). Employing imidazole as the buffer, the rate of completion of phase one is dependent on the square of the total imidazole concentration at low buffer concentration and independent of imidazole concentration at higher buffer concentration. The most logical mechanism involves the formation of a complex of the aldimine with two molecules of an imidazole species which then undergoes an intra-complex-catalyzed prototropic shift converting aldimine to ketimine. Support for the suggestion of a specific pre-equilibrium complex formation between imidazole catalyst and substrate is provided by the observation that certain bases (*e.g.*, morpholine and carbonate) are catalytically effective only when used at high concentrations. In experiments in which Al^{+++} ions were added to the reaction mixture no effect on the rate of the imidazole-catalyzed reaction was noted.
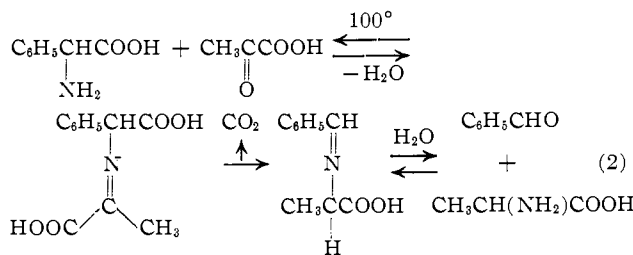
Introduction

The mechanism for the catalysis of the interconversion of azomethines, as found in the transamination reaction 1, has long held the interest of organic chemists and biochemists alike.

$$R'CHO + NH_2CHR_2 \underset{+H_2O}{\overset{-H_2O}{\rightleftarrows}} R'CH{=}NCHR_2 \rightleftarrows$$

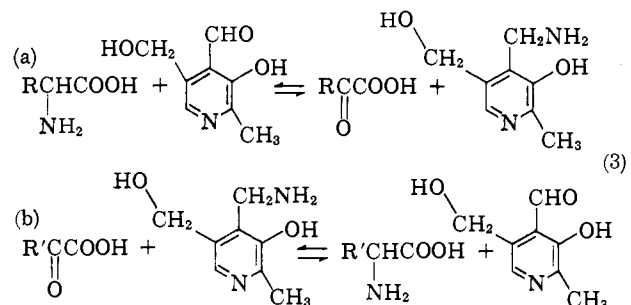$$R'CH_2N{=}CR_2 \underset{-H_2O}{\overset{+H_2O}{\rightleftarrows}} R'CH_2NH_2 + R_2CO \quad (1)$$

This, the first paper in a series dealing with the catalysis of reactions proceeding through intermediate azomethines, pertains to the imidazole catalysis of the transamination of pyridoxal by α-aminophenylacetic acid.

Interest in the biological transamination of amino acids led Herbst and Engell[2] to investigate the reaction of α-amino acids with α-keto acids. The latter studies were carried out in boiling aqueous solution, the products recovered indicating that the initially formed imine underwent decarboxylation.[3] Only in the case of glyoxylic acid reacting with α-amino acids could a transamination of type 1 be realized.[4] The glyoxylic acid reactions were carried out in water at 25° and the rate of product formation (followed chromatographically) was found to be increased by OH⊖, whereas in 2 an apparent pH optimum of about 3 was noted. The rate of the transamination of glyoxylic acid was found

(1) (a) A portion of this study has appeared in preliminary form (see T. C. Bruice and R. M. Topping, *J. Am. Chem. Soc.*, **84**, 2448 (1962)). (b) Post-doctoral Fellow of the Department of Chemistry, Cornell University.

(2) R. M. Herbst and L. L. Engell, *J. Biol. Chem.*, **107**, 505 (1934); *J. Am. Chem. Soc.*, **58**, 2239 (1936).

(3) R. M. Herbst and D. Rittenberg, *J. Org. Chem.*, **8**, 380 (1943).

(4) H. I. Nakada and S. Weinhouse, *J. Biol. Chem.*, **204**, 831 (1953).

$$C_6H_5CHCOOH + CH_3CCOOH \underset{-H_2O}{\overset{100°}{\rightleftarrows}}$$

$$\quad \underset{NH_2}{} \quad \underset{O}{}$$

to be strongly dependent on the nature of the amino acid.

Biochemical transamination reactions were shown by Braunstein[5] and Cohen[6] to be mediated by pyridoxal phosphate-requiring enzymes. Recently Snell[7] has established certain transaminases to require non-phosphorylated pyridoxamine as cofactor. The non-enzymatic transamination of pyridoxal (3a) by an α-

amino acid was first shown by Snell in 1945.[8] In the experiments of Snell, which were followed by both

(5) A. E. Braunstein, *Enzymol.*, **7**, 25 (1934).

(6) P. P. Cohen, *Biochem. J.*, **33**, 1478 (1939).

(7) H. Wada and E. E. Snell, *J. Biol. Chem.*, **237**, 127, 133 (1962).

(8) E. E. Snell, *J. Am. Chem. Soc.*, **67**, 194 (1945).