

Relative rates for chloro- and bromobenzene were also obtained from competition of chloro- and bromobenzene with fluorobenzene and that of chlorobenzene with bromobenzene.

**Determination of Isotope Effect.**—(a) Benzene- $d_6$  (0.025 mole) and toluene (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of  $\text{CH}_3\text{CO}^+\text{SbX}_6^-$  as previously described. The products were analyzed by gas-liquid chromatography. (b) Benzene- $d_6$  (0.025 mole) and benzene (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of  $\text{CH}_3\text{CO}^+\text{SbX}_6^-$  as previously described. The products were analyzed by mass spectroscopy. (c) Benzene (0.025 mole) and toluene- $d_8$  (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of  $\text{CH}_3\text{CO}^+\text{SbF}_6^-$  as previously. The products were analyzed by gas-liquid chromatography. (d) Benzene- $d_6$  (0.025 mole) and toluene- $d_8$  (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of  $\text{CH}_3\text{CO}^+\text{SbF}_6^-$  as previously. The products were analyzed by gas-liquid chromatography. (e) Benzene (0.025 mole) and toluene- $\alpha,\alpha,\alpha-d_3$  (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of  $\text{CH}_3\text{CO}^+\text{SbF}_6^-$  as described in (a). The products were analyzed by gas-liquid chromatography. (f) Benzene (0.025 mole) and toluene- $d_8$ , (0.025 mole) were acetylated as in (e). (g) Benzene (0.025 mole) and mesitylene- $d_3$ , (0.025 mole) were acetylated as in (e).

**Analytical Procedure.**—Gas-liquid chromatography was carried out on a Perkin-Elmer Model 154-C vapor fractometer, using a thermistor detector, equipped with a Perkin-Elmer Model 194 electronic printing integrator. A 4-m.  $\times$  0.25 in. stainless

steel column packed with polypropylene glycol (UCON LB 550-X) supported on diatomaceous earth was used. The column temperature was 180° for all of the determinations; 25 ml. of hydrogen per minute was used for carrier gas.

Relative response was determined by making up known solutions of acetophenone, alkylacetophenones, and haloacetophenones in excess benzene in the ratios approximating those occurring in the reaction mixtures and determining the response per mole relative to acetophenone as analyzed by gas-liquid chromatography.

Characteristic retention times of acetophenone, alkylacetophenones, and haloacetophenones are given in Table X.

TABLE X  
RETENTION TIME (MINUTES)

Acetophenone	13	3,4-Dimethylacetophenone	36.8
<i>o</i> -Methylacetophenone	16.4	2,4,6-Trimethylacetophenone	30.4
<i>m</i> -Methylacetophenone	20.0	<i>p</i> -Fluoroacetophenone	12
<i>p</i> -Methylacetophenone	21.6	<i>p</i> -Chloroacetophenone	29
2,5-Dimethylacetophenone	23.6	<i>p</i> -Bromoacetophenone	34
2,4-Dimethylacetophenone	25.6		

**Acknowledgment.**—Dr. L. B. Westover, Chemical Physics Research Laboratory, Dow Chemical Co., Midland, Mich., is thanked for the mass spectroscopic analyses, and Dr. J. S. McIntyre for the n.m.r. spectra obtained on a Varian Model A-60 spectrometer.

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## Tautomeric Equilibria. VII. Substituent Effects in Dimethylaminoazobenzenes<sup>1</sup>

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The effect of substitution on the tautomeric equilibrium in substituted dimethylaminoazobenzenes has been investigated. The tautomeric equilibrium constants for seven 4'-substituted-4-dimethylaminoazobenzenes have been obtained and have been found to follow the Hammett equation. The spectroscopic behavior of the first conjugate acid of dimethylaminoazobenzene and the comparability of  $H_0$  and  $H_+$  acidity scales were also investigated.

The structures of the first conjugate acids of 4-dimethylaminoazobenzenes have been under much discussion. A number of workers have reached widely varying conclusions on this problem.<sup>2</sup>

More recently it has become clear that there is a tautomeric equilibrium between ammonium (I) and azonium (II) forms.<sup>3</sup>

With the exception of some semiquantitative work by the method of Sawicki,<sup>3</sup> the only careful attempt at determination of tautomeric equilibrium constants has been performed in this laboratory,<sup>3i,j</sup> and only on the parent compound. We have now re-examined and improved this work, and extended it to a series of substituted derivatives.

(1) Support of this work by a research grant from the American Cancer Society is gratefully acknowledged.

(2) (a) A. Hantzsch and F. Hilsher, *Ber.*, **41**, 1171 (1908); (b) F. Kehrman, *ibid.*, **48**, 1933 (1915); (c) A. Hantzsch and A. Burawoy, *ibid.*, **63**, 1760 (1930); (d) M. T. Rogers, T. W. Campbell, and R. W. Maatman, *J. Am. Chem. Soc.*, **73**, 5122 (1951); (e) I. M. Klotz, H. A. Fiess, J. Y. Chen-Ho, and M. Melody, *ibid.*, **76**, 5136 (1954).

(3) (a) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 1888 (1954); (b) E. Sawicki and F. E. Ray, *J. Org. Chem.*, **19**, 1686 (1954); (c) E. Sawicki, *ibid.*, **21**, 605 (1956); (d) *ibid.*, **22**, 365, 621, 743 (1957); (e) G. Cilento, *Cancer Res.*, **20**, 120 (1960); (f) A. Zenhäusern and H. Zollinger, *Helv. Chim. Acta*, **45**, 1882, 1890 (1962); (g) P. Gerson and E. Heilbronner, *ibid.*, **45**, 42 (1962); (h) I. Granacher, H. Suhr, A. Zenhäusern, and H. Zollinger, *ibid.*, **44**, 313 (1961); (i) H. H. Jaffé and S. J. Yeh, *J. Org. Chem.*, **22**, 1281 (1957); (j) S. J. Yeh and H. H. Jaffé, *J. Am. Chem. Soc.*, **81**, 3283 (1959); (k) G. E. Lewis, *Tetrahedron*, **10**, 129 (1960).

## Experimental

**Dimethylaminoazobenzenes (4-DAB).**—4'-Substituted-4-DAB were prepared by diazotization of the appropriate *p*-substituted aniline and coupling of the resulting diazonium salt with dimethylaniline in an acetate buffer.<sup>4</sup> The products were recrystallized from ethanol to a constant melting point, in all cases equal to or greater than values reported in the literature (*cf.* Table I). Elemental analysis<sup>5</sup> on these compounds checked very closely with theoretical values.

**Trimethylammonioazobenzene Chlorides. N,N,N-Trimethyl-*p*-phenylazoanilinium Chloride (4-TAB).**—The 4'-substituted dimethylaminoazobenzene (3 g.) was dissolved in *ca.* 30 ml. of methyl iodide and heated under reflux for 2 to 4 days. The resulting precipitate of trimethylammonioazobenzene iodide was collected, washed with anhydrous ether, and dried. The precipitate was then dissolved in 1:1 ethanol-water and passed through a 10-g. column of Dowex 2-X8 ion-exchange resin. The solvent was then removed under aspirator vacuum and the residue dissolved in absolute ethanol and precipitated by addition of anhydrous ether. The dissolving in ethanol then reprecipitating with ether steps were repeated a number of times. The product was then dissolved in 95% ethanol and passed once more through a 10-g. column of the same ion exchange resin. After removal of solvent, the reprecipitation was repeated once more. Finally the product was collected and dried *in vacuo*. The yields were generally in the range of 60%. The purity of the compounds was checked by elemental analysis (*cf.* Table I).

(4) "Organic Syntheses," Coll. Vol. I, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 347.

(5) Elemental analyses were performed by A. Bernhardt, Mülheim (Ruhr), Germany.

TABLE I  
 ACIDITIES AND MELTING POINTS OF 4'-SUBSTITUTED 4-DAB AND OF 4'-SUBSTITUTED 4-TAB

4'-Substituent	DAB		M.p., °C.	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %		-pK <sub>s</sub> <sup>a</sup>
	M.p., °C.	-pK <sub>a2</sub> <sup>a</sup>		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
Methoxy	164-165	2.74 ± 0.01	185-186 d.	62.84	63.28	6.59	6.57	13.74	13.61	11.59	11.42	2.21 ± 0.003
Methyl	169.5-170	4.23 ± .01	178-179 d.	66.31	66.56	6.96	7.38	14.50	13.89	12.23	12.05	3.52 ± .01
None	119-120	5.34 ± .02	186-187 d.	65.32	65.17	6.58	6.43	15.24	15.02	12.86	12.85	4.43 ± .01
Chloro	158-159	5.61 ± .01	184-185 d.	58.07	58.14	5.52	5.56	13.56	13.61	22.86	23.10	4.83 ± .01
Bromo	160-161	5.70 ± .01	187-188 d. <sup>c</sup>	50.80	50.73	4.83	4.89	11.85	11.60	10.00	10.36	4.85 ± .008
Trifluoro-												
methyl	178-178.5 <sup>b</sup>	7.10 ± .02	179-180 d. <sup>d</sup>	55.90	56.02	4.98	4.90	12.22	12.07	10.31	10.16	5.85 ± .01
Nitro	230-231	8.34 ± .01	224-225 d.	56.16	55.96	5.34	5.47	17.45	17.34	11.05	11.02	6.57 ± .01

<sup>a</sup> ± Standard deviation from the mean. <sup>b</sup> Anal. Calcd.: C, 61.43; H, 4.18; N, 14.33. Found: C, 61.08; H, 5.03; N, 14.50. <sup>c</sup> Anal. Calcd.: Br, 22.53. Found: Br, 22.64. <sup>d</sup> Anal. Calcd.: F, 16.58. Found: F, 16.56.

**pK Measurements.**—All pK<sub>a</sub> measurements were carried out using a standard spectrophotometric method<sup>6</sup> with a Beckman DU quartz spectrophotometer. The H<sub>0</sub> acidity scale for 20% ethanol-sulfuric acid developed by Jaffé and Gardner<sup>7</sup> and extended by Yeh and Jaffé<sup>8</sup> was used.

### Results and Discussion

#### Comparison of the H<sub>0</sub> and the H<sub>+</sub> Acidity Scales.—

In this work the equilibrium constants for the process of protonating positively charged species to dipositively charged ones were measured. Since an H<sub>+</sub> function was not available, the H<sub>0</sub> scale was used. The applicability of this was checked by plotting log (B<sup>+</sup>)/(BH<sup>2+</sup>) vs. H<sub>0</sub> for all compounds investigated. These plots are shown in Fig. 1 and 2 and demonstrate that the

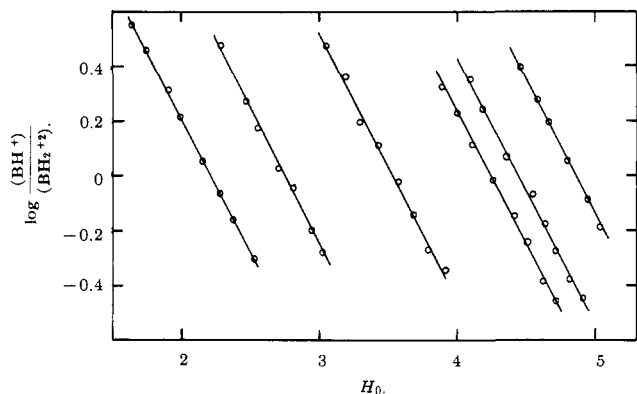


Fig. 1.—Plot of log (B<sup>+</sup>)/(BH<sup>2+</sup>) vs. H<sub>0</sub>.

slope of the line defined by the experimentally measured points is unity except for the last two compounds. This then shows that H<sub>0</sub> and H<sub>+</sub> acidity scales are identical for this system up to about H<sub>0</sub> = -7. This is not unexpected since Fuller and Schubert<sup>9</sup> have reported that H<sub>0</sub> and H<sub>+</sub> functions are parallel in low acidity regions and Deno<sup>10</sup> has suggested that, if the charge already on the molecule is insulated from the site of protonation by several atoms, the interaction energy of the charge with the solvent will cancel in the f<sub>B</sub>/f<sub>BH<sup>+</sup></sub> ratios. Since the H<sub>0</sub> function used in this work was developed using substituted azobenzenes as indicators, the present series of measurements is the first known in which it has become possible to make a careful comparison of H<sub>0</sub> and H<sub>+</sub> scales over a wide range of acidities using structurally similar compounds. This then constitutes

(6) L. A. Flexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935).

(7) H. H. Jaffé and R. W. Gardner, *ibid.*, **80**, 319 (1958).

(8) S. J. Yeh and H. H. Jaffé, *ibid.*, **81**, 3274 (1959).

(9) M. W. Fuller and W. M. Schubert, *ibid.*, **85**, 108 (1963).

(10) N. C. Deno, private communication

the establishment of a previously unavailable H<sub>+</sub> acidity function.

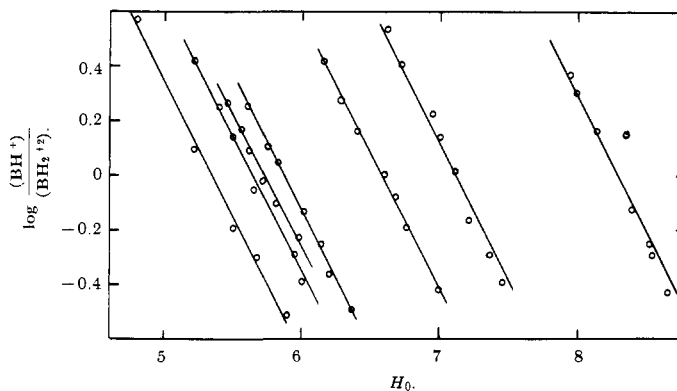


Fig. 2.—Plot of log (B<sup>+</sup>)/(BH<sup>2+</sup>) vs. H<sub>0</sub>.

**Analysis of the Tautomeric Equilibrium.**—The results of the pK<sub>a</sub> measurements are shown in Table I. These were analyzed according to the scheme shown in Fig. 3. From the equilibria shown there, the following equation can be derived

$$K_T = (K_{a_2}/K_1) - 1$$

Since K<sub>1</sub> is not experimentally obtainable, the approximation that K<sub>1</sub> ≈ K<sub>3</sub> must be made. This approximation can be justified on the grounds that inductive effects of -N<sup>+</sup>(CH<sub>3</sub>)<sub>3</sub> and -N<sup>+</sup>H(CH<sub>3</sub>)<sub>2</sub> groups be very nearly equal and since no resonance forms can be written to delocalize the positive charge, the σ-values for the two groups should be the same.<sup>11</sup> The equation then becomes

$$K_T = (K_{a_2}/K_3) - 1$$

and K<sub>T</sub> can be easily calculated.<sup>3j</sup> The tautomeric equilibrium constants are summarized in Table II, column A. For comparison K<sub>T</sub>'s obtained by other

TABLE II  
TAUTOMERIC EQUILIBRIUM CONSTANTS IN  
4'-SUBSTITUTED 4-DAB

4'-Substituent	-K <sub>T</sub>					
	A	B	C	D	E	F
Methoxy	2.39			1.27	0.53	0.60
Methyl	4.13			4.25	1.44	1.88
None	7.15	1.7	3.0	6.98	2.10	3.10
Chloro	5.02			5.29	1.80	2.40
Bromo	6.05			7.23	2.61	3.86
Trifluoromethyl	16.8			11.25	3.57	5.62
Nitro	57.9			13.10	4.36	7.00

(11) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **79**, 5804 (1957).

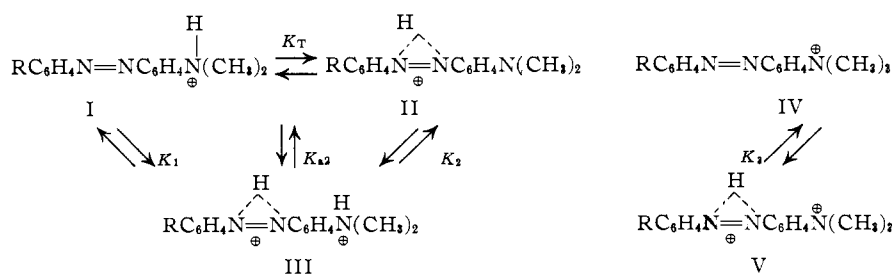


Fig. 3.—The equilibrium scheme.

methods are given in columns B through F. Columns B and C give  $K_T$ 's obtained by Yeh and Jaffé<sup>3j</sup> in 20% ethanol-sulfuric acid and sulfuric acid-water solvent systems, respectively. In the present work we have found that their values are only approximations, because the  $pK_a$  measurements were performed on trimethylammonioazobenzene methyl sulfate. In the present work it was found that the compound, when prepared by quaternization with dimethyl sulfate, is usually contaminated with dimethylaminoazobenzene methyl sulfate. This is indicated by the deep red color of the product. Consequently  $pK_a$  measurements of

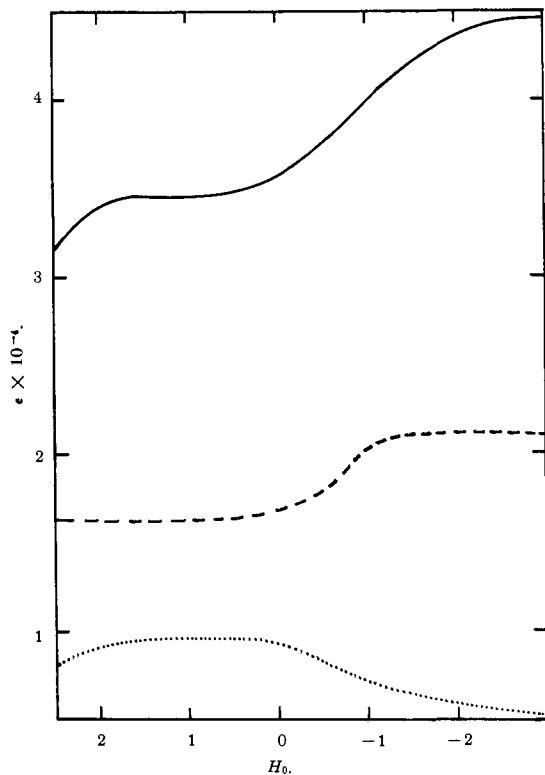


Fig. 4.—Plot of  $\epsilon \times 10^{-4}$  of 4-DAB and 4-TAB vs.  $H_0$ : ———, 518  $m\mu$  band of DAB; ·····, 318  $m\mu$  band of DAB; - - - - , 318  $m\mu$  band of TAB.

Jaffé and Yeh are only first approximations. In contrast to this, the trimethylammonioazobenzene chlorides were light yellow in color and gave perfectly consistent and reproducible  $pK_a$  measurements. Column D in Table II gives data obtained by the spectrophotometric method of Sawicki.<sup>3c</sup> Column E gives data obtained by the spectrophotometric method of Yeh and Jaffé<sup>3j</sup> and column F gives data obtained by the same method modified by a correction suggested by Wepster.<sup>12</sup> Sawicki's method assumes that substituents affect the molar extinction coefficients of the 320

(ammonium form) and 520  $m\mu$  (azonium form) bands equally. The failure of his method is no doubt due to an inadequacy of this assumption. Particularly, substituents which can give rise to cross conjugation with the dimethylamino group may be expected to violate this assumption.

The tautomeric equilibrium constants from spectroscopic data are probably invalid for the following reason: the spectroscopic behavior of 4-DAB and of its 4'-methoxy derivative was investigated *between*  $pK_{a1}$  and  $pK_{a2}$ . Instead of the expected constancy of the extinction coefficient of DAB in the acidity range where the first conjugate acid is the only significant species, an "S" shaped curve was noted in the 520  $m\mu$  peak and the 320  $m\mu$  peak of the conjugate acid of 4-TAB, as shown in Fig. 4. About the same behavior was exhibited by the 4'-methoxy derivative as shown in Fig. 5. From these data it is apparent that  $K_T$ 's from

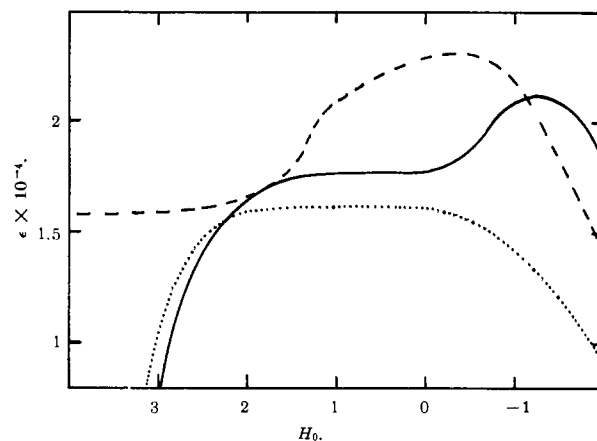


Fig. 5.—Plot of  $\epsilon \times 10^{-4}$  of 4'-methoxy-4-DAB and TAB vs.  $H_0$ : ———, 548  $m\mu$  band of DAB; ·····, 354  $m\mu$  band of DAB; - - - - , 354  $m\mu$  band of TAB.

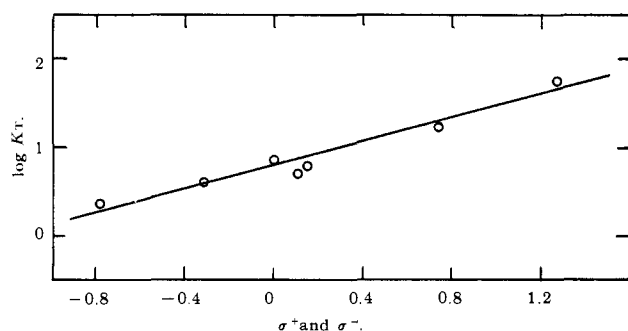
spectral data will be quite unreliable, since there will appear to be large changes in  $K_T$  with relatively small changes in the acidity of the solution. Such changes are shown in Table III when calculations are performed at different acidities.

TABLE III  
CHANGES IN  $K_T$  FROM SPECTROSCOPIC DATA WITH CHANGES IN ACIDITY

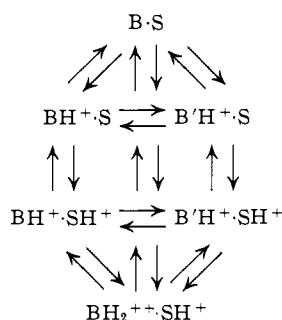
$H_0$	Compound	Method of Sawicki <sup>3c</sup>	Method of Yeh and Jaffé <sup>3j</sup>
+0.3	4-DAB	8.9	7.3
-2	4-DAB	3.7	2.0
+2	4'-Methoxy-4-DAB	1.1	0.038
0	4'-Methoxy-4-DAB	1.6	0.43

It is quite unlikely that the tautomeric equilibrium constant changes as much as indicated by these calculations. Attempts to relate these spectral changes to

(12) B. M. Wepster, private communication cited in ref. 3j.

Fig. 6.—Plot of  $\log K_T$  vs.  $\sigma^+$  and  $\sigma^-$ .

changes in  $H_0$  or to changes in total sulfuric acid concentrations<sup>13</sup> met with failure. One of the more likely explanations of this effect is the possibility that the observed spectral changes are due to protonation of the solvent shell which is solvating the azobenzene moiety. This could be analyzed as



where B and S are the base and the solvent, respectively. At the present moment not enough constants are known to allow analysis of the above system. However, work on this is in progress.

TABLE IV  
LEAST SQUARES ANALYSIS OF  $pK_a$ 'S WITH VARIOUS  
 $\sigma$  CONSTANTS

$pK$	Value <sup>a</sup>	$\sigma^-$	$\sigma^+$	$\sigma^+$ and $\sigma^-$
$pK_3$	$\rho$		2.790	
	$r$		0.999	
	$s$		.018	
	$s_p$		.015	
	$pK_0$			-4.41
$pK_2$	$\rho$	3.272	3.612	2.777
	$r$	0.951	0.996	0.994
	$s$	.635	.185	.222
	$s_p$	.477	.147	.135
	$pK_0$	-4.56	-5.26	-5.04
$pK_{a_2}$	$\rho$		3.526	2.711
	$r$		0.996	0.995
	$s$		.184	.212
	$s_p$		.146	.129
	$pK_0$		-5.34	-5.13
$\log K_T$	$\rho$		0.841	0.674
	$r$		.916	.968
	$s$		.205	.131
	$s_p$		.164	.079
	$\log K_T^0$		.830	.793

<sup>a</sup>  $\rho$  is the slope,  $r$  is the correlation coefficient,  $s$  is the standard deviation,  $s_p$  is the standard deviation from the slope, and  $pK_0$  is the calculated  $pK$  of the unsubstituted compound.

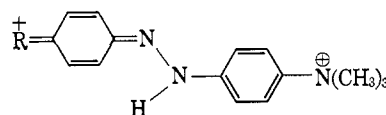
After this work was completed, we found that Kaminsky and Bernshtein<sup>14</sup> had also noted this effect

(13) W. H. Layne, H. H. Jaffé, and H. Zimmer, *J. Am. Chem. Soc.*, **85**, 1816 (1963).

and were able to show that there is a linear relationship between increase in the extinction coefficient of the 520  $m\mu$  peak and the decrease in the extinction coefficient of the 320  $m\mu$  peak of the first conjugate acid of 4-DAB with increase of the acidity of the solution. This observation they ascribe to an acidity-dependent shift from ammonium to azonium form; however, these authors fail to provide any rationale for the shift.

**Application of the Hammett Equation.**—The  $pK_3$  of the 4'-substituted 4-TAB chlorides gave an almost perfect fit with  $\sigma^+$  values. The fit was obtained by means of a least squares treatment which yielded a correlation coefficient of 0.999. The quantities found by the least squares treatment have been summarized in Table IV.

Yeh and Jaffé<sup>15</sup> observed that series of disubstituted azobenzenes, in which one substituent was held constant and the other varied, gave  $\rho$ -values which varied linearly with the  $\sigma$  of the constant substituent. The  $\rho$  of 2.79 obtained here for the trimethylammonioazobenzenes is in excellent agreement with the correlation of these authors, who also found that  $\sigma^+$  constants were necessary to obtain a good fit. This is no doubt due to contributing resonance forms such as

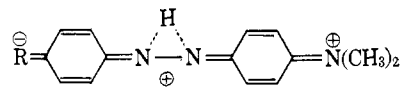


From the diagram in Fig. 3 it can be seen that  $K_2 = K_1 K_T$ . The substitution of  $K_3$  for  $K_1$  will then permit the calculation of  $K_2$ . These values are shown in Table V.

TABLE V  
CALCULATED  $pK_2$  OF 4'-SUBSTITUTED 4-DAB

Substituent	$-pK_2$	Substituent	$-pK_2$
Methoxy	2.59	Bromo	5.63
Methyl	4.14	Trifluoromethyl	7.07
None	5.28	Nitro	8.36
Chloro	5.53		

$\sigma^-$ -Values might be expected to apply to  $K_2$  since structures such as



should contribute. When this fit was attempted, the results were disappointing since a correlation coefficient of only 0.951 was found. The other quantities can be seen in Table IV. Although no valid resonance structures can be written to invoke  $\sigma^+$  constants, with these a much better correlation was found. However, when a "mixed set" of  $\sigma^+$  and  $\sigma^-$  values was used, an equally good fit was obtained. In a mixed set of values,  $\sigma^-$  is used for mesomerically electron-withdrawing substituents and  $\sigma^+$  is used for mesomerically electron-donating ones. The correlations are again shown in more detail in Table IV. It therefore appears reasonable that contributions from resonance forms which would lead to use of  $\sigma^-$  constants to the ground

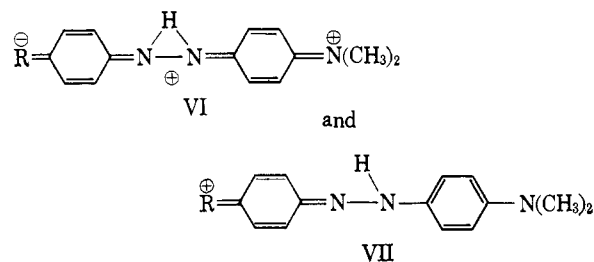
(14) I. L. Kaminsky and I. J. Bernshtein in "Lectures on Problems in Development of Correlation Equations in Organic Chemistry," Tartu Peoples University, Tartu, U.S.S.R., 1962, pp. 333-341.

(15) S. J. Yeh and H. H. Jaffé, *J. Am. Chem. Soc.*, **81**, 3279 (1959).

state energy of the molecule is a very good possibility. The  $K_T$  data indicate that in the first conjugate acid the form present in major proportions is the azonium form (II). Since  $pK_2$  is the  $pK_a$  of the azonium form, it could be expected that  $pK_{a2}$  would be quite close to  $pK_2$ . This was found to be the case. The results of the least squares analysis are shown in Table IV.

It should be noted that the Hammett plots of  $pK_3$  and  $pK_2$  are quite good straight lines. This is in contrast to work of Zollinger<sup>3f</sup> and Heilbronner<sup>3g</sup> who could obtain good fits only when points representing the more active substituents such as 4'-nitro and 4'-cyano were omitted. This is due to their basic assumption that  $K_T$  can be estimated by the spectroscopic method of Sawicki,<sup>3c</sup> as discussed above.

When the Hammett equation was applied to  $\log K_T$  it was found that, with  $\sigma^+$ , a correlation coefficient of 0.916, and with  $\sigma^+\sigma^-$ , one of 0.968, could be obtained. The appropriate data are shown in more detail in Table IV and a graphical representation is shown in Fig. 6. That the use of  $\sigma^+\sigma^-$  constants yields the better fit can be rationalized on the basis of the resonance forms



In structure VI substituents capable of exerting an electron-withdrawing effect by resonance would tend to make the dimethylamino group less basic, leaving the azo group effectively uncharged. This would tend to increase  $K_T$  and would require  $\sigma^-$ -values. Structures such as VII would demonstrate the effect of electron-donating groups in increasing the basicity of the azo group and leaving the dimethylamino group effectively uncharged. Such structures would lead to a fit with  $\sigma^+$ . Both structures tend to substantiate the view that the tautomer protonated on the azo group should be predominant.

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## Enamines as Dipolarophiles in 1,3-Dipolar Addition Reactions<sup>1</sup>

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The investigation of the reaction of phenyl azide with a series of enamines clearly demonstrates that the exclusive products of 1,3-dipolar addition, 1-phenyl-5-amino-4,5-dihydro-1,2,3-triazoles, are the result of electronic control. The negative end of the azide dipole, *i.e.*, the nitrogen bearing phenyl, is directed to that carbon atom of the unsaturated linkage bearing the electron-releasing amino group. The fact that conjugation with an amino group "activates" the olefinic linkage toward 1,3-dipolar addition supports the electrophilic nature of the reaction.

Of the varied olefinic dipolarophiles successfully employed in intermolecular 1,3-dipolar addition reactions, the predominant number involve an unsaturated linkage that is either strained or conjugated to aromatic and/or electron-withdrawing groups.<sup>3,4</sup> However, only relatively few isolated examples of the successful utilization of dipolarophiles in which the olefinic linkage is conjugated to an electron-releasing group have appeared in the literature.<sup>5</sup> The present report, describing the addition of phenyl azide to a series of enamines,<sup>6</sup> clearly demonstrates the important role that an electron-releasing substituent at the site of unsaturation can play in determining the course of 1,3-dipolar additions.

(1) Presented before the Division of Organic Chemistry at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 10, 1963.

(2) Supported by a Parke, Davis and Co. Research Scholarship.

(3) The facile intramolecular cycloaddition of nitrones to "unactivated" olefinic linkages to yield fused bicyclic isoxazolidines has been reported by N. A. LeBel and J. J. Whang, *J. Am. Chem. Soc.*, **81**, 6334 (1959).

(4) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963), provides a recent and comprehensive review of the entire field of 1,3-dipolar addition reactions.

(5) (a) K. Alder and G. Stein, *Ann.*, **501**, 1 (1933), suggest that the reactions of cyclohexanone and cyclopentanone anil with phenyl azide are explicable in terms of a 1,3-dipolar addition to the tautomeric enamine forms. (b) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962), report the cycloaddition of diphenylnitrilimine to ketene diethyl acetal. (c) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963), reports the successful addition of *p*-nitrophenyl azide to 2,3-dihydropryan.

(6) Recent papers by R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. chim. ital.*, **91**, 849 (1961) [*Chem. Abstr.*, **56**, 14019 (1962)], and G. Nathanson, E. Testa, and N. Dimola, *Experientia*, **18**, 57 (1962), which appeared after the inception of the study described in this manuscript, report the successful condensation of aromatic azides with enamines.

The directive influence of the amino group was established on the basis of the isomeric 5-(1-piperidino)-4,5-dihydro-1,2,3-triazoles,<sup>7</sup> IIa (70% yield) and IIb (91% yield), respectively, arising from the addition of phenyl azide to the isomeric piperidine enamines of acetophenone and phenylacetaldehyde (Ia and Ib, respectively). Thus the nitrogen atom of the azide dipole bearing phenyl is directed to that carbon of the unsaturated linkage bearing the amino group. Reaction was conveniently effected by mixing equimolar amounts of reactants at room temperature in the absence of solvent.

Triazoline structures IIa and IIb were assigned on the basis of elemental analysis and their facile conversion, in yields greater than 90%, to the known triazoles, 1,5-diphenyl-1,2,3-triazole (IIIa)<sup>8</sup> and 1,4-diphenyl-1,2,3-triazole (IIIb),<sup>8</sup> respectively, upon treatment with refluxing 2 *N* methanolic potassium hydroxide. It appears that the stabilization of the transition state of the elimination step provided by the incipient aromaticity of the 1,2,3-triazole system accounts for the rather facile departure of a poor leaving group. It is interesting to note that dilute aqueous acid promotes a similar quantitative elimination of piperidine in the case of triazoline IIa; the isomeric triazoline IIb gives rise to more deep-seated decomposition products under these conditions (*vide infra*).

(7) 4,5-Dihydro-1,2,3-triazoles will hereafter be designated as "triazolines."

(8) W. Kirmse and L. Horner, *Ann.*, **614**, 1 (1958).