[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

The Physical Properties of Aminoazobenzene Dyes. II. Further Studies of the Basicity[1]

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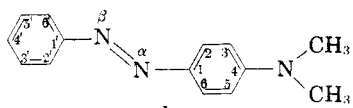
The basicity of 34 aminoazobenzene dyes was determined spectrophotometrically in 50% ethanol. The shifts in basicity by the substitution of various groups in the aminoazobenzenes are discussed. Desired groupings can now be placed into a 4-aminoazobenzene molecule to obtain compounds of a desired structure and basicity for cancer research studies. Alternatively the *p*Ka values of these azo dyes can be of value in proof of structure work with unknown azo dyes or their metabolites. The infrared spectra of 7 aminoazobenzenes were compared in the 3 μ region. Two 2-aminoazobenzene dyes were found to have 3 definite bands in this region with relative intensities characteristic only of these dyes. The long wave length band at approximately 3.04 μ is believed to be due to the N—H stretching frequency modified by intramolecular hydrogen bonding. Approximately 19 new azo dyes were prepared.

Since a large number of 4-dimethylaminoazobenzene (DAB) (I) derivatives are hepatocarcinogenic in the rat[3] and since so many aromatic amine derivatives are carcinogenic to mammals,[4] basicity studies appear to be necessary for an eventual evaluation of the relation of the physical properties of carcinogens to their biological activity. In this respect the basicity of certain alkylated 4-aminoazobenzene dyes has been investigated previously.[5]



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It was found that a 2-methyl group in DAB increased the *p*Ka 0.7 unit; a 2′-methyl group decreased the *p*Ka 0.3 unit; a 3-methyl group increased the *p*Ka 1.3 unit, while 3′- and 4′-methyl groups had a negligible effect. In the present paper the effect of other groups on the basicity is investigated, Table I.

The 2-, 3-, and 4-nitroanilines have *p*Ka's in water of −0.05, 2.52 and 1.13[19] while the analogous aminoazobenzenes have values in 50% alcohol of 1.8, 3.0 and 2.28. In both series the *ortho* derivatives have the lowest basicity while the *meta* derivatives are the most basic. Contributing to the weak basicity in these molecules are the strong inductive and resonance effects in the *ortho* derivatives, a moderate inductive effect in the *meta* derivatives and strong resonance and weak inductive effects in the *para* derivatives. Hydrogen bonding and steric strain[20] are other factors contributing to the basicity of the *ortho* derivatives. In this respect an examination of the infrared spectra of several 2-, 3-, and 4-aminoazobenzene derivatives in carbon tetrachloride solution disclosed a definite difference between the 2-aminoazobenzenes and the 3- and 4-analogs in the N—H stretching region. 2-Aminoazobenzene had bands at 2.89 μ, 2.96 μ and 3.05 μ, while 4′,5-dimethyl-2-aminoazobenzene had bands at 2.85 μ, 2.94 μ, and 3.02 μ. The low wave length band was of moderate intensity, the remaining bands were weak with the band at approximately 2.95 μ the weakest. The long wave length band is believed to be caused by the NH stretching frequency modified by intramolecular hydrogen bonding. On the other hand, 3,4′-dimethyl-4-aminoazobenzene,2′,3-dimethyl-4-aminoazobenzene,2,4′-dimethyl-4-aminoazobenzene, and 2,3′-dimethyl-4-aminoazobenzene have bands at 2.86 μ and 2.93 μ, the low wave length band being of weak and the second band, of moderate intensity. 3-Aminoazobenzene had 3 weak bands at 2.89 μ, 2.95 μ, and 3.15 μ; the middle band was the strongest while the long wave length band was, by far, the weakest.

The 4′-isopropyl-, 3′-acetylamino, and 4′-acetylamino groups had very little effect on the basicity of DAB while the 2′-methoxy group had a slight base

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TABLE I
BASICITY OF AZOBENZENE DYES

Compound	M.p., °C. (ref.)	*p*Ka 50% EtOH	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
2-AB[a]	59–60 (7)	1.8						
3-AB	64–65 (8)	3.0						
4-AB	124–125 (9)	2.28						
4′,5-Dimethyl-2-AB	118–119 (10)	2.5						
4′-Isopropyl DAB[b]	105–106	2.31	76.4	76.5	7.9	7.9	15.7	16.0
2′-Methoxy DAB	91–92	2.20	70.6	70.7	6.67	6.84	16.5	16.4
4′-Methoxy DAB	160–161 (11)	2.40						
3′-Acetylamino DAB	184–185 (12)	2.27						
3′-Acetylamino MEAB[c]	157–159	2.47	68.9	69.0	6.76	6.70	18.9	18.7
4′-Acetylamino DAB	227–228 (13)	2.25						
2′-Chloro DAB	108–109 (14)	1.74						
2′-Chloro MEAB	57–58	2.14	65.8	65.7	5.85	5.81	15.4	15.3
3′-Chloro DAB	103–104 (9)	2.01						
3′-Chloro-2-methyl DAB	89–90.5	2.67	65.8	65.9	5.85	5.79	15.4	15.3
4′-Chloro DAB	158–159 (14)	2.00						
4′-Fluoro DAB	152–153 (14)	2.00						
4′-Fluoro MEAB	117–118	2.40	70.0	70.1	6.23	6.32	16.3	16.2
3′-Trifluoromethyl DAB	81–82.5 (15)	1.84						
3′-Trifluoromethyl MEAB	68.5–69	2.15	62.5	62.4	5.21	5.12	13.7	13.6
3′-Acetyl DAB	111–112	2.03	71.9	71.7	6.37	6.60	15.7	15.5
3′-Acetyl MEAB	79–80	2.28	72.6	72.7	6.76	6.68	14.9	14.7
3′-Acetyl-2-methyl DAB	115–116.5	2.73	72.6	72.5	6.76	6.78	14.9	14.8
4′-Acetyl DAB	204–206 (16)	2.16						
4′-Acetyl MEAB	150–150.5	2.35	72.6	72.7	6.76	6.82	14.9	14.8
4′-Acetyl-2-methyl DAB	153–154	2.88	72.6	72.7	6.76	6.58	14.9	14.6
4′-Acetyl-3-methyl DAB	127.5–128	3.27	72.6	72.5	6.76	6.83	14.9	14.9
2′-Nitro DAB	127–128 (14)	1.5						
2′-Nitro MEAB	95–97	1.75	63.4	63.5	5.63	5.90	19.7	19.5
2′-Nitro-2-methyl DAB	125–126	2.12	63.4	63.4	5.63	5.65	19.7	19.6
3′-Nitro DAB	160–161 (17)	1.67						
3′-Nitro MEAB	122–123	2.00	63.4	63.6	5.63	5.85	19.7	19.6
3′-Nitro-2-methyl DAB	112–113	2.32	63.4	63.4	5.63	5.66	19.7	19.6
3′-Nitro-3-methyl DAB	72–73	3.18	63.4	63.6	5.63	5.70	19.7	19.6
3′-Nitro DEAB[d]	113–113.5	2.39	64.4	64.5	6.04	6.10	18.8	18.6
4′-Nitro DAB	231–232.5 (17)	1.81						
2′,4′,6′-Tribromo DAB	162–163 (18)	1.0						

[a] AB = aminoazobenzene. [b] DAB = 4-dimethylaminoazobenzene. [c] MEAB = 4-methylethylaminoazobenzene. [d] DEAB = 4-diethylaminoazobenzene.

weakening effect and the 4′-methoxy had a weak base strengthening effect. *o*-Methoxyaniline, *p*Ka 4.59, and *p*-methoxyaniline, *p*Ka 5.40, show approximately the same relation to aniline, *p*Ka 4.67, although it must be emphasized the solvent was water in this case.[19]

Comparison of the dialkylaminoazobenzenes with their 2′- and 3′-nitro and 3′- and 4′-acetyl derivatives disclosed the following regular relationships. A change from a 4-dimethylamino dye to a 4-methylethylamino dye caused an increase in *p*Ka of approximately 0.3 unit; the addition of a 2-methyl group to a 4-dimethylamino dye caused an increase in basicity of 0.7 ± 0.1 unit. 4-Diethylamino- and 2-methyl-4-dimethylamino-azobenzene dyes have approximately the same basicity. The addition of a 3-methyl group to DAB pushes the dimethylamino group out of the plane of the molecule and increases the basicity 1.2 units. In the previous paper[5] it was shown that the sterically hindered dimethylamino group in this molecule, as compared to the β-nitrogen atom, is, by far, the most powerful proton attractor. The addition of a 3-methyl group to 4′-acetyl DAB causes an analogous increase of 1.1 units. A similar change in structure for 3′-nitro DAB causes an increase in basicity of 1.5 units. The fairly large increase in basicity of this derivative is apparently due to the 4-dimethylamino group being pushed out of the plane of the azobenzene molecule by the 3-methyl group. Consequently the dimethylamino group is more isolated from the remainder of the molecule and the base weakening effect of the 3′-nitro group on the amino group is considerably reduced. This is consistent with the close resemblance of the spectrum of 3′-nitro-3-methyl DAB in dilute acid to the spectrum of azobenzene in alcohol.

This work is being continued.

EXPERIMENTAL[21]

Preparation of compounds. The compounds were prepared by procedures given in the literature. Each dye was crystallized from two to four different solvents to a constant melt-

(21) Melting points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Florida.

ing point. The melting point and reference of preparation are given in Table I. The new dyes were prepared by combining the properly substituted benzene diazonium chloride with the appropriate dialkylaniline by standard procedure.

Determination of the dissociation constants. Details are given in the previous paper.[5] The average deviation of the *p*Ka of most of the compounds was within ±0.05 *p*H unit; the remainder of the dyes with *p*Ka's below 1.8 and above 3.0 had deviations of approximately ±0.1 *p*H unit.

Infrared absorption spectra. The infrared spectra of all compounds were measured with a Perkin-Elmer model 21 infrared spectrophotometer using sodium chloride optics and carbon tetrachloride as a solvent.

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