without further purification, was converted into the dibromo compound by shaking for 20 hours with a solution of 2.74 g. of bromine in 20 ml. of carbon tetrachloride. The reaction mixture was washed with aqueous sulfite and then with water, and finally filtered and evaporated to dryness. The residue was taken up in petroleum ether (b.p. 35–60°) and chromatographed on a 40-g. alumina column, using more solvent as eluent. A single solid fraction consisting of 0.706 g. (18.6%, based on sulfonyl chloride), m.p. 55.0–56.5°, was isolated. Recrystallization from methanol yielded 0.409 g. (11%) of light yellow crystals, m.p. 57.0–57.5°. A mixed melting point with an authentic specimen of 4-nitro-2,6-dibromotoluene was not depressed, and the infrared absorption spectra of the two samples were identical.

4-Nitro-2,6-diiodotoluene.—Five grams (0.015 mole) of 4-nitrotoluene-2,6-disulfonyl chloride was converted to the bischloromercuri compound as described in the preceding section. The mercury compound was stirred overnight with a suspension of 4.2 g. of iodine in carbon tetrachloride. Excess iodine was destroyed by washing the mixture with aqueous sodium sulfite. The organic layer was filtered and evaporated to dryness, and the residue was taken up in a 1:4 mixture of benzene and petroleum ether (b.p. 35–60°) and chromatographed on alumina, using benzene–petroleum ether mixtures of increasing benzene content for elution. The only sizable fraction recovered was 0.293 g. (5.0%) of light yellow crystals, m.p. 116°.

Anal. Calcd. for $C_7H_5I_2NO_2$: C, 21.61; H, 1.30; I, 62.26. Found: C, 21.61; H, 1.34; I, 65.35.

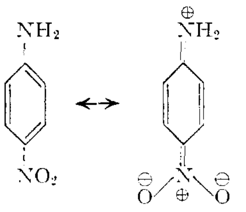
PROCTER AND GAMBLE CO.
MIAMI VALLEY LABORATORIES
CINCINNATI 31, OHIO

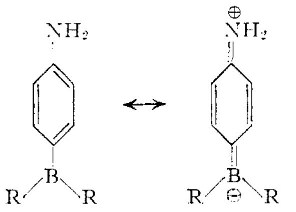
Quantum Mechanical Calculations of Electrical Effects of Substituents in *para*-Substituted Anilines

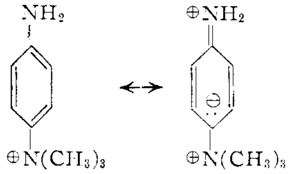
BY JOHN D. ROBERTS AND DOROTHY A. SEMENOW

RECEIVED OCTOBER 28, 1954

Base strength measurements with substituted anilines indicate direct conjugation between the amino groups and electron-attracting unsaturated substituent groups such as $—NO_2$, $—C{\equiv}N$, etc. (I). Such conjugation delocalizes the unshared electron pair of nitrogen and confers a formal (+) charge on the amino group. Somewhat analogous behavior might be anticipated for substituents which do not carry multiple bonds but which, like tercovalent boron, could accept an electron pair (II) or, like a positively charged trimethylammonium group, could stabilize an adjacent negatively charged center as in the "ylides" (III). Resonance forms may be written which symbolize each of these situations (I–III).

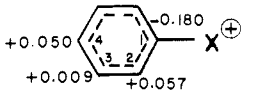

I


II

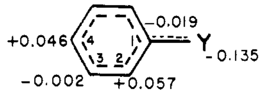

III

In order to determine whether the extent of delocalization of the unshared pair of electrons on nitrogen in *para*-substituted anilines is, at least theoretically, dependent on the character of the substituent, calculations were made by the simple molecular orbital method[1] of the charges on the amino nitrogen in such compounds where the *para*-substituent is: (1) $-X^{\oplus}$ bearing a unit positive charge (analogous to $-N(CH_3)_3^{\oplus}$); (2) $-Y$ carrying an empty p-orbital (analogous to $-BR_2$); and (3) $-\overset{|}{C}=Z$ where Z (analogous to oxygen) is more electronegative than carbon and the polarization of the $-\overset{|}{C}=Z$ p-π-bond results in an incompletely filled p-orbital on carbon. The substituent $-X^{\oplus}$ is regarded as being formally unable to "conjugate" with a *para*-amino group, whereas $-Y$ and $-\overset{|}{C}=Z$ are both able to take part in such conjugation. $-Y$ and $-\overset{|}{C}=Z$ differ from each other only in the degree of unsaturation of the p-orbitals (on Y and C, respectively) and in the electron affinities of Y and Z.

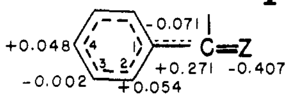
The condition was imposed that systems IV, V and VI have nearly the same charge (*e.g.*, +0.05 of an electron charge[2]) in the π-electrons at C_4 before introduction of a *para*-amino group, so that the only important variable in the *para*-substituted anilines is the electron-accepting power of the substituent.



IV



V



VI

This was achieved by assigning appropriate coulomb integrals, $\alpha + \delta\beta$, to atoms having electron affinities different from a "normal" carbon atom with coulomb integral α; $\delta > 0$ for larger and $\delta < 0$ for smaller electron affinities than a "normal" carbon atom. The δ values used for atoms adjacent to the source of polarization[3] (*i.e.*, C_2 and C_6 in IV, C_1 in V and C_7 in VI) were one-tenth the δ values for the atom at the source (*i.e.*, C_1 in IV, Y in V and Z in VI); coulomb integrals for which δ was less than 0.05 were set equal to α. Resonance integrals between non-adjacent atoms were neglected and, in general, those between adjacent atoms were assigned a value of β. Coulson[4] has stated that the deviation from β of resonance integrals involving

---

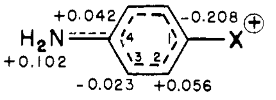
[1] (a) E. Hückel, *Z. Physik*, **70**, 204 (1931); "Grundzüge der Theorie ungesättiger und aromatischer Verbindungen," Verlag Chemie, Berlin, 1938, pp. 77–85; (b) C. A. Couson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A191**, 39 (1947); (c) H. Eyring, J. Walter and G. E. Kimball, "Quantum Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, Chap. XIII.

[2] The charge at C_4 was chosen to be equal to 0.05 of an electron charge since then a substance possessing the over-all charge distribution of VI would have a resonance moment of 0.4 *D* which is of the same order of magnitude as the experimental resonance moments, 0.3 and 0.6 *D*, for benzaldehyde and benzonitrile, respectively.

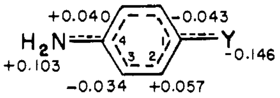
[3] G. W. Wheland and L. Pauling, THIS JOURNAL, **57**, 2086 (1935).

[4] C. A. Coulson, "Valence," Oxford University Press, London 1952, p. 242.

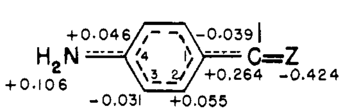
hetero-atoms is small and can be shown[4,5] to exert only a second-order effect on charge distribution. Since the orbitals of the central atom of the $-X^{\oplus}$ group in IV (like N in $-N(CH_3)_3^{\oplus}$) are used in four sp^3-bonds, the π-electron resonance integral for the C_1–$X^{\oplus}$ bond was assumed to be zero. Thus, the only electrical effect considered for $-X^{\oplus}$ was inductive generation of a positive charge on C_1, increasing the electron affinity of that atom and to a lesser extent the electron affinities of C_2 and C_6. The values of the parameters used are summarized in Table I. The resulting π-electron charge distributions in the *para*-amino derivatives are shown in VII, VIII and IX.



VII



VIII



IX

TABLE I

COULOMB INTEGRALS USED IN CALCULATIONS

System	Coulomb integral
IV and VII	$C_1 = \alpha + 0.50\beta$
	$C_2 = C_6 = \alpha + 0.05\beta$
V and VIII	$Y = \alpha - 1.40\beta$
	$C_1 = \alpha - 0.14\beta$
VI and IX	$Z = \alpha + 0.80\beta$
	$C_7 = \alpha + 0.08\beta$
VII, VIII and IX	$N = \alpha + 2.00\beta^a$
	$C_4 = \alpha + 0.20\beta$
IV–IX	Carbon atoms not otherwise designated $= \alpha$

[a] The value chosen for the coulomb integral of nitrogen is not critical; the value of $\alpha + 2\beta$ commonly is used, although it is probably not the best value for nitrogen.[4]

The calculated charges on the amino nitrogens for VII–IX are essentially the same.[6] Furthermore, the magnitudes of the calculated resonance energies for VII–IX and the corresponding anilinium ions indicate that compounds with charge distributions like VII–IX should have practically equal base strengths. Thus, $-X^{\oplus}$, $-Y$ or $-\overset{|}{C}=Z$ are calculated to be equally effective in causing delocalization of *para*-amino electrons provided that C_4 initially has the same charge in each case. It is concluded, therefore, that so far as the LCAO method is concerned, the relative basicities of amino groups *para* located with respect to electron-attracting substituents provide a reasonable measure of the charge on C_4 as postulated previously.[7] The failure of *p*-amino- and *p*-dimethylaminophenyltrimethylammonium salts to be weak bases relative to the corresponding *m*-isomers is thus regarded as strong experimental evidence against important preferential induction by the trimethylammonium group of charged centers in the 2- and 4-positions.[7b,8]

---

(5) G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

(6) If the charges on C_2, C_4 and C_6 in the $-X^{\oplus}$ and $-\overset{|}{C}=Z$ systems are initially +0.15 instead of +0.05 of an electron charge, the calculated charges on a *para*-amino group are again practically equal (approximately +0.14 of an electron charge). A comparable calculation has not been made for the —Y system, but there is no reason to expect that the result would be different.

(7) (a) J. D. Roberts, E. A. McElhill, R. A. Armstrong, THIS JOURNAL, **72**, 408 (1950); (b) J. D. Roberts, R. A. Clement and J. J. Drysdale, *ibid.*, **73**, 2181 (1951).

(8) A somewhat different interpretation recently has been expressed by C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., pp. 254, 732.

CONTRIBUTION NO. 1953
GATES AND CRELLIN LABORATORIES
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA

Reaction of Fumaric Acid with Cysteine

BY LEO PINE AND CARL L. PEACOCK

RECEIVED FEBRUARY 7, 1955

In recent studies of growth requirements of the yeast phase of *Histoplasma capsulatum* in liquid media,[1] it was observed that the presence of fumarate in a cysteine-containing medium did not affect growth of the fungus when the medium was sterilized by filtration. When the medium was autoclaved, however, growth was completely inhibited. Substitution of pyruvic acid for fumarate completely inhibited growth whether the medium was sterilized by heat or by filtration. These results appeared to demonstrate a requirement of the fungus for —SH groups in the medium, since the reaction of pyruvate with cysteine in the cold[2] and the reaction of mercaptans with unsaturated compounds[3] are known. Although Morgan and Friedmann[4] have reported the reaction of maleic acid with cysteine at low temperatures, fumaric acid did not react with cysteine under their conditions. The amorphous addition product of maleic acid and cysteine was isolated by these workers and was identified as S-cysteinosuccinic acid.

Because fumaric acid and cysteine are used in the preparation of certain culture media and in many biological systems their reaction at elevated temperatures is reported here. A simplified procedure for the isolation of S-cysteinosuccinic acid as a crystalline salt of acetic acid and some of the properties of this compound are also given.

Experimental

Ten grams of L-cysteine (free base) and 11.5 g. of fumaric acid were added to 200 ml. of 95% ethanol. The mixture was heated to near boiling until the reactants dissolved and the presence of —SH groups could no longer be detected with nitroprusside and strong alkali. The time required for the reaction to go to completion was approximately two hours. The ethanol lost by evaporation during this time was replaced with water. The solution was placed in a refrigerator at 5° overnight. The following morning, any cystine or fumaric acid which crystallized from solution was filtered off and the volume of the filtrate was reduced to approximately 25 ml. by vacuum distillation. One hundred ml. of distilled water was added, the solution was cooled to 5°, and the excess fumaric acid which crystallized from solu-

---

(1) L. Pine, *J. Bacteriol.*, **68**, 671 (1954).

(2) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936).

(3) T. Posner, *Ber.*, **40**, 4788 (1907).

(4) E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).