Kinetics and Mechanism of the Formation of Formazans by Diazonium Ion Attack on Hydrazones[1]

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Benzenediazonium ion reacts at the methine carbon with aldehyde arylhydrazones in neutral solution to give bis(arylazo)methanes, rather than tetrazenes (which would result from attack at the amino nitrogen) as previously postulated. The bisazo structure is consistent with infrared, ultraviolet, and nmr data and the reactions of such compounds. The technique used to study the rates of formation of variously substituted bis(arylazo)methanes involved measuring low (*ca.* 10^{-4} *M*) diazonium ion concentrations polarographically at a dropping mercury electrode. Under the conditions used, with 40% *t*-butyl alcohol as solvent at 20°, these were moderately fast reactions, the second-order rate constants being in the region 1–100 l. mole^{-1} sec^{-1}. Substituents in the hydrazine ring have a larger effect on the rate ($\rho = -1.3$) than those in the aldehyde ring ($\rho = -0.38$). *ortho* substituents in either ring slowed the coupling reaction, those in the hydrazine ring giving a Taft δ value of 1.06. The effect of variation in acidity of the reacting medium has shown that both neutral hydrazone and the hydrazone anion may react with the electrophile. The bis(arylazo)methanes formed isomerized rapidly in basic solution to formazans.

Formazans have recently regained considerable attention principally as they form the only route to the colorless tetrazolium salts which have wide application as selective biological staining agents.[2] However the mechanism of the reaction that provides the principal route to and also the greatest variety of formazans, namely, the coupling of diazonium salts and aldehyde arylhydrazones, has remained controversial. This controversy has centered mainly about the initial position of attack of the diazonium ion, whether it occurs at the methine carbon or at the amino nitrogen, and about the form of the hydrazone involved in the reaction and the role of base catalysis.

Busch,[3] by carrying out the reaction at pH 6–8 under carefully controlled conditions, isolated a labile, yellow intermediate which rapidly rearranged to the isomeric formazan. He formulated the structure of this intermediate as a tetrazene so that formazan formation was regarded as a two-step process involving prior attack by the diazonium ion at the amino nitrogen of the hydrazone. In a later, elegant extension of this work Hauptmann and Perisse,[4] apparently confirming Busch's mechanism, investigated the stability and acid-cleavage reactions of this type of intermediate, and showed that the rearrangement to the formazan is intramolecular. Other workers[5] have proposed that formazan formation can occur, *inter alia*, by direct methine attack.

All of these studies have been hampered by a lack of quantitative data. As part of a systematic study of electrophilic attack on the ambident system provided by hydrazones, we have now investigated the mechanism of their reaction with diazonium ions under conditions where the intermediate product isolated by Busch is formed, using a polarographic technique to measure diazonium ion concentrations.

Experimental Section

Materials.—All inorganic chemicals used were AnalaR grade. Potassium nitrate and potassium dihydrogen phosphate were dried at 120° for 3 hr before use and borax was twice crystallized from water and air dried to constant weight. The solvent used for the kinetic experiments was 40% *t*-butyl alcohol, prepared by mixing 40 volumes of *t*-butyl alcohol with 60 volumes of water. The water used had been passed through a mixed cation–anion-exchange resin and then distilled from alkaline potassium permanganate, while *t*-butyl alcohol (reagent grade) had been refluxed over sodium (3 g/100 ml) and distilled; the fraction with bp 82–82.5° was then used to prepare the reaction solvents. The buffer solutions for pH 6.0 to 8.8 were prepared by using the appropriate amounts of borax and potassium dihydrogen phosphate according to Kolthoff,[6] while the ionic strength was maintained constant at 0.1 *M* by the addition of potassium nitrate. The pH values quoted are those of the corresponding aqueous solutions. The actual defined pH values of the alcohol–water mixtures used would differ from these by a small, and probably constant,[7] amount.

Aniline (AnalaR grade) was distilled from zinc dust and then distilled *in vacuo;* the colorless product had bp 85° (20 mm).

Substrates.—The arylaldehyde arylhydrazones used as substrates were prepared by mixing equimolar quantities of phenylhydrazine hydrochloride and the appropriate aldehyde in ethanol at room temperature. The hydrazones were precipitated in approximately quantitative yields by the addition of water (after 3 hr) and thoroughly washed free of the catalyzing acid. They were crystallized several times from aqueous ethanol mixtures and, shortly before a kinetic run they were crystallized from 95% ethanol in a rigorously similar manner, thus minimizing the possible presence of different (*syn* and *anti*) isomers.[8] The hydrazones, all of which with the exception of the nitro derivatives were white, were then stored for the short period until required under nitrogen to prevent the formation of the colored hydroperoxides.[9] The following arylaldehyde arylhydrazones were used to study substituent effects (melting points in parentheses refer to ref 10 unless otherwise noted; primed numerals refer to substituents in the hydrazone ring of benzaldehyde phenylhydrazone): 4-methoxy, mp 118–120° (120°); 4-methyl, 114–

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(1) A preliminary communication describing a portion of this work has appeared: A. F. Hegarty and F. L. Scott, *Chem. Commun.*, 622 (1966). Since this was published independent work on the structure of bis(arylazo)-phenylmethane became available: R. Kuhn, F. A. Neugebauer, and H. Trischmann, *Monatsh. Chem.*, **97**, 525 (1966). Their results (based on ultraviolet and infrared data) complement ours, and their conclusions are in agreement with our findings.

(2) For comprehensive reviews on the chemistry of formazans and tetrazolium salts, see (a) A. W. Nineham, *Chem. Rev.*, **55**, 355 (1955); (b) R. Putter, "Methoden der Organischen Chemie," Bd. 10/3, Houben-Weyl-Muller, Ed., Georg Thieme, Stuttgart, 1965, p 633 ff.

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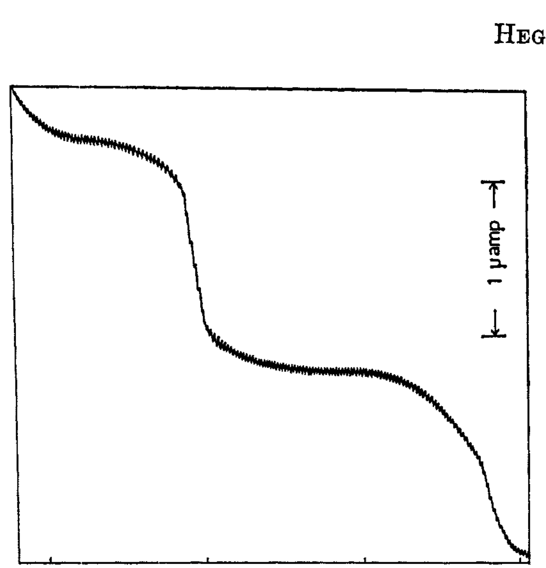

Figure 1.—Polarographic reduction of benzenediazonium ion (4×10^{-4} M) in 40% *t*-butyl alcohol at pH 7 (at 20°).

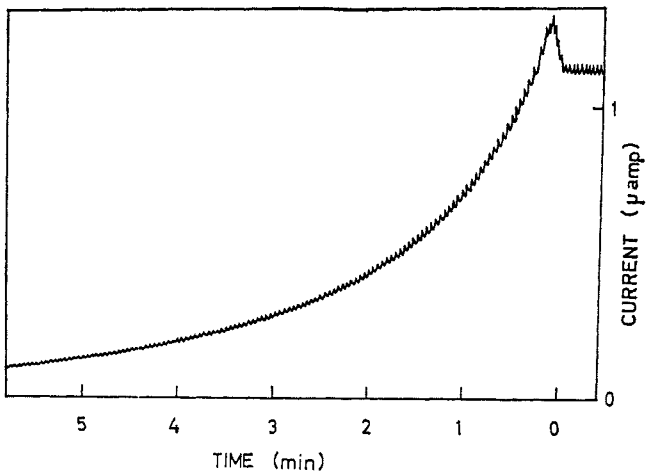

Figure 2.—Typical current (or concentration) *vs.* time curve obtained for reaction of benzenediazonium ion with benzaldehyde phenylhydrazone (initial concentrations *ca.* 4×10^{-4} M).

115° (113–114°); 2,4,6-trimethyl, 76° (lit.[11] 78°); 4-isopropyl, 128–129° (129°); unsubstituted, 158° (158°); 4-fluoro, 146° (147°); 2-fluoro, 87° (90°); 4-chloro, 128° (127°); 3-chloro, 135° (134–135°); 2-chloro, 84° (86°); 2,6-dichloro, 68° (*Anal.* Calcd for $C_{13}H_{10}Cl_2N_2$: C, 58.89; H, 3.80; N, 10.57. Found: C, 59.00; H, 3.82; N, 10.28); 4-bromo, 114° (113°); 3-bromo, 146–147° (141°); 2-bromo, 70° (*Anal.* Calcd for $C_{13}H_{11}BrN_2$: C, 56.74; H, 4.03; N, 10.17. Found: C, 57.04; H, 4.03; N, 9.89); 4-nitro, 158° (159°); 3-nitro, 124° (124°); 2-nitro, 154° (153°); 4′-methoxy, 124–125° (lit.[13] 124°); 4′-methyl, 125–126° (lit.[12] 126°); 2′-methyl, 96° (lit.[13] 97–98°); 4′-carboxy, 230–232° (lit.[14] 221°); 4′-fluoro, 141° (lit.[15] 140°); 2′-fluoro, 98° (lit.[15] 99°); 4′-chloro, 129° (lit.[12] 128°); 2′-chloro 70° (lit.[16] 73°); 4′-bromo, 127° (lit.[17] 127°); 2′-bromo, 61° (*Anal.* Calcd for $C_{13}H_{11}BrN_2$: C, 56.74; H, 4.03; N, 10.17. Found: C, 56.62; H, 4.43; N, 10.30); 4′-nitro, 194° (192°); 2′-phenyl, 124–125° (*Anal.* Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.98; N, 10.28. Found: C, 83.59; H, 5.89; N, 10.15).

The diazonium salt solutions used to study the kinetics were prepared fresh each day. A solution 0.100 M in aniline and 0.300 M in hydrochloric acid was prepared by dissolving 4.656 g (0.05 mole) of aniline and 27.43 g (0.15 mole) of 12 N hydrochloric acid in water and diluting to 500 ml. After cooling 5.00 ml of this standard solution in ice–water for 15 min, 5.00 ml of a 0.100 M solution of sodium nitrite (freshly prepared) was added dropwise from a buret. When the addition was complete, the solution was allowed to stand at 0° for 30 min after which time ice-cold water was added to make the total volume 50 ml, thus giving a 0.01 M solution of benzenediazonium chloride. Usually 1.0 ml of this solution was used in a kinetic experiment.

Kinetic Measurements.—The kinetics of the reaction between benzenediazonium ion and hydrazones were measured polarographically by following the decrease in the diazonium ion concentration at the dropping mercury electrode (dme) on the addition of the hydrazone. Several solvents, *e.g.*, ethanol, methanol, acetone, dioxane, proved unsatisfactory when used in aqueous solvent mixtures since the solvolytic decomposition of diazonium ion at the low concentrations used was too rapid (up to 50% had decomposed in 10 min) compared with the coupling reaction. The rate of decomposition was far lower, however, using *t*-butyl alcohol and correction for it had to be made only in the very slowest reactions when the pH of the solution was less than 8. The polarograph used in this investigation was a Metrohm Polarecord E261-R, with a variable sensitivity recorder, usually set at 1 μa for full-scale deflection. The mercury electrode had a dropping rate of 2.5 sec with −0.4 v, with respect to silver–silver chloride reference, applied potential at pH 7 in 40% *t*-butyl alcohol and an m value of 2.97 mg/sec (using a reservoir height of 54 cm). Under these conditions benzenediazonium ion shows two characteristic[18] waves with $E_{1/2}$ values of approximately −0.2 and −1.0 v (see Figure 1) showing that the reduction takes place in two steps. The height of the first complex wave, although due to an adsorption phenomenon, was found to be proportional to the concentration of the diazonium ion up to about 6×10^{-4} M. Thus by setting a polarizing voltage of −0.4 v across the dme and the reference electrode, the current flowing in the polarographic circuit is directly proportional to the amount of diazonium ion present. Moreover none of the compounds used has polarographic reduction waves in this region which lies well below those for the nitrite, nitro, or hydrazo reductions. This method also has the advantage that no interference is caused by the precipitation of the more insoluble formazans.

The reaction vessel was a 25-ml capacity jacketed cell about which water was circulated to maintain the temperature at 20°. Five ground-glass cones passed through the head of the cell to take, respectively, the dme, a silver–silver chloride (saturated) reference electrode separated from the reaction solution by a sintered-glass disk and an agar plug, the nitrogen inlet and outlet, and a self-sealing cap through which the substrates were introduced by means of a calibrated syringe. Since the hydrazones were not sufficiently soluble in 40% *t*-butyl alcohol to be added in concentrated form, they were made up, usually in 10^{-2} M solution in *t*-butyl alcohol at 25°. Then 1.0 ml of this solution and 1.0 ml of the aqueous diazonium ion solution were added in a kinetic experiment to 20 ml of the reaction solvent which contained sufficient water so that the final composition of the total of 22 ml was, in fact, 40% *t*-butyl alcohol. The initial concentrations of benzenediazonium ion and hydrazone used varied with the reactivity of the latter but were typically in the region 10^{-4} M.

In a typical kinetic experiment 20 ml of the reaction solvent was pipetted into the cell and a fine stream of nitrogen was passed through the solution for 15 min to remove oxygen, which both interferes with the polarographic determination having a reduction wave in the voltage region used and also may react rapidly with hydrazones to give hydroperoxides.[19a] The diazonium salt solution was then introduced and the recorder deflected and plotted a wave height which was proportional to the amount of diazonium ion introduced. Unlike the analogous bromination reactions studied with a rotating platinum electrode,[20] these deflections were reproducible to about 2% when the cell and electrodes were cleaned between runs in a rigorously similar manner. Thus the absolute concentration of the diazonium ion could be obtained directly from the recorder deflection once this had been calibrated using known concentrations of the diazonium ion. The deaerated hydrazone solution was then added and nitrogen

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TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF BENZENEDIAZONIUM ION

(A) WITH Substituted Benzaldehyde Phenylhydrazones ($XC_6H_4CH{=}NNHC_6H_5$)

X	4-OCH$_3$	4-CH$_3$	2,4,6-(CH$_3$)$_3$	4-CH(CH$_3$)$_2$	4-H	4-F	2-F
Registry no.	622-73-1	2829-25-6	10407-15-5	10407-16-6	588-64-7	352-06-7	348-14-1
k^a	2.82	2.02	1.00	1.89	1.74	1.52	0.76

X	4-Cl	3-Cl	2-Cl	2,6-Cl$_2$	4-Br	3-Br	2-Br	4-NO$_2$	3-NO$_2$	2-NO$_2$
k^a	1.36	1.14	0.62	0.65	1.34	1.20	0.68	2.97	0.98	1.58

(B) WITH Benzaldehyde Substituted Phenylhydrazones ($C_6H_5CH{=}NNHC_6H_4Y$)

Y	4-OCH$_3$	4-CH$_3$	2-CH$_3$	4-COOH	4-F	2-F
Registry no.	10407-20-2	1858-99-7	10421-79-1	10407-22-4	352-07-8	348-15-2
k^a	17.8	3.97	0.34	1.81	1.89	0.61

Y	4-Cl	2-Cl	4-Br	2-Br	4-NO$_2$	2-C$_6$H$_5$
k^a	1.22	0.19	1.16	0.11	1.16	0.04

[a] In l. mole^{-1} sec^{-1}.

was rapidly passed through the solution for 30 sec to complete mixing. The nitrogen was then turned off and the recorder plotted a diazonium ion concentration against time curve (Figure 2).

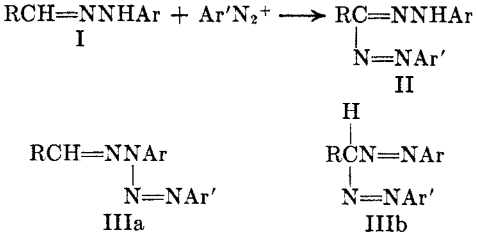
Rates were evaluated graphically using the integrated form of the second-order rate constant, $k = [2.3/(a - b)][\log(a - x) - \log(b - x)] + C$, where a and b are, respectively, the initial concentrations of the hydrazone and benzenediazonium ion, x is the concentration of the latter reacted at time t, and C is a constant. Various initial concentrations of the substrates were used, ranging from equal to a large excess of the hydrazone. Under this latter condition the reaction becomes a pseudo-first-order one, thus being independent of the initial diazonium ion concentrations used. This was used to check the calibration of the recorder since the second-order rate constants obtained from these were the same as those in which the diazonium ion concentrations entered the rate equation. Most of the runs were followed to 80% completion. Individual rate constants were estimated to be accurate to ±5%, and the values quoted (Table I) are the mean of three to six experiments.

Product Analysis.—The intermediate products (III) in formazan formation first described by Busch were prepared by the method of Hauptmann and Perisse.[4] The hydrazone (0.01 mole), while stirred in 200 ml of ethanol at 0°, was treated with 1.64 g (0.01 mole) of benzenediazonium acetate, prepared from 0.93 g (0.01 mole) of aniline, 10 ml (0.03 mole) of 3 *N* hydrochloric acid, 0.76 g (0.011 mole) of sodium nitrite, and 1.64 g (0.02 mole) of anhydrous sodium acetate. The light yellow intermediate slowly separated from the solution and was filtered off after about 30 min and thoroughly washed with ice-cold water and pentane. The unsubstituted intermediate (III, R = Ar = Ar′ = Ph) has an indefinite melting point; at about 85–90°, depending on the rate of heating it rearranges to the deep red 1,3,5-triphenylformazan and melted at 170–173° (lit.[21] 174–175°). The stability of the intermediates varied with the aryl substituents present, those with strong electron-withdrawing, *e.g.*, nitro, groups present were converted too rapidly to the formazan to be isolated. Under the conditions used to study the kinetics at pH 7 with the low concentrations of reactants used the yellow intermediate products formed so slowly that appreciable quantities had rearranged to the deep red formazan before all of the diazonium ion had reacted. On standing, the more insoluble, *e.g.*, nitro-, bromo-, chloro-substituted, formazans were precipitated and found to be identical with the corresponding formazans prepared by coupling benzenediazonium ion and the hydrazone in pyridine.[2a] At pH 8.8, however, the formation of the intermediate (III, R = Ar = Ar′ = Ph) was very rapid under the conditions used to study the kinetics (complete in approximately 30 sec) and the ultraviolet and visible spectra of this solution (measured very rapidly) were identical with the spectra of the intermediate prepared as described above. The strong characteristic formazan absorption at 495 mμ then appeared and after about 30 min the rearrangement to 1,3,5-triphenylformazan was complete.

Spectroscopic Measurements.—Ultraviolet absorption spectra were determined in 95% ethanol using a Perkin-Elmer 137UV spectrophotometer. All nmr absorption spectra were obtained in acetone solution (unless otherwise noted) with tetramethylsilane as internal reference using a Varian A-60 nmr spectrometer.

Results and Discussion

The reaction of aldehyde arylhydrazones (I) with diazonium salts may yield different products depending on the pH of the solution. In acidic solution, when the pH is maintained below about 3, ring-substitution products, *p*-phenylazohydrazones, are obtained.[4] When the reaction is carried out at pH 3–8, an unstable, light yellow intermediate (III) may be isolated, which rapidly, even in the solid state, isomerizes to the formazan (II). Above about pH 9 (depending to some extent on the reactants involved) only the formazan may be isolated. That the amino nitrogen played a vital part in the mechanism of formazan formation was quickly recognized. When this hydrogen was replaced by an alkyl group, as for example in benzaldehyde N-methyl-N-phenylhydrazone, the reaction proceeded very slowly to give, not the formazan,[22] but a product resulting from ring attack.[3a] We have confirmed this by measuring the rate of reaction between benzenediazonium ion and benzaldehyde phenylhydrazone and compared this with the reaction with benzaldehyde N-methyl-N-phenylhydrazone at pH 7–9 in 40% *t*-butyl alcohol. The N-methyl compound reacted at least 10^{-3} times as fast and its rate was, in fact, indistinguishable from solvent decomposition of the benzenediazonium ion. It is possible that this lack of reactivity of the N-methyl compound is due to its presence in an unfavorable configuration. Thus, even though the phenylhydrazone may assume either a *syn* or an *anti* configuration about the azomethine bond, the N-methyl-N-phenylhydrazone can only exist in the *syn* form because strong interactions between the N-methyl and the aldehydic phenyl group in the *anti*



$$\underset{\text{I}}{RCH{=}NNHAr} + Ar'N_2^+ \longrightarrow \underset{\text{II}}{\underset{N{=}NAr'}{RC{=}NNHAr}}$$

$$\underset{\text{IIIa}}{\underset{N{=}NAr'}{RCH{=}NNAr}} \qquad \underset{\text{IIIb}}{\underset{N{=}NAr'}{R\overset{H}{C}N{=}NAr}}$$

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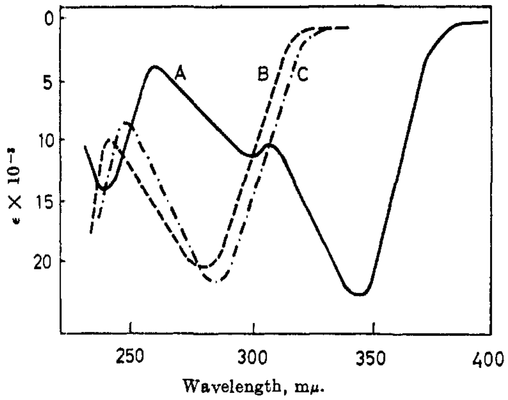

Figure 3.—Ultraviolet absorption spectra of (A) benzaldehyde phenylhydrazone, (B) bis(phenylazo)phenylmethane, and (C) 1-(*p*-tolylazo)-1-(phenylazo)phenylmethane.

isomer would force the unshared electrons to become nonparallel with the π orbital.[23]

However benzaldazine and acetophenone azine are equally unreactive with benzenediazonium ion in the same pH range and may be recovered unchanged in near-quantitative yield. These azines are analogous to hydrazones in that they contain an azomethine bond flanked by nitrogen (which, however, does not have a hydrogen attached to it), but they have a particularly open linear structure[24] so that the same reservations about the steric effects to the entry of the reagent do not apply.

Structure of the Intermediate.—Busch and Pfeiffer[3b] postulated that this failure to obtain formazans from hydrazones where the amino nitrogen is disubstituted was due to prior attack by the diazonium ion on the amino nitrogen with the formation of the tetrazene (IIIa), as the only possible route to formazans. An attempt to synthesize IIIa unambiguously, however, failed.[3b,25]

Reinterpretation of the results of the acid-cleavage experiments described by Hauptmann and Perisse[4] casts doubt on this structure. When treated with ethanolic hydrochloric acid the intermediate (III) was smoothly cleaved to give a diazonium salt and a hydrazone. However the diazonium salt released was always the least electrophilic, independent of whether it was used as electrophile or was present in the hydrazone in the initial coupling reaction to form the intermediate. Thus, if ArN_2^+ is less electrophilic than $Ar'N_2^+$, then ArN_2^+ and RCH=NNHAr′ were obtained on cleavage of the intermediate (III) formed from $Ar'N_2^+$ and I. This exchange reaction is difficult to visualize in terms of the tetrazene intermediate (IIIa) proposed. But if the structure of the isolable intermediate (III) was in fact the symmetrical bis(arylazo)methane (IIIb), then this cleavage reaction is a reversal of the initial coupling reaction, and the aryl nucleus initially in the hydrazone could end up in the diazonium salt without involving a complex rearrangement. Moreover by carrying out the rearrangement of the intermediate (III) to the formazan (II) in the presence of β-naphthol, no cross coupling was observed.[4] Later work[26] also confirmed that the rearrangement did not involve free diazonium ion in solution. For structure IIIa this would require the intramolecular shift of a diazo group, whereas for IIIb the rearrangement would rather be a simple azo to hydrazone conversion.[19]

Further chemical evidence makes the possibility of the rearrangement of IIIa to II less certain and favors IIIb as the structure of the intermediate. Many tetrazenes, *e.g.*, 1-benzylidene-2-phenyl-4-(1′H-5′-tetrazolyl)tetrazene,[27] of the type (IIIa) whose structures have been unequivocally assigned do not rearrange in basic solution to give the corresponding formazans. In this example the electron-withdrawing tetrazolyl group would be expected to speed the rearrangement to the formazan. Also diazonium ions couple with aldehyde alkylhydrazones to give tetrazenes, *e.g.*, 1-benzylidene-4-(*p*-nitrophenyl)-2-benzyltetrazene,[3b] which do not rearrange. In fact, the formazans analogous to these tetrazenes have not been prepared.[2]

The spectral data also support formulation IIIb for the intermediate. As shown in Figure 3, the ultraviolet absorption spectrum of benzaldehyde phenylhydrazone shows the characteristic bands of a simple phenylhydrazone at 236, 304, and 345 mμ. The spectrum of the intermediate (III, R = Ar = Ar′ = Ph) is quite different having a single strong absorption assigned to a $\pi \rightarrow \pi^*$ transition at 282 mμ in the ultraviolet spectrum and a weak band at 410 mμ ($n \rightarrow \pi^*$) in the visible spectrum. These two bands are characteristic of a simple phenylazo structure (IIIb).[9] Moreover the molar extinction coefficients are approximately double those reported for simple phenylazoalkanes suggesting the presence of two nonconjugated azo bonds.[28]

The infrared spectra, although showing the absence of the sharp NH stretching band at about 3.0 μ present in all benzaldehyde phenylhydrazones, were not very informative since the preparation of a disk or mulling caused considerable rearrangement of the intermediate. The resulting spectra thus contain many formazan bands.

The phenylhydrazones and the coupling products have also been examined by means of nmr absorption spectra. The absorption for the methine proton (CH=N) is often found close to or buried in the phenyl proton peaks.[29] By deuteration[30] we have established that this absorption occurs at τ 2.18 (in deuteriochloroform solution) for benzaldehyde *p*-nitrophenylhydrazone. This absorption is relatively insensitive to substituents in the aromatic rings, *e.g.*, it occurs at τ 2.13 and 2.15 in benzaldehyde phenylhydrazone, and benzaldehyde tolylhydrazone, respectively. Replacement of the amino hydrogen by a methyl group causes only a small shift (0.2 ppm) to higher fields. The value expected for this proton in the tetrazene (an N-substituted hydrazone), should not

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[27] J. P. Horwitz and V. A. Grakauskas, *J. Am. Chem. Soc.*, **77**, 6712 (1955).

[28] The extinction coefficients are close to those reported by T. W. Milligan and B. C. Minor [*J. Org. Chem.*, **27**, 4663 (1962)] for 1,2-bis(phenylazo)-1,2-diphenylethane.

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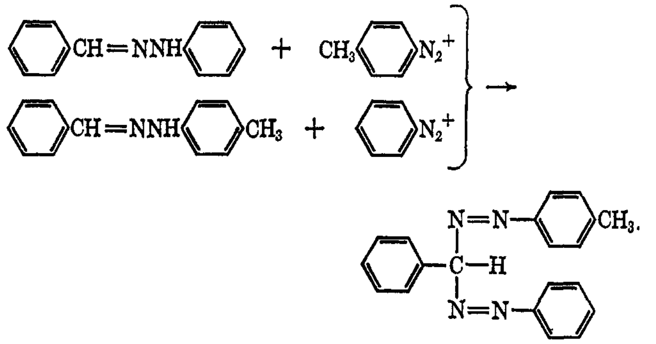
[30] A. F. Hegarty and F. L. Scott, *J. Chem. Soc., Sect. B*, 1031 (1966).

differ appreciably from about 2.3 ppm. However, the intermediate (III, R = Ar = Ar′ = Ph) gives, in addition to the complex aromatic region absorptions, a singlet at τ 3.75 corresponding to one proton. The $CH_2N{=}N$ peak of benzylazo compounds is at 4.3 ppm[28] while the replacement of one of the hydrogen atoms by an OOH group shifts the proton peak of the remaining H atom to 4.0 ppm.[19,31] The =NNH peak of the hydrazone at τ 0.63 is also absent in the intermediate. These data are consistent with structure IIIb rather than IIIa for the intermediate.[32]

Moreover the same intermediate is obtained either by coupling benzaldehyde phenylhydrazone and *p*-tolyldiazonium ion or benzaldehyde *p*-tolylhydrazone and benzenediazonium ion. This intermediate has a benzylic proton in its nmr spectrum at 3.8 ppm; it melts at about 60° when prepared either way, and when converted to 1-(*p*-tolyl)-3,5-diphenylformazan on crystallization from aqueous ethanol it had mp 153–155° (lit.[33] 155.5°); its ultraviolet spectrum is given in Figure 3. This identity of product formed by the two coupling routes again confirms structure IIIb for the intermediate.



Substituent Effects.—The observed effect of substituents in the aldehyde arylhydrazones on the ease of formazan formation may be rationalized in terms of the prior formation of an intermediate with the structure IIIb proposed. The coupling reaction between benzenediazonium ion and hydrazones variously substituted in both aromatic rings was studied in 40% *t*-butyl alcohol at pH 7 with ionic strength 0.1 *M* under which conditions the light yellow bis(arylazo)methane (IIIb) was the initial product. As this reaction proceeded the bis(arylazo)methane formed isomerized (most rapidly with electron-withdrawing substituents in the hydrazone) to the corresponding formazan and the reaction solution became deep red with the appearance of the characteristic[2a] formazan absorption at 495 mμ. However this color change did not interfere with the measurement of the initial coupling reaction to form the bis(arylazo)methanes since diazonium ion concentrations (and not coupling product) were measured and the formazans were not reduced at the dme in the voltage region used.

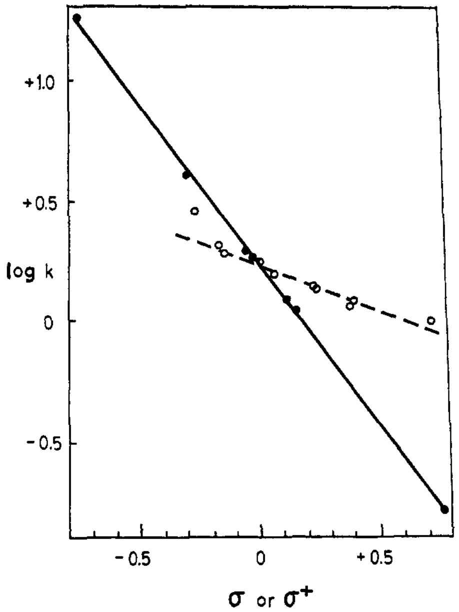


Figure 4.—Plot of log *k* for the reaction of benzenediazonium ion with hydrazones in 40% *t*-butyl alcohol at pH 7 against σ for substituents in the aldehyde ring (broken line) and σ^+ for substituents in the hydrazine ring (solid line) of the benzaldehyde phenylhydrazone.

For the six *para*- and three *meta*-substituted benzaldehyde phenylhydrazones studied (Figure 4) a plot of the log of the observed rate constant against the corresponding σ values of McDaniel and Brown[34] gave a ρ value of -0.38. A least-squares treatment gave a satisfactory correlation coefficient (r = 0.984) and standard deviation (s = 0.048) with log k_0 = 0.225. The data for the *p*-methoxy substituent were not included since its log *k* value did not improve the correlation coefficient using either σ or σ^+ values. The enhanced reactivity of this compound is probably due to a small intermediate resonance contribution to the stabilization of the transition state.[35] The ρ value obtained, although negative as expected for an electrophilic substitution reaction, is small when compared with typical[36] values (-4 or -5) obtained for solvolysis reactions considered indicative of a highly electron-deficient carbon with considerable carbonium ion character adjacent to the aromatic ring. This implies that a major portion of the charge involved in the transition state of the reaction is delocalized away from the reaction site along the hydrazone system toward the amino nitrogen. This view was confirmed since substituents in the hydrazine ring have a far greater effect on reactivity in the coupling reaction, a similar Hammett plot, using σ^+ values,[37] for the eight *para* substituents giving a ρ value of -1.3 with r = 0.999, s = 0.018, and log k_0 = 0.240. The use of σ^+ values in a reaction where *para* substituents capable of electron release by resonance cannot interact in any simple way with the charged center visualized in the transition state, an immonium ion, is justified only by the excellent fit of the data. With ordinary σ values a correlation coefficient of 0.925 was obtained.

The relatively large rate acceleration (instead of the rate depression expected from the ρ value) of a *p*-nitro group in the aldehyde ring was due to a small contribu-

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[31] E. Fahr and H. D. Rupp [*Angew. Chem. Intern. Ed. Engl.*, **3**, 693 (1964)] have shown that the 1-azo-1-hydrazinoalkane formed by the reaction of azido formates with aldehyde phenylhydrazones gives an α-benzyl proton peak at 3.2 ppm.

[32] A similar conclusion was drawn independently by S. G. Plovan, Ph.D. Thesis, Kansas State University, 1960.

[33] L. Hunter and C. B. Roberts, *J. Chem. Soc.*, 820 (1941).

[34] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[35] H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **78**, 815 (1959).

[36] J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 163.

[37] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

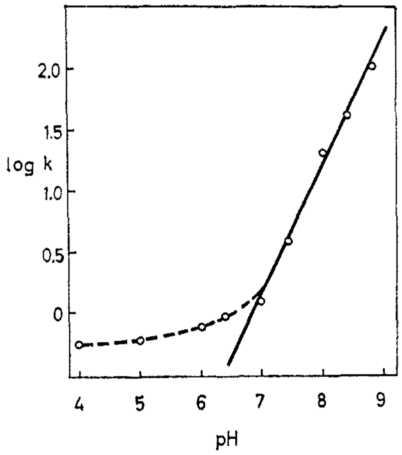

Figure 5.—The effect of pH on the rate of coupling of benzenediazonium ion with benzaldehyde phenylhydrazone. The solid line has unit slope.

tion of a reactive anion (see below) of the hydrazone (IV) resonance stabilized by the nitro group. This was shown by reducing the anion concentration by adjusting the pH of the solution (to 6.0) when *p*-nitrobenzaldehyde phenylhydrazone now reacted slower than the unsubstituted compound. A similar rate

$$\underset{\text{IVa}}{\mathrm{ArCH{=}N\bar{N}Ar'}} \longleftrightarrow \underset{\text{IVb}}{\mathrm{Ar\bar{C}HN{=}NAr'}}$$

enhancement was noted in the reaction of *o*-nitrobenzaldehyde phenylhydrazone, but not with *m*-nitrobenzaldehyde phenylhydrazone or indeed benzaldehyde *p*-nitrophenylhydrazone. The nitro groups in these two last compounds are not suitably placed for strong resonance interaction in IVb, presumably the reactive anion involved.

Large substituents in the *ortho* position in the hydrazone ring have been reported[4] to hinder the formation of the bis(arylazo)methanes (IIIb). Formazans containing such groups have been obtained only in forcing conditions using strongly basic media. Quantitative examination of the kinetics of coupling of benzenediazonium ion with such hydrazones has shown that this retardation may be explained in terms of steric repulsions toward the approaching reagent. Thus for the six benzaldehyde *ortho*-substituted hydrazones studied, a plot of log k against $\rho^*\sigma^* + \delta E_{s'}$ using the ρ value already evaluated from data for *para* substituents (-1.3) and the E_s and σ^* values reported by Taft[38] for the hydrolysis of *ortho*-substituted benzoates, gave a steric susceptibility constant, $\delta = 1.06$. The precision of the correlation ($r = 0.980$; $s = 0.09$), despite the approximations used in the parameters, indicates that the substituents exert a simple steric effect.

The data for *ortho*-substituted aldehyde hydrazones may not be correlated so readily. The rates of reaction between benzenediazonium ion and the six 2- and 2,6-disubstituted benzaldehyde phenylhydrazones studied (with the exception of the *o*-nitro aldehyde hydrazone noted above) were approximately the same (they varied from 0.6 to 0.7 l. mole^{-1} sec^{-1}) independent of the substituent used and approximately one-third of the rate of reaction of benzaldehyde phenylhydrazone. This rate depression observed for *ortho*-substituted aldehyde hydrazones is reflected in literature reports[39] of failures in attempts to synthesize formazans from such hydrazones; however such formazans may, in fact, be isolated if sufficiently electrophilic diazonium salts are used.[40]

pH Effect.—The response of the reaction between benzenediazonium ion and benzaldehyde phenylhydrazone to the hydrogen ion concentration was studied by the variation of the pH of the solution over the range 4.0 to 8.8 at constant ionic strength. At pH 4.0 the reverse reaction, namely, the acid-catalyzed cleavage of the intermediate to regenerate the hydrazone and the diazonium ion, was appreciable and, in fact, an equilibrium was reached with about 70% of the diazonium ion, reacted. The rate constant quoted, therefore, was calculated from data for the first 10% reaction. In the lower pH region the rate of coupling did not vary greatly but above about pH 7.5 there was a steep rise with increasing pH. In this latter region the rate increases roughly ten times when the pH is increased by one unit so that log k was linear with pH, the slope of the line being close to 1 (Figure 5). This shows[41] that the coupling of benzenediazonium ion, the active electrophile in solution,[42] with hydrazones may occur either at the free hydrazone or, in sufficiently basic solution with the hydrazone anion, both reactions giving the same product.

Pyridine has been shown in many instances to be a powerful specific catalyst[43] in diazo coupling reactions due to the acceleration of the loss of a proton from the intermediate. However it is relatively ineffective in the present instance even when locked in a position close to the amino hydrogen as in benzaldehyde 2-pyridylhydrazone. The reaction of this compound with benzenediazonium ion (k = 0.22 l. mole^{-1} sec^{-1}) at pH 7 was far slower than the same reaction with benzaldehyde phenylhydrazone but close to that of benzaldehyde *p*-nitrophenylhydrazone where electronic effects would approximate those of the 2-pyridyl group. Thus with the neutral hydrazone species, diazonium ion attack, rather than loss of a proton from the intermediate, is rate controlling.

Conclusion.—Formazan formation is a two-step reaction, the first step involving electrophilic attack by diazonium ion at the methine carbon, the second a tautomeric shift of hydrogen from carbon to nitrogen giving the stabilized cyclic formazan structure. The first step is faciliated by electron-donating, the second by electron-withdrawing substituents. The quantitative data presented here for the rates of formation of bis(arylazo)methane intermediates in the coupling reaction in aqueous butyl alcohol are in accord with the qualitative observations about substituent effects in formazan formation in the literature,[2a] suggesting that the first step, namely, attack by the diazonium ion on the hydrazone, is rate determining. Moreover it is reported that even when the reaction is carried out in basic pyridine solution the transitory yellow coloration

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[38] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newmann, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 156.

[39] F. R. Fichter and J. Frohlich, *Chem. Zentr.*, 426 (1903); A. W. Nineham, D. L. Pain, and R. Slack, *J. Chem. Soc.*, 1568 (1954).

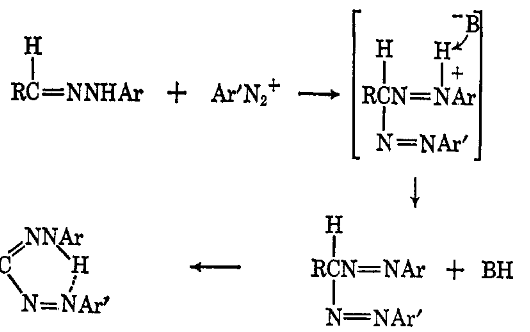
[40] A. F. Hegarty and F. L. Scott, to be published.

[41] R. Pütter, *Angew. Chem.*, **63**, 188 (1951).

[42] C. Wittwer and H. Zollinger, *Helv. Chim. Acta*, **37**, 1954 (1954).

[43] H. Zollinger, *ibid.*, **38**, 1597 (1955).

characteristic of the bis(arylazo)methane is observed.[4] Formation of the intermediate occurs most rapidly with the anion of the hydrazone, but the neutral molecule also has considerable reactivity. For this latter reaction the relative magnitudes of the ρ values obtained for substituent variation in the hydrazone and aldehyde rings compare with the reported[20] values for the bromination of hydrazones. Thus, even though the absolute magnitudes of the substituent responses, as measured by ρ values, are quite different for the two reactions, as expected since they involve different reagents and were measured under different solvent conditions, the ratio of the ρ values (3.4 for diazonium ion attack, 3.5 for bromination) obtained for both reactions are remarkably similar. This suggests a similar distribution of the available electronic charge along the hydrazone system in the transition states of both reactions.



Registry No.—$C_{13}H_{10}Cl_2N_2$, 6579-24-4; $C_{13}H_{11}BrN_2$, 10407-11-1; $C_{19}H_{16}N_2$, 1047-12-2.

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Substituent Electronegativity and the Thermodynamic Stabilities of Isomeric Substituted Propanes and Butenes

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Literature data on equilibrium mixtures of isomeric substituted propanes and of isomeric substituted butenes have been summarized. The relative free energies derived from the propyl equilibria are to a first approximation linearly related to the Pauling electronegativity of the substituent atom bonded to the propyl system. A similar linear correlation is found for the butenyl system.

In organic reactions which may yield isomeric products, both kinetic and thermodynamic factors can influence product compositions. A knowledge of the relative free energies of the isomeric products fixes the equilibrium composition and is, therefore, of great value in planning synthetic procedures and in the analysis of kinetic data. In principle, relative free energies can be obtained from tabulated standard heats and entropies of formation of individual compounds from thermochemical measurements. In fact the precision demanded when thermochemical data are used for comparison of isomers often taxes, even now, the experimental techniques available. Much of the currently available data is too inaccurate for use in calculating relative free energies of isomeric substances.

A more direct, experimentally less demanding, procedure is to equilibrate the isomeric substances and to determine equilibrium composition as a function of temperature. Unfortunately, side reactions often frustrate attempts to reach equilibrium. In spite of the excellent early book of Parks and Huffman,[1] reports on such equilibria have been rare. In the past few years, however, useful equilibrium data have begun to appear in the literature, primarily on the propyl and butenyl systems. Examination of the available data has led us to propose a linear correlation between substituent electronegativity and relative free energies of isomers in these two systems which is useful for predicting equilibrium compositions.

In the isomeric monosubstituted propanes complete

$$CH_3CH_2CH_2X \rightleftarrows CH_2CHXCH_3$$

thermodynamic data from equilibrium measurements are available for chloro-[2] and bromopropanes.[3,4] Reliable thermochemical data are available for butane and isobutane[5] and an approximate equilibrium constant at one temperature is available for a di-n-propylboron substituent.[6] The data on the propyl alcohols are contradictory. A recent study of the heats of combustion of n-propyl and isopropyl alcohols[7] has given $\Delta H°$ (isomerization) as -2.98 ± 0.11 kcal/mole at 25° in the liquid phase, much less than the -5-kcal/mole value implied by direct measurements of the equilibrium between n-propyl and isopropyl alcohol[8,9] together with estimated entropies of isomerization.[10] The equilibrium measurements were in strongly acidic media and could be misleading. Pending experimental resolution of this conflict, preferably by vapor phase equilibrium measurements, no choice is made between the two results.

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(5) "Lange's Handbook of Chemistry," 8th ed, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p 1672.

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