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Effect of Substituent in Diazotized Orthanilic Acid on the Azo Coupling with 7-Acetylamino-4-hydroxynaphthalene-2-sulfonic Acid in Citrate–Phosphate Buffers

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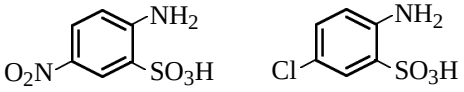
Abstract—Effect of substituent in the *para* position with respect to the diazo group in diazotized orthanilic acid derivatives on the rate and selectivity of azo coupling with 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid was studied in citrate–phosphate buffers. The selectivity of azo coupling at the 3-position of the azo component almost does not depend on the nature of electron-donor substituent. Electron-acceptor groups considerably reduce the selectivity of formation of the 3-isomer. Previous conclusions, according to which the rate-determining stages are different depending on the site of azo coupling of diazotized orthanilic acid with 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid, were found to be also valid for some 5-substituted orthanilic acid derivatives. The rate-determining stage in the azo coupling at the 3-position can change upon introduction of strong electron-acceptor substituents capable of interacting with the diazo group. The contribution of the multicenter mechanism of deprotonation of the σ-complex with participation of water molecules was presumed to increase in going to the diazo components having electron-donor substituents.

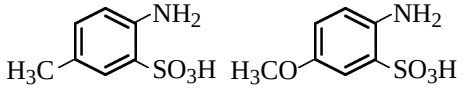
We previously studied the effect of steric and electronic factors on the azo coupling of diazotized orthanilic and sulfanilic acids, as well as of *N*,*N*-dialkylamides derived therefrom [1, 2], with 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid. In continuation of these studies, we have focused on the electronic effect of substituent in the diazo component on the rate and selectivity of azo coupling. According to published data [3, 4], such an effect may be quite considerable, especially when the substituent gives rise to π-electron interaction with the reaction center. Probably, electron density redistribution in the diazo group and effective positive charge on the terminal nitrogen atom affect the kinetics of azo coupling to a greater extent, as compared to steric and electrostatic obstacles created by the sulfo group in diazotized orthanilic acid derivatives.

With the goal of elucidating the role of electronic properties of substituents, as model compounds we selected 5-substituted orthanilic acid derivatives, in which the substituent affects the electronic structure of the diazo group but exerts no additional steric hindrance.

Compounds **I** and **IV** possess, respectively, electron-acceptor (NO_2) and electron-donor (OCH_3) substituents which are conjugated with the amino group subjected to diazotization. The influence of the above groups originates from their strong mesomeric effects

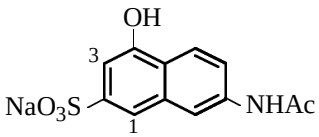


I **II**



III **IV**

having the opposite signs. The substituents in the *para*-position with respect to the amino group in **II** and **III** exert mainly inductive effect on the aromatic system. Therefore, variation of the selectivity and rate of azo coupling in the series **I**–**IV** could provide information on the character and magnitude of the electronic structure effect on the azo coupling at positions *1* and *3* of 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid (**V**).



V

Figure 1 show the dependence of the selectivity of azo coupling Φ_3 on the pH value of buffer solution.

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Table 1. Partial second-order rate constants (l mol^{-1} s^{-1}) for azo coupling of diazotized orthanilic acid derivatives **I**–**IV** with 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid (**V**) in citrate–phosphate buffer

Diazo component	Rate constant, l mol^{-1} s^{-1}	Azo coupling at C^3	Azo coupling at C^1
2-Amino-5-nitrobenzenesulfonic acid (**I**)	k^{ROH}	16.3	11.9
	k^{RO^-}	6.04×10^4	1.35×10^5
2-Amino-5-chlorobenzenesulfonic acid (**II**)	k^{ROH}	0.465	0.0571
	k^{RO^-}	2780	588
2-Amino-5-methylbenzenesulfonic acid (**III**)	k^{ROH}	8.72×10^{-2}	3.13×10^{-3}
	k^{RO^-}	39.3	2.99
2-Amino-5-methoxybenzenesulfonic acid (**IV**)	k^{ROH}	–	–
	k^{RO^-}	4.97	0.83

It should be noted that introduction of electron-donor substituents into position 5 of the diazo component almost does not affect the selectivity of azo coupling with acid **V**. In neutral and alkaline media, the selectivity of the azo coupling of diazotized 5-methylorthanilic acid (**III**) at the 3-position of **V** is lower by 4–5% than the selectivity found for diazotized unsubstituted orthonilic acid. This value exceeds by only 1–2% the error in spectrophotometric determination of the corresponding quantities, so that it can hardly be taken into account. The selectivities for orthanilic acid and 5-methoxyorthanilic acid (**IV**) are experimentally indistinguishable.

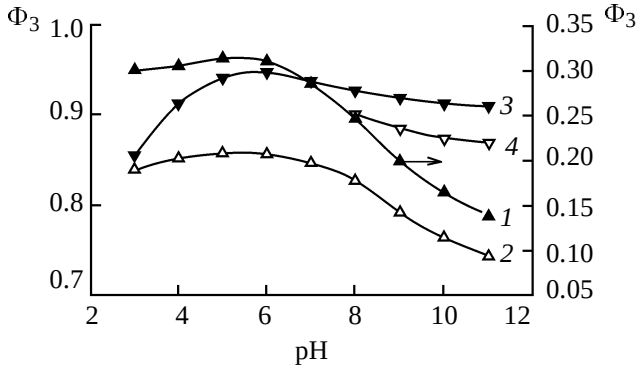


Fig. 1. Selectivities of the azo coupling at position 3 of 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid versus pH of buffer solution: (*1*) 2-amino-5-nitrobenzenesulfonic acid (**I**), (*2*) 2-amino-5-chlorobenzenesulfonic acid (**II**), (*3*) 2-amino-5-methylbenzenesulfonic acid (**III**), and (*4*) 2-amino-5-methoxybenzenesulfonic acid (**IV**).

A different pattern is observed in going to diazo compounds having electron-acceptor substituents. The selectivity of azo coupling at the 3-position of acid **V** with diazotized 5-chloroorthanilic acid (**II**) is lower by 7–17% than the corresponding value for orthanilic acid. In the reaction with diazotized 5-nitroorthanilic acid (**I**), the major product is that formed by azo coupling at the 1-position of acid **V** throughout the examined range of pH. Here, the selectivity Φ_3 is lower by a factor of 2.4–6.2, as compared with diazotized orthanilic acid.

Our results are consistent with the data obtained while studying azo coupling of substituted benzenediazonium salts with 1-naphthol [4, 5]. Assuming that the conclusions drawn in [4, 5] are also valid for the series of compounds under study, base catalysis of the azo coupling at position 3 of acid **V** is likely to be much less effective than at position 1. The rate of deprotonation of the σ-complex increases relative to the rate of its formation as the electron-acceptor power (*–M* effect) of the conjugated substituent rises, for the latter strongly enhances acidic properties. In the limiting case, the azo coupling of diazotized 2-amino-5-nitrobenzenesulfonic acid at both activated positions of acid **V** could involve the second stage of the process as rate-determining.

On the basis of the pH dependences of the apparent rate constants and selectivities of azo coupling with diazotized compounds **I**–**IV**, we calculated the partial rate constants for substitution at positions 1 and 3 of sulfonic acid **V** (Table 1). The rate of azo coupling with diazotized compound **IV** in neutral and acid media is so small that it becomes comparable with the rate of side transformations of the diazo compound. For that reason, we failed to determine the selectivity Φ_3 at pH <8 and the rate constant k^{ROH}. Taking into account that alkaline medium gives rise to base catalysis of the deprotonation of σ-complexes with hydroxide ions, the k^{RO^-} values for 2-amino-5-methoxybenzenesulfonic acid could be somewhat overestimated.

Some general trends in the substituent effect on the reactivity of diazotized orthanilic acid derivatives in the azo coupling at positions 1 and 3 of acid **V** can be determined by analysis of the obtained data using the Hammett equation $\log k_R = \log k_H + \rho\sigma$. For this purpose, we have plotted the dependences of $\log(k_R/k_H)$ on the constants σ_p for the following substituents R: OCH_3, CH_3, H, Cl, NO_2. Although the number of points is too small to obtain rigorous correlations, the observed trends in the variation of the rates of azo coupling at positions 1 and 3 allowed us to make some presumptions concerning the reaction mechanism.

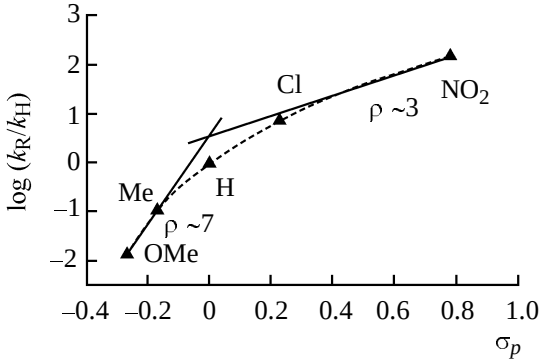


Fig. 2. Semilog plot of the reduced rate constants for the azo coupling in position 3 versus substituent constants σ_p.

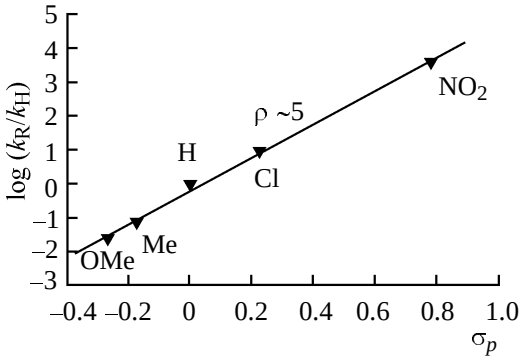
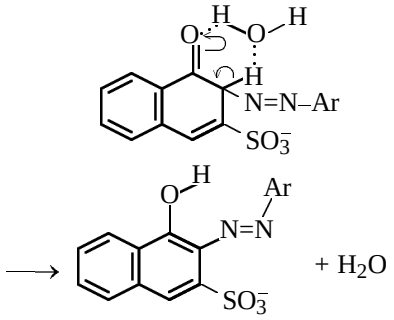


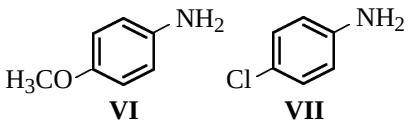
Fig. 3. Semilog plot of the reduced rate constants for the azo coupling in position 1 versus substituent constants σ_p.

The $\log (k_R/k_H)$–σ_p plot for the azo coupling at position 3 is a smooth curve having two asymptotic tangents which cross at a point with $\sigma_p \approx 0$ (Fig. 2). The slope of the asymptote relative to the σ axis is ~7, and it approaches a value of 3 in the region corresponding to electron-acceptor substituents. In keeping with the theoretical data [6], this pattern suggests either change of the rate-determining stage or different contributions of the multicenter mechanism of deprotonation of the σ-complex with water molecules in the azo coupling at position 3, depending on the electronic structure of the diazo component.

The excellent correlation (r = 0.996) between the rate constants for azo coupling at position 1 and constants σ_p for all diazo components **I**–**IV** clearly indicates that the rate-determining stage does not depend on the substituent (Fig. 3). The above two relations provide one more support to the assumption that the rate-determining stages in the azo couplings at positions 1 and 3 of acid **V** are different. The substituent in the diazo component has no appreciable influence on the previously [1, 2] established relations holding in the azo coupling at position 3 of azo component **V**.



In order to estimate the effect of the sulfo group in *ortho* position with respect to the diazo group, we measured the rates of azo coupling and determined the selectivities of azo coupling at position 3 of 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid (**V**) for diazotized 4-methoxyaniline (**VI**) and 4-chloroaniline (**VII**).



VI **VII**

Only traces of the corresponding 1-isomer were detected by chromatography among products of azo coupling of diazotized 4-methoxyaniline, and we failed to isolate it and determine its yield by spectrophotometry. The selectivity of azo coupling at position 3 for diazotized 4-chloroaniline ranges from 0.611 to 0.940, depending on the pH value; the maximal selectivity is observed in neutral medium. The second-order rate constants, calculated from the apparent partial rate constants for azo coupling in the pH range from 3 to 11, are given in Table 2. It should be noted that the rate constants for azo coupling at position 1 almost do not change in going from 4-chloroaniline (**VII**) to 2-amino-5-chlorobenzenesulfonic acid, while the azo coupling at position 3 is characterized by reduction of the partial rate constants: k^{ROH} decreases by a factor of 2, and k^{RO^-}, by a factor of 3. The rate constant k^{RO^-} for the azo coupling at position 3 for 4-methoxyaniline is greater by a factor of 2.2 than the corresponding rate constant for 2-amino-5-methoxybenzenesulfonic acid.

Obviously, the presence of a sulfo group in the *ortho* position with respect to the diazo group does not effect the rate of substitution at position 1; the strongest inhibitory effect in the azo coupling at position 3 is observed when the hydroxy group in **V** is ionized. These data may be explained only in terms

Table 2. Partial second-order rate constants for azo coupling of diazotized orthanilic and sulfanilic acids with 7-acetylamino-4-hydroxynaphthalene-2-sulfonic acid (**V**) in cutrate–phosphate buffers

Diazo component	Rate constant, $l\ mol^{-1}\ s^{-1}$	Azo coupling at C^3	Azo coupling at C^1
4-Chloroaniline (**VI**)	k^{ROH}	0.954	0.0558
	k^{RO^-}	8530	574
4-Methoxy-aniline (**VII**)	k^{ROH}	0.0208	–
	k^{RO^-}	10.9	–

of our previous conclusions implying different rate-determining stages in the azo couplings at positions 3 and 1 of acid **V**, as well as in terms of appreciable contribution of steric and electronic effects of the sulfo group in each of the above stages.

EXPERIMENTAL

All kinetic and spectrophotometric measurements were performed in citrate–phosphate buffers [7]. The pH values were measured with the aid of a pH-121 pH meter equipped with glass and silver chloride electrodes and calibrated against standard buffer solutions with pH values of 1.69, 4.01, 6.86, and 9.18.

The ratio of isomeric azo compounds was determined from the electronic absorption spectra which were recorded on a Specord M-400 spectrophotometer (Carl Zeiss, Jena) at pH 2.0. The IR spectra were measured on a Specord M-80 spectrometer (Carl Zeiss, Jena) from samples dispersed in mineral oil. The ^1H NMR spectra were obtained at 333 K in DMSO-d_6 using a Bruker CXR-200 spectrometer (200 MHz); tetramethylsilane was used as internal reference.

Primary kinetic dependences of optical density of the reaction mixtures were obtained on a Spekol-210 spectrophotometer (Carl Zeiss, Jena) equipped with a Serial Box Interface external AD converter (Vernier Software) which was connected to a serial port of an IBM-compatible PC. The measurements were performed in a 1-cm static cell equipped with a stirrer and maintained at a constant temperature. The cell was charged with 0.5 ml of a solution of the azo component and 1.0 ml of citrate–phosphate buffer. A solution of aqppropriate diazo component, 0.485 ± 0.005 ml, was then added through a calibrated syringe. The optical densities were measured at 20°C, the initial concentration of azo component **V** being $(7.3–8.0) \times 10^{-4}$ M. The initial concentration of the diazo components was $(4.3–4.6) \times 10^{-5}$ M.

Sodium 3-hydroxybenzenesulfonate. 3-Aminobenzenesulfonic acid, 87 g, was dissolved in 1 l of water while adding 40% aqueous sodium hydroxide to pH 7.5–8.5. A 30% solution of sodium nitrite (35 g) was then added, the mixture was cooled to 5–10°C, and a cold solution of 23 ml of 94% sulfuric acid in 100 ml of water was added at such a rate that the temperature did not exceed 15–18°C (the mixture should be acidic according to Congo Red). The mixture was kept for 30 min at room temperature, and excess nitrous acid was decomposed by adding solid sulfamic acid. The mixture was heated to 60–70°C, kept at that temperature until negative test for diazo compound with an alkaline solution of H-acid (more than 15 h), neutralized with barium carbonate, and filtered to remove barium sulfate. The yellow–brown solution was evaporated to dryness, and the residue was extracted with 2 l of 96% ethanol. Removal of the solvent from the extract left 60 g (61%) of sodium 3-hydroxybenzenesulfonate as a light yellow powder. IR spectrum, cm^{-1}: 1250 (SO_2, asym.); 3600, 1200 (OH); 1050 (SO_2, sym.).

5-Hydroxy-2-(phenylazo)benzenesulfonic acid. Sodium 3-hydroxybenzenesulfonate, 38.5 g, was dissolved in 100 ml of water, the solution was adjusted to pH 8.9–9.5 by adding 40% aqueous sodium hydroxide, and the mixture was cooled to 0–5°C. Freshly distilled aniline, 12 ml, was diazotized according to the procedure described in [8]. Just before azo coupling, excess nitrous acid was decomposed by adding solid sulfamic acid to the solution of benzenediazonium chloride. The latter was then added in portions over a period of 3 h with stirring to the solution of the azo component, maintaining the pH at 8.9–9.3 by adding 20% aqueous sodium hydroxide. The misture was left overnight at 0–5°C, heated to 60°C, stirred for 30 min, and filtered. The filtrate was adjusted to pH 9.5 by adding a 10% solution of NaOH, sodium chloride was added in portions to a concentration of 15 wt %, the mixture was cooled to room temperature, and colored impurities were filtered off. The filtrate was acidified to pH 2 with 15% hydrochloric acid, and the precipitate was filtered off. Yield 11.5 g (64%), violet powder, R_f 0.35 (Silufol UV-254, pyridine–isopentyl alcohol–25% aqueous ammonia, 7 : 4 : 4). IR spectrum, ν, cm^{-1}: 1250 (SO_2, asym.); 3600, 1200 (OH), 1050 (SO_2, sym.). UV spectrum (water), λ_{max}, nm ($\log \varepsilon$): pH 1.0: 350 (4.13); pH 11.0: 400 (4.18).

Sodium 5-methoxy-2-(phenylazo)benzenesulfonate. Sodium 5-hydroxy-2-(phenylazo)benzenesulfonate, 21.4 g, was dissolved in 50 ml of water, the

solution was adjusted to pH 9.0 by adding 40% aqueous NaOH, and the mixture was heated to 60°C. Freshly distilled dimethyl sulfate, 20 ml, was added over a period of 5 h under vigorous stirring; during the addition, the initial pH value was maintained intermittently by adding 20% aqueous NaOH. The mixture was kept for 12 h, and the fine crystals were filtered off, washed with 100 ml of water, and dried. Yield 22 g (90%). IR spectrum, ν, cm^{-1}: 1250 (SO_2, asym.), 1050 (SO_2, sym.). UV spectrum (water), λ_{max}, nm (log ε): pH 1.0: 350 (4.16); pH 11.0: 350 (4.17).

2-Amino-5-methoxybenzenesulfonic acid (IV). Sodium 5-methoxy-2-(phenylazo)benzenesulfonate, 20.0 g, was dissolved in 300 ml of water heated to 80–85°C, 22.0 g of $Na_2S_2O_4$ was added, and the mixture was stirred for 30 min (until it became colorless), heated to 90–95°C, and kept for 10–15 min at that temperature. The mixture was cooled to 35–40°C and extracted with benzene until the extracts no longer contained aniline. The aqueous phase was acidified to pH 5.0 with hydrochloric acid, and the precipitate was filtered off, washed with 50 ml of 0.1 N hydrochloric acid and 50 ml of water, and recrystallized from water. Yield 6.3 g (51%) of chromatographically pure compound **IV**. Further acidification of the filtrate obtained after separation of the first portion gave an additional 2.7 g (22%) of the producta containing a little of impurities. ^{1}H NMR spectrum, δ, ppm: 7.17 d (1H, 6-H), 6.89 d.d (1H, 4-H), 6.71 d (1H, 3-H), 5.47 br.s (NH_2), 3.65 s (3H, CH_3).

2-Amino-5-methylbenzenesulfonic acid (III). A 5.6-ml portion of 95% sulfuric acid was slowly added with stirring to 10.7 g of 4-methylaniline. The salt thus obtained was ground and uniformly applied to the bottom of a round-bottom flask. The flask was immersed into a metal bath heated to 90–100°C, and water was distilled off under reduced pressure (water-jet pump). The bath temperature was slowly raised to 170–180°C, and the mixture was kept for 3 h at that temperature. The end of the process was determined by dissolution of a sample of the mixture in 10% aqueous NaOH (the solution should be homogeneous, and it should not contain appreciable amounts of 4-methylaniline). The mixture was cooled to 60–70°C, 10% aqueous NaOH was added until alkaline reaction (phenolphthalein), and the mixture was heated to 90–95°C and was stirred until it became homogeneous. A small amount of unreacted 4-methylaniline was removed from the solution by steam distillation. The solution was cooled to 70–80°C, 1 g of charcoal was added, the mixture was stirred for 30 min and quickly filtered on a Büchner funnel, and the charcoal was washed on a filter with 15 ml of hot water. The filtrate was combined with the washings and acidified with hydrochloric acid (Congo Red). The precipitate was filtered off, washed with water (2 × 50 ml), recrystallized first from 0.1 N hydrochloric acid and then from water, and dried at 60°C. Yield 13.1 g (70%), colorless finely crystalline powder. IR spectrum, ν, cm^{-1}: 1250 (SO_2, asym.), 1060 (SO_2, sym). Anilinium salt $C_7H_9NO_3S \cdot C_6H_7N$: mp 235–239°C (from 96% ethanol); published data [9]: mp 237–241°C.

2-Amino-5-chlorobenzenesulfonic acid (II). A 7.5-ml portion of 92% sulfuric acid was added with stirring to 16.7 g of 4-chloroaniline (see above). The salt was sulfonated by sintering at 170–180°C over a period of 5 h. The end of the reaction was determined as described above. Removal of unreacted 4-chloroaniline and isolation and purification of 2-amino-5-chlorobenzenesulfonic acid were performed following the procedures described above for 2-amino-5-methylbenzenesulfonic acid. Yield 25.2 g (60%), light grey crystals. IR spectrum, ν, cm^{-1}: 1250 (SO_2, asym.), 1060 (SO_2, sym). Anilinium salt $C_6H_6NO_3S \cdot C_6H_7N$, mp 210–212°C (from 96% ethanol); published data [10]: mp 211–212°C.

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