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Textbook Errors, 65

The Coupling of Diazonium Salts

"The coupling of diazonium salts to aryl rings is a typical electrophilic substitution, analogous to sulfonation or nitration, involving attack by the diazonium ion. As is the case for HNO_2, the diazonium ion is a weak electrophile and displaces hydrogen only from highly activated rings, e.g., amines and phenols. Coupling does not take place in strongly acid solution because the active phenoxide ion becomes a phenol and the active amine an anilinium ion." This statement, or a similar one, appears in many recent texts of organic chemistry, both elementary and advanced.[2]

Such statements are often elaborated by the addition of charts or diagrams depicting the typical electrophilic attack of a generalized diazonium species on a nucleophilic receptor (usually N,N-dimethyl aniline) at high, moderate, and low pH values. Such elaborations then often lead to statements as to the impossibility of attack on hydrocarbons or on arylamines at high pH because of the formation of the "non-electrophilic hydroxide" $Ar—N=N—OH$. Further, the student is often left with the impression that diazo coupling is unknown or unlikely in the aliphatic series.

The student's puzzlement begins with the memory that nitration and sulfonation proceed well in strong acid. In fact he knows of virtually no other media for these reactions. Why not diazonium coupling? Oh well, he reasons, it's "weak," although he is still vaguely disturbed that any cation which is said to form completely dissociated salts should be called weak.

A few pages along he discovers that methyl orange is customarily synthesized from the diazonium salt of sulfanilic acid and N,N-dimethyl anilinium acetate in acetic acid as a solvent. Finally, if he synthesizes methyl orange in the laboratory, according to directions in his laboratory manual (*1*), he discovers that the reaction medium is, in fact, not only largely aqueous but about 0.2 M in excess HOAc and 0.75 M in excess HCl. At that, the reaction is complete within a few minutes. Or, if methyl red is prepared (*2*), that the medium is about 1.4 M in HOAc and about 1.1 M in excess HCl.

The serious student can find (*3–5* for example) that hydrocarbons, phenyl ethers, and many aliphatic compounds couple well and even rapidly in acid media, that diazo hydroxides are electrophilic and probably best represented as $Ar—N=N—O^-$ in aqueous media and that aryl amines couple in strongly basic media.

Among the more special cases he might find the facile coupling of a quaternary ammonium ion, e.g., a quaternary benzothiazole (*6*), and the increased yield of cinnolines produced by diazo coupling in strong, warm HCl (*7*). Actually the former involves the deprotonated form of the ion, not the ion itself. For the latter, acid-promoted enolization of the acetyl group would be expected to facilitate subsequent coupling. In either case, though, the student might well be confused.

More generally, many classical amine and phenol couplings proceed fairly rapidly in acid, even in concentrated H_2SO_4 (*8, 13*), and a number of dyes and pigments are produced commercially by couplings in strong acid (*9*).

Historically, the situation seems to have arisen by qualitative extension of the now classical mechanism proposed in 1941 by Wistar and Bartlett (*10*) as a result of kinetic measurements made at pH values from 2 to 6 (*10, 11*). In this range a classical electrophilic attack

$$ArN_2^+ + ArO^- \rightarrow Ar—N=N—ArO^- + H^+$$
$$ArN_2^+ + ArN(CH_3)_2 \rightarrow Ar—N=N—ArN(CH_3)_2 + H^+$$

seemed both valid and general. Although objections have been raised, and a number of alternative mechanisms proposed (*12*) or suggested, current opinion supports the classical mechanism over the entire pH range (*5*).

Two experimental approaches have been employed to demonstrate clearly the involvement of the diazonium *ion*. Zollinger (*14*) investigated the effects of ionic strength on the coupling of diazo salts and their mono- and disulfonic acid derivatives. Negative, zero, and positive salt effects respectively were observed. These were in precise quantitative agreement with the predictions of Brönsted's equation applied to the diazonium ion.

Further studies have also shown (*15*) that the diazo hydroxide, $Ar—N=N—OH$, can only be a metastable intermediate in the diazo equilibrium,

$$Ar—N=N^+ + OH^- \rightleftharpoons Ar—N=N—OH \rightleftharpoons$$
$$Ar—N=N—O^- + H^+$$
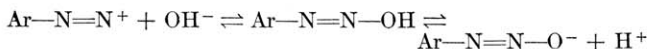
and one possessing an essentially infinitesimal lifetime. In consequence, one would expect the rate of coupling to rise approximately one power of ten per pH unit from very low pH values (zero or less) to some value characteristic for the above rearrangement (about 10), then to decrease by *two* powers of 10 per pH unit. This behavior is, in fact, what is usually observed (*5*).

If, then, the classical mechanism is correct why is there an evident discrepancy between text statements and experimental observation? The difficulty seems to lie in an inadequate presentation of the admittedly complex kinetics, combined with a form of "temporal solipsism." It is not at all uncommon for diazo coupling reactions to possess such high *intrinsic* rates that the maximum *observed* rate under ordinary laboratory conditions is chiefly limited by diffusion, by rate of mixing, and by human reaction times which have become conditioned to relatively slow organic reactions. Thus, a drop of 6 orders of magnitude in true rate can still leave an apparent rate so high as to afford complete reaction in a few hours or, possibly, minutes. Since this time domain lies well within the span of human patience the apparent rate, although "slow" relative to its maximum, is nevertheless quite "fast" to the attending student.

The concept of the diazo hydroxide as a chief reactive intermediate has had a long and curious history, which has been reviewed better elsewhere (*3, 5*). It derived its chief support from the painstaking and brilliant work of Hantzsch. Despite the evolution of more appropriate ionic mechanisms since that time, however, it remains uncorrected in many texts and even monographs. For example, it is often incorrectly asserted that the *syn*-diazotate couples but that the *anti*-diazotate does not. In fact the apparent reactivity of the *syn*-diazotate is due to the fact that it takes part in a rapidly established equilibrium with the diazonium ion, while the *anti*-form only slowly produces the diazonium via rearrangement (*16*).

A number of other anomalies from the older literature, although not properly errors, are still to be found in recent texts. Although very adequately discussed by Zollinger (*5*) it might be pertinent to call attention to them here. Thus, Huisgen's original observation (*17*) that diazonium acetates couple almost instantaneously in pure benzene was interpreted as evidence for the existence of a covalent diazo acetate. Present interpretations regard this rather as evidence for a concerted mechanism involving intramolecular base catalysis (*5, 18*). Similarly, the coupling behavior of *p*-tetrazo benzene in strong and weak acid (*19*), originally interpreted as evidence for an asymmetric form, has been reinterpreted in terms of the relative activating influence of the diazo groups (*5*). Finally, the stability of the diazonium nitrogens themselves, deduced from N^{15} experiments (*20*), requires some revision in the light of more recent work (*21*).

Recent studies of coupling at extremes of *p*H (*5, 8, 13*) have served to demonstrate both the applicability of the classical mechanism and inadvisability of predicting real rates without a careful consideration of quantitative aspects. Thus, at *p*H values below zero,

coupling to phenols decreases in rate until a plateau is reached. The plateau, attributable to coupling to the free phenol, persists until formation of the oxonium ion brings about a further decrease. Amines, on the other hand, show no plateau in this region but do demonstrate one in the regions of high *p*H where formation of the anion begins. Thus, completely analogous results are obtained for phenols and amines which correspond to the equilibria

$$Ar\overset{+}{O}H_2 \rightleftharpoons ArOH \rightleftharpoons Ar\overset{-}{O}$$

$$Ar\overset{+}{N}H_3 \rightleftharpoons ArNH_2 \rightleftharpoons Ar\overset{-}{N}H$$

and to the expected constants for these equilibria.

What is unexpected is the avidity of the coupling species which is so marked that coupling occurs not merely with anionic species but with neutral and possibly even cationic ones as well. Such behavior suggests that the characterization of the diazo reactant as simply a weak electrophile, often done in texts, is probably inadequate. One may, perhaps, best conclude by quoting Zollinger (*4*): "Whereas the fundamental principles concerning the reactivity of amines and phenols are today rather clear, the situation regarding the diazo reactant still presents many interesting problems."

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