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Preparative Organic Chemistry

With Contributions by
J. Káš, E. M. Kosower, P. Rauch,
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With 41 Figures and 21 Tables

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Azo Coupling Reactions
Structures and Mechanisms

Ivanka Szele and Heinrich Zollinger

Technisch-Chemisches Laboratorium, Eidgenössische Technische Hochschule (ETH),
CH-8092 Zürich, Switzerland

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Ivanka Szele and Heinrich Zollinger

1 Introduction

Diazonium ions are Lewis acids in which the β-nitrogen atom is the centre of electrophilic character. The addition of nucleophiles at the β-nitrogen is called an azo (or diazo) coupling reaction and depending on the atom which provides the lone pair of electrons, C-, N-, O-, P- or S-coupling can occur.

In this paper reactions of aromatic, heteroaromatic and related diazonium ions with nucleophiles are discussed. In such reactions substitution by the diazonium ion of an electrofugic atom or group bonded to carbon takes place. Occasionally reference is made to N- and P-coupling. In Section 4 the respective substitution at nitrogen (formation of diazoamino compounds) is included for comparative purposes.

The products of these substitution reactions at carbon are azo compounds; azo coupling is the reaction by which about 50 % of all industrial dyes manufactured in the last 100 years have been produced.

The industrial aspects of this reaction will, however, not be discussed in this paper. We will concentrate on structural and mechanistic problems which, to our knowledge, have not been summarized in detail in the last two decades. In the 1950's work on azo coupling reactions with aromatic substrates, e.g. wih phenols, naphthols, naphthylamines, as well as with activated methylene compounds such as enols, demonstrated that azo coupling reactions are, in many respects, ideal systems for mechanistic investigations of electrophilic aromatic substitutions: Azo coupling reactions can be run in dilute aqueous buffer solutions, and therefore acid-base phenomena can be studied better than with other electrophilic aromatic substitutions, which often take place in less familiar systems such as concentrated sulfuric acid for nitrations, or apolar solvents for Friedel-Crafts reactions. A clear differentiation between specific and general base catalysis in electrophilic aromatic substitutions was made possible for the first time using an azo coupling reaction. The same is true for a quantitative evaluation of kinetic hydrogen isotope effects.

These results were previously discussed in a monograph published in 1961 [1], but were later dealt with only briefly by various authors. In the last twenty years some effects, found many decades ago in coupling and other substitution reactions, could be elucidated with respect to their structural and mechanistic basis, e.g. product ratios due to mixing effects — a phenomenon which was not understandable at all only a few years ago.

This review summarizes such investigations. We hope that it will give suggestions for further work on the understanding and the expansion of the scope of the azo coupling reaction as well as catalyze the transfer of methods used successfully in investigations of the azo coupling to other reactions in organic chemistry.

In order to keep this review to a manageable size we do not discuss in detail related reactions, e.g. additions of diazonium ions to simple anions like OH^-, CN^-, and N_3^-, or the so-called oxidative azo coupling reaction, discovered by Hünig in which electrophilic reagents comparable but not identical with diazonium ions are obtained by oxidation of heteroaromatic hydrazones.

2 Structure of Reagents in Azo Coupling Reactions

2.1 Diazo Components

By far the most important azo coupling reaction, i.e. the reaction of arenediazonium ions with aromatic coupling components, has been known for many decades and has been extensively reviewed [1]. Therefore, in this section we shall concentrate on reactions of aliphatic diazonium ions, diazoalkanes and diazocarbonyl compounds which have not been known previously as well as on coupling reactions which have gained in importance more recently, specifically those of heterocyclic diazonium ions.

2.1.1 Aliphatic Diazonium Ions

Aliphatic diazonium ions are formed as intermediates in deamination reactions of aliphatic amines. Due to the extremely good leaving group ability of nitrogen, however, they usually cannot be trapped by an azo coupling reaction, but rather undergo rapid dediazoniation to give carbocation intermediates [2]. Recently, however, it has been found that in some alkanediazonium ions azo coupling successfully competes with dediazoniation. All the examples known up to now concern cyclopropanediazonium ions [3-5] and bridgehead diazonium ions [6-9] in which the loss of nitrogen would lead to a very unstable carbocation.

Kirmse and coworkers have studied the reaction of alkanediazonium ions with amines [3,4] and with lithium azide [3,5]. Cyclopropanediazonium ions [2] give azo coupling products *6* and *7* with dimethylamine and with ethylamine, respectively (1) [3,4]. However, no azo coupling of *1* with phenols was observed. In the reaction

$$(1)$$
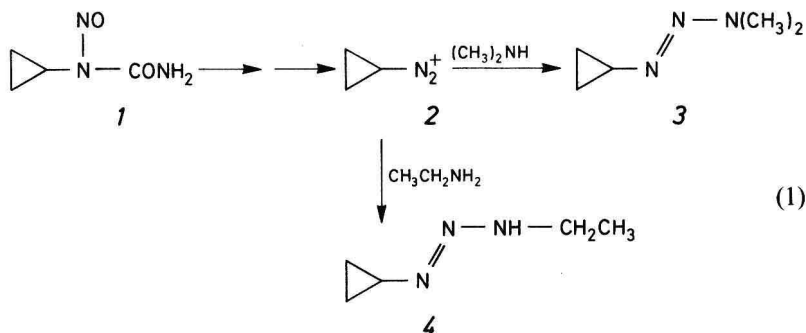
with lithium azide Kirmse and coworkers [3,5] determined by ^{15}N-labelling of the α-nitrogen atom in *1* that only 3% of the product (cyclopropyl azide) was formed by direct substitution of the diazonio group by azide ions, while the major pathway (97%) was an addition of N_3^- to the β-nitrogen of the intermediate diazonium ion *2* and dediazoniation of the pentazene formed.

Curtin and coworkers have observed the azo coupling of the bridgehead diazonium ion *6* with 2-naphthol at low temperature (2) in 50% yield.

$$R-NH_2 \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{NOCl}} R-N_2^+ \xrightarrow{\text{(naphthol)}} \text{(product)}$$

5		**6**		**7**

$$R = \qquad\qquad\qquad\qquad (2)$$
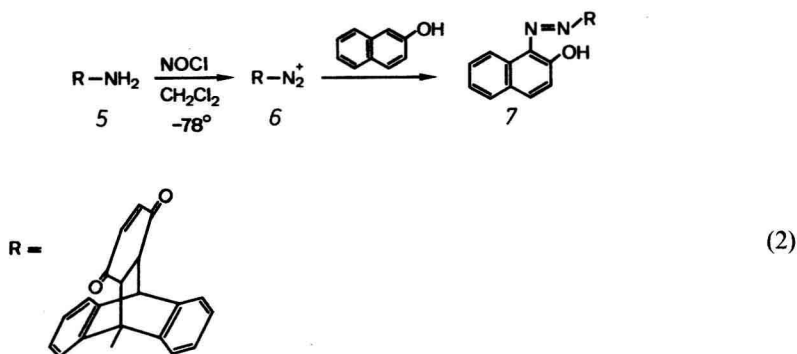
Also Scherer and Lunt [7-9] could demonstrate the azo coupling of the extremely electrophilic bridgehead polychlorinated homocubanediazonium ion *8* with several aromatic coupling components (3). The dediazoniation of *8* surprisingly yields radical intermediates [9], thus reflecting the high energy content of the bridgehead perchlorinated homocubyl cation. The hydrogenated analogue of *8*, on the other hand, yields 'normal' ionic intermediates under the same reaction conditions [10].

$$R-NH_2 \xrightarrow{\text{HNO}_2} R-N_2^+ \rightarrow R\cdot$$

$$\mathbf{8}$$

$$\downarrow \text{ArH}$$

$$\underset{Ar}{\overset{R}{N=N}} \qquad (3)$$

$$\sim 90\%$$

$$R-NH_2 = \text{(polychlorinated cage, Cl}_9\text{, NH}_2\text{)} \qquad ArH = \text{(2-naphthol)}, \text{(anisole, OCH}_3\text{)}, \text{(1,3,5-trimethylbenzene)}$$
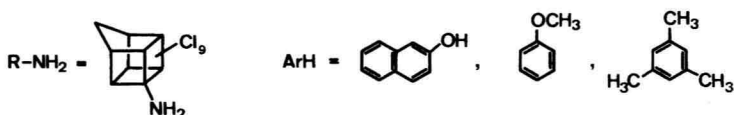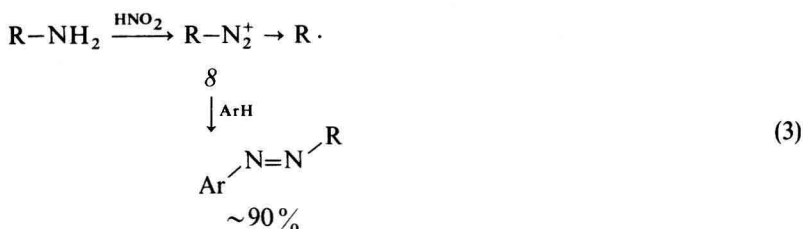
Other alkanediazonium ions, including the bridgehead bicyclo[2.2.1]heptane-1-diazonium ion *9*, do not undergo azo coupling reactions but give only nucleophilic substitution products [4,5]. In addition to the examples given above, some alkene-diazonium ions generated from nitrosooxazolidones can also add azide ions [5,11].

$$\mathbf{9}$$

It is interesting to compare the behavior of short-lived diazonium ion intermediates with that of the relatively stable and isolable alkenediazonium ions first prepared

4

by Reimlinger [12] and by Bott [13,14]. Until now there has been no conclusive evidence that the latter compounds undergo an azo coupling reaction. The reaction of alkene-diazonium ions *10* with primary amines, which gives triazoles *11* in reasonable yield [15,16], can be rationalized in terms of an azo coupling reaction (Path A), as well as of a nucleophilic attack on the β-carbon atom of the C—C double bond (Path B) (4).

$$\text{(4)}$$

R^1 = H , 4—O$_2$NC$_6$H$_4$

R^2 = OEt , —N⟨ ⟩

R^3 = H , Alkyl , Aryl
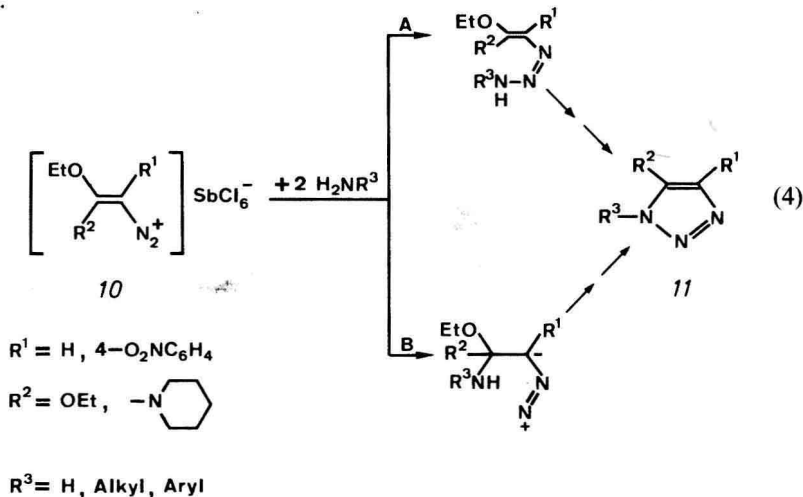
The extremely electrophilic alkenediazonium salt *12* was shown to react with nucleophiles, e.g. with anisole, at the β-carbon atom (5) [14]. Compound *12* and other

$$\text{(5)}$$
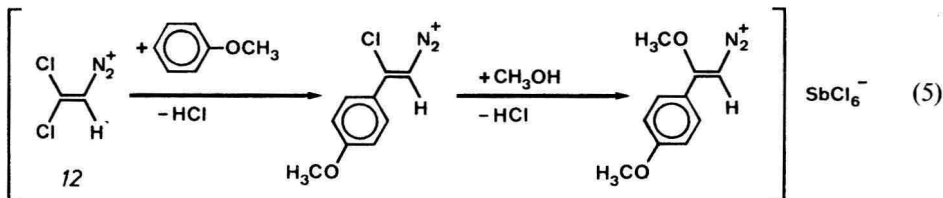
substituted ethenediazonium ions [17] do not give azo compounds with typical aromatic coupling components.

On the other hand, the diazonium substituted acetyl-acetone complex [18] *13* as well as the mixture of diazonium salts [19] *14* and *15* seem to react with 2- and 1-naphthol, respectively, to give the corresponding azo dyes, which could, however, not be isolated as pure compounds.

13

14

15

5
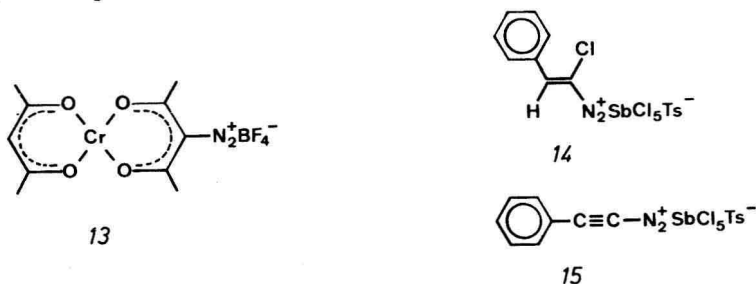
In conclusion it can be said that alkane- and alkenediazonium ions react with nucleophiles by a variety of pathways, one of them, in certain cases, being the azo coupling reaction. Small changes in the substrate structure, as well as in the reaction conditions, can drastically change the reaction pathway, indicating that the energy requirements for the competing reactions are rather similar.

2.1.2 Diazoalkanes, Diazoketones and Diazoesters

Compared to diazonium salts, diazo compounds are generally much less reactive towards nucleophiles than towards electrophiles. As a result of this azo coupling reactions of diazo compounds are the exception rather than the rule. Electron withdrawing substituents on the diazo carbon increase the reactivity towards nucleophiles. Consequently the ability to undergo azo coupling reactions increases from diazomethane to diazocarbonyl- and 2-diazo-1,3-dicarbonyl compounds. Among the earliest reactions known were those with cyanide and sulfite ions [1,20].
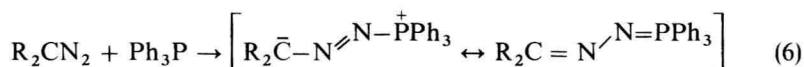
Tertiary phosphines, as opposed to amines, can form stable addition complexes with diazoalkanes [21,22], probably due to the ability of phosphorus to stabilize the betaine with its empty d orbitals (6).
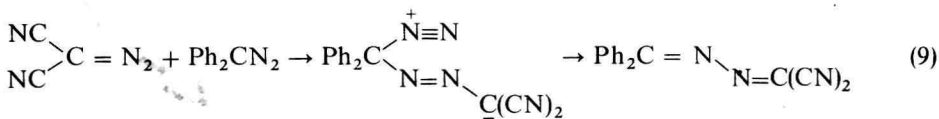
$$R_2CN_2 + Ph_3P \rightarrow \left[R_2\bar{C}-N{\overset{\nearrow N-\overset{+}{P}Ph_3}{}} \leftrightarrow R_2C = N{\overset{\nearrow N=PPh_3}{}} \right] \quad (6)$$

Carbanions derived from organometallic reagents react with aryldiazoalkanes [23 to 25], diazoketones [26] and diazoesters [27] to yield hydrazones after hydrolysis (7).

$$Ph_2C = N_2 + PhMgBr \rightarrow Ph_2\bar{C}-N{\overset{\nearrow N-Ph}{}} \rightarrow Ph_2C = N-NHPh \quad (7)$$
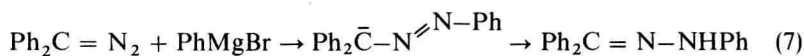
2-Diazo-1,3-dicarbonyl compounds are electrophilic enough to give azo coupling products with reactive aromatic azo coupling components [28,29], as well as with CH acidic compounds [30] such as β-diketones and β-keto-esters.

Dicyanodiazomethane [31] even gives an azo-coupling product with dimethylaniline (8) and also reacts with diaryldiazomethanes to give the mixed azines (9).

$$\underset{NC}{\overset{NC}{>}}C = N_2 + \langle\!\!\!\bigcirc\!\!\!\rangle - NMe_2 \longrightarrow \underset{NC}{\overset{NC}{>}}C = N - NH - \langle\!\!\!\bigcirc\!\!\!\rangle - NMe_2 \quad (8)$$

$$\underset{NC}{\overset{NC}{>}}C = N_2 + Ph_2CN_2 \rightarrow Ph_2C{\overset{\overset{+}{N}\equiv N}{\underset{N=N}{\diagdown}}}C(CN)_2 \rightarrow Ph_2C = N{\overset{}{\diagdown}}N=C(CN)_2 \quad (9)$$
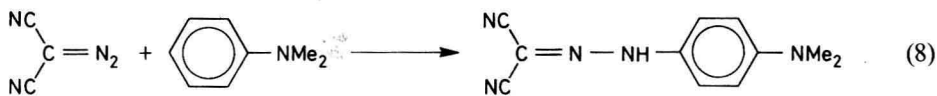
Bisarylsulfonyldiazomethanes can also react with diphenyldiazomethane and the azine is formed without passing through a carbene intermediate (10) [32].

$$Ph_2CN_2 + N_2C(SO_2Ph)_2 \rightarrow Ph_2C = N{\overset{}{\diagdown}}N=C(SO_2Ph)_2 \quad (10)$$
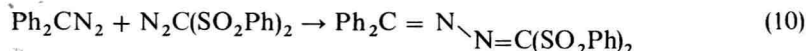
In 1969 the first example was reported of a coupling reaction of diazomethane with

(11)
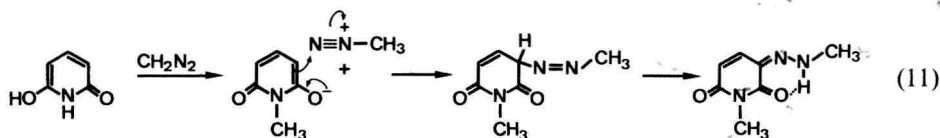
a heterocyclic coupling component [33] (11). Compounds *16* to *18* can be synthesized in a similar manner [34-36].
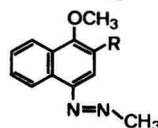
16	*17*	*18*

An interesting dichotomy of reaction paths was recently observed by Huisgen and coworkers [37] in reactions of diazocarbonyl compounds with enamines: While diazomonocarbonyl compounds react with 2,5-dimethyl-1-pyrrolidinocyclopentene *19* in a cycloaddition reaction to give 2-pyrazolines *20*, dimethyl diazomalonate undergoes an azo coupling reaction and the hydrazone *21* is formed (12). This nicely
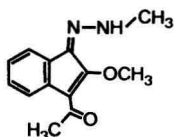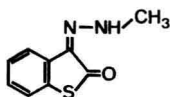
$R = COPh, CO-C_6H_4-NO_2\ p,$
CO_2CH_3

(12)
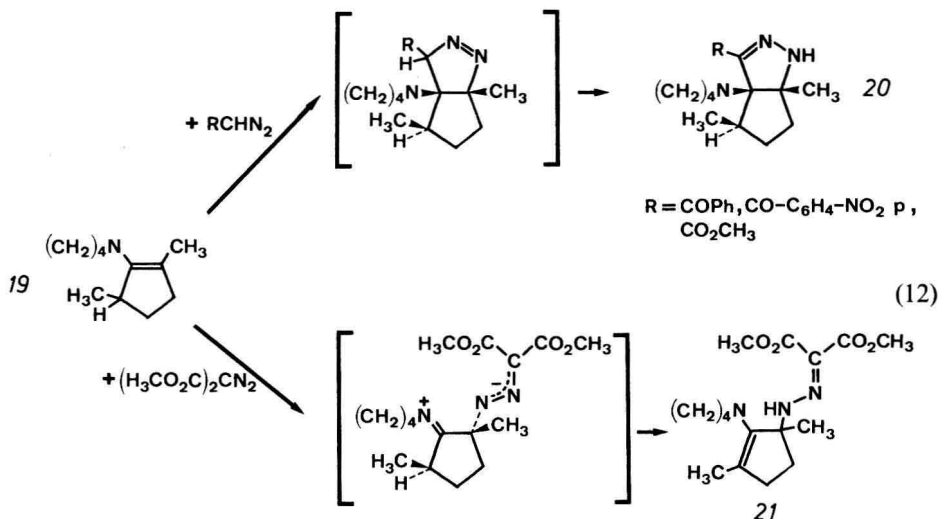
substantiates the statement that the reactivity of substituted diazo compounds in 1,3-dipolar additions decreases with increasing delocalization of the negative charge on the carbon atom into the substituents. The opposite trend is observed for the reactivity in azo coupling reactions.

Another interesting coupling reaction with enamines was recently observed with bis(methylsulfonyl)diazomethane *22* [40].

$(CH_3SO_2)_2C = N_2$

22

+

H5C6\C=CH2 (morpholine, **23**)

⟶

H5C6\C=CH—N=N—CH(SO₂CH₃)₂ (morpholine, **24**)

| $-\bar{C}H(SO_2CH_3)_2$ ↓

H5C6\C=CH—$\overset{+}{N}\equiv N$ (morpholine, **25**)

| +**23** ↓

H5C6\C=CH—N=N—HC=C(morpholine)(C₆H₅) (**26**)
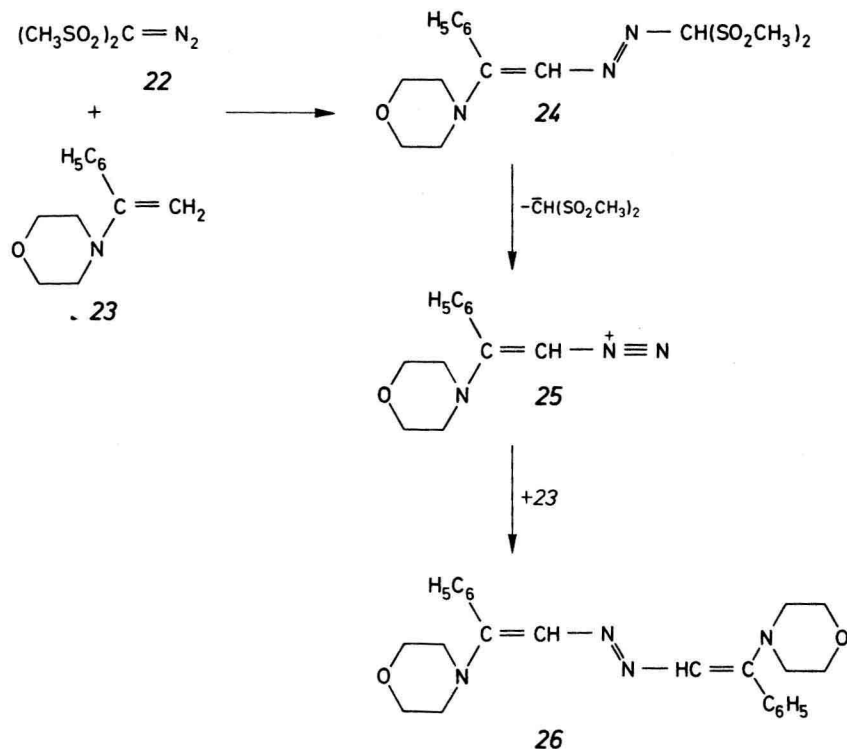
The azo compound **24** is probably formed initially. It decomposes to give the vinyldiazonium ion **25** that in its turn couples with another molecule of **23** to give the final product **26** (13) [40]. Actually the diazodiester **22** acts as a diazo-transfer agent.
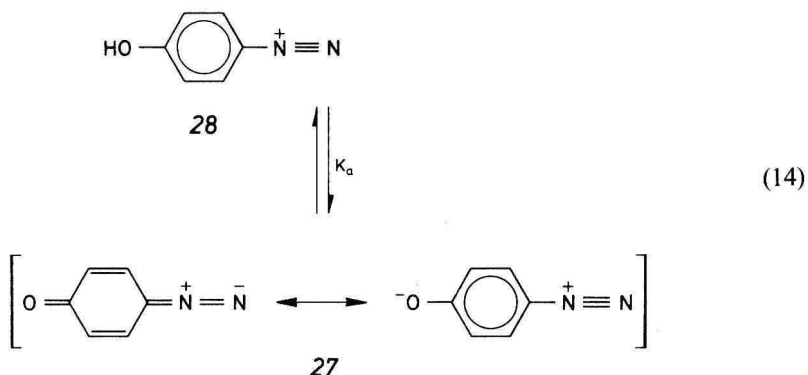
2.1.3 Diazooxides[1]

p-Diazooxides **27** and their o-isomers simultaneously display the properties of both aliphatic and aromatic diazo components. They can be considered as analogues of conjugated diazoketones. On the other hand, a specific feature of many of their reactions is their conversion to hydroxyarenediazonium ions **28** in the presence of acids (14). The pK_a value of the p-hydroxybenzenediazonium ion **28**, for example, is 3.19 [42], so the reactivity of compounds of this type will depend a lot on the acidity of the reaction medium. **28** is much more electrophilic than **27**, and the measured rate therefore depends on the position of equilibrium (14). Recently a comprehensive review on diazooxides has appeared [43], also including azo coupling reactions, and therefore only a few selected reactions will be mentioned here.

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1 In this review the name diazooxides will be used for compounds of the type **27**, since it seems to be in best agreement with the IUPAC [41] Rules (C10.1 and C84.2). Other names also encountered in the literature are: diazoquinones, quinonediazides and diazophenols.

$$HO-\langle\bigcirc\rangle-\overset{+}{N}\equiv N$$

28

$$K_a \qquad (14)$$

$$\left[O=\langle\bigcirc\rangle=\overset{+}{N}=\overset{-}{N} \longleftrightarrow \quad {}^{-}O-\langle\bigcirc\rangle-\overset{+}{N}\equiv N \right]$$

27

Diazooxides react with hydroxyaromatic coupling components in the same manner as diazonium salts, giving dihydroxysubstituted azo compounds. An interesting feature of this reaction is the fact that the reaction rate increases with medium acidity, reaches a maximum (between 50–80% H_2SO_4 in reactions with resorcinol, depending on the diazooxide under study) and then decreases [44,45].

Basically the reactivity in azo coupling reactions of diazonium salts is larger than that of diazooxides [46] (1,4-diazooxides again are more reactive than the 1,2-species), and therefore the concentration of the more reactive form is increasing with the medium acidity. Up to a certain point this compensates for the parallel decrease in the concentration of the more reactive coupling component, the phenolate ion. In principle, however, there are no qualitative differences in the behavior of diazooxides and arenediazonium salts in azo coupling reactions with hydroxyaromatic compounds. This is also supported by a thorough study of the coupling with 2-naphthol [46]: in a Hammett plot of log k vs. σ^+, data for diazonium salts and diazooxides fall on one straight line ($\varrho = 2.55$) [42], indicating a uniform mechanism of the azo coupling process.

Substituted 1,4-diazooxides react with secondary aliphatic amines to give the corresponding triazenes (diazoamino compounds) in high yield, while the products with primary amines are surprisingly unstable and decompose by a radical mechanism [47]. Reactions with diazoalkanes yield asymmetrical azines *29* (15) in the case of 1,4-diazooxides, and cyclic benzoxadiazines *30* with 1,2-diazooxides (16) [48].

$$(15)$$

29

$$(16)$$

30

9