Azobenzenes—synthesis and carbohydrate applications

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1. Introduction

Advances in molecular and supramolecular organization are a major challenge in organic chemistry. The control of molecular and supramolecular assembly may be obtained under ambient conditions by external inputs such as electricity, pH, redox potential, magnetic fields, and light. Various photochemical reactions are described in the literature: E/Z isomerization, tautomerization, electrocyclic reactions, heterolytic cleavage, and homolytic cleavage. The use of light-powered reactions is the most reliable strategy to convert photochemical energy into reversible physical motion without waste (Fig. 1).

Azobenzenes have been used as photosensitive functional devices utilized as smart polymers, liquid crystals, and machines. Azobenzenes derivatives have received considerable experimental and theoretical attention. Azobenzenes exist as two isomers: the isomer E (or trans) and the isomer Z (or cis) (Fig. 2). The E isomer is 50 kJ mol⁻¹ more stable thermodynamically than the Z form. Consequently, the different spatial arrangements lead to different physical and chemical properties. The E to Z- photoisomerization of azobenzene induces a change of the dipole moment (μ E-azobenzene=0.5 D vs μ Z-azobenzene=0.2 D).
Z-azobenzene (3.1 D), which in turn determines the hydrophobic and hydrophilic nature of the \( E \) and \( Z \) isomers.

The structure of \( E \)-azobenzene is not planar; the dihedral angle \( \text{N,N,C,C} \) is around 17.5°, whereas one of the benzene rings of the \( Z \)-isomer occupies a plane tilted by 56° from the plane of the other ring. Thus, the distances between the two carbon atoms in the 4- and 4'-positions are 9.0 and 5.0 Å for the \( E \)- and \( Z \)-isomer, respectively (Fig. 3).

The UV-visible absorption spectra of \( E \)-azobenzene is characterized by three major bands: (i) a band at 228 nm originates from \( \pi-\pi^* \) transitions localized on the phenyl groups; (ii) a band at 318 nm originates from symmetry-allowed \( \pi-\pi^* \) transitions, which are delocalized through the molecule including the two nitrogen atoms; and (iii) a band at 440 nm originates from symmetry-forbidden \( n-\pi^* \) transitions occurring at the central nitrogen atoms (Fig. 4). It is notable that the UV-visible absorption spectrum of the \( Z \)-isomer is quite different from that of the \( E \)-isomer, with a band at 260 nm originating from symmetry-allowed \( \pi-\pi^* \) transitions (318 nm for the \( E \)-isomer).

The mechanism of photoisomerization of azobenzene has been a fundamental subject and two pathways have been described. It is accepted that the photoirradiation step from \( E \) to \( Z \) has a rotational pathway and/or an inversion pathway, whereas the heating step from \( Z \) to \( E \) has an inversion pathway (Scheme 1).

The Rau classification of azobenzene distinguishes three families of compounds: (i) the azobenzene derivative 1; (ii) the amino-azobenzene derivative 2; and (iii) the push–pull azobenzene...
The synthesis of symmetrical azobenzene derivatives has been described in the literature but recent investigations from aniline derivatives, but these reagents have not been used recently.

The use of manganese dioxide (MnO₂) for the oxidation of aniline derivatives 4 and 5 in refluxing hexane was realized to furnish the corresponding azobenzene analogues 1 and 6 in 69 and 61% yields, respectively (Scheme 2).

More recently, Gilbert et al. reported the dimerization of 4-chloroaniline (5) via oxidation with MnO₂ in refluxing toluene to afford the corresponding azo compound 6 in a lower yield (49 vs 61%).

Starting from the aniline derivatives 7–9 having halogen atoms in the meta or para position, application of this procedure permitted the formation of the corresponding azobenzene analogues 10–12 in 89, 88, and 79% yields, respectively (Scheme 3).

The synthesis of azobenzene derivatives having a protected hydroxyl group in the para position of the aromatic ring has been described. The protection of the aromatic hydroxyl group was realized by treatment of 4-aminophenol (13) with triisopropylsilyl chloride. The silylated derivative 14 in the presence of MnO₂ in refluxing benzene furnished the azobenzene derivative 15 in 34% overall yield (two steps) (Scheme 4).

Woolley et al. described the synthesis of the azobenzene derivative 18 with an ethyl(2-hydroxyethyl)amino substituent in the para position starting from the commercial benzeneaminium hydrogenosulfate 16 (Scheme 5). Treatment of the salt 16 with sodium bicarbonate generated the amine 17 in 62% yield. Then, oxidation of 17 with MnO₂ gave the azobenzene derivative 18 in 29% yield. It was notable that the primary hydroxyl group was not protected during the oxidation step.
Recently, the synthesis of azobenzene derivatives with steric hindrance has been described. Yamaguchi et al. reported the synthesis of a cycloalkyne dimer 20 linked by an azo group. Oxidative coupling of 19 with MnO₂ in benzene generated the azobenzene 20 in 64% yield (Scheme 6).23

The use of potassium permanganate absorbed onto copper(II) sulfate pentahydrate was studied. This oxidizing reagent offered several practical advantages, namely better yields, a simpler experimental procedure, and utilization of a commercially available oxidant that is safe to handle. Starting from the aniline derivatives 4, 21, and 22, Noureldin et al. reported the synthesis of azobenzenes 1, 23, and 24 using the supported permanganate in 77–87% yield (Scheme 7).24

A few years later, Flatt et al. described the synthesis of compound 24 in 15% yield using CHCl₃ instead of CH₂Cl₂ (Scheme 8).25

In order to limit the use of solvents and to have applications in combinatorial chemistry and in green chemistry, the synthesis of azobenzene derivatives by solvent-free permanganate oxidation was developed.26 Treatment of the primary aromatic amines 4, 5, and 25 with KMnO₄, Al₂O₃, and CuSO₄·5H₂O afforded the corresponding azobenzene derivatives 1, 6, and 26 in 75, 80, and 70% yields, respectively (Scheme 9).

The use of sodium perborate for the oxidation of aromatic amines has been reported. Abelt et al. reported the oxidation of aniline derivative 27 with sodium perborate tetrahydrate in the presence of boric acid in acetic acid to give the azobenzene 28 in 64% yield (Scheme 10) and various amounts of the azoxy compound.27 It was notable that the amino group and the carboxy group, respectively, in the para and meta positions of the aromatic ring, were protected.

Recently, Naeimi et al. reported the synthesis of 4,4'-di-aminooazobenzene (30)28 as described by Stubbings et al. (Scheme 11).29 Starting from the p-aminoacetonilide (29), treatment with...
sodium perborate tetrahydrate and boric acid in glacial acetic acid followed by treatment with HCl in methanol furnished the azo compound 30 in 52% overall yield (two steps).

\[
\begin{align*}
\text{Scheme 11. Reagents and conditions: (a) } & \text{NaBO} \text{3$\cdot$4H}_2\text{O, B(OH)}_3, \text{AcOH then HCl, MeOH} & (52\%).
\end{align*}
\]

The synthesis of azobenzenes was described by oxidation with a mercury(II) oxide/iodine reagent. Orito et al. reported the synthesis of azobenzene derivatives 32 by dimerization of aniline derivatives 31 in 87% yield (Scheme 12). 30 As described above, the protection of the carboxy group of the compounds was established before the oxidation reaction.

\[
\begin{align*}
\text{Scheme 12. Reagents and conditions: (a) } & \text{HgO, I}_2, \text{CH}_2\text{Cl}_2 & (87\%).
\end{align*}
\]

The authors proposed a plausible mechanism involving a nitrogen–nitrogen coupling of an initially formed cation radical (or aminyl radical), which is probably produced by a one-electron transfer, followed by a two-electron oxidation of the resultant hydrazobenzene 33 (Scheme 13). 30

\[
\begin{align*}
\text{Scheme 13. Mechanism of oxidation of aniline (4) with HgO and I}_2.
\end{align*}
\]

Flatt et al. described the synthesis of azobenzene 35 from 2-nitro-4-iodoaniline (34) by oxidation using mercury(II) oxide and iodine (Scheme 14). 32 The poor yield (4%) was presumably due to the low reactivity of the electron-deficient aniline and the sterically hindered azo product.

As described in this section, the oxidative coupling of amines was used for the synthesis of symmetrical azobenzene. One example was reported in the literature concerning the oxidation of the primary aromatic amines for the preparation of dissymmetrical azobenzenes. Oxidative hetero-coupling of free base aminoporphyrin 36 and aminoacetal 37 using MnO2 as the oxidant was utilized to furnish the dissymmetrical azobenzene 38 in 50% yield (Scheme 15). 31

\[
\begin{align*}
\text{Scheme 15. Reagents and conditions: (a) } & \text{MnO}_2, \text{toluene, 110 °C} & (50\%).
\end{align*}
\]

2.2. Reduction reactions of aromatic compounds having nitro groups

The synthesis of azobenzene derivatives has been reported via the reduction of nitro compounds using zinc in a basic medium, via catalytic transfer hydrogenation using HCO2H, NEt3/Pb, and via reduction using glucose in a basic medium. Hecht et al. reported the synthesis of azobenzene-core amphiphilic oligo(meta-phenylene ethynylene)s. 33 After bromination of methyl 3-nitrobenzoate (39), treatment of 40 with zinc under basic conditions yielded the desired azobenzene bis-acid 41 in 63% yield (two steps) (Scheme 16).

Cyclic azobenzenes were prepared by reduction reaction using Zn. Sukwattanasinitt et al. reported the synthesis of azobenzene derivative-bridged crown ether p-tert-butylcalix[4]arenes. 33 Reductive coupling of p-tert-butylcalix[4]arene derivative 42 with zinc in the presence of NaOH in isopropanol and water furnished the azobenzene 43 in 8% yield (Scheme 17). Starting from the isomer 44, application of this strategy using high-pressure method (3 atm nitrogen) gave the azo compound 45 in 59% yield (Scheme 17). It was notable that the 4,4'-derivative was unstable and none of the desired product could be isolated.

\[
\begin{align*}
\text{Scheme 14. Reagents and conditions: (a) } & \text{HgO, I}_2, \text{CH}_2\text{Cl}_2 & (4\%).
\end{align*}
\]
The synthesis of azo compounds by catalytic transfer hydroge-
nation of nitroarenes has been studied in order to limit the use of
flammable hydrogen gas and pressure equipment. Nitrobenzene (46)
and lead powder in methanol in the presence of triethylammonium
formate furnished the azobenzene (1) in 92% yield (Scheme 18).34
Gowda et al. proposed34 that the initial reduction of the nitro com-
pound furnished a hydroxylamine as a reaction intermediate.

The synthesis of azobenzene derivatives having an unprotected
carboxy group in the aromatic ring could be effected using glucose
as a carbohydrate reducing agent.35 Starting from 4-nitrobenzoic
acid (47) in an aqueous solution of NaOH, treatment with an
aqueous solution of glucose gave the corresponding azo compound
48 in 76% yield (Scheme 19). Recently, different teams have applied
the above synthesis for the preparation of 4,4'-azodibenzoic acid
(49) in 44% yield.36

2.3. Coupling of primary arylamines with nitroso compounds
(Mills reaction)

The synthesis of dissymmetrical azobenzene derivatives has
been reported by treatment of aromatic nitroso compounds and
primary arylamines via Mills reactions.37–52 Compound 52 was
obtained starting from the nitroso compound 50 and the aniline
derivative 51 in acetic acid at 60 °C in quantitative yield (Scheme
20).51 It was notable that, using the Mills reaction, different elec-
tron-withdrawing and -donating groups could be present in the
ortho-, meta-, and para-positions of both the aromatic nitroso
compounds and the aromatic amines.

Nishihara et al. have described the synthesis of ferrocenylazob-
enzenes.53 3-Ferrocenylazobenzene (54) was prepared by the re-
action of 3-ferrocenylaniline (53) and nitrosobenzene (50) in acetic
acid in 24% yield (Scheme 21). Application of this strategy per-
mitted different ferrocenylazobenzenes 55–60 to be obtained
(Fig. 6). It was notable that the azobenzene 60 was obtained in the
Z configuration.

2.4. Diazo-coupling via diazonium salts

The synthesis of dissymmetrical azobenzene derivatives has
been reported by the coupling of diazo compounds and diazonium
salts in an acidic or basic medium. Due to the size of the attacking species, substitution is mostly para to the activating group. When the para position is already occupied, ortho substitution takes place. The pH of the solution was important both for the amine and phenol. In general, the use of an aromatic amine needed a mildly acidic or neutral solution. If the solution was too acidic, the reaction did not occur because the concentration of free amine became too small. Phenol was not active enough for the reaction, but, in slightly alkaline solution, the more reactive phenoxide ion afforded the target azobenzene. Neither amines nor phenols, however reacted in moderately alkaline solution because the diazonium ion was converted into the corresponding diazo hydroxide. Yang et al. reported the formation of the azobenzene derivative by the reaction of phenol (61) and diazo compound 62 in AcONa at 0 °C (Scheme 22).

Contemporary calixarene chemistry has involved the synthesis and development of biologically active compounds. The structures of calixarenes are convenient for performing diazonium coupling. Parola et al. described the diazo-coupling reaction of thiacalix[4]arenes. Starting from thiacalixarene 64, the synthesis of the tetraakis(phenylazo) derivative 65 was realized by treatment with the corresponding diazonium salt in pyridine and THF in 71% yield (Scheme 23).

Using a similar procedure, Parola et al. and Lhotak et al. reported the synthesis of the tetraazo compounds 66–70 (Fig. 7). Bolte et al. reported the synthesis of an azobenzene derivative of thiacalix[4]arene 72 by coupling the monoalkylated thiacalix[4]arene 71 with p-nitrophenyldiazonium tetrafluoroborate in 84% yield (Scheme 24). It was notable that the coupling reaction was carried out on the aromatic ring having a free hydroxyl group in the phenol ring.

Kim et al. reported the diazo-coupling reaction of calix[4]arene 73 with p-nitrobenzenediazonium tetraborate in the presence of pyridine and THF to give the bis-azobenzene derivative 74 in 42% yield (Scheme 25). Application of the above methodology permitted the preparation of calix[4]arene derivatives 75 and 76 with two propyl groups and a monocrown-6 moiety, respectively (Fig. 8).

Dumazet-Bonnamour et al. described the synthesis of azocalix[4]arenes containing bipyridyl subunits. A diazo-coupling reaction of calix[4]arene 77 with the diazonium salt led to the corresponding azobenzene derivative 78 in 66% yield (Scheme 26).
In 2000, Lamartine et al. reported the selective synthesis of new phenylazocalixarenes. A coupling reaction between the tetrazonium salt 81 and calix[4]arene 79 in pyridine and THF gave the azo dimer 80 in 15% yield (Scheme 27). Using the same procedure, compound 82 was also synthesized (Fig. 9).

Pritchard et al. reported the first synthesis and structural characterization of a tertiary phosphine containing an azo linkage. After treatment of the phosphine 83 with NaOH in ethanol, the arenediazonium tetrafluoroborate salt in MeCN was added to furnish the azo compounds 84 and 85 in 70% yield (Scheme 28). Isolation of arenediazonium salt was essential before addition to the anion of the tertiary phosphine in order to prevent undesirable reactions such as oxidation at the phosphorus atom or decomposition of the diazonium salt by quaternization.

Three years later, Pritchard et al. described the synthesis of some azo-containing phosphine chalcogenides. Treatment of the phenoxide anion of the phosphine derivative with benzenediazonium tetrafluoroborate did not lead to the azo compound but only the diphenylphosphine oxide was isolated. In order to obtain the target azobenzene derivative, the phosphorus atom was protected and the derivative 86 gave the corresponding azobenzene 87 in 60% yield (Scheme 29).

Having established that p-hydroxyphenyl(diphenyl)phosphine chalcogenides underwent azo-coupling reactions, Pritchard et al. then investigated the coupling reaction with a m-hydroxy analogue 88 (Scheme 30). Using the same procedure, the coupling reaction of 88 with the diazonium salt furnished a mixture of two azo compounds 89 and 90. The coupling reaction occurred at the expected ortho-positions to the meta-directing Ph2PS group. Using the non-selectivity of this coupling reaction, the authors described the synthesis of the bis-azobenzene derivative 91 in 58% yield.

Replacing the Ph2PS moiety with a formally ortho/para-directing methyl group was also studied by Pritchard et al. In contrast to compound 88, treatment of compound 92 with the diazonium salt gave selective coupling to afford the azobenzene derivative 93 in 56% yield. Starting from the azo compound 93, a second coupling gave the bisazobenzene 94 in 40% yield (Scheme 31).
2.5. Oxidation of hydrazo derivatives

The preparation of azobenzene derivatives has been reported by a stoichiometric oxidation process of hydrazo compounds using H$_2$O$_2$, O$_2$, MnO$_2$, sodium hydroxide, triarylphenol/potassium ferricyanide/sodium hydroxide, iron chloride, periodate resin, NaNO$_2$ in acetic anhydride, polyethylene glycol/nitrogen dioxide, and NaNO$_2$/NaHSO$_4$ on silica support. H$_2$O$_2$, O$_2$, MnO$_2$, sodium hydroxide, triarylphenol/potassium ferricyanide/sodium hydroxide, iron chloride, periodate resin, NaNO$_2$ in acetic anhydride, polyethylene glycol/nitrogen dioxide, and NaNO$_2$/NaHSO$_4$ on silica support.

The oxidation of hydrazine derivatives using H$_2$O$_2$ as oxidant was studied. Oxidation of hydrazobenzenes 95–97 with pyridinium tribromide gave the corresponding azobenzenes 98–100 in 100, 89, and 26% yields, respectively (Scheme 32). Similarly, the use of t-BuOCl as oxidant furnished the azobenzenes 98 and 99 in 61 and 45% yields. It was notable that hydrazobenzene 97 bearing a phosphine selenide moiety was not oxidized by t-BuOCl.

The oxidation of hydrazines using iron chloride was reported by Wang et al. Treatment of hydrazobenzene 33 with FeCl$_3$ as dehydrogenating agent in acetone furnished azobenzene (1) in 90% yield (Scheme 33). Application of this methodology permitted the preparation of the azo compounds 6 and 101–104 in 81–99% yields (Fig. 10).

Oxidation of hydrazobenzene was realized using a periodate resin by Rademann et al. The authors reported the synthesis of azobenzene (1) (88% yield) starting from hydrazobenzene (33) by treatment with the oxidizing periodate resin 105 (Scheme 36).

Much effort has been directed toward the development of sustainable chemistry by reduction of the solvent or the use of the resin. Recently, Mihara et al. reported the synthesis of azobenzene derivatives by dehydrogenation of hydrazo compounds using solvent-free conditions. Commercially available KF/alumina and hydrazobenzene (33) furnished the corresponding azobenzene (1) in 85% yield (Scheme 34).

2.6. Reduction of azoxybenzene derivatives

Selective deoxygenation of organic N-oxides is a subject of considerable interest in heterocyclic chemistry. In particular,
azoxybenzene derivatives were reduced with various reducing agents and with sulfuric acid via a Wallach rearrangement. Aly reported the synthesis of trans-azoxybenzene 111 by the reduction of a mixture of the E and Z azoxy compounds 110 with LiAlH4 in 82% yield (Scheme 38).92

Sanz et al. described the chemoselective deoxygenation of N-oxides 112 and 113 under mild conditions with common phosphines in the presence of dichlorodioxomolybdenum(VI) to furnish the corresponding azo compounds 1 and 114 in 97 and 96% yields, respectively (Scheme 39).93

Various metals were used to deoxygenate azoxybenzene derivatives. These methods were efficient, simple, and selective. Yus et al. reported the reduction of azoxy compounds using combinations of NiCl2/Li/DTBB as reducing agents.94 Starting from the azoxybenzenes 112 and 113, the corresponding azobenzenes 1 and 114 were obtained in 83 and 79% yields, respectively (Scheme 40). It was notable that the final products depend upon the reaction conditions used: for a short reaction time (1 h), the target compounds were isolated, whereas a longer reaction time (10 h) led to full reduction to the corresponding primary amines.

Konwar et al. described an efficient general system for the deoxygenation of azoxybenzene derivatives in aqueous media.95 Starting from the azoxybenzenes 112, 115, and 116, treatment with AlCl3·6H2O/KI in acetonitrile and water led to the azobenzenes 1, 11, and 103 in 71–75% yields (Scheme 41).

Reduction of azoxybenzene (112) using ruthenium(III) chloride in acetonitrile was described by Sandhu et al. to furnish the deoxygenated compound 1 in 82% yield (Scheme 42).96

A mild and efficient deoxygenation of azoxybenzene 117 was reported by Singh et al. using CuI and Zn powder in ethanol to give the azo compound 118 in 95% yield (Scheme 43).97

With an increasing focus on green methodologies, Sandhu et al. reported a safe and environmentally friendly procedure for the deoxygenation of azoxybenzene 112 using Zn(OTf)2 to give the corresponding azobenzene (1) in 70% yield. In this work, the use of Cu(OTf)2 instead of Zn(OTf)2 furnished compound 1 in 75% yield (Scheme 44).98
It was notable that the Wallach rearrangement using sulfuric acid induced the direct conversion of azoxybenzene $\textit{112}$ into the corresponding 4-hydroxyazobenzene ($\textit{119}$) (Scheme 45).99

2.7. Other methods

Different methods to obtain azobenzenes were reported using isocyanates or aryldiazonium salts and metal reagents or aryl hydrazines and quinones. Recently, only the last two methods were studied. In 1998, Fochi et al. developed the synthesis of azobenzene by an electrophilic coupling reaction of arenediazonium salts with Grignard reagents.100 Thus, treatment of the arenediazonium o-benzenedisulfonimide $\textit{120}$ with a solution of phenylmagnesium bromide ($\textit{121}$) afforded azobenzene ($\textit{1}$) in 71% yield (Scheme 46).

In order to find new organometallic compounds useful in organic synthesis, Dughera et al. studied the aforementioned strategy by replacing the Grignard reagent with a triorganoindium compound.101 Quinone chemistry is well documented, but only a few studies have been described for the synthesis of azobenzene starting from benzoquinone.102 Starting from the commercial bis-dimethyl acetal of p-benzoquinone ($\textit{122}$), the direct reaction of arylhydrazine $\textit{123}$ afforded the azobenzene $\textit{124}$ in 99% yield (Scheme 47).

In order to enhance the yield of the azobenzene derivatives, the presence of a one-electron oxidant such as a CAN reagent gave a remarkable increase in the reaction rate and yield. Tobe et al. reported the synthesis of azobenzene ($\textit{126}$), which was prepared by the reaction of 2-p-tolylsufinyl-1,1,4,4-tetramethoxy-2,5-cyclohexadiene ($\textit{125}$) and the hydrazine $\textit{123}$ in the presence of CAN in acetonitrile in 85% yield (Scheme 48).102

Recently, Kaneda et al. reported the treatment of p-nitrophenylhydrazine ($\textit{127}$) with benzoquinone $\textit{128}$ having an 18-crown-6 moiety to furnish the azobenzene $\textit{129}$ in 25% yield (Scheme 49).103

In 2006, azocalix[4]arene having azobenzene ($\textit{131}$) has been synthesized by Chawda et al.104 A non-diazo-coupling route was also used to synthesize azocalix[4]arene derivatives containing two free phenolic groups. Treatment of dibenzoylated calix[4]arene diquinone $\textit{130}$ with 4-nitrophenylhydrazine in the presence of sulfuric acid furnished the bis(nitrophenylazophenol) derivative $\textit{131}$ in 78% yield (Scheme 50).

Application of this strategy permitted the synthesis of the corresponding azobenzenes $\textit{132}–\textit{134}$ in 78–84% yields (Fig. 12).
3. Synthesis of azobenzene carbohydrates

Although many glycosides and azobenzene compounds have been studied over the past century, a surprisingly small number of reports regarding azobenzene derivatives having a glycone moiety are available. The different structures described in the literature associate an azobenzenyl group with one or several glycone moieties with or without a linker. The following two routes have been reported in the literature: (i) an azobenzene derivative was directly bound to the glycone part; and (ii) the azobenzene was prepared using standard methods starting from the glycosyl part bearing an aromatic substituent. The carbohydrate moiety comprises modified or natural pentoses, hexoses or cyclodextrins.

3.1. Carbohydrate derivatives having one azobenzene moiety

In order to control the color of dye aggregates, a novel azobenzene glycopyranoside 136 was reported starting from p-aminophenyl-α-D-glucopyranoside (135). This compound was an amphiphilic glycopyranoside containing an azobenzene chromophore and an amide-benzene auxochrome. Treatment of the azobenzene derivative 137 with oxalyl chloride and addition of the glycoside 135 furnished the target compound 136 in 35% yield (Scheme 51). It was notable that the carbohydrate derivative was used without protection. Compound 138 was obtained according to a similar method (Fig. 13).

Boullanger and Goodby have described the synthesis of amphiphilic azobenzene glycosides and a study of their liquid crystal properties. The authors described the synthesis of the
azobenzene moiety using the diazonium strategy in the area of carbohydrate chemistry. Starting from the per-O-acetylated 4-aminophenyl glycoside 139, formation of the corresponding phenyldiazonium tetrafluoroborate 140 was obtained in quantitative yield. Then, the salt 140 was condensed with N,N-didodecylaniline under phase-transfer conditions and the per-O-acetylated compound was fully de-O-acetylated by the Zemplen method to furnish the azobenzene 141 in 57% yield (two steps) (Scheme 52). Application of this methodology permitted the synthesis of the phenylazophenyl glycosides 142–145 (Fig. 14).

The synthesis of azobenzene-containing multivalent ligands has been described. Selective amide bond formation between an amine-tethered mannopyranoside derivative 146 and 4,4'-azobenzene dicarbonyl chloride (149) was performed in the presence of triethylamine to obtain the dissymmetrical compound 147 in 76% yield (Scheme 53). Classical deprotection of the glycone moiety furnished the targeted azobenzene 148 in quantitative yield. Development of this methodology led to the isolation of the monoamide 150 (Fig. 15).

In 2007, Dotz et al. described the synthesis of amphiphilic carbohydrate-functionalized Fischer carbene complexes having an azobenzene moiety as the hydrophobic part of the molecule.108 Starting from the azobenzene 151, the iodine/lithium exchange in diethyl ether followed by transmetallation to zinc, addition of hexacarbonylchromium and O-alkylation afforded the azobenzenechromium carbene 152 in 36% yield. Aminolysis of the methoxy-carbene complexe 152 with the glucamine derivative 153 furnished the protected itol 154 in 28% yield. Classical deprotection of the hydroxyl groups of compound 154 afforded the targeted azobenzene derivative 155 in 30% yield (Scheme 54).
Using the same methodology, Dotz et al. reported the synthesis of the amphiphilic azobenzene metal carbene 156 (Fig. 16). Novel cyclodextrins bearing azobenzene functional groups were reported in the literature. These structures associate the cyclodextrin moiety with the azobenzene via either O-ether, amido functions or via different links. Liu et al. reported the synthesis of novel cyclodextrins possessing an azobenzene functional group having an O-ether bond. Starting from the O-tosylate 157, etherification with alcohol 119 gave the corresponding ether 158 in 78% yield (Scheme 55).

Similar etherifications were reported in the literature starting from α- and β-cyclodextrins optionally methylated for the synthesis of the azobenzene derivatives 159–163 in 40–74% yield (Table 1).

Tian et al. reported the synthesis of azobenzene-modified β-cyclodextrin at the 2-position (165) starting from the corresponding 2-O-tosylate 164 by the addition of the azobenzene derivative 166 (Scheme 56). In 2008, Gin et al. described the synthesis of a novel azobenzene-modified β-cyclodextrin 168 in order to prepare a light-gated synthetic ion channel. Compound 168 had a butyl link.

Table 1
Synthesis of azobenzenes 159–163 starting from corresponding O-tosylate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>159</td>
<td>74</td>
<td>109</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>76</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>161</td>
<td>40</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>162</td>
<td>nd</td>
<td>111</td>
</tr>
<tr>
<td>5</td>
<td>163</td>
<td>38</td>
<td>112</td>
</tr>
</tbody>
</table>

Scheme 55. Reagents and conditions: (a) 4-phenylazophenol (119), DMF (78%).

Scheme 56. Reagents and conditions: (a) 4-iodophenylazophenol (166), K2CO3, DMF (nd).

In 2008, Gin et al. described the synthesis of a novel azobenzene-modified β-cyclodextrin 168 in order to prepare a light-gated synthetic ion channel. Compound 168 had a butyl link.
between the arene moiety and the CD derivative. The attachment of the tether at the secondary face of the β-cyclodextrin (167) was effected by deprotonation with sodium hydride and addition of the bromobutylazobenzene (169) to give the target modified β-cyclo-
dextrin 168 in modest yield (7%) (Scheme 57).

Kuwabara et al. reported similar work for the synthesis of azo-
benzene-modified cyclodextrins with various lengths of spacer be-
tween the cyclodextrin and the azobenzene.114 Starting from the
6-deoxy-6-amino-β-CD 170, treatment of a dimethylacetamide of 4-
hydroxyazobenzene-2-carboxylic acid, dicyclohexylcarbodiimide,
and 1-hydroxybenzotriazole furnished the corresponding azo-
benzene (Scheme 58).

Application of this strategy also permitted the synthesis of
the corresponding azobenzene-modified cyclodextrins 172–176 (Table 2).

Harada et al. described the synthesis of poly(ethylene glycol)-
substituted with an azobenzene group at the chain end. 115 Starting
from the poly(ethylene glycol) derivative 177, amidation using
p-aminoazobenzene (179) in water and DMF gave the corre-
sponding modified cyclodextrin 178 in 15% yield (Scheme 59).

The click chemistry116 was applied to the synthesis of an azo-
benzene-modified cyclodextrin starting from the azido compound
180.117 Using 4-propargylazobenzene (183), Huisgen 1,3-dipolar
cycloaddition was applied in hydrothermal conditions to give the
analogue 181 in 69% yield (Scheme 60). The isomer 182 was
obtained using a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition
in 71% yield. It was notable that Vargas-Berenguel et al. reported
the synthesis of the modified cyclodextrin 181 in 74% yield using
a similar method.112

Table 2
Synthesis of azobenzenes 172–176 starting from corresponding amine 170

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>172</td>
<td>nd</td>
<td>114</td>
</tr>
<tr>
<td>2</td>
<td>173</td>
<td>nd</td>
<td>114a</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>1</td>
<td>114b</td>
</tr>
<tr>
<td>4</td>
<td>175</td>
<td>15</td>
<td>114b</td>
</tr>
<tr>
<td>5</td>
<td>176</td>
<td>23</td>
<td>114b</td>
</tr>
</tbody>
</table>

Scheme 58. Reagents and conditions: (a) HABA, DCC, HOBt (nd).

Scheme 59. Reagents and conditions: (a) compound 179, H2O, DMF (15%).

Scheme 60. Reagents and conditions: (a) compound 183, EtOH, H2O, 85 °C (69%); (b) compound 183, CuSO4 5H2O, sodium ascorbate, EtOH, H2O (71%).
3.2. Dimers and polymers linked with one azobenzene moiety

The synthesis of azobenzene-containing multivalent ligands has been described. Amide bond formation between an amine-tethered mannopyranoside derivative 184 and 4,4'-azobenzene dicarbonyl chloride 149 was performed in the presence of triethylamine to obtain the symmetrical diamide 185 in 89% yield. Classical deprotection of the glycone moiety furnished the targeted azobenzene 186 in quantitative yield (Scheme 61).

The same strategy was applied to extend the series of compounds to include the mannopyranoside and lactoside derivatives 187–189 (Fig. 17).107 Similarly, azobenzene 3,3',5,5'-tetracarbonyl chloride (190) led to the azobenzene derivatives 191–193 (Fig. 18).107

Recently, dimers of cyclodextrin linked by an azobenzene moiety were reported in the literature. Liu et al. described the synthesis of bridged bis(β-cyclodextrin) with an azobenzene dicarboxylate linker starting from native β-cyclodextrin 194.118 Treatment of β-cyclodextrin 194 with 3,3'-azodibenzoic acid 196 in presence of

![Scheme 61](image1.png)

![Scheme 62](image2.png)

Figure 17. Azobenzene derivatives 187–189 having glycone part.

Figure 18. Azobenzene 3,3',5,5'-tetracarbonyl chloride (190) and derivatives 191-193 having glycone part.
DCC and molecular sieves afforded the corresponding dimer 195 in 25% yield (Scheme 62).

In order to obtain a bisdansyl-modified \( \beta \)-cyclodextrin dimer linked by azobenzene, Hamada et al. reported the synthesis of dimer 198.\(^{119}\) Starting from 4,4’-azidobenzoic acid (49) in the presence of DCC and HOBr, addition of the modified cyclodextrin 197 furnished the dimer 198 in 32% yield (Scheme 63).

```
\[
\begin{align*}
\text{NH} & \quad \text{NH}_2 \\
\beta-\text{CD} & \quad a \\
\text{NH} & \quad \text{NH}_2 \\
\beta-\text{CD} & \quad b
\end{align*}
\]
```

Scheme 63. Reagents and conditions: (a) 4,4’-azidobenzoic acid (49), DCC, HOBr, DMF (32%).

In 2008, Vargas-Berenguel et al. reported the synthesis of dimer 199 via the click chemistry strategy.\(^{112}\) A \( \beta \)-cyclodextrin moiety was bound to the azobenzene moiety by the reaction of 6-deoxy-6-azido-\( \beta \)-cyclodextrin (180) with 4,4’-dipropargyloxyazobenzene (200) in the presence of (EtO)\(_2\)P\(\text{Cu} \) in DMF to afford the corresponding 1,2,3-triazole-linked azobenzene-cyclodextrin derivative 199 in 72% yield (Scheme 64).

```
\[
\begin{align*}
\text{N}_3 & \quad \text{O} \\
\beta-\text{CD} & \quad a \\
\text{O} & \quad \text{N} \\
\beta-\text{CD} & \quad b
\end{align*}
\]
```

Scheme 64. Reagents and conditions: (a) 4,4’-dipropargyloxyazobenzene (200), (EtO)\(_2\)P\(\text{Cu} \), DMF (72%).

4. Conclusions

Azobenzenes and carbohydrates are two families of organic compounds widely developed but few studies have associated them. This review updates the major preparations of azobenzene derivatives and the association of a phenylazophenyl group with a glycone moiety such as monosaccharides, itol, and cyclodextrins covering the literature from 1998 to 2009. Although a lot of effort has been devoted to the development of azobenzenes, no general reaction was obtained. Two methods of choice for the synthesis of azobenzenes were developed: (i) creation of the azo bond by coupling two identical or non-identical aromatic compounds;\(^{19–71}\) and (ii) creation of the azo bond by oxidation of hydrazo compounds\(^{22,73,76,77,78}\) or by reduction of azoxybenzene derivatives.\(^{92–99}\)

Between the two methods described above, two classes of derivatives can be obtained: the symmetrical and the disymmetrical azobenzenes. The synthesis of symmetrical azobenzene derivatives was effected by: (i) oxidation reactions of aromatic primary amines;\(^{19–30}\) (ii) reduction reactions of aromatic compound having nitro groups;\(^{32–36}\) (iii) diazo-coupling via diazonium salts;\(^{54–71}\) and (iv) coupling reactions with arenediazonium salts.\(^{100,101}\) The synthesis of disymmetrical azobenzene derivatives was effected by: (i) oxidation reactions of aromatic primary amines;\(^{31}\) (ii) coupling of primary arylamines with nitroso compounds (Mills reaction)\(^{37–55}\) and (iii) coupling reactions with arenediazonium salts.\(^{100,101}\) Starting from hydrazo compounds, the oxidation furnished symmetrical azobenzenes\(^{72,73,76,77}\) and disymmetrical azobenzenes.\(^{72,73,76,77}\)

Starting from azoxybenzene compounds, the reduction furnished symmetrical azobenzenes\(^{92–99}\) and disymmetrical azobenzenes.\(^{94}\)

The association between a glycone moiety (e.g., monosaccharides, itol, and cyclodextrins) and a phenylazophenyl group with or without a linker was described, furnishing photomodular structures. Two target families were reported having either one glycone moiety and one phenylazophenyl group\(^{105–115,117}\) or two glycone parts and one phenylazophenyl group.\(^{107,112,118,119}\) All of these syntheses were effected by coupling between azobenzene derivatives and carbohydrate derivatives.\(^{106,105–115,117–119}\)

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Francis Barbot was born in Saint-Front (France) in 1946. He received his Ph.D. (1972) and his "Doctorat-ès-Sciences Physiques" (1980) from the University of Poitiers (France) under the supervision of Professor Ph. Miginiac in the field of organometallic chemistry. Since 1974, he has been a chemist ingenior (C.N.R.S.). Up to 2000, he worked on the reactivity of \( \alpha \)-unsaturated organometallic compounds with carbonyl derivatives with particular attention to organoaluminum compounds. Since 2000, he joined UMR 6514 and worked first on dipolar cycloaddition reactions with Professor G. Bashiardes, then on the synthesis of azobenzene derivatives with Professor Ch. Len using, whenever possible, microwave-assisted synthesis. He has 42 publications in international journals.

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