Azo group(s) in selected macrocyclic compounds

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Abstract
Azobenzene derivatives due to their photo- and electroactive properties are an important group of compounds finding applications in diverse fields. Due to the possibility of controlling the trans–cis isomerization, azo-bearing structures are ideal building blocks for development of e.g. nanomaterials, smart polymers, molecular containers, photoswitches, and sensors. Important role play also macrocyclic compounds well known for their interesting binding properties. In this article selected macrocyclic compounds bearing azo group(s) are comprehensively described. Here, the relationship between compounds’ structure and their properties (as e.g. ability to guest complexation, supramolecular structure formation, switching and motion) is reviewed.

Keywords Macrocyclic compounds · Azo group · Trans–cis isomerization · Host–guest interactions · Molecular switches

Introduction
The year 2017 appears to be a very special for supramolecular chemistry. 50 years ago Charles Pedersen [1] published papers describing the syntheses and completely untypical and unknown until that time intriguing complexing properties of macrocyclic polyethers, i.e. crown ethers [2, 3]. The discovery turned out to be a milestone in chemistry that changed the whole chemical world, gave new fascination and opened up new perspectives for science and technology. Crown ethers are excellent example of unexpected discovery that gained worldwide fame. Since discovery of crown ethers, many their applications have been developed, for example in chromatography [4, 5], sample preparations [6], catalysis [7–9], and chemical sensing [10].

Macrocyclic compounds had entered the laboratories all over the world, in particular after the discovery of macrocycles containing oxygen and nitrogen electron donors, being the base for three dimensional cryptands, synthesized and studied by Lehn [11, 12] and spherands, obtained and investigated by Cram [13–16]. All these discoveries initiated host–guest [17, 18] and supramolecular chemistry [19–22]. For their achievements Pedersen [23], Cram [18] and Lehn [20] were honored in 1987 with a Nobel Prize. The Nobel Prize in Chemistry 2016 was awarded to: Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Ben L. Feringa “for the design and synthesis of molecular machines” [24–26], which have close relationship with the above mentioned branches of chemistry.

A year after Pedersen’s publication on crown ethers and their unique metal cation binding abilities, Park and Simmons published work on macrobicyclic amines i.e. catapinands, the first anion receptors [27–29]. Since that time supramolecular chemistry of anions for many years seemed to be almost forgotten, but last two decades were a renaissance of anion recognition studies [30–33].

Within the last 50-years a lot of macrocyclic compounds of sophisticated structures have been synthesized and investigated [34]. The skeleton of the vast majority of macrocycles can be more or less easily modified by introducing functional groups, which bring about additional chemical or physical features in comparison to the parent compounds as well as...
to the respective supramolecular species. Functionalized supramolecular systems can be applied in many branches of science and life [35], including e.g. the development of new analytical [36–41] and therapeutic [42–44] systems, modern, intelligent (nano)materials [45–50] and molecular devices and machines [51–57].

One of the most convenient and useful functionalization of macrocyclic compounds is the introduction of azo group(s): incorporated in the ring or on its periphery. Azo moiety due to its ability to alter the geometry upon photochemical or thermal trans–cis isomerization can be utilized as a light triggered switch in vast variety of functional materials such as for example molecular containers, polymers, supramolecular protein channels, and sensors. As upon photoisomerization process of azo bearing molecules electromagnetic radiation is converted to mechanical work, those compounds can be used in light-driven molecular machines. Here, we present an extensive review of selected azomacrocyclic compounds with the special focus on supramolecular interactions (host–guest complex formation, self-assembly) and trans–cis isomerization of azo group.

Azobenzene and its derivatives

The properties and functions of the supramolecular systems can be controlled by external stimuli such as changing of pH, temperature, irradiation with the selected wavelength, action with electric or magnetic field. For specific goals, moieties sensitive to one or more of the above factors must be present or introduced to macrocycle structure upon its functionalization. The synthetic routes leading to macrocyclic compounds are often laborious, hence additional functionalization preferably needs relatively simple procedures. A nice example of relatively easy-to-implement functional unit with photo- and redox active properties is the azo group –N\(=\)N–, which is also pH sensitive.

Azo compounds are one of the oldest synthesized organic compounds, being produced till now on a large scale in dye industry [58]. The main synthetic approach is based on diazotization reaction discovered by Peter Griess in nineteenth century. The most common methods of azo group incorporation are schematically shown in Fig. 1. Nowadays, diverse modifications of the original process of diazocoupling are available; also new, synthetic procedures are proposed for preparation of azo compounds for varied purposes [59–66], including methods identified as environmentally friendly [67–69].

Colored azobenzenes and their more sophisticated derivatives, among others, can undergo light-driven reversible trans–cis (\(E\Rightarrow Z\)) isomerization. The reversible \(E\Rightarrow Z\) photoisomerization of azobenzene presents well-understood process widely used for construction of light-driven functional molecules for energy storage or conversion of light energy into mechanical motion, exemplified by molecular devices and machines [70]. cis isomer of azobenzene was discovered in 1937 by Hartley [71]. Trans (E) and cis (Z) azobenzene isomers are shown in Fig. 2 that also illustrates the reversible isomerization.

Trans isomer of azobenzene is thermodynamically more stable than the cis isomer. In most cases trans\(\rightarrow\)cis isomerization occurs upon irradiation with UV light (Fig. 2a). However, azobenzene derivatives undergoing reversible trans\(\Rightarrow\)cis isomerization upon visible light illumination have been also reported [72–74]. Such molecular switches are more applicable and safer for biological uses where harmful ultraviolet light should be avoided.

The cis\(\Rightarrow\)trans isomerization may occur by spontaneous thermal back reaction or reverse photoisomerization cycle.

The light-driven reversible \(E\Rightarrow Z\) isomerization of azobenzene is associated with substantial changes of structure, size, geometry and physical properties. Structural changes of azobenzene moiety inbuilt into a larger or more complicated compound affect also the behavior and properties of the azo-functionalized molecular systems like it is for example in photoswitches.

Dipole moment of trans isomer of azobenzene is near zero. cis isomer of azobenzene has dipole moment 3.1 D, what determines hydrophobic/hydrophilic character of isomers. Trans (E) azobenzene is almost planar, opposite to...
cis (Z) isomer. In solid state in cis azobenzene the parallel phenyl rings are twisted 56° out of the plane of the azo group (Fig. 2). The different geometry of trans and cis isomers of azobenzene affects their UV–Vis spectra. The spectra (Fig. 2c) of trans and cis isomers are overlapping, but differ significantly. Band at ~440 nm originating from n→π* transition is more distinct for cis isomer. Strong absorption band at ~320 nm for trans isomer can be attributed to π→π* transition. In a spectrum of cis-azobenzene less intensive π→π* transition bands are observed at lower wavelength. The spectral differences cause different colors of both isomers, what makes the observation of isomerization process possible also in non-instrumental manner (by naked eye). Spectral properties of azobenzene derivatives are strongly dependent on the substituents in phenyl rings.

Azobenzene can also act as an important functional unit if incorporated into electrochromic materials (ECMs), which properties can be stimulated by applied potential. Such substances are outstanding candidates for materials used for production of electronic paper [75–78] or dual-stimuli-responsive systems [79, 80].

The electrochemistry of azobenzene and its derivatives in different solvents was studied exhaustively in details for both trans and cis isomers [81–85]. It was found that the electrochemical reduction of azobenzene is strongly dependent on conditions, such as type of the solvent, pH or reagent concentrations. However, in general it can be summarized that the reduction of azobenzene occurs in a single two electrons, two protons process with a final formation of hydrazobenzene. The simplified way of the electrochemical reduction of azobenzene is shown in Scheme 1.

The properties of self-assembled monolayers of azobenzene derivatives—also macrocyclic—on different surfaces [86–92] showed, that such materials are promising candidates for molecular devices for energy storage and conversion.

**Cyclic and macrocyclic derivatives of azobenzene(s)**

**Small rings**

Derivatives of cinnoline 1, e.g. benzo[c]cinnoline 2 (Scheme 2) can be considered as structural, cyclic analogs of azobenzene. These compounds are used in manufacturing of dyes, electrochromic polymers, coloured polyamide fibers and have microbial and herbicidal activities [93, 94]. Cinnolines were also studied as potential anticancer agents [95, 96]. The reduction of 2,2′-dinitrobiphenyl to
3,4-benzocinnoline (benzo[c]cinnoline) 2 (Scheme 2) was first described by Wohlfart [97] and later by other groups [98–107].

The crystal structure of benzo[c]cinnoline complex with ytterbium Yb(BC)₃(thf)₂ (BC = benzo[c]cinnoline) was described [108]. Fe₂(BC)(CO)₆ complex was examined as a candidate for a new structural and functional model for [FeFe]-hydrogenases [109, 110].

Modified with benzo[c]cinnoline or its derivatives surfaces of e.g. glassy carbon [111, 112], gold [113] or platinum [114, 115] are often used in organic, inorganic, and biochemical catalytic transformations.

Öztürk et al. [116] reported an amperometric lactate biosensor based on a carbon paste electrode modified with benzo[c]cinnoline and multiwalled carbon nanotubes. Its characteristics showed, that it can be used for determination of lactate in human serum. Incorporation of benzo[c]cinnoline moieties into poly[2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene] (MEH-PPV) indicated that p-type semiconductors based on the above polymer can be transformed into n-type materials [117].

Larger analog of cinnoline, (5,6-dihydrodibenzo[c,g][1,2]diazocine) (Fig. 3, compound 3) comprising azobenzene moiety joined by ethylene bridge at 2,2′-positions was identified as a molecular switch with interesting photochemical characteristics [118–120].

Interestingly, in this case cis isomer is thermodynamically more stable than trans isomer. Remarkably, both isomers of 3 have well pronounced n→π* bands in UV–Vis absorption spectra. Reversible trans to cis photoisomerization occurs with efficiency close to 100% under the illumination with visible light of 480–550 nm. The back process of rapid kinetics can be achieved at near ultraviolet at 380–400 nm.

**Cyclic oligomers of azobenzene (oligoazobenzenophanes)**

Oligoazobenzenophanes are compounds consisting of at least two or more azobenzene units forming macrocycles. Azobenzene moieties can be joined in para-, meta- or ortho-positions by sp³ hybridized spacers with or without heteroatoms forming relatively flexible, non-conjugated azobenzenophanes (Fig. 4a). More rigid, conjugated azobenzenophanes are obtained by joining azobenzene units without sp³ tether. As an example of conjugated azobenzophane the simplest cyclotriazobenzene is shown in Fig. 4b.

Synthetic procedures leading to azobenzenophanes involve also approaches typical for macrocyclization, e.g. high dilution technique or template synthesis. The formation of azo group can be the final step of ring closure or can be achieved from substrate(s) bearing functional group(s) by substitution or condensation reactions. An exhaustive review on synthetic protocols was published by Reuter and Wegner [121] that shows preparation of vast varieties of azobenzophane skeletons by cyclizations based on nucleophilic reactions, Schiff bases condensations, reductive or oxidative azocouplings, palladium catalyzed N-arylations, and electrophilic aromatic substitutions of diazonium salts.

The utility of azobenzenophanes lies in reversible photoisomerization. Opposite to azobenzene for which only two possible states Z or E can be achieved by photoisomerization, macrocyclic azobenzenophanes offer multiple molecular states, depending on the number of azo units. For example, for azobenzophane composed of two azobenzene fragments three states can be considered: E,E, E,Z and Z,Z (Fig. 4c) with the ratio of the isomers depending on e.g. the structure of macrocycle and photoisomerization conditions. The simplest conjugated azobenzophane cyclotriazobenzene 4 (Fig. 4b) exits only in all-E form and has no tendency to be converted into Z form under illumination [121]. Unusual behavior of cyclotriazobenzene was exhaustively

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**Fig. 3** a 5,6-dihydrodibenzo[c,g][1,2]diazocine (3): equilibrium structures of 3Z and 3E in the electronic ground states from quantum chemical calculations at the B3LYP/def2-TZVP level of theory using the TURBOMOLE program and b colors of 3Z before irradiation and color 3E upon irradiation in n-hexane. Adapted with permission from [119]. Copyright 2009 American Chemical Society

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investigated by Dreuw and Wachtveitl [122]. According to experimental and theoretical studies on ultrafast dynamics of this macrocycle the authors stated that the structural constraints prevent isomerization of azo units. The azo bonds respond elastically to the motion along the isomerization coordinates leading to complete and ultrafast dissipation of the UV excitation as heat. It was proposed that the molecules of this type can be used as UV absorbers e.g. in sunscreens.

Azobenzophanes of various structures are studied inter alia as metal cation complexing reagents. Tamaoki and co-workers [123] have obtained a series of azobenzophanes 6–8 (Fig. 5) by reductive macrocyclization of bis(3-nitrophenyl) methane under high dilution conditions. Macrocycles constructed of two, three or four azobenzene units with methylene linkers were isolated as all-E isomers. For comparative studies trans-3,3′-dimethylazobenzene 5 was prepared (Fig. 5).

![Fig. 4](image_url) Azobenzophanes, schematic view: a joined in para-, meta- and ortho- positions (E,E isomers), b the simplest conjugated azobenzophane: cyclotrisazobenzene, c reversible isomerization of azobenzophanes

![Fig. 5](image_url) a Azobenzophanes 6–8 and acyclic compounds 5 and 5′ obtained by Tamaoki and co-workers [123, 124], b the position of π→π* and n→π* absorption bands in UV–Vis spectra (benzene) of macrocyclic compounds 6–8 and acyclic analogs 5 [123]
The position of UV–Vis absorption maxima for compounds 6–8 and 5 registered in benzene are ring size dependent. The shift of the main band (π→π*) towards longer wavelength can be ordered as follows: 8 > 7 > 6 and reverse order for n→π* (cf. Fig. 5b) and can be associated with steric distortion of the azobenzene moieties. The position of the main absorption band of the largest compound 8 is comparable to a spectrum of open chain analog trans-3,3’-dimethylazobenzene.

The UV–Vis spectra of all-trans 6 macrocycle and all-trans isomer of acyclic dimer 5’ (Fig. 5a) in acetonitrile are compared in Fig. 6 [124]. The same Figure shows also changes upon irradiation with 313 nm wavelength light.

Photoisomerization of macrocycles 6–8 (Fig. 5) and acyclic compound 5′ from all-trans(E) to all-cis(Z) isomers proceeds gradually via respective trans(E)/cis(Z) isomers (depending on the number of azo groups). Comparison of UV–Vis spectra of macrocycle 6 trans/trans, and its acyclic analog 5′ is shown in Fig. 6 (left). Photoisomerization studies of all-trans isomers of compounds 6–8 showed that the ratio of all-cis isomers is irradiation wavelength dependent. The increase in quantity of cis azobenzene units upon irradiation at 366 nm and decrease at 436 nm was observed for 7 and 8 in chloroform. Similar behaviour was found for photoisomerization of 6 in acetonitrile. The ratios of isomers at the photostationary state for compounds 6–8 are schematically shown in Fig. 7a–c [123].

It was found that macrocyclic compounds 6–8 form complexes with alkali metal cations in methanol (determined by mass spectrometry, MS ESI). For all-trans isomers the highest peak in mass spectra was observed for cesium complexes; peak intensities for particular macrocycles can be ordered as: 6 > 7 > 8. The observed trend was disturbed upon irradiation when cis isomers also participate in complex formation. It was explained by the softer character of trans isomers. However, the clear relationship: the intensity of peaks versus ion diameter in correlation with the size of macrocycle ring was not defined. It was concluded that other factors than only host–guest geometrical complementarity affect the binding strength of metal cations by azobenzophanes 6–8 [123].

Norikane et al. [125] obtained azobenzophanes 9 and 10 (Fig. 8), having structures similar to 6–8 (Fig. 5). The modification of the macrocyclic skeleton by attaching...
long alkoxy chains resulted in photoresponsive liquid crystallinity.

The effect of different bulky substituents on the properties of azobenzophanes having the same macroring size was investigated by Mayor and co-workers [126]. Four $m$-terphenyl compounds 11–14 (Fig. 9) comprising different peripheral substituents were synthesized by multistep reactions, and different strategies, with the final step of reductive macrocyclization (LiAlH$_4$, THF, r.t.) of the respective nitro compounds. Compounds 11–13 are symmetric opposite to derivative 14 with two different substituents at peripheral positions.

Fig. 7 The ratios of isomers at the photostationary state (PPS) at various wavelength irradiation for a 6 in acetonitrile, for b 7 in chloroform and c 8 in chloroform [123]

Fig. 8 Azobenzophanes obtained by Norikane et al. [125]

Fig. 9 Bulky azobenzophanes synthetized by Mayor and co-workers [126]
The structures of obtained macrocycles were confirmed spectroscopically and the molecular weights of oligomers were determined by vapor pressure osmometry. UV–Vis spectra registered for macrocycles 11–14 in THF are shown in Fig. 10 (left) [126].

Similar shape of spectra, i.e. $\pi \rightarrow \pi^*$ $\sim$350 nm and $n \rightarrow \pi^*$ $\sim$450 nm was found for all compounds, although below 300 nm in UV–Vis spectra of macrocycles 11–14 the differences are more pronounced. The blue shift of absorption bands for compounds 12 and 13 can be attributed to the effect of substituents on the central phenyl rings. UV–Vis spectra of 11–14 undergo changes upon illumination (313 nm, in THF). For all compounds comparable changes were observed, what is exemplified for 11 in Fig. 10 (right). The photostationary state was reached within 8 min. Photoisomerization is observable in UV–Vis spectra by the decrease of the $\pi \rightarrow \pi^*$ and the increase in the $n \rightarrow \pi^*$ absorption bands upon irradiation over time. These changes are associated with the formation of Z isomer. Photoisomerization was monitored by $^1$H NMR measurements along with UV–Vis experiments (Fig. 11). By integration of the corresponding $^1$H NMR signals the amounts of E isomer at the photostationary state was determined to be 15%. In all cases no intermediate $E,Z$ isomer was observed as it was in the case of similar systems studied by Tamaoki [123]. This property can be attributed to the extremely rigid structure of macrocycles 11–14. The back $Z \rightarrow E$ isomerization proceeds upon illumination or thermally. The Z isomers of the
macrocycles 11–14 are stable pointing to very slow thermal back-reaction (the rate constant $1.15 \times 10^{-6}$ s$^{-1}$). The reversibility of the photoisomerization was investigated under illumination (450 nm). Contrary to the thermal-back process, under which macrocycles were fully converted back to $E$ isomers, upon light stimuli ~15% remain in their $Z$ form. However, this process seems to be reversible what was confirmed by experiments performed in several cycles.

The effect of the strain in azobenzophanes on the photoisomerization of azobenzene unit is well seen in cyclotriazobenzenes, a special class of azobenzenophanes, in which all azobenzene units are conjugated. The simplest compound of this class has been already shown in Fig. 4b. Wegner and co-workers [127] prepared bromo- and $t$-butyl derivatives of the simplest cyclotrisazobenzene 4 using o-phenylenediamine as a substrate (Scheme 3).

Irradiation of 4, 15 and 16 (Scheme 3) showed no isomerization under various conditions. The unfavorable change of geometry upon possible photoisomerization should result in extreme strain in the macrocyclic skeleton, thus 4, 15 and 16 exist only as all-$E$ isomers [cf.122]

Light controlled sol–gel transition of azobenzene bismacrocycle 17 (Fig. 12) was described by Reuter and Wegner [128].

Due to significant $\pi-\pi$-stacking interactions macrocycle 17 forms 3D networks. Its gelation was observed in aromatic solvents, attributable to the incorporation of the solvent molecule inside the 3D $\pi$-stacking network. After UV irradiation at 365 nm the gel in o-xylene slowly liquefies as a result of dissociation of 3D network. The gel–liquid conversion of 17 upon irradiation till now is the first example of switchable 3D system which was controlled by two factors: incorporation of azobenzene units and non-covalent interaction, namely $\pi$-stacking of the azobenzene macrocycles. The proposed system can be potentially used in process where small molecules are released from the 3D network upon light stimulation.

In photoswitchable cyclic azobenzenes several factors such as ring strain and the number of azo units are crucial for photochemical properties. These features depend also on rigidity and the position of linkers connecting the azobenzene units, the symmetry of the macrocycle and the degree of bonds conjugation. If at the beginning, i.e. before the illumination, a compound with several azo units is fully symmetrical in all-$E$ configuration, the change of one of the azo groups into $Z$ isomer affects the geometry of the macrocycle. The more azo units in macrocycle the more configuration variations (number of isomers) and geometrical changes can be expected. Wegner and co-workers [129] investigated the effect of symmetry changes on the photostationary state upon $E \rightarrow Z$ isomerization stimulated by both light and temperature. For this purpose they used macrocycle 18 with four azo moietyes shown in Fig. 13. The isomerization of 18 was monitored by UV–Vis measurements and $^1$H NMR spectroscopy with in situ light irradiation. 18 in THF exists in the form of all-$E$ isomer. Upon irradiation of this solution (125 μM) at 424 nm for 73 min. a mixture of five among six possible isomers was detected: the starting all-$E$ (21%), $E,E,E,Z$ (49%), $E,E,Z,Z$ (19%), $E,Z,E,Z$ (7%), and $E,Z,Z,Z$ (4%). Under elevated (50 °C) temperature, at photostationary state, much higher ratio of the all-$E$ isomer (55%) was detected, but lower quantities of $E,E,E,Z$ (32%), $E,E,Z,Z$ (4%) and $E,Z,Z,Z$ (1.7%) isomers and almost unchanged

![Scheme 3](image.png)

**Scheme 3** The general synthetic route for preparation of cyclotrisazobenzenes 4, 15 and 16 reported by Wegner and co-workers [127]
amount of E,Z,E,Z (6.8%) isomer. It was concluded that at photostationary state the E,E,Z,Z isomer is favored over the E,Z,E,Z isomer. Comparison of the rates of thermal back isomerization reveals that the E,Z,E,Z isomer has the highest and the E,E,Z,Z isomer the lowest thermal stability. This can be ascribed to the ring strain of the particular forms. Different states can be achieved by the arrangement of the azo groups in macroring reflecting the overall symmetry of the molecule without introduction of additional substituents or applying different wavelength of the light used for illumination.

Interesting, well organized system utilizing highly ordered pyrolytic graphite (HOPG) based on the photosensitive macrocycle 19 (4NN-M, Fig. 14) immobilized in the TCDB network was obtained and investigated by Wang and co-workers [130]. Upon UV illumination of the prepared material E,E,Z and E,Z,E,Z isomers are present at photostationary state. The proposed methodology was found to be useful for fabrication of nanostructures and can be valuable for production of photosensitive nanodevices.

A ternary switch utilizing chiral macrocycle was presented by Reuter and Wegner [131]. They obtained both enantiomers R and S and racemic form of chiral bimesitylclootrisazoiphenyl compound 20 (Fig. 15) in about 40% yield.

Three different photostationary states were gained by irradiation of 20 with different UV (302 and 365 nm) and visible light. The photoisomerization was investigated by CD spectroscopy. A large increase in the optical rotation angle for (S)-20: [α]20_D = 2128° and for (R)-20: [α]20_D = −2077° in comparison with acyclic 3,3′-diaminobismesityls come from the helical shape of macrocyclic compounds. All E-isomer was obtained by heating samples of (S)-20 and (R)-20 at 45 °C overnight. CD spectra of two all-E enantiomers are mirror images with four different absorption maxima. Upon irradiation of all E-isomer of (S)-20 with three different wavelength the photostationary state was reached after ~15 min. For (S)-20 seven different isomers were detected by 1H NMR measurements: six species being different E/Z isomers (one (E,E,E), two (E,E,Z), two (E,Z,Z), and one (Z,Z,Z)). The seventh one was described as a stable conformer of the (E,E,Z)-isomer with azo bond next to the bimesityl unit in Z-form. The different ratio of these isomers at particular photostationary state is manifested in CD spectra that varied mostly in intensities, but with preserved similar overall shape. However, a difference can be observed at 275 nm, when irradiating sample with mentioned above three different wavelengths: at 302 nm—positive value, visible light—no dichroism, at 365 nm negative value what is promising for ternary switch with +, − and 0 output (Fig. 15, bottom).
Crown ethers with azobenzene moiety(-ies)

Azobenzene unit incorporated into crown ethers skeleton was first reported by Takagi and co-workers almost 40 years ago [132, 133]. Azo bearing crowns 21–24 (Fig. 16a) were obtained by Williamson reaction from dihydroxyazobenzene and alkylating agents. The synthesis of this type of compounds (21–23, Fig. 16a) was also elaborated in details by Biernat and co-workers [134–140]. Reductive macrocyclization of dinitropodands allowed the preparation of vast number of macrocyclic compounds showing diverse properties. By this method azoxycompounds are formed next to azocompounds. They were studied e.g. as ionophores in ion-selective membrane electrodes and chromogenic agents for metal cation complexation. At first glance—these simple compounds bring a great potential in supramolecular chemistry not only as metal cation complexing properties, but also due to photosensitivity. There are also known crown ethers with azo group located at the periphery of the molecule with brilliant example of so called “butterfly crown ethers” obtained and investigated by Shinkai et al. [141, 142]. These photo-switchable compounds were used for light-driven transport of potassium and sodium. Figure 16b shows the scheme of light-driven transport of potassium cations across organic bulk membrane with the use of photoresponsive azobis(benzo-15-crown-5) 25.

These early works on azo group bearing crown ethers inspired further development of synthetic methods, challenging functionalization, and studies (both experimental and theoretical) of properties and finally applications of macrocyclic polyethers.

Crown ethers with inherent azobenzene group(s)

Among the first synthesized crown ethers with azo unit incorporated into the macrocycle were so called “all or nothing” crown ethers exemplified by 26 (Fig. 17) obtained by Shinkai et al. [141, 143]. These photoswitchable
compounds form complexes with metal cations with affinity that depends on the geometry of azo group. The *cis* isomer obtained by illumination binds cations, whereas in the dark the cation is released due to decreasing the cavity size being a consequence of isomerization to *trans* form. The spectral behavior of "all or nothing" crowns of different size of the macrocycle and their ability to form complexes with alkali metal cations was later studied theoretically.

Fig. 16  a Crown ethers 21–24 with inherent azo group (Takagi’s and Biernat’s group) [132–140] (b) 25 - azobis(benzo-15-crown-5) an example of butterfly crown ethers obtained and studied by Shinkai [141, 142]

Fig. 17  Example of “all-or nothing” photoswitchable crown ether 26 [141, 143]

Fig. 18  Azobenzene embedded *N*-(11-pyrenyl methyl)aza-21-crown-7, 27 studied by DFT by Wang and co-workers [145]
using density functional theory (DFT) [144]. The results showed good agreement between experimental and computational attempts.

Computational methods were also used by Wang and co-workers [145] to study trans-azobenzene embedded N-(11-pyrenyl methyl)aza-21-crown-7 27 (Fig. 18) as a fluorogenic receptor for alkaline-earth metal cations.

According to density functional theory using B3LYP/6-31G(d) it was determined that the ether chain of trans isomer of the compound becomes almost a straight line forming a strip crown ring. Calculated structure of cis isomer shows cavity enables coordination of metal cation inside the macrocycle. The optimized structures of complexes of the host molecule and alkaline earth metal cations (Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, and Ba$^{2+}$) indicate that the ligand binds calcium cations the strongest due to the best match of ion radius to the cavity size. These results showed, that proposed system can act as molecular device of double function.

Tamaoki and co-workers [146] studied the effect of trans–cis isomerization of [5.5](4,4′)azobenzeno(1,5)naphthalenophane 28 (Fig. 19) on silver(I) complexation. The resolved crystal structure of 1:1 complex showed that two silver cations are complexed to form dimeric structure with azobenzenonaphthalenophane in trans form (Fig. 19 left).

$^{1}$H NMR studies showed that complexion of silver cation is controlled by reversible trans–cis isomerisation of azo moiety; photoisomerization of trans to cis isomer causes the cleavage of the π–cation interaction. The opposite change was found under reverse isomeriation (Fig. 19, right).

Kirichenko and co-workers [147] described synthesis and complexing properties of four crownophanes 29–32 (Fig. 20) containing 2,7-dioxyfluorenone and 4,4′-azobiphenoxy groups joined with di-, tri-, tetra-, and pentaethylene glycol moieties. Based on NMR, UV–Vis, and X-ray data it was concluded that all macrocycles exist in solution and in solid state in trans-configuration of azobenzene unit. The trans to cis isomerization of 30 can be achieved by UV-light (365 nm) irradiation.

Macrocycles 30–32 bind 4,4′-dimethylbipyridinium (paraquat) bis(hexafluorophosphate), an electron-deficient model compound. The derivatives of this compound are used in synthetic procedures leading to interpenetrating complexes (pseudorotaxanes). Complex formation of paraquat with macrocycles is based on π–π interactions between π-donor aromatic moieties of cyclophanes and π-acceptor dipyridinium core of the guest. $^{1}$H NMR and MS measurements showed the formation of 1:1 inclusion complexes of pseudorotaxane type. The stability of complexes changes in the order: 31 ≫ 30 ≫ 32. The smallest macrocycle 29 does not complex the guest due to lack of complementarity between size of the guest and cavity of the host.

Described by Takagi’s and Biernat’s groups 13- and 16-membered crown ethers 22 and 23, as it was stated earlier, form complexes with metal cations. The X-ray structure of complexes of 13-membered crown with lithium bromide [148] and sodium iodide [149] were described. Metal cation complexes of larger, 16-membered crowns were also obtained. In solid state 16-membered crown forms sodium complex of 1:1 stoichiometry [150] while with potassium salt sandwich type 2:1 (crown:ion) complex [151] is created. In all cases the azo group is in trans configuration. It was
also shown that the analysis of crystal structures of complexes of azobenzocrown ethers with alkali metal cations can be helpful in interpretation of the selectivity of ion-selective electrodes doped with particular macrocycle [152].

The X-ray structures of uncomplexed trans isomers of crown 22 and 23 were also investigated [153]. In the unit cells there are two independent molecules 22A and 22B or 23A and 23B (Fig. 21).

The kinetics of the buildup and decay of photoinduced birefringence of crown ethers with inherent azo groups 21–24 (Fig. 16a) of different size of the macrocycle was suitably described by a sum of two exponential functions, the time constants (being function of the pumping light characteristic) and sample thickness. The dark decays were described the best by the stretched exponential function, with the characteristic parameters (time constant and stretch coefficient) being practically independent of the type of crown ether. The time constants of the signal decay were orders of magnitude shorter than the respective constants of the dark isomerization of the azo crown ethers. Thus it indicates that the process controlling the decay was a relaxation of the polymer matrix and/or a rearrangement of the flexible parts of the crowns.

The introduction of the azo group into compounds results not only in photoresponsive but also redox active properties. An example can serve 16-membered crown 33 (Fig. 22) [155] with naphthalene joined by two oxyethylene chains. This macrocycle was used for the preparation of Langmuir–Blodgett (LB) film deposited onto solid ITO substrate. The complexation of metal cations on these electrodes can be successfully observed by cyclic voltammetry (CV). Figure 22 shows CV obtained for a 22-monolayers LB film on an ITO electrode in solutions of KCl, NaCl and LiCl (0.1 M). Bare ITO shows no redox peaks in the presence of K⁺, Na⁺ or Li⁺ ions. For the LB film based on crown 33 film, an electrochemical response in the presence of metal salts was observed. The change of observed signal was attributed...
to the specific interactions between the film and the metal ions. The peaks in voltammograms can be ascribed to the electro-reduction of the azo moiety to the hydrazo group, which consumes two electrons and two protons according to the overall reaction. The strongest effect was observed in the presence of lithium cation, showing the possibilities of its electrochemical sensing.

Similar experiments were performed for a number of macrocyclic compounds, e.g. larger 29-membered macrocycle 34 (Fig. 23), bearing two n-octyl substituents in benzene rings and two azo groups as a part of macrocycle [156]. Langmuir–Blodgett (LB) and physical vapor deposition (PVD) films on ITO showed electrochemical response towards metal cations. Cyclovoltamperometric curves registered for LB films of 29-membered compound 34 point out that among alkali metal cations Li+, Na+ K+, potassium ion was preferentially complexed under applied conditions suggesting the best host and guest size complementarity.

The selectivity of crown ethers and other host molecules towards metal cation can be controlled also by changing the type of donor atoms. 16- and 18-membered azo- and azoxythiacrown (forming next to azo compounds) ethers 35–40 (Fig. 24, right) were obtained in satisfactory yields by Kertmen and Szczygelska-Tao [157] using reductive macrocyclization procedure. Thiacrowns were tested as ionophores in ion-selective, graphite screen printed electrodes. Opposite to their oxygen analogs, sulfur containing compounds preferentially supposed to form complexes with softer metal cations. All electrodes doped both with azo- and azoxythiacrowns 35–40 (Fig. 24) showed high sensitivity towards heavy metal cations. The effect of softer sulfur donor atom in the skeleton of macrocycles on the response of ISE with membrane doped with 35–40 can be visualized by comparison of the order of potentiometric selectivity of thia-crown and its oxaanalog [137], shown in Fig. 24 (right, in a frame).

Potassium selectivity of electrodes based on derivatives of 16-membered crown ether 23 was well-proved over years of working with ISEs. 13-membered azobenzocrowns, derivatives of compound 22 (Fig. 16a) are sodium ionophores [134, 136–138, 158–160]. To improve the characteristic of the sodium and potassium sensors, important for clinical analyses, new derivatives of both 13- and 16-membered crowns were prepared and at the same time new technical solutions, including miniaturization of the sensors, were applied. Recently, a series of bis-(azobenzocrown)s (compounds 41–48, Scheme 4) based on the skeleton of parent 13- and 16-membered crowns were prepared and at the same time new technical solutions, including miniaturization of the sensors, were applied. These bis-crowns were synthesized from the respective hydroxyazobenzocrowns obtained in reaction analogous to Wallach rearrangement elaborated by Luboch [161].

![Fig. 24](image-url)

**Fig. 24** Left: Thiaazo- (35–37) and thiaazoxy (38–40) crown ethers obtained by Kertmen and Szczygelska-Tao. Right: comparison of the trend of potentiometric selectivity coefficients of electrodes with crown 36 and its oxygen analog shown is in a frame [157]

![Scheme 4](image-url)

**Scheme 4** Synthetic route for preparation of bis-(azobenzocrown)s 41–48 from hydroxyazobenzocrowns as substrates [162]
The unique structure of intermolecular of 2:2 stoichiometry sandwich-type complex of bis-(azobenzocrown) with sodium iodide was obtained [162]. It is presented in Fig. 25.

Bis-(azobenzocrown)s 41–48 were used as ionophores both in classic and miniature, all-solid state, screenprinted, graphite ion-selective electrodes. New sodium and potassium sensors feature by short response times, stable potential and high selectivity, in particular high K/Na selectivity.

Bis-(azobenzocrown)s 41–48 form complexes with metal cations also in acetonitrile. The increase of stability constant values comparing analogous monocrown bearing alkoxy substituent proves beneficial effect of the presence of two binding sites in one molecule.

Another example of biscrowns are diester derivatives of dodecylmethylmalonic acid joining two 13-membered azobenzocrown moieties obtained in Luboch group [163] (compounds 49 and 50, Scheme 5). Biscrowns were obtained using bromoalkoxy derivatives of azobenzocrowns [164] and potassium salt of dodecylmethylmalonic acid in ~40% yield. For comparative studies monoester derivative 51 was synthesized.

For biscrowns 49 and 50 three isomers trans-trans, trans-cis and cis-cis can be considered. From 1H NMR spectra registered in d-acetone it was found that in solutions of 49 and 50 trans-trans and trans-cis isomers dominate representing altogether ~90% of the total amount of compounds. The presence of cis-cis isomer of 49 was observed upon irradiation with UV light. For monoester...
derivative 51 the ratio of trans to cis isomer was evaluated as 6:4. Trans–trans and trans–cis isomers of 49 and especially of 50, differ significantly in TLC properties. This can be associated with different complexation properties of both isomers [166]. Trans isomers of azobenzocrowns show higher affinity towards metal cations than cis forms. Thus trans–trans isomer is probable able to form intramolecular sandwich type complexes (Fig. 26) with metal cations whereas for trans–cis isomer rather intermolecular complexes are expected. This hypothesis finds confirmation in previously published works of the above authors and in articles published by other groups [149, 166, 167]. Formation of sodium complex by trans–trans isomer of 49 was confirmed also by 1H NMR measurements. Stability constant value of (1:1) complex of 49 in acetone was estimated as logK ~ 3.0 from UV–Vis titrations.

Bis-crowns 49 and 50 based on 13-membered rings, were tested as sodium ionophores in classic and miniature, solid contact: screen-printed and particularly glassy carbon membrane ion-selective electrodes. Plasticizers 2-nitrophenyl octyl ether (o-NPOE) and more lipophilic di(2-ethylhexyl) sebacate (DOS) can be successfully used for bis(azobenzocrown) containing membranes. It was proved that possible isomerization under usual conditions does not significantly affect the characteristics of the prepared electrodes. The influence of UV irradiation on the properties of glassy carbon electrode with ionophore 49 is shown in Fig. 27. After exposition to UV light (1 h, 365 nm), the electrode regains its properties practically after 2 h conditioning in NaCl solution.

Electrodes with the tested biscrowns 49 and 50 were found to have better selectivity coefficients K_{Na/K} than the electrodes with the monocrown 51. The best selectivity coefficient Na/K was achieved for the screen printed graphite electrode with the addition of carbon nanotubes into the membrane (50 as the ionophore, logK_{Na,K} = −2.6). No significant differences were also observed between the selectivities of the classic and solid contact electrodes. In the last case lower detection limits (LDL) may be obtained. The membrane doped with carbon nanotubes deposited onto graphite screen-printed electrodes results in the better potential stability, detection limit and selectivity of bicrown-based electrodes. The electro-conductive material was introduced directly into the membrane in a manner analogous to that proposed by Ivaska and co-workers [168]. For glassy carbon electrodes to improve the conductivity, between the membrane and glassy carbon the conductive PEDOT/PSS polymer blend was introduced by electropolymerization. Such electrodes have better (lower) LDL than plain glassy carbon electrode. Electrodes with ionophores 49 and 50 characterize with response times not longer than 10 s, illustrated in Fig. 28 for membrane electrode doped with 49.
Electrodes based on 49–51 characterize by stable potential in a wide range of pH, depending on the type of the used plasticizer, e.g. electrodes with compound 49 and DOS show stable potential in the pH range 2–10 (0.1M NaCl). Proposed sodium sensor (based on 50) fulfills requirements for electrodes used in clinical analysis [169]. The response of electrodes based on 50 for sodium in the presence of interfering metal cations corresponding to their blood plasma levels are shown in Fig. 29.

The electrodes were tested for sodium in blood plasma giving consistent results with independent measurements carried out in clinical analytical laboratory.

Crown ethers with peripheral azo group

The interactions between photoswitchable azobis-(benzox-18-crown-6) and alkaline earth metal cations were studied by DFT and reactive molecular dynamics (reactive MD) by Pang et al. [170]. Optimized structures of complexes revealed that in the case of Ba2+ complex the distance between two cations is the largest among tested complexes in their trans form, and the shortest among cis complexes. Macrocycles become face-to-face when complexing Ba2+ ions. Small energy difference between Ba2+ complex in its trans and cis form indicates facile cis to trans thermal conversion. Calculation the Ba2+ complex allows to conclude that it is a suitable candidate for photocontrolled catalysis.

To mimick the structure and function of biological ion channels the light-regulated transmembrane system was proposed using tri(macrocycle) system based on diaza-18-crown-6 joined by azobenzene photoswitchable moieties 52 (hydraphile 1, Fig. 30) [171]. The liposome-based ion transport assays revealed that compound 52 displays an efficient transmembrane activity with Y_{max} around 0.7 at 40 μmol/L of 52 in DMSO. Due to the presence of azobenzene moieties the potassium ion transport by the molecule across bilayer membranes can be regulated by applying of external source of light. The photoisomerization of azo groups induces changes of transmembrane length of the ion channel and this way regulating the efficiency of the ion transport.

In many chemical and photochemical processes donor–acceptor complexes (D-A complexes) play an important role. Such systems are also investigated as organic conductors and photoconductors that find applications in nonlinear optics. D–A complexes of a series of bis(crown)
stilbenes, and also of bis(crown)azobenzene with salts of alkylammonium viologen derivatives were studied in solution and in a solid state by Gromov and co-workers [172]. X-ray structure of complex of bis(18-crown-6)azobenzene 53 (Fig. 31) with viologen derivative 54 showed that the central parts of donor and acceptor molecules feature planar geometry. The proposed systems can be used for the design of optical sensors and molecular devices.

**Colorimetric and spectrophotometric ion receptors**

Molecular recognition can be utilized in many branches of science and technique if the information about host–guest interaction could be converted into analytically useful signal, e.g. optical or electrochemical. Optical signaling in the visible range of the electromagnetic spectrum draws special attention because it enables non-instrumental sensing of various chemical species such as ions or neutral molecules, e.g. for monitoring of ions of biological or environmental importance. The receptor molecule besides binding site...
should be equipped with additional signaling unit, a functional group joined via linker or chromophoric/fluorophoric moiety forming an integral part of the molecule. Schematically, the idea of chromo- and fluorogenic molecular receptors is shown in Scheme 6. The mechanism of sensing depends on the nature of both the host and the guest. The binding mode, selectivity and sensitivity can be also influenced or controlled by the effect of the solvent and/or receptor immobilization on solid surfaces of various properties.

Inter alia functionalized macrocyclic compounds bearing azo moiety belong to this relatively popular group of sensing materials.

In the case of para- and ortho-hydroxy derivatives of azo-compounds the color signaling mechanism may be associated with the change in the tautomeric equilibrium upon complexation. This is well illustrated by tautomeric switch based on functionalized azacrown ether 55 (Fig. 32) synthesized and investigated by Antonov and co-workers [173]. Uncomplexed ligand in acetonitrile exists in azophenol form stabilized by intramolecular hydrogen bond between phenolic OH group and nitrogen atom of crown ether residue. In the presence of alkali and alkaline earth metal cations—the color of the solution turns from yellow to orange-red, what is a result of bathochromic and hyperchromic effects in UV–Vis spectra. The complex formation is connected with the shift of the tautomeric equilibrium towards ketone (quinone-hydrazone) form. Metal cations are complexed by ether oxygen donor atoms and by carbonyl oxygen atom of ketone form.

Lithium and sodium cations form complexes of 1:1 stoichiometry with azacrown 55 (Fig. 33). For magnesium and calcium initially 1:1 complex is formed. Under an excess of a metal salt 2:2 complex dominates. Direct 2:2 complex formation was found for barium perchlorate. Absorption spectra of azacrown registered in the presence of metal perchlorates are shown in Fig. 33a. In Fig. 33b the values of the stability constants of 1:1 and 2:2 metal complexes with discussed azacrown 55 are presented.

Aza-15-crown-5 56 (Fig. 34) skeleton is a hopeful building block for colorimetric sensors. Lincoln and Sumby [174] used this macrocycle to synthesize N-[4-(phenyldiazenyl)naphthalen-1-ol 55 synthesized by Antonov et al. exemplified by sodium complexation [173].

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**Scheme 6** Schematic: the idea of chromo- and fluorogenic molecular receptors

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**Fig. 32** The mechanism of color change of azacrown ether modified with 4-(phenyldiazenyl) naphthalen-1-ol 55 synthesized by Antonov et al. exemplified by sodium complexation [173]
of 1:1 complexes of sodium and potassium cations with 57 are higher than for the parent aza-15-crown-5 56 [174–178]. The solved X-ray structure of [Na(57)(H2O)]2(ClO4)2 complex showed that it is a dimer with the sulfonamide oxygen atom engaged in cation complexation. This indicates the cooperation of sulfonamide side arm and crown ether moiety in ion binding and explains the higher values of the stability constant compared with data for unsubstituted aza-15-crown-5.

The selectivity of metal cation binding can be controlled by using macrocycles with softer, sulfur donor atoms. Lee and Lee [179] synthesized, under high dilution conditions, macrocyclic derivatives incorporating aromatic moiety, i.e. benzene 59 or pyridine 60 (Scheme 7) within the macroring. Chromogenic character of macrocycles was achieved by extending the structure by diazocoupling of the obtained in the first step N-phenylated macrocycles 58 with p-diazonium salt.

Both compounds 59 and 60 selectively bind mercury(II) in acetonitrile forming 1:1 complexes. Complexation of Hg2+ causes hipochromic shift of absorption bands from 480 to 339 and 378 nm for 59 and 60, respectively. Among other investigated metals only copper(II) cations cause bathochromic shift of absorption band of 59, whereas spectral behavior of 60 remains intact. Color and spectral changes of 59 and 60 in acetonitrile solutions in the presence of metal salts are shown in Fig. 35. The crystal structure of 60 complex with mercury(II) ion showed metal cation located inside the macrocycle cavity. The difference in selectivity towards mercury ions versus other metal cations was explained by the engagement of the pyridine nitrogen atom in complex formation in case of 60.

Spectral and color changes in the presence of Hg2+ were found to be anion dependent (Fig. 36). Addition of perchlorates or nitrates to the acetonitrile solution of mercury(II) complexes of 59 and 60 causes spectral and color changes,
which can be attributed to the ability of mercury to coordinate these anions. The obtained results indicate that proposed macrocycles can be used not only as mercury, but also as anion sensing molecules.

Spectral and color changes caused by complexation of heavy metal cations were also found for macrocycle \( \text{61} \) bearing as chromogenic substituent \( p \)-nitroazobenzene \([180]\) that was obtained in multistep reaction shown in Scheme 8.

Red acetonitrile solution of \( \text{61} \) changes color to yellow upon addition of metal salt, which is a result of metal cation induced hypsochromic shift of absorption band. The largest spectral and color changes among investigated metal cations causes copper(II) \( (\Delta \lambda_{\text{max}} = 174 \text{ nm}) \). The spectral and color changes of \( \text{61} \) in the presence of metal nitrates are shown in Fig. 37.

Compound \( \text{61} \) forms two types of solid state complexes, which differ in color: \([\text{Cu}(\text{61})\text{NO}_3\text{Cl}])\text{NO}_3\cdot\text{CH}_2\text{Cl}_2\), a pale-yellow and dark red \([\{\text{Cu}(\text{61})\}\cdot2(\mu\text{OH})\text{ClO}_4\text{Cl}]\cdot2\text{CH}_2\text{Cl}_2\cdot2\text{H}_2\text{O}\). The effect of counter ion on spectral changes upon copper(II) complexation was investigated using chloride, nitrate, perchlorate, acetate, and sulfate salts. A blue shift was observed and the influence of anion can be set in the following order: \( \text{NO}_3^- > \text{ClO}_4^- > \text{Cl}^- \).
AcO$^{-} > \text{SO}_4^{2-}$, which is in accordance with the Hofmeister series of relative anion lipophilicities.

Colored systems can be also used for preparation of sensing materials by immobilization of the respective receptor(s) on a chosen solid surface. For example, macrocycle 62 (Scheme 9) bearing azo unit, was immobilized on a silica nanotubes (SNT) using sol–gel method [181]. The described system (SNT-62) was presented as a heterogenous “naked-eye” and spectrophotometric metal cation sensor.

Inorganic–organic nanomaterial (SNT-62) shows in water selective response by color change from yellow to violet towards $\text{Hg}^{2+}$ among all other investigated metal cations: $\text{Ag}^{+}$, $\text{Co}^{2+}$, $\text{Cu}^{2+}$, $\text{Cd}^{2+}$, $\text{Pb}^{2+}$, $\text{Zn}^{2+}$, $\text{Fe}^{3+}$, $\text{Cu}^{2+}$. The color of suspensions also changes in the presence of nitrate and perchlorate anions from yellow to pink and violet, respectively. The addition of $\text{Cl}^{-}$, $\text{Br}^{-}$, $\Gamma$-, $\text{SCN}^{-}$, or $\text{SO}_4^{2-}$ salts does not cause color change. It was also shown that modified silica nanotubes can act not only as colorimetric sensor for mercury(II) cation, but also for preparation of stationary phases for ion chromatography. The use of suspensions can be sometimes troublesome, thus a portable chemosensor kit was prepared by modification of the glass surface with SNT-62. The material also in this form exhibits selective response towards $\text{Hg}^{2+}$ with color change from yellow to violet upon dipping.

**Scheme 8** Synthesis of chromogenic macrocyle 61 [180]
in solution of mercury(II) salt. Color changes of the water suspensions of SNT-62 upon addition of mercury(II) nitrate at different concentrations are shown in Fig. 38 (left). The color change of the glass sensor modified with SNT-62 upon immersion into mercury(II) and for comparison copper(II) aqueous solutions is shown in Fig. 38 (right).

Environmentally hazardous mercury(II) sensing based on dithiaazadioxo crown ether system with peripheral azo unit was described by Ha and co-workers [182]. Compounds 63 and 64 (Fig. 39) were investigated as Hg$^{2+}$ receptors in solvents of diverse polarity (acetonitrile, its mixture with water and in chloroform). It was found that host–guest interaction strongly depends on the solvent nature. According to $^1$H NMR and spectrophotometric measurements it was stated that both ligands in acetonitrile form 1:1 complexes, if Hg$^{2+}$ is coordinated inside the macrocyclic cavity (Fig. 39). As a consequence of molecular recognition solutions of both ligands undergo discoloration in the presence of Hg$^{2+}$ ions. In less polar chloroform, different mechanism of ligand-ion interaction was proposed. Two molecules of 63 probably bind one mercury(II) cation forming sandwich complex. This is manifested by color change from yellow to pink. In the case of macrocycle 64 in chloroform complexes of 2:2 stoichiometry are formed.

Ha and Jeon continued the work on selective mercury(II) sensing using compound 63 (Fig. 39) [183]. The colored

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**Scheme 9** Schematically: modification of silica nanotubes with chromogenic macrocyclic derivative 62 (SNT-62) [181]

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**Fig. 37** Changes in the UV–Vis spectrum of 61 on addition of metal nitrates in acetonitrile (ligand concentration, 5.0×10$^{-5}$ M; and added metal ion, 3.0 equiv). Number of compound in reproduced material corresponds to following number of compound in this work: L$^2$ = 61. Reprinted with permission from [180]. Copyright 2009 American Chemical Society

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**Fig. 38** Left: pictures of the suspensions: a SNT-62, b SNT-62 +0.01 mM Hg(NO$_3$)$_2$, c STN-62 + 1.0 mM Hg(NO$_3$)$_2$. Right color changes of glass plates coated with SNT-62: a before immersion and after immersion in b Hg$^{2+}$ (0.01 mM) and c Cu$^{2+}$ (0.01 mM) solution in water. Reprinted from [181]. Copyright 2007 with permission from John Wiley and Sons

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A macrocycle was applied for recognition of Hg$^{2+}$ ions in aqueous solution. The effect of two surfactants cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS) on spectral and color behavior of 63 was investigated. In the presence of CTAB the solution of 63 is yellow, while pink color is observed in the presence of SDS (Fig. 40). In the presence of Hg$^{2+}$ the pink solution of 63-SDS system becomes colorless enabling naked-eye ion recognition with detection limit 1.6 μM. The 63-SDS based system was also used for preparation of the mercury sensitive cellulose test strips.

**Functionalized azobenzocrowns (azo moiety as a part of the macrocycle)**

This chapter highlights the preparation and properties of azobenzocrowns, of different size of the macrocycle, equipped with additional functional groups in benzene rings: hydroxyl, amino, and dimethylamino, as well as pull–push type azobenzocrowns with nitro and dimethylamino groups. 13-, 16- and 19-membered crowns bearing electron donating (dimethylamino) 65–67 or two different electron donating/accepting groups (dimethylamino and nitro) 68–70.

**Fig. 39** Proposed mechanism of mercury(II) complexation by macrocycles 63 and 64 depending on the solvent type [182]

**Fig. 40** Color and spectral changes of 63 in various concentrations of a CTAB and b SDS. Reprinted from [183] Copyright 2015 with permission from John Wiley and Sons. (Color figure online)
Compounds 65–70 exist only in E form, both in the solid state and in solution. In Fig. 41 X-ray structure of 70·2H2O is presented, showing the E geometry of the azo unit with aromatic moieties in the trans-positions and proved the existence of a molecular diaqua-complex [159].

The absorption spectra of 65–70, opposite to the parent azobenzocrowns 22–24 (Fig. 16a) have sharp and well pronounced maxima (Fig. 42).

The UV–Vis studies of alkali and alkaline metal cation complexation by compounds 65–70 showed magnesium selectivity of 19-membered azobenzocrown 67 in acetonitrile. Only in this case the complexation is characterized by significant spectral shift (Fig. 43) and by distinctive color change from orange to pink.

Another set of synthesized and investigated functionalized azobenzocrowns consists of derivatives with a hydroxyl substituent. Azobenzocrowns with hydroxyl group located in one of the benzene rings, in the para position to the azo group, have been synthesized prior to 2002 [158] and are also a part of current works carried in Luboch’s group.
A simple method for the synthesis of 13- and 16-membered azobenzocrown ethers, derivatives of 4-hexylresorcinol with two peripheral groups, i.e. nitro and hydroxyl groups at two opposite sides of the conjugated chromophoric system has been described by Luboch et al. (Scheme 11) [160].

Typical for 13-membered azobenzocrowns, including compounds 71 and 72 is selective binding of lithium cations. The most significant, among all investigated so far compounds of this type, is the spectral shift of 95 nm and color change from yellow to pink found for 72 (Fig. 44) in basic acetonitrile (Et₃N) solution. Crown 73 is more lithium sensitive, but less selective, versus sodium and potassium (Fig. 44) giving the color change. The chromoionophoric behavior of the compounds potentially allows their application, under selected conditions, for construction of optical sensors.

As shown in Scheme 12 the hydroxyazobenzocrowns undergo tautomeric equilibrium to quinone-hydrazones. The tautomeric equilibrium of hydroxyazobenzocrowns is affected by the size of the macrocycle. The larger the cavity size the lower the tendency to occur in the quinone-hydrazone form. This can be explained by weaker hydrogen bonds in macrocycles of larger cavity. 13-membered macrocyclic p-hydroxyazobenzene derivative—compound 74 (Scheme 11), in the solid state and in solvents of different polarity (chloroform, acetonitrile, acetone or methanol) exists in the quinone-hydrazone form. The azophenol form was observed (~30%) in DMSO.

16-Membered crown 75 in chloroform and in acetonitrile exists, like 74, in the quinone-hydrazone form, but in DMSO only the azophenol form was found. Compound 76 of 19-membered ring entirely exists in the azophenol form in DMSO and chloroform. In acetonitrile no less than 75% of this form was detected [159], but in acetone both forms exist in comparable amounts.

p-Hydroxyazobenzocrown ethers can be obtained from O-protected podands by reduction [158] or directly from dihydroxyazocompounds as shown for sterically hindered crowns 71–73 [160]. The reaction analogous to the Wallach rearrangement was proposed as a method for preparation of
p-hydroxyazobenzocrowns using azoxybenzocrowns as substrates [161]. However, the reaction carried out in the mixture of concentrated sulfuric acid and ethanol suffers from the formation of side products and large amounts of used reagents [162]. Exhaustive synthetic research on the applicability of Wallach rearrangement allowed to conclude that the decrease of the side-products formation, lower amounts of reagents and finally, the most importantly, significant yield increase is obtained by carrying out the Wallach rearrangement in a mixture of concentrated sulfuric acid and dimethylformamide [165]. Under elaborated reaction and isolation conditions a series of hydroxyazobenzocrowns 74, 75 and 77–83 were successfully obtained (Scheme 13).

In contrast to the Wallach rearrangement conducted under strongly acidic conditions where mostly p-hydroxyazo compounds are formed, the photochemical rearrangement leads also to ortho-hydroxyazo compounds 84, 85 (Scheme 14) [162]. Under fixed conditions the ratio of para to ortho hydroxyazobenzocrown isomers was dependent on the solvent. In toluene o-substituted compounds were dominating, p-substituted crowns were the main product in ethanol, whereas in DMF a mixture of comparable amounts of both isomers were obtained.

The spectral properties of o-hydroxyazobenzocrowns opposite to p-substituted analogs, exist mainly in azophenol form. The spectral properties of o-hydroxyazobenzocrowns 84 and 85 were compared with 74 and 75, and unsubstituted crowns 22 and 23 (Fig. 16a) [165]. Their normalized UV–Vis spectra (acetonitrile) (solid lines) and the corresponding protonated forms (dashed lines) are shown in Fig. 45a, b. Protonation constants in acetonitrile solutions are compared in Fig. 45 (right). The protonation constants can be ordered: p-hydroxyazobenzocrowns > o-hydroxyazobenzocrowns > unsubstituted azobenzocrowns ~ acyclic analog of azobenzocrowns 86.

p-Hydroxyazobenzocrowns were used as substrates in the synthesis of bisazobenzocrowns (Scheme 15) of different lipophilicity, where two macrocyclic residues are
joined via dioxymethylene group. Biscrowns (87–93) were obtained in yields up to 72%.

Bisazobenzocrowns were used as ionophores in classic and miniature (screen-printed) ion-selective electrodes. A selectivity coefficient $\log K_{\text{Na},\text{K}} = -2.5$ (SSM, $10^{-1}$ M) for electrode with crown 87 as ionophore was one of the best result obtained for the whole group of the electrodes based on the 13-membered azobenzocrowns. Within the investigated 16-membered bisazocrowns the best potassium over sodium selectivity coefficient for potassium electrodes was $\log K_{\text{K},\text{Na}} = -3.5$ (SSM, $10^{-1}$ M) for compound 88.

13- and 16-Membered azobenzocrowns (Scheme 16) with aromatic amino (94, 95), amide (96, 97), ether–ester (98–103) or ether–amide (104–107) residue in para position to an azo moiety were synthesized and investigated [184].

The studies of tautomeric equilibrium of aminocrowns 94 and 95 showed that in majority of solvents, similarly to open chain aminoazocompounds [185] they exist in aminoazoform (Scheme 17). It is opposite to discussed above hydroxyazobenzocrowns for which tautomeric equilibrium was found to be more solvent dependent [158, 159, 186].

The protonation of aminoazobenzocrowns shifts the tautomeric equilibrium towards protonated iminohydrazone form.

13-Membered crown 94, as expected, in acetonitrile preferentially complexes lithium ions. Stability constant of this 1:1 complex is $\log K = 4.0$. This value is comparable with the value for unsubstituted 22 ($\log K = 4.1$), but it is higher than for the corresponding 13-membered hydroxyazobenzocrown 74. The stability constant obtained for magnesium complex, $\log K = 6.43$, is the highest value for magnesium complex among all studied so far azobenzocrowns. Changes in the absorption spectra upon spectrophotometric titration of a solution of 94 with lithium and magnesium perchlorates in acetonitrile are illustrated in Fig. 46a, c. Fig. 46b shows limiting spectra for 94 upon titration with alkaline earth metal perchlorates.

![Fig. 45 Left: comparison of normalized UV–Vis spectra of (a) 13-membered (b) 16-membered azobenzocrowns (solid) and their protonated forms (dashed lines) Right: proton binding constants for 22, 84, 74 and 23, 85, 75 azobenzocrowns and for acyclic analog 86 in acetonitrile. Number of compounds in reproduced material correspond to following numbers of compounds in this work: 10 = 74; 10a = 22; 23 = 84; 11 = 75; 11a = 23; 24 = 85; 22 = 86. Reprinted from [165]. Copyright 2013 with permission from Elsevier. (Color figure online)](image)

![Scheme 15 Synthesis of bisazobenzocrowns 87–93 with dioxymethylene spacer [165]](image)
16-Membered aminoazobenzocrown forms 1:1 complexes with alkali and alkaline earth metal cations. In all cases, with exception for potassium, the values of the corresponding stability constants are higher than for parent azobenzocrown, which are in turn higher than for complexes of hydroxyazobenzocrown. The introduction of electron-donor amino group into the benzene ring in para position to azo moiety enhanced binding properties of azobenzocrowns.

Lithium binding was investigated for a series of 13-membered azobenzocrown with oxyalkylcarbonester moiety as side chain (Scheme 16) and was compared with properties of 22 and its alkoxy derivative (Fig. 47).

The general trend of spectral changes upon lithium complexation for oxyalkylcarbonester derivatives is similar as for 108. The length of aliphatic acid chain has some effect on the binding strength of the lithium ions, however it cannot be the complexation of the same type as for lariat type crowns. The side chain seems to be too short to participate in complex formation. This is to some extent confirmed by the crystal structure of sodium iodide complex (Fig. 48).

Vast majority of azo compounds, with few exceptions [105, 187–190] show no fluorescence. Protonated azobenzocrowns exhibit orange-red fluorescence. The position of emission band, and the value of the Stoke’s shift is dependent on the presence and nature of the substituent in the para position to the azo group [184].

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**Scheme 16** Synthesis of a amino (94, 95), b amide (96, 97), c ether–ester (98–103) or ether–amide (104–107) derivatives of azobenzocrowns [184]

**Scheme 17** Comparison of tautomerism of 13-membered hydroxy- and aminoazobenzocrowns [184]
spectra for protonated forms of 13-membered azobenzo-
crowns 22, 94 and 96 are shown in the Fig. 49a, b.

Changes in the UV–Vis and emission spectra of com-
pound 96 solution upon titration with solution of p-tolu-
esulfonic acid in acetonitrile are shown in Fig. 50a, b. Photos show a color change and red fluorescence of 96 caused by protonation.

Selected functionalized azobenzocrowns (Scheme 16) were tested as ionophores in ion-selective membrane elec-
trodes. Ether-ester 100–103 and ether-amide 104–107, similarly to described earlier alkyl and dialkyl derivatives [136, 137, 158] are good ionophores in membrane electrodes. The mechanism of ion selectivity can be explained by forma-
tion of “sandwich” type complexes with the main ions [149, 151].

The 1H NMR studies of tautomeric equilibrium of hydroxyazobenzocrowns with phenyl substituents in benzene rings (Fig. 51) showed that 13-membered crown 109 in acetonitrile exists in quinone-hydrazone form [191]. 10% of azophenol form was detected in DMSO. For 16-membered crown 110 the presence of quinone-hydrazone form was stated in acetone and chloroform [191] and also in DMSO (50%).

For 13-membered hydroxyazobenzocrown 109 spectral response with spectral shift ~ 40 nm (Fig. 52a) and color change from yellow to orange (Fig. 52, top) caused by the presence of lithium salt was observed only in basic solution (Et3N) of acetonitrile. This corresponds to lithium com-
plex formation by ionized hydrazone form of 109. Lithium response is observed also in the presence of the excess of sodium salt (Fig. 52b).

For 13-membered hydroxyazobenzocrown 109 (Scheme 12) forms complexes both in neutral and basic ace-
tonitrile solution. In pure acetonitrile the presence of alkali and alkaline earth metal cations causes a blue spectral shift corresponding to shift of tautomeric equilibrium and forma-
tion of complex in azophenol form. Under the same con-
ditions no spectral changes were observed in the presence of lithium and sodium for 110. In basic acetonitrile (Et3N) for both 75 and 110 the presence of lithium and sodium salts (no changes in the presence of potassium) causes red shift of absorption band. This corresponds to formation of complexes by quinone-hydrazone forms. The comparison of the stability constants (logK), determined by UV–Vis titra-
tions, of lithium and sodium complexes of 75 in neutral and basic acetonitrile and 110 in basic acetonitrile are shown in Fig. 53. Stability constant values of complexes of 23 in neutral acetonitrile were also included for comparison.
Lithium cation is stronger complexed by the ionized quinone-hydrazone form than by azophenol tautomer. For 109 and 110 the presence of phenyl rings appears to be important factor affecting tautomeric equilibrium driven by metal cation complexation and the strength of ion–azobenzocrown interactions.

Spectrofluorimetric titrations of 109 with lithium and sodium perchlorates causes the decrease of fluorescence intensity, especially in the presence of organic base. The value of Stern–Volmer \( (K_{SV}) \) constant was the highest for lithium in the presence of triethylamine \( 222 \text{ M}^{-1} \). For comparison this value for 74 is \( 80 \text{ M}^{-1} \). For 16-membered diphenyl derivative 110 Stern–Volmer constants in the presence of triethylamine were also higher than for compound without phenyl substituents in benzene rings 75, both for lithium and sodium. In pure acetonitrile quenching constants caused by metal perchlorates were higher for 75 than for 110, what can be connected with complex formation by this compound in azophenol form in neutral solvent.

Acid-base properties of hydroxyazobenzocrowns were compared with their analogs without hydroxyl substituent by determination of proton binding constants in acetonitrile.
Protonation constants of hydroxyazobenzocrowns 109, 110 and 74, 75 are higher than for compounds without hydroxyl group (111, 22, 112, 23) and among hydroxyazobenzocrowns are higher for macrocycles without phenyl substituents in benzene rings 74 and 75.

X-ray structure of 109 was solved confirming the existence of this compound in quinone-hydrazone form in solid state (Fig. 55).

p-Hydroxyazobenzocrowns can be considered as universal substrates for azobenzocrowns skeleton modifications. 13- and 16-membered azobenzocrowns 113–118 with peripheral thiol moieties (Scheme 18) were obtained from hydroxyazobenzocrown via the respective bromoderivatives (113a-118a) as substrates under optimized reaction conditions [164]. The most effective preparation method of thiol

(Fig. 54). Protonation constants of hydroxyazobenzocrowns 109, 110 and 74, 75 are higher than for compounds without hydroxyl group (111, 22, 112, 23) and among hydroxyazobenzocrowns are higher for macrocycles without phenyl substituents in benzene rings 74 and 75.

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derivatives turned out to be a relatively simple thiourea route giving functionalized crowns in yields 27–46%.

Selected thiol derivatives were anchored onto the surfaces of Gold NanoParticles (GNPs) and studied as plasmonic sensors. The stable systems, which can be stored without change for several month were obtained by bifunctionalization of GNPs with thiol and lipoic acid. GNPs modified with 16-membered thiol derivatives and lipoic acid, showed spectral and visual response towards potassium cations in aqueous environment. In Fig. 56 the comparison of the spectrophotometric response of GNPs of different concentrations modified with thiol derivative 116 and lipoic acid (Au-116) towards potassium chloride is shown.

Scheme 18  Synthesis of thiol derivatives of azobenzocrown ethers 113–118 [164]

Fig. 56  Changes in UV–Vis spectrum of: Left: Au-116 (2.3 mL, 0.095 mM) upon titration with KCl solution (0.05 M, titration step: 0.15 mL). Right: Au-116 (2.2 mL, 0.022 mM) upon titration with KCl solution (0.05 M, titration step: 0.1 mL). Bottom: Au-116 solutions (1.5 mL) at concentration of 0.36 mM containing increasing aliquots of 0.05 M KCl: (1) 0 mL; (2) 0.1 mL; (3) 0.2 mL; (4) 0.3 mL; (5) 0.4 mL; (6) 0.5 mL; (7) 0.6 mL; (8) 0.7 mL; (9) 0.8 mL. Photograph taken 5 min after addition of KCl solution. Reprinted from [164]. Copyright 2015 with permission from Springer Publishing Company
The appearance of new absorption band ~ 600 nm in the presence of potassium is more distinct for diluted solutions GNPs. Color changes of Au-116 system upon addition of potassium salt are shown in Fig. 56 (bottom). The presence of magnesium and calcium salts do not cause spectral changes, moreover, selective potassium response was found in the presence of these two ions (Fig. 57, left). Color of Au-116 system in the presence of sodium, magnesium and calcium and color change upon addition of potassium salt is shown in Fig. 57 (right). This behavior is important from practical point of view when considering possible applications of modified GNPs in biomedical analysis.

Among investigated 16-membered crowns the most promising results as potential potassium plasmonic sensor—regarding the stability of the system and fast response—were obtained for GNPs modified with crown 117 (Au-117). In Fig. 58 changes in absorption spectrum for the highest, among all tested, concentration of colloid is shown.

Azo group(s) in macrocyclic compounds bearing azole rings

Azo group(s) as integral part of the macrocyclic ring

The first series of crown analogs, mainly 18-membered, consisting of two azo groups and heterocyclic (pyrrole or imidazole) residues (compounds 119–121, 126 and 127 Fig. 59) were obtained and studied since 2003 [192].

The further studies including 21-membered pyrrole derivatives (compounds 122–125 Fig. 59) showed the lead(II) selectivity of this class of compounds [193]. Complexation of lead(II) in acetonitrile solution was connected with large, bathochromic shift resulting in color change from orange to blue. High lead(II) selectivity of these compounds, over other studied metal cations, was also confirmed by experiments on transport through the liquid membranes [193]. Membrane electrodes doped with 21-membered pyrrole derived crowns 123–125 (Fig. 59) also exhibited lead(II) sensitivity with the best parameters for sensor in which lipophilic derivative 123 was used as ionophore.

The relatively high yields of macrocyclization and attractive properties of the initially synthesized azomacrocycles with heterocyclic unit(s) motivated to expanded investigation of this class of compounds. The modification of the skeleton of macroring in different parts of the molecule (schematically drawn in Fig. 60) allowed to obtain macrocycles featuring with many interesting properties.

The structure of 23- and 21-membered macrocyclic pyrrole derivatives 128–131 shown in Fig. 61a comprise chromogenic and fluorogenic character [194]. Pyrrole containing
Macrocycles were prepared in multistep reactions; the final step was the azocoupling of the respective bisamines with pyrrole that proceeds with moderate yields.

Azocrowns bearing pyrrole residue 128–131 are lead(II) selective with the highest values of the stability constants and the most significant spectral shifts. The comparison of the color change in the presence of lead(II) and other metal cations is shown in Fig. 61b. The comparison of the stability constants of 2:1 (L:Pb) complexes of crowns 128–131 with lead(II) perchlorate in acetonitrile [195] is presented in Fig. 61c.

The incorporation of the fluorescent moieties into the structure of azomacrocycles 125 (Fig. 59) and 128–131 (Fig. 61a) results in compounds for which lead(II) complexation is associated with quenching or increase of the fluorescence intensity, depending on the type of substituent. The changes of fluorescence intensity for crowns 125 and 128–131 in the presence of 100-fold excess of metal perchlorates in acetonitrile are shown in Fig. 62 (left).

The binding properties and associated changes in fluorescence spectra of crowns 125 and 128–131 can be to some extent explained by analyzing their X-ray structures (Fig. 62, right). Naphthalene fragment(s) influences the geometry of 125 and 130. Particularly, the introduction of the naphthalene unit into the oxyethylene chain affects the conformation of this part of the molecule leading to the significant distortion of its shape. On the other hand the arrangement of the two naphthalene moieties in compound 130 causes molecule to be more flat, resembling a flying butterfly.

For the above-described compounds 119–125 (Fig. 59) the characteristic constituent of the structure is polyether chain coexisting with heterocyclic residue and two azo groups. More “soft” nitrogen atom donor, instead of the polyether fragment pyridine was inserted and the effect of such structure modification on metal cation binding was investigated [196]. Crown 132 (Scheme 19) constitutes of two heterocyclic residues: pyrrole and pyridine, and two azo groups forming inherent part of the macroring.

Metal cation complexation by 132 was studied using UV–Vis spectroscopy in acetonitrile and in its mixture with water. In acetonitrile, spectral and color changes were not observed in the presence of alkali metal ions and

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Fig. 59 Chromogenic crown ethers with pyrrole (119–125) and with imidazole (126, 127) heterocyclic residue and with two azo groups in macroring [192, 193]

Fig. 60 Schematically: the general formula of macrocyclic compounds with two azo groups and heterocyclic residue(s) as inherent part of the macroring
Fig. 61  
(a) Chromo- and fluorogenic macrocyclic derivatives with pyrrole residue in the macroring [194]; 
(b) Color changes of acetonitrile solution of compound 131 in the presence of the excess of metal perchlorates. Reprinted from [194]. Copyright 2011 with permission from Elsevier; 
(c) The comparison of the stability constants of 2:1 (L-Pb) complexes of compounds 128–131 in acetonitrile [195]. (Color figure online)

Fig. 62  
(a) The changes of fluorescence intensity for crowns 125 and 128–131 in the presence of 100-fold excess of metal perchlorates in acetonitrile. Right: the side view of the X-ray structure of the macrocycles a 125 and b 130. Numbers of compounds in reproduced figure correspond to following numbers of compounds in this manuscript: 1 = 125, 2 = 128, 3 = 129, 4 = 130, 5 = 131. Reprinted from [194]. Copyright 2011 with permission from Elsevier. (Color figure online)

Scheme 19  
The synthesis of crown 132 with two heterocyclic residues: pyrrole and pyridine as inherent part of the macrocycle [196]
magnesium, but the presence of calcium, strontium and barium affected the absorption spectra of 132. Among heavy metal cations in the case of nickel(II) and cobalt(II) slow kinetics of complex formation was observed. The presence of zinc(II) and lead(II) caused the most significant color changes of acetonitrile solution of 132 from red to violet. In reaction carried out without γ-CD compounds 136 and 133 were obtained in ~45% yield.

Besides imidazole, also 18- (119a, 119b) and 21-membered (122) pyrrole derivatives were obtained by cyclodextrin assisted synthesis. The size of used cyclodextrin affects the total yield and the ratio of isomeric crowns 119a and 119b. The overall yield of the two macrocyclic compounds formed simultaneously reached 87% in the presence of β-CD. In the absence of β-CD the cumulative yield of both isomers is ~40%. Cyclodextrins assisted syntheses of azomacrocycles bearing pyrrole or imidazole confirmed the role of CDs as a molecular reactors.

Metal cations binding by 21-membered imidazole crown 137 was investigated as a model compound by UV–Vis spectroscopy in acetonitrile, methanol, and methanol–water (4:1) mixture. In acetonitrile, only calcium, strontium and barium among alkali and alkaline earth metal cations cause spectral change, i.e. hypsochromic shift, with simultaneous color changes from orange–red to yellow. In the presence of heavy metal salts the color of acetonitrile solution of 137 turns to pink-purple. Schematically, these color changes are illustrated in Fig. 65a. From spectrophotometric measurements it was concluded that complexes of 137 have different stoichiometry depending on the complexed metal cation. Alkaline earth metal ion complexes have 1:1 stoichiometry; in the case of cobalt(II) and nickel(II) 2:1 (L:M) complexes dominate. In systems containing 137 and zinc(II), lead(II) and copper(II) salts two 1:1 and the 2:1 (L:M) complexes exist under equilibrium. The values of stability constants (logK) and the most probable stoichiometry of the formed complexes are shown in Fig. 65b. It was found (1H NMR) that polyether chain plays a bigger role in the case of barium ion complexation.

![Fig. 63](image-url) The comparison of the values of the stability constants of 2:1 (L:M) complexes of compound 132 with metal perchlorates in acetonitrile [196]

![Fig. 64](image-url) Imidazole bearing macrocyclic azo compounds [197]

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than in the case of lead(II) complex, where imidazole residue was supposed to be engaged. In methanol, only barium, among alkaline earth metal cations, and zinc(II), lead(II) and copper(II), among heavy metal cations, caused significant changes in UV–Vis spectra. For barium and zinc(II) 1:1 complexes dominate, whereas lead(II) and copper(II) form complexes of 2:1 (L:M) stoichiometry. The values of the complex stability constants of 137 with metal perchlorates in methanol are shown in Fig. 65c. Comparing with acetonitrile, in methanol larger spectral shift, particularly for lead(II) complex was observed. The further increase of solvent polarity by water addition to methanol (mixture 4:1, methanol:water) resulted in increase of molar absorption coefficient of 137 and further increase of the selectivity. Only copper(II) complex with spectral shift of 55 nm and lead(II) with spectral shift of 61 nm caused spectral changes in water containing system. The values of the stability constants (logK) 4.75 and 5.51 for lead(II) and copper(II) 1:1 complexes are lower than in acetonitrile and methanol.

Macrocyclic imidazole derivatives (Fig. 64) were also tested as ionophores in membrane ion-selective electrodes. The obtained potentiometric sensors were lead(II) sensitive. Selected macrocyclic derivatives of imidazole crowns 126 (Fig. 59), 135 and 137 (Fig. 64) were entrapped in silica xerogel matrix and tested as optical recognition elements for metal cations in water [199]. Among prepared materials, elements based on 21-membered derivatives of imidazole 135 and 137 showed spectral response (change of reflectance) in the presence of lithium salt in aqueous solution.

Structurally similar to the macrocyclic derivatives of imidazole discussed above is compound 142 (Fig. 64), N-acetylhistidine based macrocycle with two azo groups [200]. This is an example of crown ether containing azo group and –COOH mobile protons of unique pH controlled properties. The electrochemical behavior of imidazole derivative 126 (Fig. 59) and N-acetylhistidine azocrown ether 142 adsorbed on the electrode surface was investigated under different pH conditions. At pH ~ 12 similar voltammograms for 126 and 142 were obtained, but different changes were noticed under acidic conditions. It was concluded, that at pH higher than 4 the adsorbed compound 142 is present in electrochemically reducible azo form on the electrode surface. In voltammograms the first step of reduction for N-acetylhistidine azomacrocycle 142 was not observed below pH 4.0. This suggests that transformation to the hydrazine form occurs in chemical pathway, not by means of an electrode process. This is a unique example of pH dependent on/off process due to the presence of azo group.
Tetrapyrrolic macrocyles with azo moiety as a part of macroring, compounds 143 and 144, (Fig. 66) were obtained by Tsuda and co-workers [201].

$^1$H NMR experiments performed in chloroform-$d$ showed that after exposure of 143 solution onto UV-light (350 nm) a mixture of isomers was present. In the photostationary state the trans to cis ratio was 6:4. Higher conversion to the cis isomer was obtained for compound 144 with the trans to cis isomers ratio 4:6. According to theoretical calculations for cis isomer of 143 the photoisomerization results in a larger structural distortion of the macrocycle. Reverse cis to trans reaction for both compounds occurs thermally and can be accelerated upon irradiation with visible light. The half-life at 25 °C of thermal back reaction for 143 was estimated to be 8 days in toluene solution, whereas for 144 the time is much shorter (14 h). Taking into account the values of activation energy for 143 and 144 obtained from van’t Hoff plots it was stated that the thermal stability of cis-144 is lower than cis-143 having less overcrowded structure. The obtained tetrapyrrolic derivatives were suggested to be used for photoswitchable molecular devices.

The reversible trans–cis isomerization of host molecules, as it was shown in relatively early works of Shinkai [141] can be used for light-driven transport of guest molecules. Scherman and co-workers [202] described the synthesis and complexing properties of macrocycle 145 (Fig. 67) containing bis(imidazolium)-azobenzene motifs.

According to $^1$H NMR analysis, compound 145 exists as all-trans isomer ($E,E$-145). UV-light-promoted isomerization generates a mixture of stereoisomers: $E,E$-145 (18%), $E,Z$-145 (38%) and $Z,Z$-145 (44%). Visible light illumination causes the reversible process; the isomer $E,E$-145 (64%) prevails in the photostationary state. Macrocycle 145 in all-trans form interacts with 4,4′-dipyridyl-$N,N'$-dioxide (4DPDO). According to quantum mechanical calculations, in the complex the ligand adopts cage-like conformation and the guest is encapsulated inside the host cavity. Each of the oxygen atoms of 4DPDO are hydrogen-bonded by two of...
the four acidic protons from imidazole rings. Exposure of the complex to UV light induces trans to cis isomerization of the macrocycle azo groups resulting in the guest release from the cavity, what was detected by $^1$H NMR spectroscopy. The studies revealed that the Z-predominant isomeric mixture of 145 interacts with the guest very weakly due to significant decrease of the 145 cavity size and change of the ligand conformation resulted from trans to cis isomerization. Irradiation of the mixture with visible light increases the ligand affinity to 4DPDO and ensures the guest encapsulation inside the macrocycle cavity. Thanks to these properties ligand 145 can be considered as photoswitchable molecular container.

**Azo group(s) as peripheral part of the macrocycle**

Thanks incorporation of azo group “spectroscopically silent” in the visible range compounds gain the chromogenic character and photoactivity. Ballester and co-workers [203] reported dimerization of urea-based calix[4]pyrrole with four appended azobenzene units 146 (Fig. 68) templated by the encapsulation of 4,4′-dipyridyl-$N,N'$-dioxide (4DPDO). The assembly can be observed only when all azo groups are in trans form. Light-induced trans to cis isomerization of a single azo moiety is probably sufficient to trigger the disassembly of the capsule. The subsequent back isomerization conducted in the dark or upon visible light irradiation results in the quantitative recovery of the complex.

Molecular switches or molecular devices can be based on porphyrins and phthalocyanines skeletons. An azobenzene moiety was joined at the meso position of expanded porphyrins, called also smaragdyrins [204]. Azobenzene-smaragdyrin conjugates were obtained using dipyrromethane bearing azo unit as precursor. Smaragdyrins 147–154 (Fig. 69) were synthesized by acid-catalyzed [3 + 2] oxidative coupling of dipyrromethene precursors with para-substituted 5,10-diphenyl-16-oxatryptyrans in ~25% yields. The spectroscopic and electrochemical measurements showed that the azobenzene residue covalently linked to the meso carbon atom leads to interaction between the azobenzene residue and the macrocyclic π-system. In solid state compound 151 azo group is in trans form. The reversible trans cis isomerization for smaragdyrin–azobenzene conjugate was studied for compound 151 in toluene by irradiation (360 nm) and monitored by UV–Vis spectroscopy. In UV–Vis spectrum upon illumination the following changes were observed: a decrease of absorption intensity of band at 350 nm and some increase in the absorption band at 450 nm with a sharp decrease of the band intensity in the Soret band region. These changes were attributed to the trans to cis isomer conversion. Upon continuous irradiation within about 5 min a green color characteristic for smaragdyrin disappeared indicating decomposition of the system.

The linkage of porphyrin—both free and in form of zinc(II) complex—and fullerene C₆₀ moieties (Scheme 20) with a central azobenzene moiety gave dyads 155 and 156 which properties can be controlled by photoinduced changes only of the azo moiety [205]. The properties of obtained macrocycles were exhaustively studied by spectroscopic and electrochemical methods. Unfortunately, no evidence of photoinduced cis–trans isomerization was found; moreover the photochemical decomposition of the azo dyads was noted upon continuous irradiation.

**Calixarenes with azo group**

Calixarenes—cyclic oligomers are obtained by base or acid-induced condensation of phenol with aldehyde. Since the first synthesis of calixarenes by Gutsche [206], calixarenes have been used in many branches, e.g. in prevention of the oxidation of organic substances [207, 208]. However, the main applications are due to their ability to form complexes with metal cations, neutral species [209–212] and anions [213, 214]. Calix[ₙ]arenes are popular host...
molecules, which properties can be modified towards chromogenic, photoswitchable and redox active compounds by introducing an azo moiety. Modification of calixarenes skeleton can lead to conformational and structural changes and can affect the binding properties of these macrocyclic compounds.

The conformation of calix[4]arene, i.e. cone, partial cone or 1,3-alternate depends inter alia on the number and type of substituents of the macroring. Calix[4]arenes in the cone conformation with azo moieties at the meta position (in relation to the alkoxy groups) (Fig. 70) were obtained via nitroso derivatives obtained by preceded mercuration [215]. The effect of the unique for calixarenes substitution pattern and introduction of two bulky residues is rigidified molecular structure. In solution pinched cone – pinched cone interconversion is stopped (found by temperature dependent 1H NMR in dichloromethane), meaning that modified calix[4]arene adopts only one of the two possible pinched cone conformations. The resulting meta position modified calix[4]arenes can be considered as molecular receptors exhibiting cation-π binding properties.

A series of azocalix[4]arenes 161–164 with one, two, three, and four free phenolic groups were synthesized in reaction of 4-nitro- and 2,4-dinitrophenylhydrazines with calix[4]arene diquinones and also in diazocoupling reactions of calix[4]arenes [216]. As an example, the synthesis of dialkyl azocalix[4]arenes with two free phenolic groups by diquinone route is shown in Scheme 21.

The relationship between the conformation of azocalix[4]arene and the number of free phenolic OH groups was established by X-ray studies. It was concluded that azocalix[4]arene adopts a cone conformation if it contains at least one free phenolic OH group. Partial cone or 1,3-alternate conformers of azocalix[4]arenes were found in macrocycles with all substituted phenolic groups. The possibility of the controlling the conformation of calix[4]arenes is very important in design of the complementary hosts to a particular guest molecules. Additional benefit is the introduction of chromogenic groups useful in preparation of spectrophotometric and naked-eye sensing reagents.

Dendricalixarenes 165–169 (Fig. 71) [217] with azo groups at the upper rim of calix[4]– or calix[6]arene can be next examples of the structural consequences of attaching photoactive azo moieties. For preparation of azo derivatives, a method of direct diazocupling of the diazonium salt with calixarene core was elaborated. The expected effect of the introduction of photoswitchable azo groups was to control the flexibility and accessibility of the inner spaces of the dendrimers by trans–cis isomerization. It was found that receptors 166, 167, and 169 (with the azo groups in the trans configuration) do not form complexes despite the increased accessibility of the inner spaces of the dendrimers.
Complex formation was not observed also upon photoinduced conversion into \textit{cis} forms. However a model compound 170 forms a stable complex of high binding constant with 4-(4-dimethylaminostyryl)-\(N\)-methylpyridinium iodide (DASPMI) of rod-like geometry.

Photoactive azo residue was also used for joining two molecules of calix[4]arenes to form dimeric structures (Fig. 72) [218]. Azo linked calix[4]arene 171 exists in a locked \textit{trans} form [219]. The modification of the structure by providing azobenzene linker between two calix[4]arene molecules results in more flexible structure, for which the reversible \textit{trans–cis} isomerization can be achieved. UV illumination of 172 solution in chloroform leads to photostationary state with 35:65 \textit{trans : cis} ratio (according to \(1^H\) NMR measurements). The reverse \textit{cis–trans} isomerization rate of 172 in the dark, is solvent polarity, viscosity and pH dependent. These properties of dimeric calix[4]arene make it useful as a light-responsive molecular container.

Calixarene skeletons with crown ether functionality form metal cation complexes with the involvement of the macrocyclic polyether unit. Complexation of metal cations by azobenzene crown ether \textit{p-tert}-butylcalix[4]arene 173 (Fig. 73) was analyzed using DFT calculations [220].

The optimized structures of crown ether \textit{p-tert}-butylcalix[4]arene showed that more stable is this form in which azo moiety has \textit{trans} configuration. Proposed models also showed that for both \textit{trans} and \textit{cis} isomers better complexation efficiency for alkali metal cations characterizes crown-ether with benzene-rings (\textit{exo}) pockets. The obtained models also proved the higher affinity of macrocycle for sodium over potassium ion. Preferential sodium cation complexation was found for the \textit{trans}-complex in the \textit{exo}-binding mode comparing the \textit{cis-exo} analogue.

Calix[4]biscrown compound bearing azobenzene unit 174 was described as a colorimetric receptor for \(\text{Hg}^{2+}\) ions in acetonitrile (Fig. 74) [221]. According to UV–Vis analysis it was stated that complexe of 1:1 stoichiometry is formed.
Complexation is manifested by change of color from red to pale yellow only when perchlorate anions are used as the counterion. X-ray analysis of $\text{Hg(NO}_3\text{)}_2$ complex shows crystal structure with the formula $[\text{Hg(NO}_3\text{)}_2]_\text{n}$ where each of $\text{exo}$-coordinated $\text{Hg}^{2+}$ is in a distorted tetrahedral surroundings with its coordination sites occupied by two sulfur atoms from two different ligand molecules and two $\text{NO}_3^-$ anions. Addition of potassium salt to $\text{Hg}^{2+}$ solution in acetonitrile affects its UV–Vis spectrum indicating formation of heterodinuclear complex.

Supramolecular systems, where ionic species are transported across bilayer lipid membranes are used as artificial models for natural photo-excitable membranes. It was demonstrated that ether derivative of $p$-$\text{tert}$-butylcalix[4]arene $173$ studied analyzed by DFT calculations [220].

Macrocyclic compounds with azo groups are interesting objects not only as molecular receptors or building blocks in molecular devices or machines. Some of them show antibacterial activity. An example can be azocalix[4]arene $176$ (Fig. 75) obtained by diazo-coupling of tetradiazonium salt of calix [4] arene and 2,6-diaminopyridine, which shows strong activity against Gram-positive bacteria $\text{Bacillus cereus}$, while the activity against $\text{Escherichia coli}$ is mild; the $\text{Pseudomonas aeruginosa}$ shows resistance [223].

Cyclodextrins with anchored azo moiety

Cyclodextins (CDs) known since the Villiers discovery [224] for more than 125 years, are cyclic oligosaccharides that consist of $\text{d}$-glucopyranose units linked by $\alpha$-(1,4)-glycosidic bonds. Depending on the number of glucopyranose units CDs can be classified as $\alpha$-, $\beta$- and $\gamma$-CD with six, seven and eight units, respectively (Fig. 76).

Hydrophilic outer surface and a hydrophobic cavity of the native CDs and their derivatives cause that these compounds form inclusion complexes with a number of guest molecules: organic, inorganic, biological molecules and ions [225]. The versatile career of CDs is due to their availability, biocompatibility, biodegradability and industrial scale production. That is why complexes of CDs with various molecules have found multitude applications in many branches of science and industry, for example: in supramolecular polymers [226–228], hydrogels [229], bioactive materials [230], drug delivery [231–234], dynamic materials [235], catalysis [236] and separation methods.
Substituted cyclodextrins give the possibility of the more specific modification of different type of substrates, molecules and surfaces [240], changing their physical and chemical properties, which opens the way to the new applications of such hopeful systems [241]. Among them, derivatives bearing azobenzene moiety at various locations of the cyclodextrin(s)' containing architectures, are intensively studied due to their chromogenic character and unique photo-responsive properties induced by the photochemical trans–cis isomerization.

Cyclodextrins are often utilized in a construction of the nanometer-scaled supramolecular architectures. The properties and the organization of self-assemblies can vary, inter alia, depending on reaction conditions. This allows to control the structure of supramolecular frameworks by tuning the conformation of the building blocks. The interesting example of systems of the same chemical composition, but different conformations was given by Liu and co-workers [242]. In Huisgen’s cycloaddition, (Fig. 77) using the same reactants, but carrying out the reaction under different conditions two conformations: 177a—self-locked and 177b—self-unlocked were identified. The structures of obtained products were confirmed by X-ray and spectroscopic studies. In self-locked conformer—in solution and in solid state—azobenzene moiety is located in the own cavity. It presents a unique [1]rotaxane without a stopper part. Conformer 177b was found to exist as a linear supramolecule.

[1]Rotaxanes 178 and 179 (Fig. 78) based on β-cyclodextrin skeleton, bearing azo moiety were also efficiently prepared via self-inclusion complexation and Suzuki-coupling capping in aqueous solution [243]. Obtained [1]rotaxanes 178 and 179 were characterized by absorption and induced circular dichroism spectra. [1]Rotaxane 179 undergoes photo- and thermal reversible trans–cis isomerization.

Scheme 22 Synthesis of a photoresponsive ion carrier 175 based on calix[4]arene [222]
The goal of the introduction of azo moiety while modifying the cyclodextrins is the possibility of using them as photoswitchable systems. The efficient modification of the cyclodextrins' skeleton requires the elaboration of the appropriate synthetic procedures. Huisgen's [3 + 2] cycloaddition was used for the efficient synthesis of azobenzene bridged β-cyclodextrin 180 (Fig. 79a) which was obtained in a click reaction in 72% yield [244].

An oxidative coupling in Sonogashira-type reaction has been used in synthesis of β-cyclodextrin derivative bearing an azobenzene group on the secondary face 180 (Fig. 79b) [245]. Optimized reaction conditions (degassing of the reaction mixture, the use of [Pd(PPh₃)₄], pre-heated oil bath, diluted reductive H₂ atmosphere) allowed to diminish the formation of the dimeric side product. Such conditions resulted in 62% yield of the demanded azocompound.

Not only assembly/disassembly processes of supramolecular systems can be photocontrolled, but also morphological transformations of supramolecular assemblies can be light-induced. Liu and co-workers [246] described the nanotube–nanoparticle morphological conversion for the

![Fig. 75](image1)  
**Fig. 75** Azocalix[4]arene showing antibacterial activity [223]

![Fig. 76](image2)  
**Fig. 76** α-, β- and γ-CD and schematically their hydrophilic surface and a hydrophobic cavity

![Fig. 77](image3)  
**Fig. 77** The scheme of Huisgen’s cycloadditions carried out under diverse conditions leading to different conformers 177a and 177b. Numbers of molecules in reproduced material correspond to following numbers in this manuscript: 1 = 177a; 2 = 177b. Reprinted with permission from [242]. Copyright 2008 American Chemical Society
secondary assembly of amphiphilic porphyrin (182, guest molecule) mediated by azobenzene-bridged bis(permethyl-β-CD) (183, host molecule; Fig. 80). Azo-bridged β-CD, both as trans and cis isomer, forms complexes of 1:1 stoichiometry with guest molecule, porphyrin 182. The estimated binding constant value for complex of cis-isomer is higher than for trans isomer. This can be a result of cooperative binding of the porphyrin derivative by two β-cyclodextrin cavities in cis-complex (the sandwich type complex). The interaction of trans-azobenzene-bridged bis(permethyl-β-cyclodextrin) 183 with amphiphilic porphyrin derivative 182 in aqueous solution (pH 7.2) leads to aggregate formation with hollow tubular structure. According to TEM images the average inner and outer diameters of obtained nanotubes were about 45 and 61 nm with a wall thickness of about 8 nm. It was deduced that interior and exterior surfaces of nanotubes are composed of units of trans-183-182 complexes, whereas the alkyl chains of 182 interlace with each other in the middle of tubular walls. UV-light irradiation (at 365 nm) of trans-183-182 solution induces morphological conversion being a result of trans to cis isomerization of the azobenzene moiety. TEM analysis confirmed that upon photoisomerization long trans-183-182 nanotubes turn to nanospheres of average diameter of 180–220 nm. Subsequent irradiation of complex with the cis isomer enables nanotubes reconstruction. This photocontrolled process was found to be reversible and repeatable. TEM and DLS experiments confirmed that morphological switching can be repeated by irradiation for tens of times.

Photochemical properties of bis-β-cyclodextrin bearing azobenzene unit 184 was reported by Djedaini-Pilard and co-workers [247]. It was found that 184 can form two different inclusion complexes with adamantyl derivative 185 depending on 184 photoinduced isomers (Fig. 81). The cis-184 complex of 1:1 stoichiometry is created when two cyclodextrin cavities bind simultaneously two adamantyl units of the guest. It was deduced that formation of supramolecular polymers with n:n stoichiometry for trans-184 is the most probable.

Azobenzene attached to the secondary face of β-CD was utilized as gated synthetic ion channel (Fig. 82) [248]. β-CD works as a channel for ionic species transport, whereas photoresponsible azobenzene unit acts as a gate, opening or closing upon irradiation. Dependent on trans or cis conformation of azobenzene moiety, cations or anions are preferentially transported.

Permethylated α-cyclodextrin-6A-monoalcohol modified with azophenol 186 (Fig. 83) was used [249] for colorimetric detection and differentiation of primary, secondary and tertiary amines. Chloroform solutions of 186 change color in the presence of 1° and 2° amines as a consequence of spectral shift from 380 to 580 for primary and to 530 nm for secondary amines. Tertiary amines do not cause spectral changes. The values of the stability constants of 186 complexes with primary amines were found to be higher than with secondary amines. It was deducted that the number of possible hydrogen bonds formed between the oxygen atoms of crown ether and amine protons is crucial for the binding strength of the guest molecule.

Azobenzene bearing γ-cyclodextrin derivative 187 (Fig. 84) was tested as a probe for derivatives of phosphoric acid [250]. It was proved that the described host molecule reveals high selectivity towards ATP over other tested
phosphoric acid derivatives (mono-, pyro-, and triphosphate, AMP, ADP) in aqueous solution at pH 7.4. Compound 187 forms with ATP complexes of 1:1 stoichiometry with binding constant $6640 \pm 890 \text{ M}^{-1}$. The estimated value is 2.5 times higher than for complex without cyclodextrin unit, what indicates significant role of macrocyclic cavity in the guest complexation. On the basis of $^1$H NMR experiments it was suggested that adenine moiety of the guest is bound inside cyclodextrin cavity, thanks to what it is in close proximity to the azobenzene unit making $\pi-\pi$ interactions between adenine and azobenzene stronger than in the case of ligand without cyclodextrin residue. Additionally, recognition of phosphoric moieties of ATP is provided by dipicolylamine—Cu$^{2+}$ unit. These multipoint interactions are probably responsible for high selectivity of ATP recognition.

Photoswitching properties of azobenzene make it an interesting candidate for controllable drug therapy. For example, azobenzene units were used in fabrication of a triple-layer nanocomposites tested in vitro anticancer therapy as a drug.
delivery system [251]. The single particle consists of gold nanobipyramids (the core), mesoporous silica nanoparticles (the middle layer), and hyaluronic acid functionalized with α-cyclodextrin and azobenzene. Inside the silica pores anticancer drug—doxorubicin is loaded. Experiments carried out for human squamous carcinoma cells (representative cancer cells) and human keratinocyte cell (representative normal cells) revealed that these nanocomposites are able to specifically accumulate around the tumor tissue due to noncovalent interactions between hyaluronic acid and CD44 receptor overexpressed in cancer cells. Localized irradiation with near-infrared light (780 nm) converts cis-azobenzene to its trans isomer what leads to hydrogel formation due to noncovalent interactions between α-cyclodextrin and trans-azobenzene. Thanks to the presence of specific enzyme—hyaluronidase around the tumor cells the network in the hydrogel is degraded resulting in the anticancer drug release and its transport to the cancer cell nuclei.

The association of artemisinin (ART) 188 with an azobenzene bridged bist(β-CD) derivative with an azobenzene 6–6’ linker 189 in aqueous solution was investigated by circular dichroism (CD) spectroscopy (Fig. 85) [252].
It was shown that bis(β-CD) with \textit{trans}-azobenzene unit binds artemisinin (1:1 complex) and this process can be light controlled. Upon irradiation at 363 nm \textit{trans–cis} isomerization causes loss of the binding ability of artemisinin.

**Polymers bearing macrocycle(s) and azo motif(s)**

Azo derivatives found a vast range of applications in polymer science. Polymers containing azobenzene moiety have been intensively studied due to their photoreponsive properties ensuring the obtainment of functional materials. An azo group can be a part of a supramolecular system in polymer matrix (non-covalent interactions) or can be covalently bound within a polymer chain. Polymers, responding to light irradiation are widely investigated systems due to reversible (or irreversible) changes of physical properties [253]. This can be utilized in many branches of science.

The change of the polymer properties can be very often achieved by using molecules, which act as molecular containers. Elegant molecules of such properties are cyclodextrins, described earlier, which can be also used for design and synthesis of functional polymers.

A system utilizing noncovalent interactions between synthesized in a click reaction AZO-β-CD (Fig. 86), which interacts as a “dimer” with azo bearing polyester obtained in reaction of ε-caprolactone with \textit{p}-aminoazobenzene (AZO-PCL) (Fig. 86a), was described by Ma et al. [254]. It was suggested that in aqueous solution micellar aggregates are formed due to host–guest interaction between (AZO-β-CD) and AZO-PCL (Fig. 86b). On the basis of \textsuperscript{1}H NMR spectra it was suggested that the guest molecule in its \textit{trans} form is included shallowly into cyclodextrin cavity from its wider site. After UV-light irradiation the transparent opalescence solution becomes turbid, what is a result of decomplexation followed by disaggregation. The uniform vesicles are reformed upon exposure of the solution to visible light. Authors propose possible use of the system in the control or release of drugs.

Photosensitive hydrogel based on α-CD, dodecyl-modified poly(acrylic acid), and a photoresponsive competitive guest [255] inspired further studies of self-assembling systems with polymer side chains. Poly(acrylic acid)s (pAA) with p3αCD and p6αCD functionalities and pAA carrying azobenzene moieties (pC12Azo), were used for the construction of the photoresponsive system based on polymer–polymer interactions (Fig. 87) [256]. The properties of obtained systems were studied in details among others by steady-shear viscosity (η) measurements. The method was chosen because the interaction of the CD polymers with pC12Azo (formation of inclusion complexes of CD moieties in the CD polymers with side chains of guest polymers) may cause an increase of solution viscosity. The mixture of the p3αCD/pC12Azo and p6αCD/pC12Azo has shown contrast η changes upon photoirradiation: decrease in the case of the p3αCD/pC12Azo mixture, and increase of η for p6αCD/pC12Azo mixture. Irradiation with visible light causes the reverse process in the above cases, i.e. η values became similar to those before the UV exposure. The differences in η values were explained by the fact that UV light causes dissociation of inclusion complexes for the p3αCD/pC12Azo mixture, and the formation of interlocked complexes for the p6αCD/pC12Azo mixture (Fig. 87, bottom).

PEG-substituted CD with an azobenzene residue at the end of the PEG chain (6-Az-PEG600-HyCIO-β-CD) was obtained by Harada and co-workers (Fig. 88) [257]. The photochemically and thermally induced conformational changes in aqueous solutions were studied by 1D and 2D NMR analyses. It was found that at low concentration, 6-\textit{trans}-Az-PEG600-HyCIO-β-CD forms different types of intermolecular, self-inclusion complexes or exists in an uncomplexed form depending on the temperature. An intermolecular complex is formed at high concentration. Regardless of the concentration, irradiation by UV light promotes complexation with the CD including the azobenzene part.

The attaching of azobenzene groups to side-chains of liquid crystalline polymers results in light-controllable polymer materials. Such films and coatings can be applied for example as optical molecular devices. One group of such materials are derivatives of crown ethers bearing residues able to form liquid crystalline (LC) phases. Complex formation by crown ether moiety can lead to the appearance or disruption of supramolecular structures. A series of photochromic azobenzene-crown-containing compounds forming crystalline and nematic phases were described by Shinkai and co-workers [258]. Photochromic crown ether-containing LC homopolymers and copolymers based on azobenzenes were later described also by Bobrovsky and co-workers [259]. The complexation of metal ions by these compounds cause the decrease of clearing temperature and sometimes the transition into the amorphous state. The investigation of the relationship between molecular architecture of this type polymers and their photo-optical properties and phase behavior was the main scope of studies. Bobrovsky and co-workers [260] described among others the synthesis and properties

![Fig. 85 Azobenzene bridged bis(β-CD) 189 and the formula of artemisinin 188 [252]](image-url)
of two types of polymers differing in the position of the crown ether in relation to the photoresponsive azobenzene residues (Fig. 89). Macrocyclic moiety was linked directly to chromogenic residue (Fig. 89, left) or via carboxymethylene spacer (Fig. 89, right). Phase behavior, spectral properties and kinetics of photo-orientation processes inside thin films of polymers shown in Fig. 89 were found to be dependent on the location of crown ether with respect to the residue bearing azo group. In the case where a crown ether was introduced as separated non photochromic side group the decrease of the degree of photoinduced orientational order was found. Complex formation with potassium ions by compound shown in Fig. 89 (left) results in the decrease in degree of the photoinduced order. Possible application in the creation of new sensing materials was suggested.

Zhu and co-workers [261] described linear and cyclic (Scheme 23) amphiphilic polymers containing azobenzene moieties. Macrocyclic polymers were obtained in Cu(I)-catalyzed azide-alkyne cycloaddition to achieve intramolecular macroring closure process, one of the most popular and powerful “click” synthetic reaction [262].

According to the obtained results, azomacrocycles exhibit increased glass transition temperatures, faster trans–cis–trans photoisomerization, and enhanced
fluorescence intensity in comparison to their acyclic analogues. In water:THF mixture (1:1, v/v) both macroyclic and linear polymers self-assemble into spherical nanoparticles. The size of aggregates formed by cyclic compounds are significantly smaller than those of corresponding linear analogues due to more dense and compact packing of macrolcycle-bearing particles. Alternating irradiation of nanoparticles with ultraviolet (365 nm) and visible (435 nm) light causes isomerization of the azo group located in polymer main chain. This induces reversible shift of the hydrophilic-hydrophobic balance of macromolecules and leads to the dissociation and reaggregation of the particles. The photosensitive behavior is slower for nanospheres containing cyclic polymers than in the case of particles with materials of linear structure.

The skeleton of the photosensitive polymers also can be enriched with other functionalities that for example are able to form complexes with metal cations. Wiktorowicz et al. [263] prepared polymers comprising dibenzo-18-crown-6 moieties joined by azo bridges using reductive coupling procedure (Fig. 90). Spectrophotometric measurements showed that the polymers are pH-sensitive and exhibit solvatochromic properties. Alternating irradiation of the polymers with UV and visible light induces reversible trans–cis–trans photoisomerization. Due to the presence of crown ether cavity, the described polymers interact with Ba\(^{2+}\) ions and also with low molar mass pyridinium type guests, leading to complex-induced phase separation in solvents of lower polarity. In alcohols the polymers reveal thermo-responsive behavior exhibiting the upper critical solution temperature type transitions. This effect depends on the polymer concentration and the degree of polymerization.

Cozan and co-workers [264] described the preparation of copoly(ether sulfone)s with azocrown ether and fluorene fragments. The polymers 196–200 (Fig. 91) showed good solubility in solvents of different polarity. Thermogravimetric analysis showed the lowest thermal stability of the copolymer 196 among all investigated polymers as it contains only azo-crown ether units that are sensitive to thermal degradation. The insertion of fluorene moieties into a polymer chain significantly enhances thermal stability. The trans to cis isomerization of the polymers in DMSO occurs after irradiation with UV light (at 375 nm). The rate constant of the first order photoisomerization increases with decreasing the number of azobenzene units. It was also found that complexation of K\(^+\) inside the macrocyclic cavity increases trans to cis isomerization rate.

Photo-induced structural transitions of azo compound bearing dibenzo-24-crown-8 (DB24C8) moiety, dibenzylammonium salt (DBA), and 1,2,3-triazole groups were tested by Dong et al. [265]. Due to host–guest interactions between DB24C8 and DBA from separated molecules linear supramolecular polymers of 1:1 threaded structures (pseudorotaxanes) are formed. The presence of azobenzene moiety allows to control the complex formation, as trans-azobenzene-appended DBA interacts with DB24C8 stronger than its cis isomer. After addition of [PdCl\(_2\)(PhCN)\(_2\)]\(_-\), 1,2,3-triazole rings of different polymer chains are linked together by the metal coordination, what leads to the formation of cross-linked supramolecular polymers. In dichloromethane the cross-linked assemblies have a form of red gel. UV irradiation (365 nm) of linear and branched polymers induces trans to cis isomerization, resulting in weaker host–guest interactions and, in consequence, dissociation of supramolecular polymers. The structural change of cross-linked supramolecular polymer is manifested by naked eye observable decrease.
of viscosity. The reformation to the gel state is achieved by exposing the solution to visible light (430 nm).

The photoisomerization of a series of macrocyclic oligomers containing azobenzene moiety in the main chain and their linear analogs was studied by Zhu and co-workers [266] (Scheme 24). Tetraethylene glycol (TEG) was chosen as the building block for the preparation of amphiphilic polymers of good solubility. According to the UV–Vis spectrophotometry it was shown that the trans to cis and reverse process are the first order reactions for both linear 201 and cyclic 202 compounds. The estimated values of rate constants for macrocyclic oligomers are distinctly higher (for trans to cis isomerization) and slightly higher (for cis to trans isomerization) in comparison with results for linear ones, especially for \( n = 1 \). This can be
explained by the more stable conformation of cyclic cis-azobenzene than linear trans analog.

In turn, poly(ethylene glycol)methyl ether was used as building block for other amphiphilic copolymers with cyclic azobenzene unit \(203\) [267]. For comparative purposes a linear analog \(204\) was also obtained. The synthetic route is shown in Scheme 25. The obtained copolymers assemble in phosphate buffer solution (pH 7.4) into stable vesicles with hydrophobic blocks containing the azobenzene moieties aggregated in the membranes of the vesicles, and the hydrophilic PEG arrangements on the outer and inner surface of the vesicles. Due to presence of azo moiety the obtained polymers are not only photoresponsive, but also sensitive towards reducing reagents. These properties were used for the investigation of the encapsulation and release of Nile Red (NR - a model compound for drug delivery system) and anticancer drug doxorubicin (DOX). NR-loaded vesicles are fluorescent. The intensity of fluorescence can be controlled by illumination with UV light (365 nm). The reverse cis–trans process occurs upon irradiation with visible light at 435 nm.

Azo compounds can be reduced by azoreductase or popular reducing reagents, such as for example sodium dithionite. The result is azo bond cleavage, which can be used in effective drug transport. DOX-loaded vesicles were investigated in reductant-release of the encapsulated substance. The release rate of DOX from cyclic polymer \(203\) is higher compared with the linear analog \(204\). This points out the importance of investigated copolymers—particularly cyclic compounds—as potential agents in the treatment of colon disease.

Combination of cyclodextrin and azobenzene units bearing polymer were used by Winnik and co-workers [268] to obtain molecular “charm bracelets”. The cyclic poly(N-isopropylacrylamide) with azobenzene inserted in the main chain \(205\) (Fig. 92) was synthesized by the “click” ring closure of \(\alpha\)-azobenzene \(\omega\)-azido poly(N-isopropylacrylamide) in the form of inclusion complex with \(\alpha\)-cyclodextrin. UV-light irradiation of aqueous solution of \(205\) (at 365 nm) induces motion within the molecule as cis-azobenzene unit obtained upon photoisomerization, due to its size, is expelled from the \(\alpha\)-cyclodextrin cavity pushing the host to the other sections of the polymeric ring. The trans to cis photoisomerization does not affect the temperature of phase transition of the polymer, whereas in the case of the analog without cyclodextrin the temperature increases by 1.7 °C. This may be explained assuming that the enhanced polarity due to trans to cis isomerization in polymer \(205\) is overshadowed by the strong hydrophilicity of \(\alpha\)-cyclodextrin.

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\(\text{Scheme 24}\) The synthesis of the molecularly-defined linear \(201\) and cyclic oligomers \(202\) (\(n = 1–6\)) [266]

\(\text{Scheme 25}\) Poly(ethylene glycol)methyl ether based amphiphilic copolymers with cyclic azobenzene unit \(203\) and its linear analog \(204\) [267]. The chemical formulas of doxorubicin and Nile Red are also shown.

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Moiety interlocked along the polymer ring and no change of the phase transition temperature is observed.

**Miscellaneous macrocyclic systems bearing azo group(s)**

Molecular containers such as pillarenes are promising blocks for building of photoswitchable assemblies. Ogoshi et al. [269] obtained supramolecular polymers consisting of trans-azobenzene-bridged pillar[5]arene dimer 206 and bispyridinium cations linked by hexamethylene unit 207 (Fig. 93). On the basis of $^1$H NMR spectroscopy it was stated that in dichloromethane at low concentration (2 mM) complexes of 1:1 stoichiometry are formed, in which pyridinium cation moiety 207 is included inside the cavity of 206. At higher concentration (100 mM) supramolecular assemblies were detected according to DOSY $^1$H NMR experiments. Irradiation of diluted solution with UV light induces trans to cis isomerization of component 206. At the photostationary state the ratio of trans to cis isomer is 26:74. At high concentration nearly half of trans-206 does not convert into the cis form. Efficient reverse process occurs after exposure to visible light (436 nm). Under equilibrium the ratio of trans to cis isomer is 93:7.

It was demonstrated that photoisomerization from trans to cis form weakens the host–guest interactions, probably due to the steric hindrance caused by the cis isomer of 206. As a consequence, the created at high concentration, supramolecular polymers disassembly after UV-light irradiation. Photo-switching between assembly and disassembly of supramolecular system looks completely reversible by alternating irradiation between visible and UV light.

Cavitands 208 and 209 (Scheme 26) bearing azo moiety integrated with macrocyclic [270] structure undergo trans–cis photoisomerization upon illumination with UV light (365 nm). cis–trans conversion proceeds by heating to 164 °C for 5 min or irradiating with 450 nm light for 20 min. Trans–cis and cis–trans cycles can be repeated 5 times without degradation of the system. Both the trans isomers of 208 and 209 have deep cavities able to bind guest molecules. In fact, 208 and 209 were found to form complexes with small molecules of adamantane series in $d_{12}$-mesitylene. The highest values of stability constants were found for 1-adamantanecarbonitrile and 2-adamantanone. It was explained assuming the possibility of stabilization of formed complexes by hydrogen bonding and polar interactions with the upper rim of the cavitands. The complexation of adamantane guests can be light controlled, namely irradiation controls uptake and release of guest for 208.

Fig. 92 Cyclic azo-poly(N-isopropylacrylamide) with interlocked α-cyclodextrin 205 and photoinduced molecular motion within the polymer [268]
Azo moieties can constitute part of macrocyclic Schiff bases, as for example fluorescent product of \([2 + 2]\) condensation of \(N,N'\)-bis-(2-hydroxybenzaldehyde-5-yl)-benzene-1,3-diazene and benzene-1,2-diamine (Fig. 94) [271]. The stoichiometry of complexes of 210 with zinc(II), copper(II) and nickel(II) is 1:2 (L:M) as showed by elemental analyses and spectral studies. Fluorescence spectra registered in DMSO showed quenching of fluorescence of Schiff base upon metal binding.

Another example of azo derivative of Schiff base type can be chiral macrocycle 211 (Fig. 95), with three azobenzene residues [272]. This compound was obtained by \([3 + 3]\) condensation reaction of enantiomERICALLY pure \(trans\) 1,2-diaminocyclohexane with azobenzene-4,4'-dicarbaldehyde in dichloromethane. The subsequent sodium borohydride reduction of 211 produces macrocyclic hexaamine 212, also with three azobenzene units. Irradiation of chloroform solution of \((R,R,R,R,R,R)\)-211 with 365 nm light for 30 min, causes the decrease of absorption peak at 348 nm and increase of bands intensity at 273 and 450 nm. The back process occurs upon leaving the solution at room temperature for 48 h. Similar observations were made for reduced analogs.
Interesting properties were found for \( \textit{211} \) dissolved in benzene. In this solvent a translucent and orange colored gel was obtained. Scanning electron microscopy (SEM) measurements of the obtained material showed the presence of elongated fibers with diameters of around 1 \( \mu \text{m} \) in the dried gel. The illumination of the gel with UV light for several hours led to gel–sol transformation. The reverse process occurs upon heating the sol. Macrocycle \( \textit{212} \) forms inclusion complexes with various aromatic organic guest molecules. Complexes of 1:1 stoichiometry were found for benzene and toluene as the guests and 2:1 (\( \textit{212} \):guest) when \( o-, m-, \) and \( p- \)-xylenes were complexed. This can indicate better complementarity of the host and benzene or toluene than in the case of larger xylene molecules.

Not always photoinduced transformations are reversible. Red colored compound \( \textit{213} \) (Fig. 96) obtained in reaction of 3,3\(^{\prime}\)-dihydroxy-4,4\(^{\prime}\)-bipyridine and \( \textit{azobenzene-2,2\text{\textprime}-dicarboxylic acid in dichloromethane is a highly-strained cyclophane 213} \) comprising azobenzene and methyl viologen units [273]. Cyclic voltammperometric measurements showed its unique irreversible electrochemical behavior. \textit{Trans–cis} isomerisation upon visible light illumination of \( \textit{213} \) is also irreversible.

The photo- and redox properties of azo compounds can be extended to more sophisticated systems due to incorporation of transition metal cations into their structure. In such cases both the photoisomerization of azo compounds and chemical and physical properties of transition metal cations (optical, redox, magnetic etc.) can be utilized for construction of functional systems. Among the others, tetraneur nuclear macrocyclic gold(I) alkynyl phosphine complexes with two azobenzene moieties, were obtained (shown schematically in Fig. 97) and investigated as photoswiciable system [274]. It was found that the photo switching of gold(I) complex could be locked or unlocked with a second input: by the addition or removal of silver(I) ions.

The conformational change of the molecule which is a consequence of the reversible \textit{trans–cis} isomerization and the red-ox properties of iron are good examples of construction block for multi-stimuli molecular devices. The interlocking of a ferrocene-based rotary module with a photochromic azo unit of molecular machines operating \textit{via} power-conversion mechanisms can be constructed. Such systems resemble daily used devices such as pliers \( \textit{214} \) shown in Fig. 98 [275].

Azov et al. [276] investigated macrocyclization of tetrathi-fulvalene dithiolates with \textit{bis-bromomethylazobenzenes}
(Ab) under high dilution conditions (Fig. 99). The reaction afforded [1 + 1] cyclization product 215 with m-Ab and [2 + 2] cyclization product 216 with p-Ab in good yields (above 66%). Irradiation of p-Ab with UV light (365 nm, 0°C) before reaction results in obtainment of cis-azobenzene bearing product 217 (1 + 1 cyclization type). Analysis of cyclic voltammograms registered in dichloromethane/0.1 M Bu4NCIO4 showed that the electrochemical properties of tetrathiafulvalene moiety strongly depend on configuration (trans or cis) of azobenzene unit.

Banerjee and co-workers [277] synthesized and compared properties of two covalent organic frameworks (COFs) (Fig. 100) being derivatives of triformaldehydroleinol and 4,4′-azodianiline (Tp-Azo) or 4,4′-diaminostilbene (Tp-Stb). Azo-functionalized COF Tp-Azo exhibits better stability, porosity and crystallinity than stilbene-bearing analogue Tp-Stb. The analysis of N2 absorption isotherm of Tp-Azo treated with 9 M HCl indicates the retention of intrinsic porosity of the azo-functionalized COF, whereas in the case of Tp-Stb decrease of porosity after the acid treatment was observed. According to TGA experiments it was stated that Tp-Azo possesses higher acid loading (5.4 wt%) than Tp-Stb (2.8 wt%). Doping of H3PO4 to the azo-functionalized COF leads to immobilization of the acid inside the framework pores, what enables proton transfer in both the anhydrous (σ = 6.7 × 10−5 S cm−1 at 340 K) and hydrated state (σ = 9.9 × 10−4 S cm−1 at 332 K under 98% relative humidity). Stilbene-bearing COF shows almost zero proton conductivity in anhydrous milieu and a poor proton conductivity value (σ = 2.3 × 10−5 S cm−1) at 332 K under 98% relative humidity.

Azobenzene isomerization has been also utilized to drive functional changes in biomolecules such as: peptides, proteins, lipids, nucleic acids and carbohydrates. Comprehensive review of such applications can be found in the work of Beharry and Woolley from 2011 [72]. To apply azobenzene to direct protein conformational change in biological systems several requirements need to be fulfilled such as: (i) substantial structural change of azo bearing unit upon isomerization that can be coupled to protein conformational change, (ii) stability of the azo unit in a cellular environment, (iii) a suitable for cells and tissues irradiation wavelength and rate of thermal relaxation. Photocontrol of cyclic peptides was investigated among the others by Schutt et al. [278]. The authors described cyclization of a heptapeptide containing the Arg-Gly-Asp (RGD) sequence with 4-amino-methylphenylazobenzoic acid (AMPB). Studies of the cyclic peptide affinity to the cell surface receptor αVβ3 integrin

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**Fig. 96** Highly-strained cyclophane 213 comprising azobenzene and methyl viologen units [273]

**Fig. 97** Schematic diagram demonstrating the “locking” and “unlocking” mechanism brought about by the addition and removal of Ag⁺ ions in preventing and facilitating trans–cis isomerization of [Au₄(P²P)₂(C≡C–L–C≡C)]. Reprinted with permission from [274]. Copyright 2007 American Chemical Society.
show that RGD binds target protein stronger when azo unit is in its trans form. The cell adhesion can be also controlled by tethering of RGD peptide to a surface via azobenzene linker. 3-((4′-aminomethyl)phenylazo)benzoic acid was used to control the conformation of a cyclic peptide based on nNOS β-finger [279]. The trans isomer shows binding affinity towards target protein—α-1-syntrophin. Irradiation of the system with light at 330 nm enables the protein recognition. According to FTIR and NMR experiments, the isomerization azobenzene unit induces the formation of secondary, antiparallel β-type structure of the peptide ensuring the efficient interactions with α-1-syntrophin. Incorporation of azobenzene unit into protein disulfide isomerase via bis-cysteinyl active site was used to the obtainment of a simple model for allosteric conformational rearrangements [280]. It was stated, that the geometric changes accompanying isomerization of the azo group induce a rearrangement of peptide sequence changing energy landscape of the peptide and both isomers trans and cis exist in defined conformational states stabilized by disulfide bridge. Derda et al. [281] proposed bis(allenamide) functionalized azobenzene reagents for conversion of cysteine containing peptides to light responsive macrocycles. In comparison with typically used bis-alkyl halides containing azobenzene the allenyl amide derivatives ensure 2–3 order of magnitude faster macrocyclization by cysteine ligation in model peptide and those displayed on M13 phage. Woolley and co-workers [282] incorporated a thiol reactive azobenzene cross linker 218 into peptide backbone receiving cyclic azopeptides 219–221 (Fig. 101). Upon irradiation of the peptides in aqueous solution with blue light at 400–450 nm trans to cis isomerization occurs. Obtained cis isomers relax thermally with a half-life
of about 1 s. It was stated, that azobenene linker 218 can be used to control of helical content of attached peptide, as in its \textit{trans} form the linker bridges Cys residues spaced $i, i+15$ (peptide 219) in an $\alpha$-helix. Switching 218 to its \textit{cis} isomer causes the decrease of the helix content of 219 and the increase of the helix content of 221. After photoisomerization no helix content of 220 is detected.

Jaeschke and co-workers [283] described carbohydrate-based macrocycles obtained from isothiocyanate-armed bis-azobenzenes glycosides and piperazine. Isomerization of glycoazobenzene precursor molecules before the reaction ensured more efficient macrocyclization (yields: 48–65%). Obtained \textit{trans} macrocycles isomerize into their \textit{cis} forms upon UV-light irradiation what results in tremendous change of chirality with a strong helical induction in the \textit{cis} state. The isomerization process is fully reversible by thermal relaxation, whereas upon irradiation with blue light only partially recovery of \textit{trans} isomer is obtained.

**Summary**

The above review article is a subjective point of view on the current state of art in the synthesis and properties of selected azomacrocyclic compounds. It covers mainly the last 10 years, however, many of the previous works were also cited, to give more comprehensive background of the subject. Our intention was to underline the importance of very simple, seemingly tiny, functional $\text{--N=N--}$ group, which can be incorporated into almost any molecule (material) giving extraordinary properties, especially when macrocyclic compounds are regarded. The presence of macrocyclic scaffold
can have an enormous influence on switching properties of azo group due to ring strain and substituent effects. Photochemical characteristic of cyclic azobenzenes depends also on other factors, such as the number of azo units in the macrocycle, the symmetry of total molecule and the degree of conjugation, what makes the design of azomacrocyclic compounds a challenging task. Reversible trans–cis isomerization gives an opportunity to control the macrocycles structures at the molecular level what can be utilized for instance in the development of light-induced assembly/disassembly processes of supramolecular systems or in morphological transformation of assemblies. Binding properties of macrocyclic hosts e.g. crown ethers or cyclodextrins can be regulated by photoswitching of azo moiety, what finds applications among the others in ion transport through membranes and controlled drug release systems. Chromogenic and electroactive properties of azo group enable effective macrocycle use in optical and electrochemical sensors development. In the above manuscript we wanted to signalize the multifarious areas of science, technology and medicine where macrocyclic azo compounds can find applications. We believe the review will be helpful for readers interested in organic, analytical and practical aspects of supramolecular chemistry.

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