REVIEW ARTICLE

Cyclodextrin-based rotaxanes

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Abstract Selected examples of cyclodextrin-based rotaxanes are described in the aspect of their syntheses and possible applications, especially in the design of molecular devices and sensors.

Introduction

Cyclodextrins (CDs) are intensively studied, mainly in view of their receptor abilities; they have a hydrophilic exterior and a hydrophobic interior which enable formation of inclusion complexes via hydrophilic–hydrophobic interactions. It should be pointed out that they are the relatively easily achieved, and environmentally friendly species. A valuable property of CDs in the facile functionalization of their wide and narrow rims. The chemistry and applications of CDs are a topic of an enormous number of works [1–10].

Rotaxanes, as the systems representing supramolecular chemistry are today widely investigated in view of their possible applications in domain of molecular machines and switches [11–18]; the development of polyrotaxanes promising for use in various areas also received recently a considerable attention [19–24].

It is noteworthy that CDs are suitable macrocycles for formation of rotaxanes; the capping of encapsulated guest molecule by bulky end groups affords the [2]rotaxane. Many CD-based rotaxanes, further referred to as CD rotaxanes are known [25–28], along with CD polyrotaxanes [29–35]. One should point out that CD polyrotaxanes are large family which may be divided into species containing long polymer chains (such as PEG, PEO, PANI, PNIPA etc.) [36–41], and species without a long polymer chain, mainly oligorotaxanes [42–47]. The CD polyrotaxanes are a separate class of compounds and are not included here.

Some CD rotaxanes are described in the present paper; since the number of reports concerning these species is very large, only selected examples are shown. The paper is a continuation of our works on chemistry of CDs [48–54]. The presented CD rotaxanes are described in the aspect of their syntheses and potential usefulness in the design of sensors and molecular devices.

Investigation of rotary movement of a ring in CD rotaxanes

It is known that microscale mechanic or electronic devices may mimic the biological molecular motors, existing in nature [55]; such artificial molecular motors received a great attention in recent years and are a topic of an enormous amount of reports [56]. The experimental results have shown that rotaxanes are suitable systems for investigation of controlled rotary molecular movement; the performed works enable to understand action of biological molecular motors. In this section two examples of such studies are presented.

Rotaxanes **1a**–**1c** consisting of α-CD rings bearing benzamide (**1b**) and stilbene amide (**1c**) substituents and diphenylacetylene as a thread have been synthesized for investigation of the rotary movement of a ring relative to a

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thread. The synthesis of rotaxanes **1a–1c** involves the reaction of α-CDs with 4,4′-diaminodiphenylacetylene and sodium 2,4,6-trinitrobenzene-1-sulfonate in aqueous solution.

The study of rotary movement was performed using two-dimensional ^{1}H NMR techniques (TOCSY, COSY, ROESY, HMQC and HMBC). The protons of α-CD in rotaxane **1a** did not show splitting, however in rotaxanes **1b** and **1c** the resonance peak shifts and splitting for the corresponding protons of α-CD units was observed by the shielding and

deshielding effects from a diphenylacetylene axis molecule. The splitting of resonance peak was closely related to the rotary movements of α-CDs and axis molecule.

The rotational correlation time τ_c of rotaxanes was measured by ^{13}C NMR spectroscopy. It was observed that α-CD ring in **1a** rotates freely around the thread, however in **1b** and **1c** the rotary movement is restricted by steric repulsion between the α-CD substituent and the stopper. The rate of the rotary movement of α-CDs decreases in the order **1a** > **1b** > **1c**, i.e. is lower for bulky R groups [57].

Scheme 1 Syntheses of rotaxanes **1** and **2**
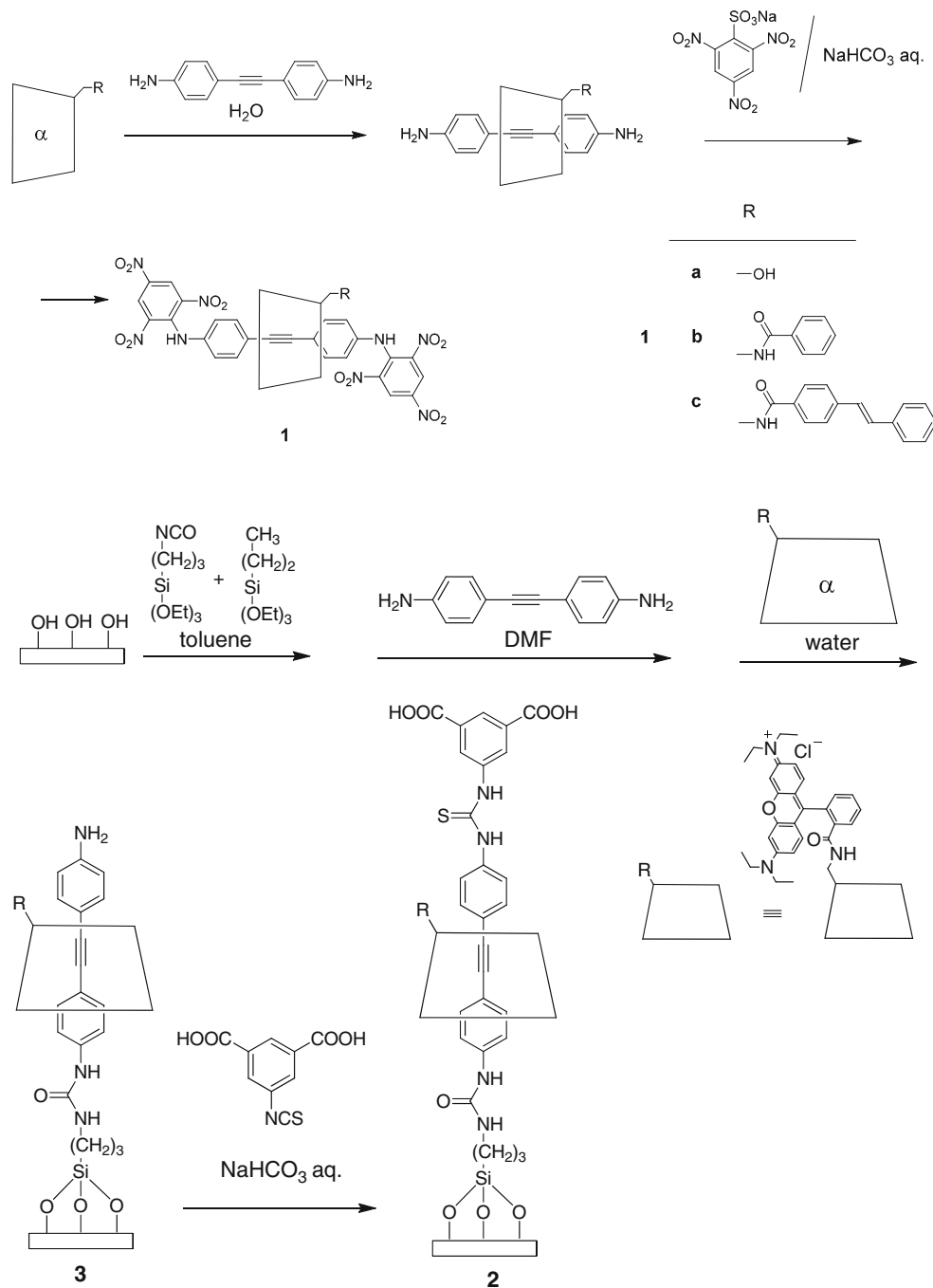
In the investigation of rotaxanes suitable for construction of molecular machines, the rotaxane **2** containing α-CD ring modified with rhodamine B as a fluorescent probe, was immobilized on a glass substrate. For this purpose the glass substrate coated with 3-(triethoxysilyl)propyl isocyanate and *N*-propyltriethoxysilane was immersed in DMF solution of 4,4′-diaminodiphenylacetylene and then in aqueous solution of α-CD modified with rhodamine B. The formed pseudorotaxane **3** was immersed in a solution of 5-isothiocyanate isophthalic acid to give the rotaxane **2** [58].

The rotary movement of α-CD ring was estimated by total internal reflection fluorescence microscopy (TIRFM). In experiments the defocused wide-field imaging technique was employed; the rotary movement of α-CD was observed by measuring the emission dipole orientation of the chromophore. Moreover it was found that rotaxane **2** in dry state shows no rotation of α-CD ring, whereas in the wet state the fast rotary movement was observed (Scheme 1).

CD rotaxanes containing azo and cyanine dyes

In this section examples of CD rotaxanes containing azo or cyanine dyes serving as threads are presented. Moreover there are described two other CD rotaxanes obtained by Suzuki coupling, similarly as rotaxanes with cyanine threads.

Pseudorotaxane **4**, i.e. **β-CD·(E)-5** contains β-CD as a ring and azobenzene derivative *(E)*-**5** as a thread [59]. To encode the threading and dethreading of **4**, the formation of inclusion complex **β-CD·A** may be used (**A** is 1-bromonaphthalene); this process causes the room temperature phosphorescence.

It was observed that the 360 nm irradiation of **4** in aqueous solution results in E→Z photoisomerization of **5**. Since *Z*-**5** is too bulky to remain in pseudorotaxane, the dethreading occurs; the subsequent formation of inclusion complex of dethreaded β-CD with **A**, i.e. **β-CD·A** induces emission of room temperature phosphorescence. The process is reversible, the 430 nm irradiation of **Z**-**5** and of inclusion complex **β-CD·A** restores the formation of **4** and of free **A**, i.e. the threading of **4** occurs [60]. These results show that the E/Z photoisomerization of **5** controls the threading and dethreading of **4**, that is, the threading and dethreading of **4** can be driven by external photostimuli (Scheme 2).

Analogs of modified β-CDs bearing long and rigid azobenzene units i.e. **6** and **7** which adopt self-locked and self-unlocked conformations, respectively, have been obtained using Huisgen 1,3-dipolar cycloaddition from the same reactants **8** and **9** but under different conditions, i.e. by the hydrothermal synthesis and by the click reaction.
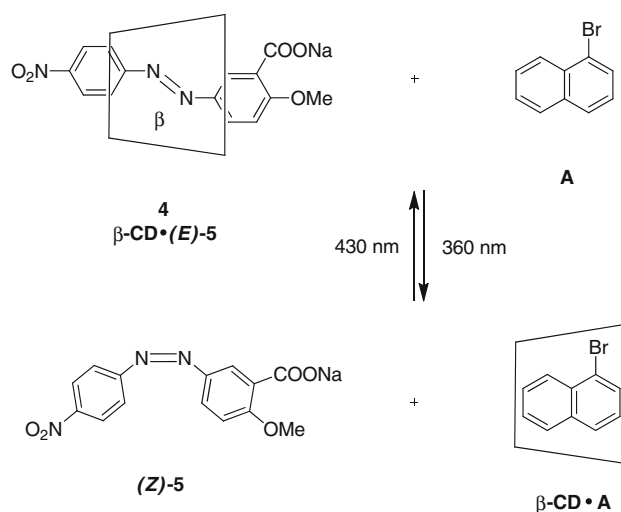

Scheme 2 Threading and dethreading of pseudorotaxane **4**

The hydrothermal 1,3-dipolar cycloaddition reaction of azido-CD **8** with azobenzene **9**, containing ethynyl group afforded the self-locked **6**, whereas their Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition (click chemistry) gave the self-unlocked **7**. A possible mechanism for the synthesis of **6** involves the primary formation of the inclusion complex of cyclodextrin **8** with **9**, and the subsequent reaction between the azido group of **8** with the ethynyl group of **9** affording product **6**.

The self-locked conformer **6** may be regarded as a new type of [1]rotaxane (without a stopper); two molecules of **6** may assemble to a dimeric capsule **10** in aqueous solution and in solid state. In the dimeric capsule the azobenzene moiety is included both in its own cavity and in the cavity of the second CD ring. The self-unlocked conformer **7**, however, self-assemblies to a linear supramolecule **11** [61].

The above study shows that **6** and **7**, having the same composition but different conformations behave differently, i.e. that the conformational factors influence their self-assembling behavior (Scheme 3).

The synthesis of [2]rotaxane **12** containing heptamethine cyanine dye thread has been performed in one step by a gram-scale procedure using α-CD, glutaconaldehyde acetate **13** and tetramethylindolium iodide; the trimethylindole terminal groups are sufficiently bulky to serve as stoppers. It was found that the encapsulation of cyanine dye improves its stability against photobleaching and increases the kinetic chemical stability of the radicals formed by oxidation and reduction of the dye, therefore the rotaxane radical dication may be observed by ESR and UV–Vis-NIR spectroscopy. One should point out that **12** is kinetically robust; investigation of its crystal structure shows that α-CD is tightly encircled around the thread [62].
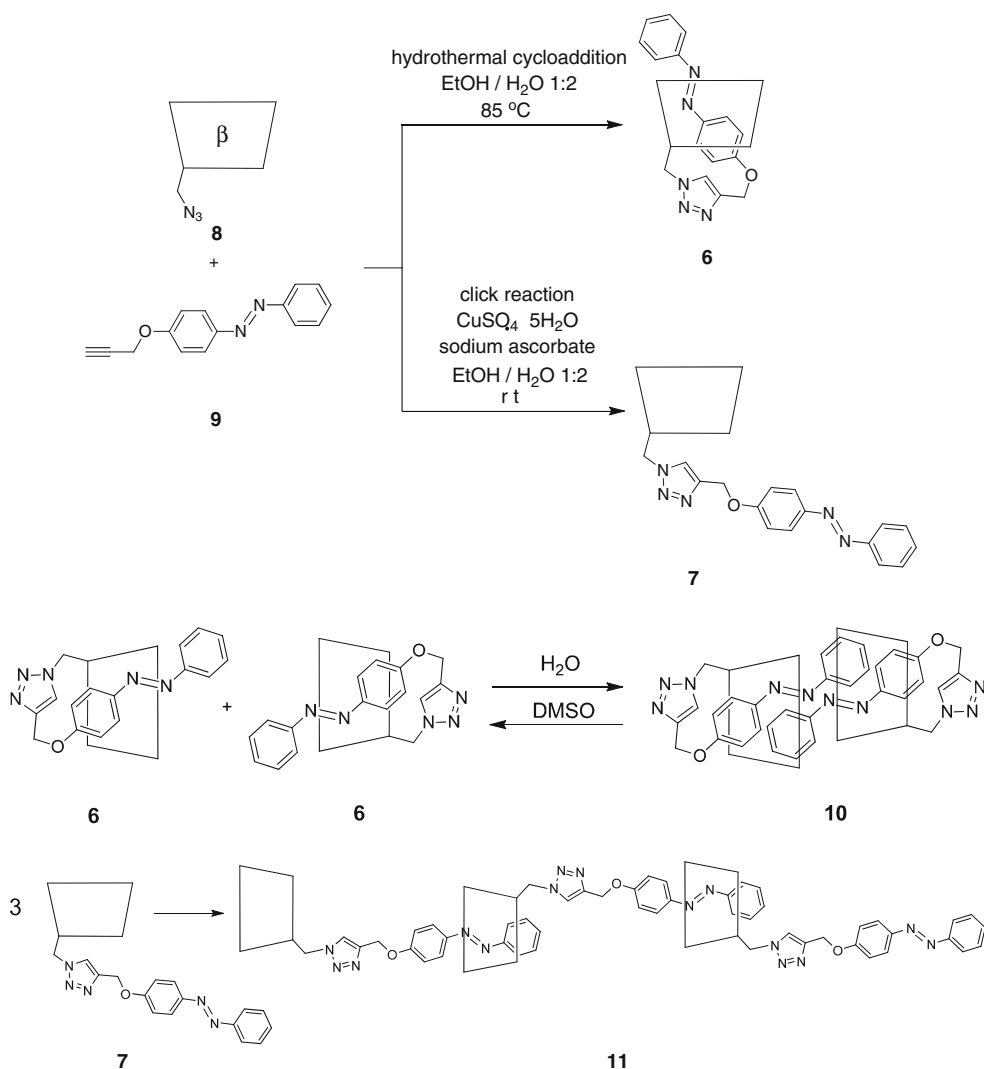
Scheme 3 Syntheses of conformers **6** and **7**, and their self-assembling behavior

Cyanine dyes are valuable chromophores due to their strong absorption and fluorescence, however the use of longer cyanines is often limited by their poor chemical and photochemical stability. It was established that the above described method improves chemical stability of the chromophore and can be used for stabilization of longer cyanine dyes, containing $(CH)_9$ and $(CH)_{11}$ polymethine bridges. One should note that rotaxane formation increases the water solubility of the dye enabling its medical application [63, 64].

In the study of [3]rotaxanes built from one macrocycle and two threads, the hetero-[3]rotaxane **14** consisting of γ-CD encircling one stilbene and one cyanine dye as threads was synthesized using Suzuki coupling. One should underline that Suzuki coupling is a very useful method for synthesis of CD rotaxanes.

It was established that the encapsulation of chromophores by CDs decreases the quenching of the luminescence

[65, 66]. Upon inclusion of organic molecules into CD rings the hydrophobic effect promotes their penetration into CD cavities, affording stable complexes. The inclusion proceeds preferentially in water, therefore Suzuki coupling in water is a convenient approach to CD rotaxanes [34, 44].

The process begins by reaction of γ-CD in aqueous solution with stilbene diboronic acid **15** and iodoterphenylene stopper **16**; the resulting dumbbell **17** upon threading through γ-CD affords [2]rotaxane **18**, i.e. **γ-CD·17**. The calculation of van der Waals surface of rotaxane **18** has shown that it has a large affinity for hydrophobic guests in aqueous solution, for example it binds cyanine **19** more strongly (association constant = $1.0 \pm 0.2 \times 10^5$ M^{-1}) than native γ-CD does (association constant = 87 ± 15 M^{-1}), this fact being due to the presence of stilbene in **18**. It is noteworthy that the presence of stilbene in **18** adds a hydrophobic floor to the cavity of CD, resulting in the increase of its affinity to suitably shaped guests.

Scheme 4 Syntheses of [2]rotaxanes **12** and **18** and of [3]rotaxane **14**
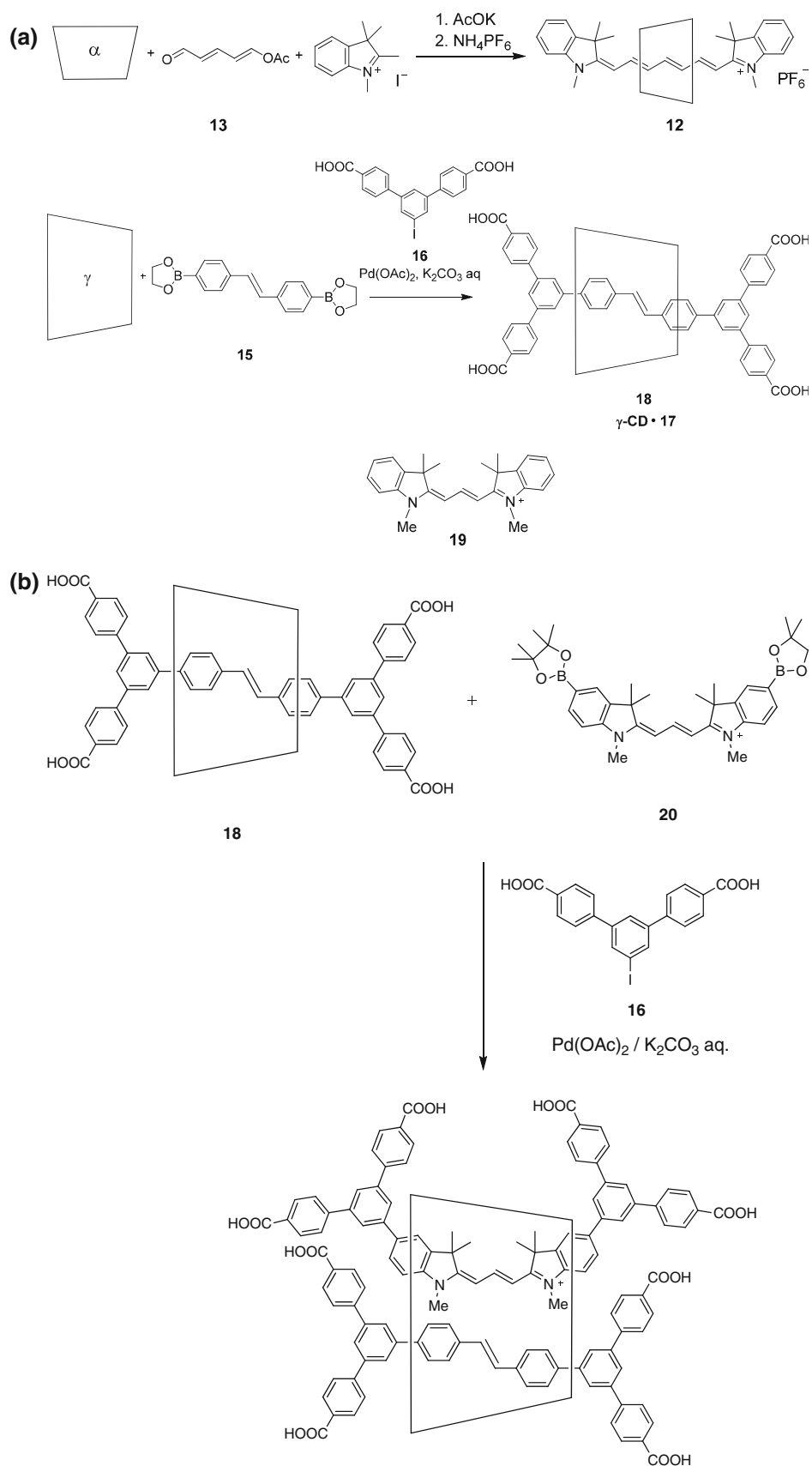
Scheme 5 Syntheses of rotaxanes **22** and **23**
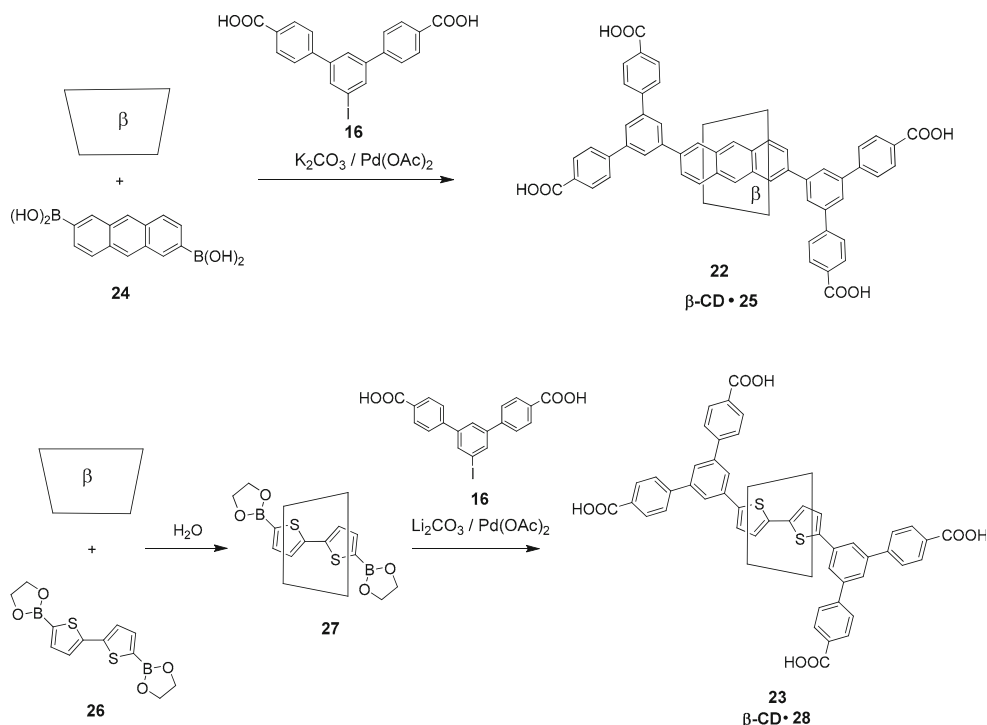
The second Suzuki coupling of cyanine diboronic acid **20** with stopper **16** yielded the dumbbell **21** which in the presence of rotaxane **18** afforded hetero-[3]rotaxane **14**, i.e. γ-**CD·17·21**, containing cyanine and stilbene threads [67]. Similarly, Suzuki coupling of **15** and **16** in the presence of **18** afforded homo-[3]rotaxane γ-**CD·17·17**, containing two stilbene threads. It is noteworthy that in these both cases, the synthesis of [3]rotaxane is highly efficient, because the presence of stilbene favors introduction of a second thread.

One should point out that the above results offer a convenient route for synthesis of homo- and hetero-[3]rotaxanes which are promising in the design of sensors (Scheme 4).

Using Suzuki coupling, two CD rotaxanes **22** and **23** containing anthracene and bithiophene threads, respectively, have been obtained.

The synthesis of [2]rotaxane **22** having anthracene as a thread involves the Suzuki coupling of anthracene-diboronic acid **24** with iodoterphenylene **16** in the presence of β-CD. Linear acenes are used as organic materials for field-effect transistors and light emitting diodes (LEDs). It is known that the molecular insulation may increase the chemical stability of dyes and of conducting polymers [34, 68]. Having this in mind the above synthesis of rotaxane **22** on an example of a short acene was made to characterize its physicochemical properties.

The experimental results indicate that rotaxane **22** i.e. **β-CD·25** is more resistant to fluorescence quenching

and photobleaching than the dumbbell **25**. The examination of fluorescence behavior of rotaxane **β-CD·25** and its dumbbell **25** has shown that the difference between the fluorescence emission of both compounds in aqueous solution may be observed by naked eye under a 365 nm UV lamp, the rotaxane is blue whereas the dumbbell is yellow. The spectrum of rotaxane showed to be independent on concentration, while that of the dumbbell is concentration dependent. This concentration dependence of the dumbbell is probably due to its aggregation which is disrupted by presence of β-CD in rotaxane [69].

The synthesis of CD rotaxane **23** containing 2,2′-bithiophene as a thread, and capped by terphenylene stoppers begins with the reaction of β-CD with dithiophene diboronic ester **26** to give pseudorotaxane **27** which upon Suzuki coupling with iodoterphenylene **16** affords rotaxane **23**, i.e. **β-CD·28** [70].

It is known that organic π-conjugated molecules containing electron-rich thiophene units are semiconductors [71]; due to their charge transport ability, oligothiophenes serve as building blocks for light emitting diodes (LED) and solar cells. The encapsulation of conjugated molecules by macrocycles in the form of rotaxanes prevents their aggregation and improves rigidity.

The experimental results have shown that so in rotaxane **23** as in the dumbbell **28** the aggregation is disfavored, presumably due to relatively short length of the dithiophene backbone and to the presence of carboxylic groups of stoppers. One should point out that the rotaxane **23** i.e.
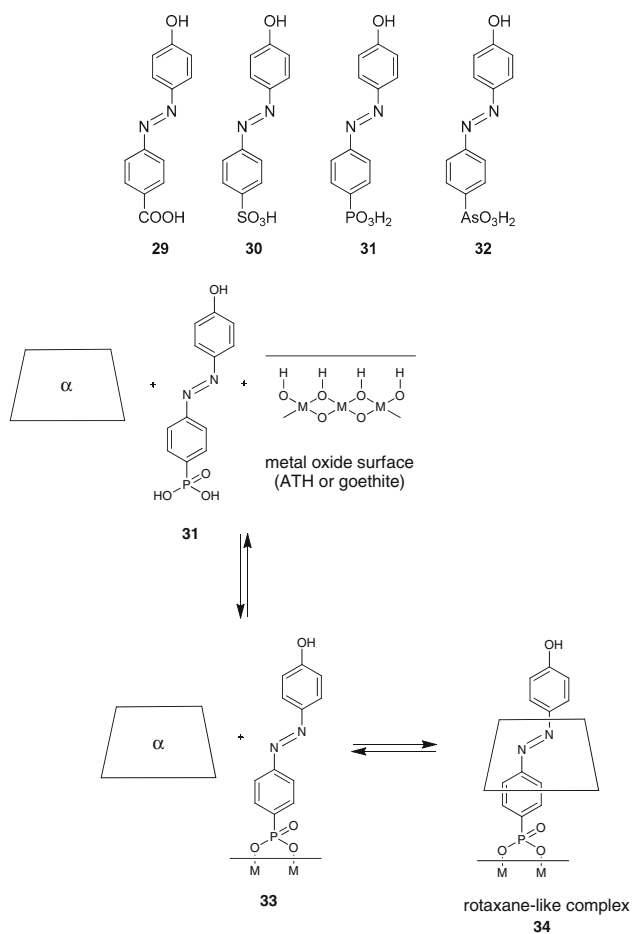
Scheme 6 Structures of azo dyes 29–32 and formation of rotaxane-like CD complex 34

β-CD·28 may be considered as a model system for investigation of optoelectronic properties of molecular wires (Scheme 5).

In investigation of the inkjet printing it was found that during this process the ternary rotaxane-like complexes α-CD/dye/aluminium trioxide or goethite surface are formed. In the experiments four azo dyes 29–32 bearing carboxylic, sulfonic, phosphonic and arsonic groups, respectively, were used; the high surface area aluminium trihydroxide (ATH) served as a model of oxide treated photo papers. For comparison purposes the goethite surface was examined. It should be noted that goethite, albeit not used for paper treatment is an important pigmentary material.

The inkjet printing involves the binding of oxides which are present in photo papers, with ligating groups of the dyes. The resulting binary complexes afford with α-CD the ternary rotaxane-like complexes. It was established that dyes forming such rotaxane-like complexes show higher light fastness when printed onto alumina coated paper in an ink formulation containing α-CD.

The inkjet printing process is shown for the phosphonic dye 31. The complex 33 formed from 31 on the metal oxide surface gives with α-CD the rotaxane-like complex 34. The adsorption isotherm measurements have shown formation of the rotaxane-like ternary complexes α-CD/dye/surface; the inclusion complex α-CD/dye is tethered to the ATH or goethite surface by a ligating group of the water soluble dye [72]. For the existence of a stable rotaxane-like ternary complex CD/dye/surface, the dye should strongly bind to the oxide surface and the inclusion complex α-CD/dye should be stable.

It was found that azo dyes bearing phosphonic (31) and arsonic (32) groups bind more strongly to ATH and goethite than azo dyes containing carboxylic (29) or sulfonic (30) groups; due to this fact, the results of the humidity fastness investigations of 29–31 show for 31 a smaller

Scheme 7 Formation of [2]pseudorotaxane 41
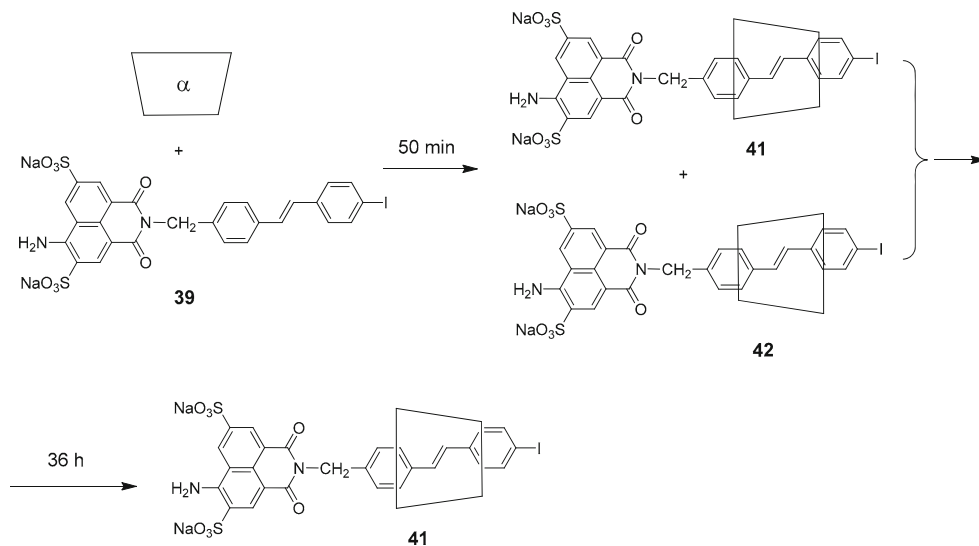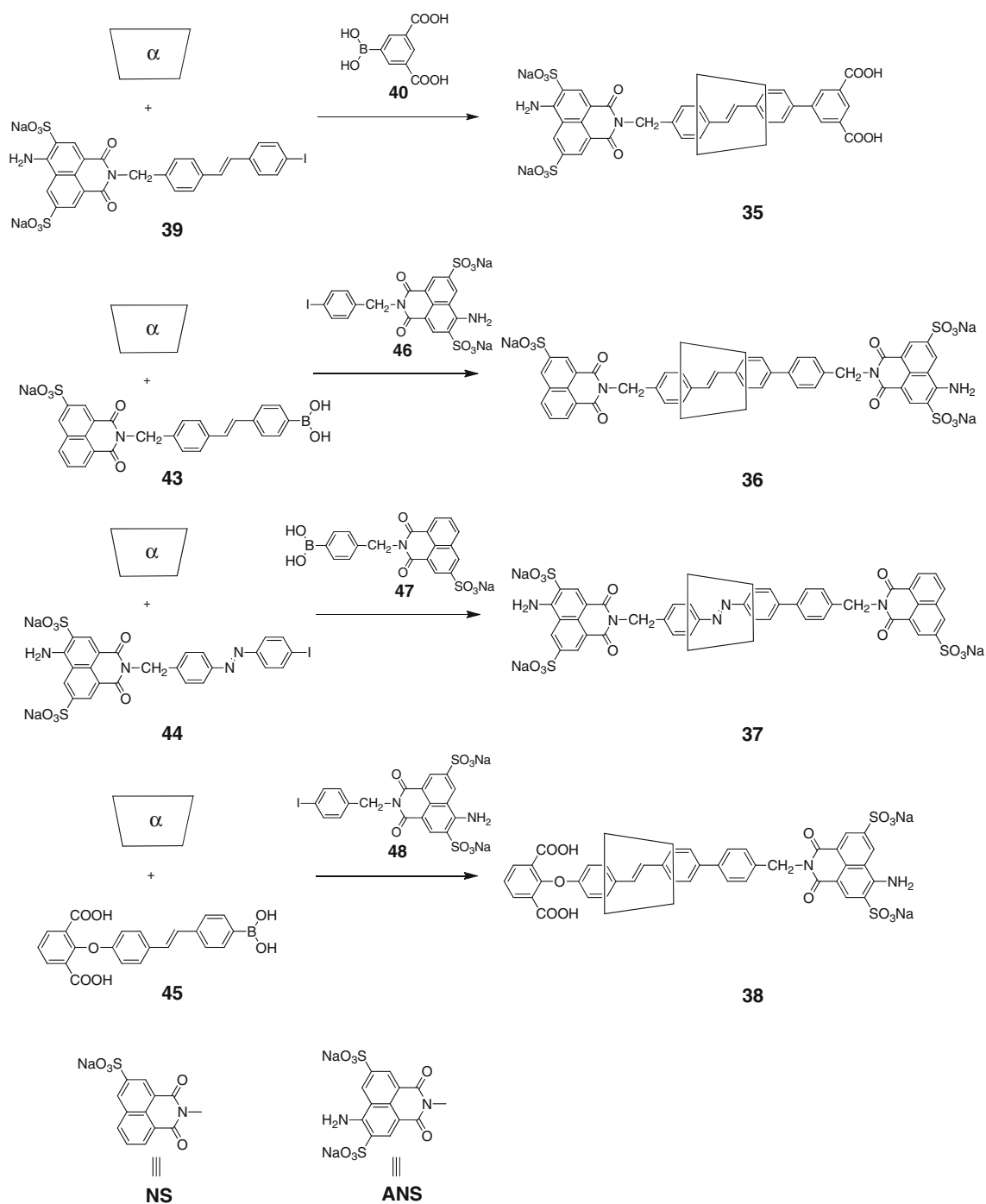
**Scheme 8** Syntheses of rotaxane **35**–**38**

degree of dye migration on alumina coated papers than for **29** or **30** (Scheme 6).

CD rotaxanes undergoing E/Z photoisomerization

The CD rotaxanes containing threads with double bonds, mainly consisting of stilbene or azobenzene derivatives,

may undergo E/Z photoisomerization; this process is often accompanied by shuttling of the CD ring. Due to above properties they are promising for design of sensors and molecular devices.

In this section selected examples of CD rotaxanes undergoing E/Z photoisomerization are shown. There are described also molecular muscles, containing stilbene or azobenzene groups.
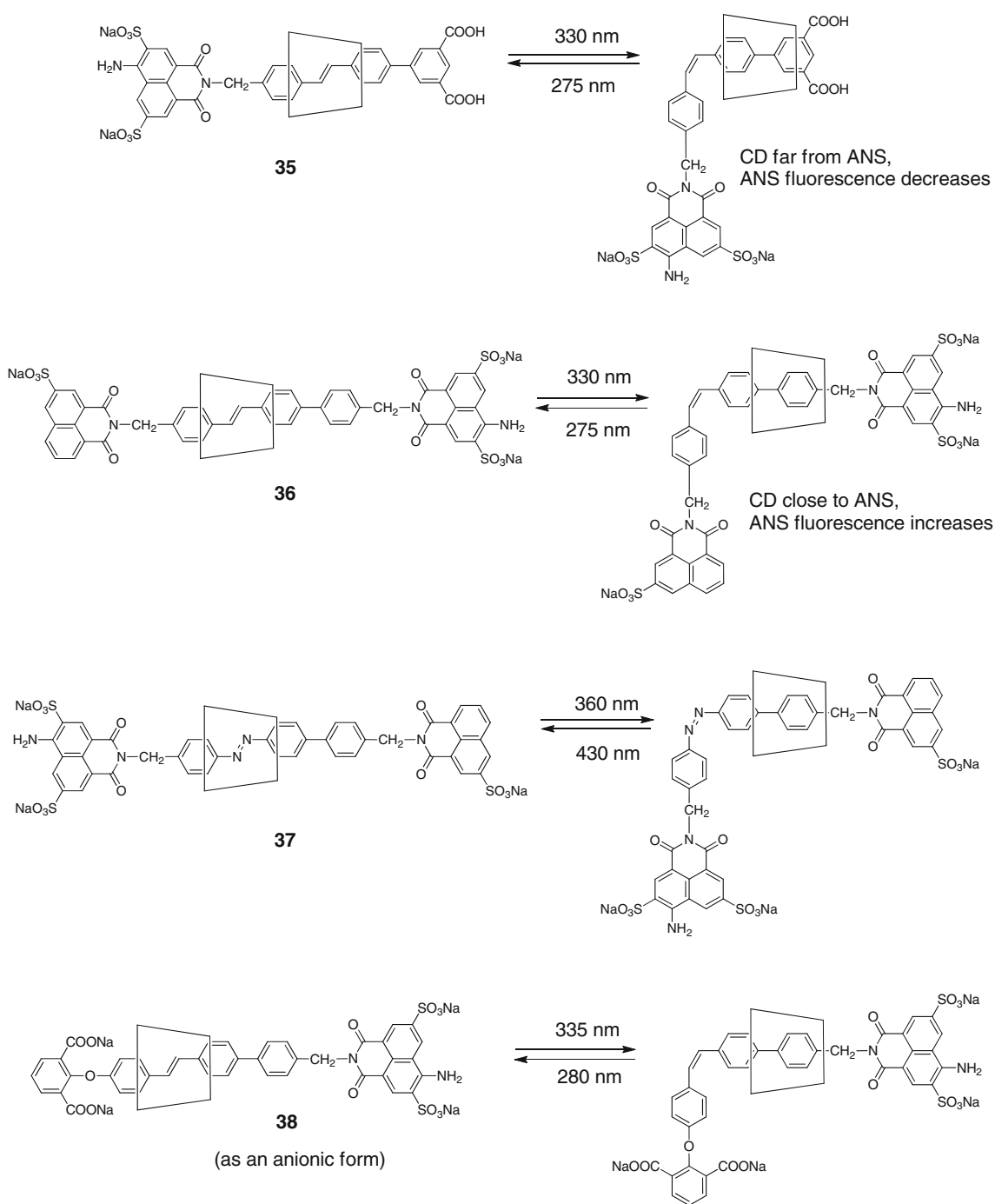
**Scheme 9** Shuttling of CD rings in rotaxanes 35–38

Shuttling of a ring in CD rotaxanes

It is known that the threading of an unsymmetrical dumbbell through CD affords two isomeric [2]rotaxanes of a different orientation of the CD ring. For synthesis of *unidirectional* [2]rotaxanes the Suzuki coupling of iodides and boronic acid derivatives in an aqueous α-CD solution has been performed. The obtained unidirectional

[2]rotaxanes 35–38 upon irradiation show E/Z photoisomerization and shuttling motion of the CD ring [73].

Rotaxanes 35–38 were synthesized by the Suzuki coupling. For example in order to obtain rotaxane 35 the reaction of α-CD in aqueous solution with stilbene 39, followed by coupling with boronic acid derivative 40 was performed. This synthesis begins with stirring of α-CD with 39 in water during 50 min to form the mixture of two

**Scheme 10** Synthesis and photoisomerization of [3]rotaxane *(E)*-49
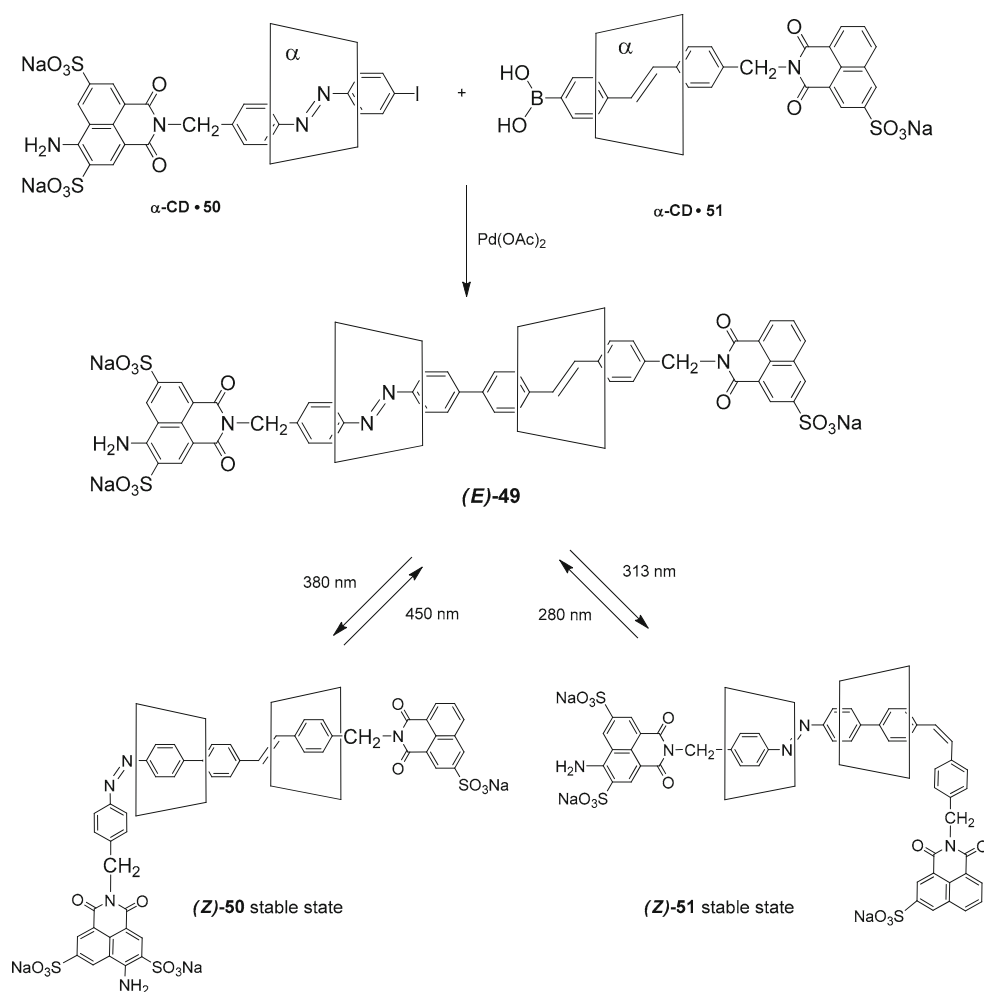
isomeric [2]pseudorotaxanes **41** and **42**. However after 36 h the isomer **42** disappears, and the remaining **41** was submitted to a Suzuki coupling (Scheme 7).

Syntheses of rotaxanes **35–38** involve the reactions of α-CD: with stilbene **39** and **40** the rotaxane **35** was obtained, while with stilbene **43** and iododerivative **46** the rotaxane **36** was formed; the reaction of α-CD with **44** and **47** afforded **37**, and with **45** and **48** yielded rotaxane **38** (Scheme 8).

Shuttling of the CD rings in rotaxanes **35–38** was investigated by irradiation of their aqueous solutions; these E/Z photoisomerization processes result in the shuttling motion of CD rings and are reversible. When in the shuttling process the α-CD ring moves away from the luminescent stopper, the fluorescence intensity of the stopper decreases; this behavior was observed in **35**; α-CD is shifted away from ANS. However in **36** during shuttling the α-CD ring comes closer to ANS, therefore the fluorescence intensity of ANS increases. The ICD spectra of **35–38** resulting from the photoisomerization accompanied by shuttling were discussed in terms of Harata and Kodaka rules (Scheme 9).

An example of the light-driven [3]rotaxane molecular shuttle is *E*-49 containing two α-CD rings, a thread consisting of azobenzene and stilbene units, and two different fluorescent naphthalimide stoppers. The synthesis involves the Suzuki coupling reaction of **α-CD·50** with **α-CD·51**. It was confirmed that in **α-CD·50** and **α-CD·51**, as well as in the [3]rotaxane **49**, the wide rims of CD rings are directed toward stoppers.

The azobenzene and stilbene units of **49** can be E/Z photoisomerized separately by light at different wavelengths. Irradiation of *(E)*-49 at 380 nm results in the E→Z photoisomerization of its azobenzene unit leading to the formation of one stable state of the rotaxane **49**, namely *(Z)*-50. Irradiation of *(E)*-49 at 313 nm results in the E→Z photoisomerization of its stilbene unit, leading to the formation of another stable state of rotaxane **49**, namely *(Z)*-51. The irradiation of the *(Z)*-50 isomer at 450 nm and irradiation of the *(Z)*-51 isomer at 280 nm recover *(E)*-49. These processes are fully reversible, the photo-induced shuttling motions of α-CD rings can be repeated, therefore the shuttling of CD in *(E)*-49 can be characterized by the fluorescence changes. When the fluorescent stopper is

Scheme 11 Syntheses of rotaxanes **56**, **58** and **60**
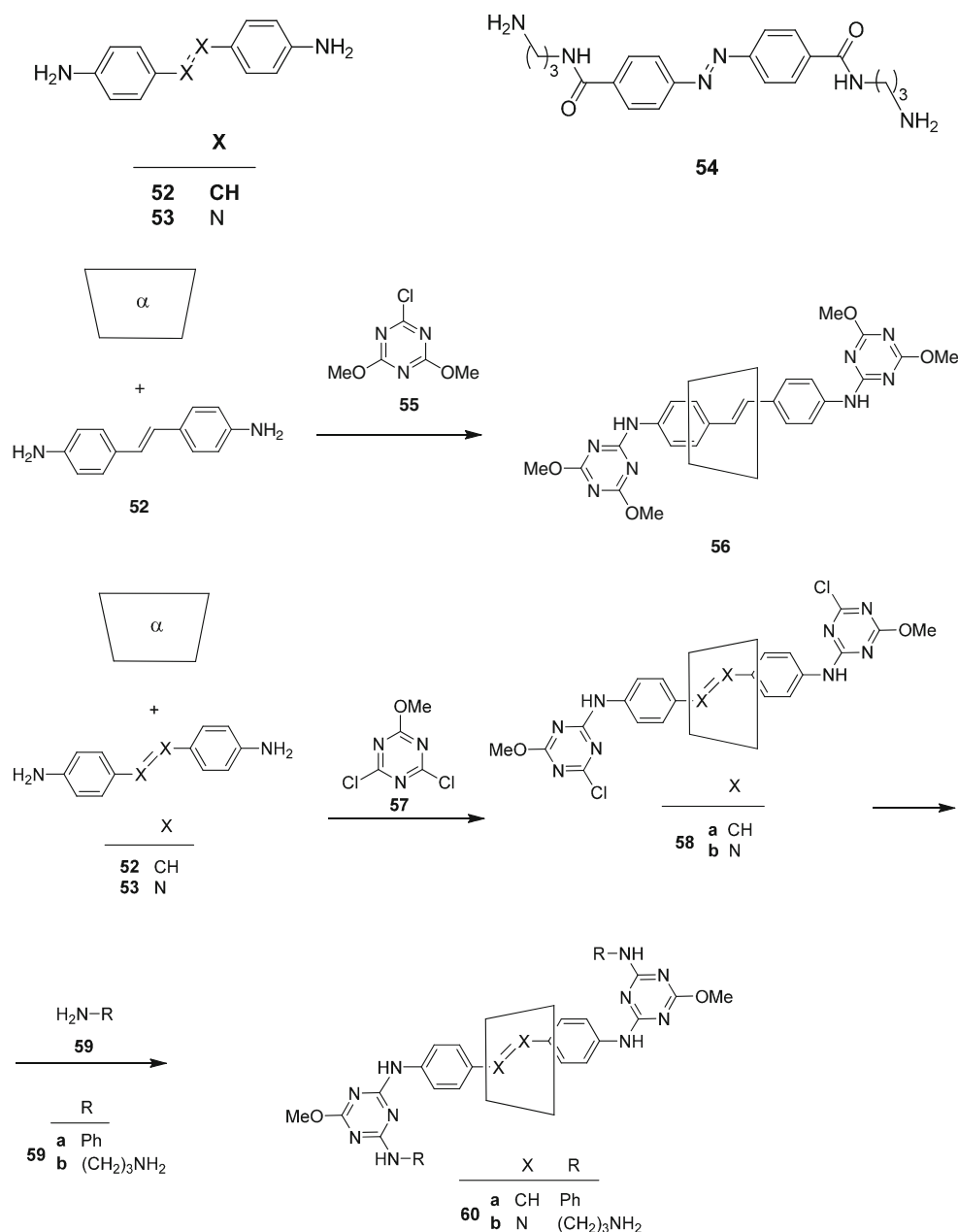
situated close to α-CD, the fluorescence intensity of stopper increases [74].

The [3]rotaxane **49** can be regarded as a light-driven molecular shuttle with three stable states: *(E)*-**49**, *(Z)*-**50** and *(Z)*-**51**. In **49**, the input is photochemical energy, more advantageous than chemical or electrochemical input due to its cleanness; the output is a fluorescence signal which allows the easy reading. The above results are promising for design of molecular devices (Scheme 10).

In order to study shuttling processes, the CD rotaxanes containing stilbene or azobenzene threads capped by 1,3,5-triazine stoppers were synthesized using compounds **52–54**. The reaction of α-CD and stilbene **52** with chlorotriazine **55** afforded rotaxane **56**. The reaction of

α-CD, stilbene **52** or azobenzene **53** with dichlorotriazine **57** yielded rotaxanes **58a** and **58b**, which were treated with aniline **59a** or 1,3-diaminopropane **59b** to give rotaxanes **60a** or **60b**, respectively (Scheme 11).

Reactions of α-CD and azobenzene **54** with chlorotriazine **55** and with dichlorotriazine **57** afforded rotaxanes **61** and **62**, respectively; the subsequent treatment of **62** with allylamine yielded rotaxane **63** [75] (Scheme 12).

Having in view the design of molecular devices, the rotaxane **61** was chosen for study of its photochemical behavior. In the experiments rotaxane *(E)*-**61** was irradiated at 350 nm to give *(Z)*-**64**; the process is reversible, the irradiation at 420 nm restored the *E* isomer [75]. The NMR measurements have indicated that in the obtained *Z*-isomer the
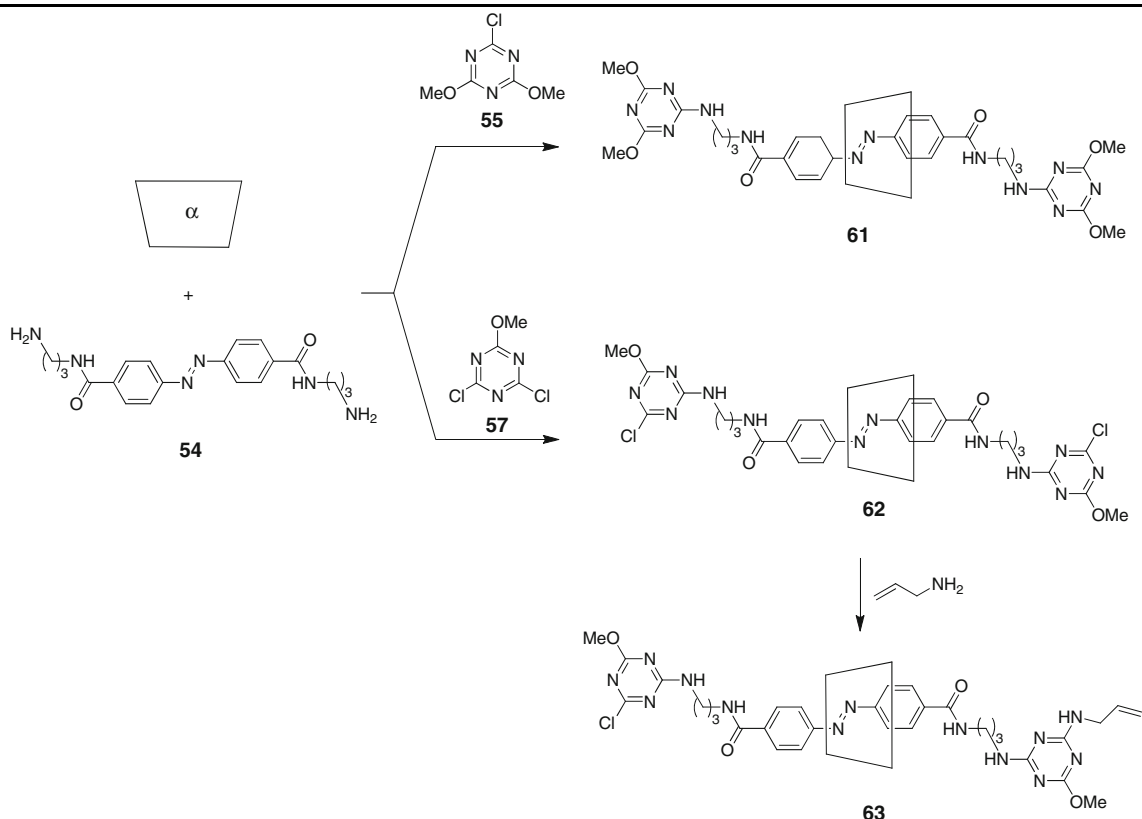
Scheme 12 Syntheses of rotaxanes **61**–**63**

shuttling of CD ring occurs, i.e. the rotaxanes **(Z)-64a** and **(Z)-64b** are in equilibrium. It was observed, as in former investigations, that α-CD does not accommodate the azo group of *(Z)*-azobenzene so readily as the azo group of the *E*-isomer (Scheme 13).

Molecular muscles basing on CD rotaxanes

Molecular muscles basing on CD Janus rotaxanes containing stilbene and azobenzene units will be presented; they are able to reversibly contract and expand upon irradiation at different wavelengths. At first, the CD daisy rotaxanes, i.e. Janus rotaxanes capped by stoppers should be mentioned; an example is [c2]daisy rotaxane **65** obtained by the reaction of two molecules of stilbenyl-α-CD **66** with dichlorotriazine **57** [75, 76]. Then two kinds of light driven molecular muscles basing on CD Janus rotaxanes, i.e. those containing stilbene and azobenzene groups, respectively, are described.

Molecular muscle containing stilbene groups

As an example of molecular muscle containing stilbene groups may serve CD Janus[2]rotaxane **67**. It is known that CDs form complexes with *E*-stilbenes more readily than with *Z*-stilbenes. The irradiation of **(E,E)-67** at

350 nm affords the **(E,Z)-67**, and subsequently the **(Z,Z)-67**; this transformation results in decrease of the distance between stoppers, i.e. in contraction (a > b > c). The irradiation at 254 nm reverses the isomerisation leading to recovery of **(E,E)-67**, i.e. to the expansion [77] (Scheme 14).

CD molecular muscle containing azobenzene groups

An example of molecular muscle containing azobenzene groups is CD Janus[2]rotaxane **68**. The synthesis of **68** begins with the condensation of two molecules of permethylated α-CD **69** which contains azobenzene group, leading to their self-assembly. The subsequent reaction with two molecules of aniline **70** as stoppers affords **(E,E)-68**. The irradiation of **(E,E)-68** forms the photoisomer **(Z,Z)-68**, in which the distance between the two amide nitrogen atoms is shorter than in **E,E-68** (a > b); the isomerization is reversible. This behavior, i.e. contraction (*E,E→Z,Z*) and extension (*Z,Z→E,E*) of **68** shows similarity to a muscle [78] (Scheme 15).

The reaction of **68** with NaH in DMF, followed by *p*-bis(bromomethyl)benzene afforded the linear *N,N'-p*-xylene linked oligorotaxanes **(E)-69a-d** showing behavior of molecular muscles; upon irradiation they form *Z*-isomers of a contracted structure [78] (Scheme 16).
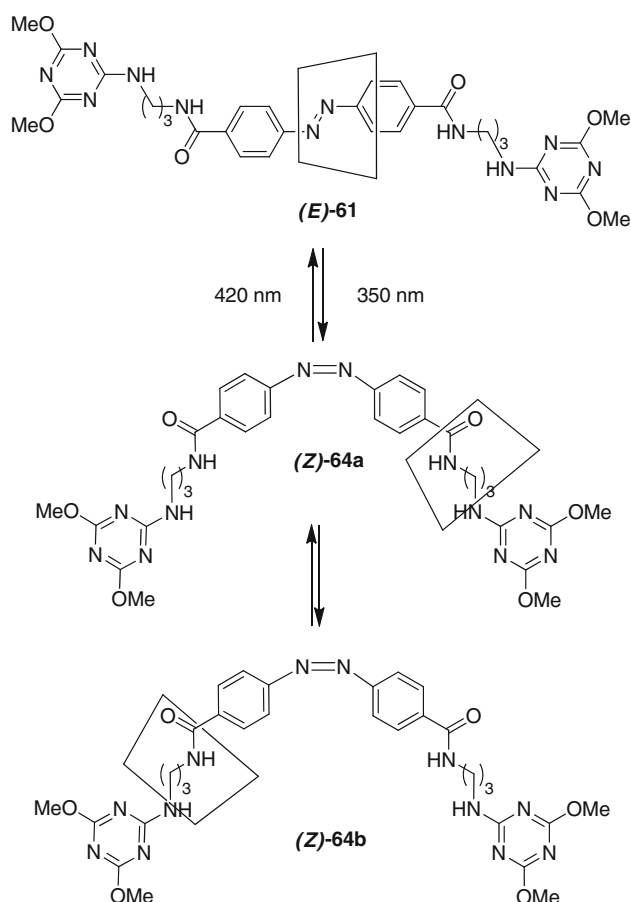
Scheme 13 Photoisomerization and shuttling of rotaxane *(E)*-61

Peptide and carbohydrate linked CD rotaxanes

Peptide and carbohydrate linked CD rotaxanes are interesting in the biological domain. For example the studies of peptide linked CD rotaxanes may be useful for understanding of increased affinity of the peptide for the enzyme in the presence of CD, while the carbohydrate linked CD rotaxanes are promising as potential lectin inhibitors. In this section the selected examples of peptide and carbohydrate linked CD rotaxanes are presented.

Peptide linked CD rotaxanes

In the study of enzymatic preparation of rotaxanes, the chymotrypsin-catalyzed synthesis of the Phe Arg peptide linked rotaxane **70** was performed along with its photoswitchable enzymatic cleavage [79]. Such rotaxanes are known to undergo the reversible *Z/E* photoisomerization, accompanied by shuttling of the CD ring along the rotaxane thread. It was established that the photoisomerization of **70** can serve to prevent its chymotrypsin-catalyzed hydrolysis.

One should point out that contrary to only few works concerning enzyme-catalyzed rotaxane *synthesis*, the enzyme-catalyzed rotaxane *cleavage* was widely investigated for drug delivery in which the naturally existing enzymes are used to dethread the rotaxane. It is noteworthy that photoswitchable rotaxane cleavage is very convenient for this purpose, since it can deliver a drug selectively to cells having a specific enzyme, which are irradiated with light of a suitable wavelength.

Synthesis of rotaxane 70

In the synthesis of rotaxane **70**, the serine protease α-chymotrypsin has been used as a catalyst. For the efficient peptide coupling the acyl donor, i.e. ester, and the acyl acceptor, i.e. amine should suit the active site of the enzyme and match the S_1 and S_1' specifities.

The S_1 and S_1' are the binding sites for amino acid residues on the donor and acceptor sides of the new amide bond, respectively. For α-chymotrypsin the S_1 site prefers large hydrophobic side chains whereas the S_1' site prefers cationic amino acid residues. Therefore the phenylalanine-based acyl donor, i.e. **71** and the arginine-substituted acyl acceptor, i.e. azo dye *(E)*-72 were chosen as substrates for the enzyme-catalyzed rotaxane synthesis.

The α-chymotrypsin-catalyzed acylation of *(E)*-72 by the acyl donor **71** in the presence of α-CD afforded the rotaxane **70**, i.e. **α-CD·(E)-73** after 20 min. When the dumbbell with non-equivalent ends such as *(E)*-73 is threaded through a CD with of course non-equivalent rims, the formation of two stereoisomers is possible, it was found however that rotaxane **α-CD·(E)-73** was obtained as a single isomer. It is noteworthy that at reaction times longer than 20 min the enzyme hydrolyzed the rotaxane back to *E*-72 by selective cleavage of the Phe Arg link.

Photoisomerization of rotaxane 70

The reversible E/Z photoisomerization of **α-CD·(E)-73** and of its dumbbell **73** was studied. The irradiation of these *E* isomers at 368 nm afforded mixtures in which *Z* isomers prevailed, while the irradiation at 445 nm shifted the equilibrium back toward *E* isomers.

The dark thermal Z/E isomerization of the rotaxane **α-CD·(Z)-73** and of the dumbbell *(Z)*-1 in aqueous solution was also investigated. It was observed that the isomerization is faster in the rotaxane than in the dumbbell. Therefore it may be established that the presence of CD destabilizes the Z isomer and decreases the activation energy of its thermal isomerization (Scheme 17).

Scheme 14 Synthesis of daisy [2]rotaxane **65** and action of the molecular muscle **67**


daisy [2]rotaxane **65**

(E,E)-**67**

254 nm ⇅ 350 nm

(E,Z)-**67**

254 nm ⇅ 350 nm

(Z,Z)-**67**
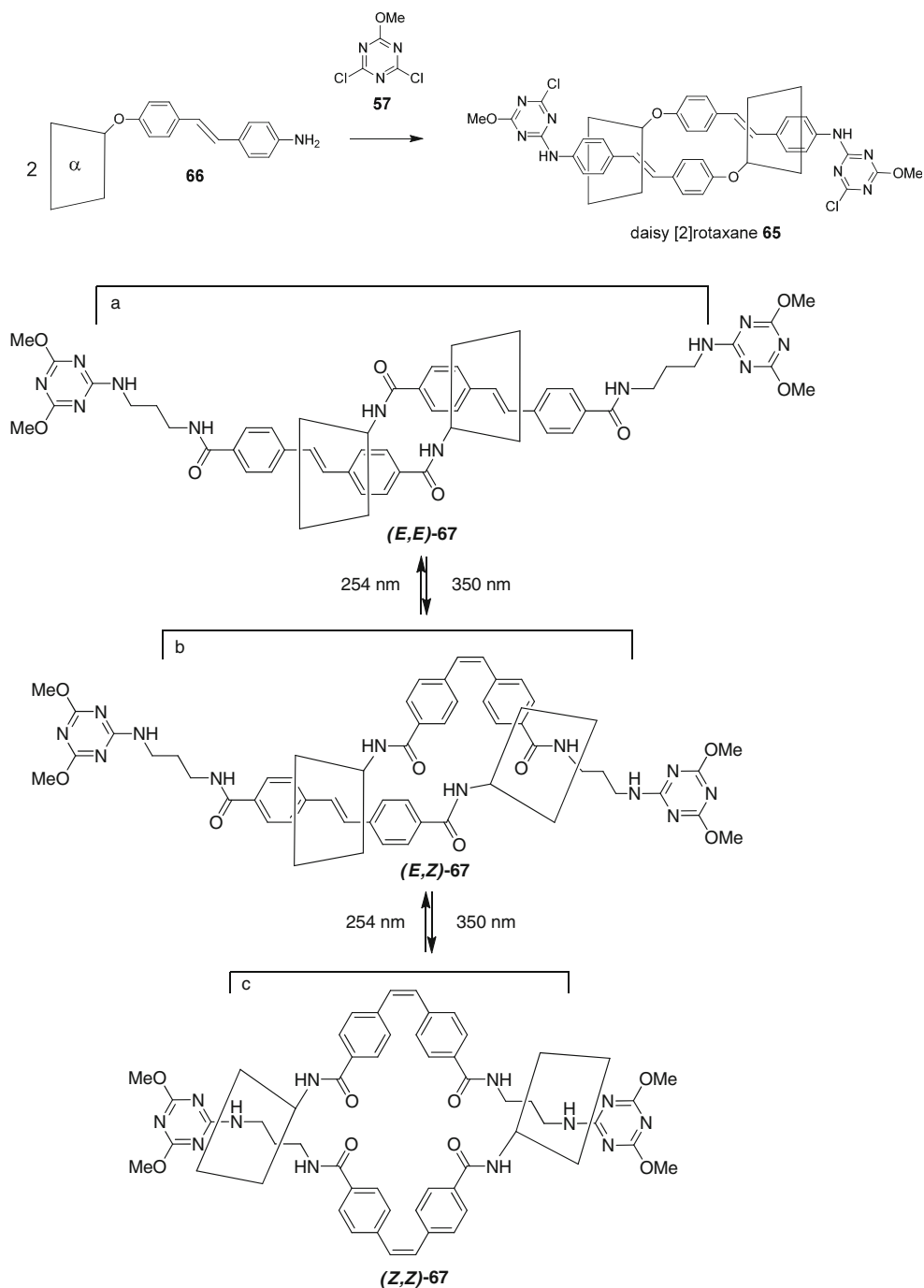
Hydrolysis of rotaxanes α-CD·(E)73 and α-CD·(Z)-73

Examining the enzyme-catalyzed hydrolysis of rotaxanes **α-CD·(E)73** and **α-CD·(Z)-73** along with their dumbbells, **(E)-73** and **(Z)-73**, the relative rates were tested by HPLC to see whether photoswitching can be used to control enzymatic hydrolysis. It was found that the *E* and *Z* isomers of the dumbbell **73** are hydrolyzed at the same rate, while **α-CD·(E)73** is hydrolyzed faster than **α-CD·(Z)-73**, i.e. the presence of CD accelerates hydrolysis of the *E* isomer and

prevents hydrolysis of the *Z* isomer. The slower hydrolysis of the *Z* rotaxane shows that the CD shift toward the peptide link hinders interaction with the enzyme; this fact indicates that the reactivity of the peptide can be controlled by photoisomerization.

It was observed that the bulky rotaxane **α-CD·(E)73** is hydrolyzed faster than the corresponding dumbbell **(E)-73**. This rather unexpected behavior suggests that the CD enhances the affinity of the peptide for the active site of chymotrypsin. The molecular mechanics study of the
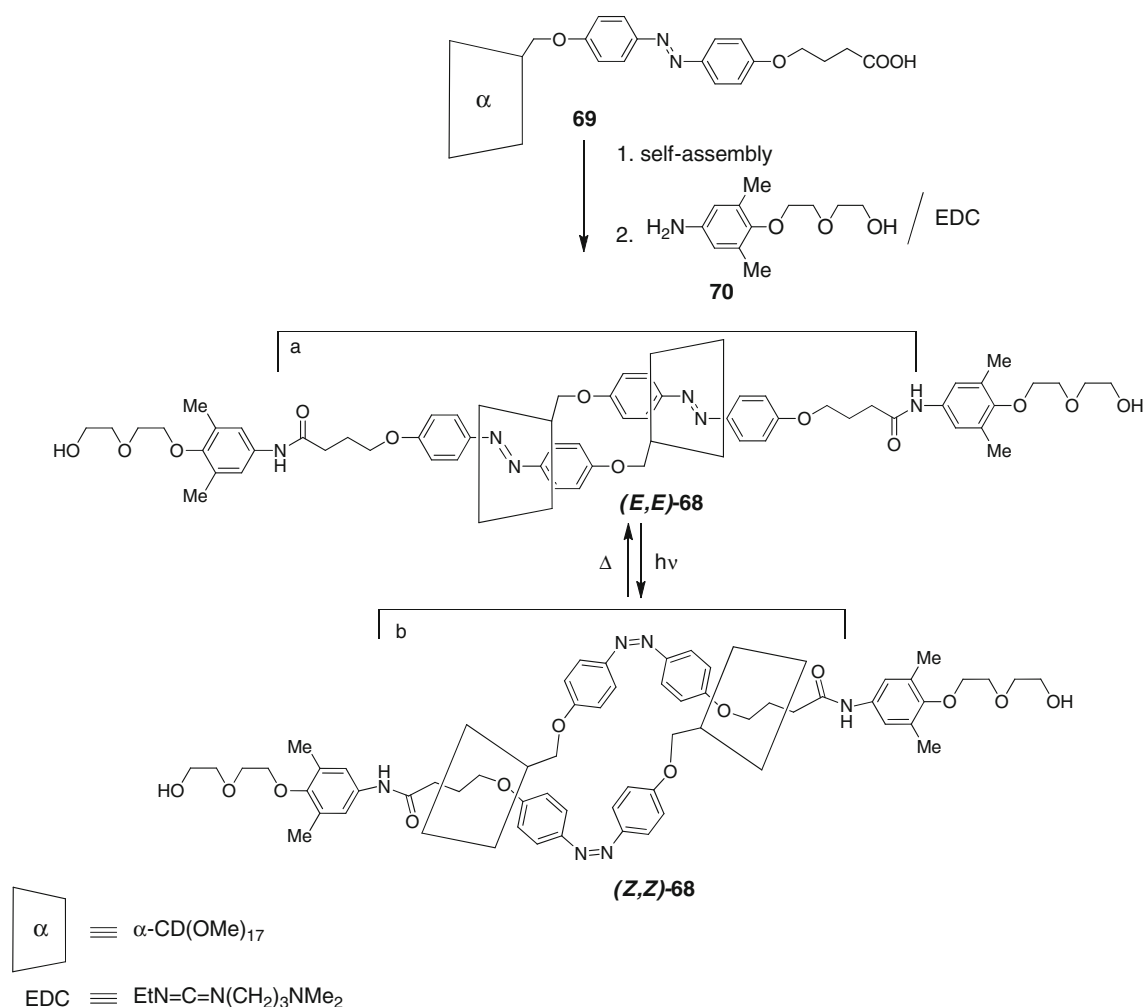
Scheme 15 Synthesis and action of the molecular muscle **68**

α-chymotrypsin/α-CD·(*E*)-**73** complex with the Phe Arg peptide bound to the active site of the enzyme allows to calculate the factors stabilizing this complex and may explain why the presence of CD increases the affinity of the peptide for the enzyme [79].

The above experiments show that enzymes can be used to synthesize CD rotaxanes rapidly and selectively under mild conditions. The results are promising for the synthesis of encapsulated dyes and insulated molecular wires and are interesting in the design of photoswitchable rotaxane-mediated drug delivery.

Carbohydrate linked CD rotaxanes

Syntheses of polyvalent carbohydrate clusters with various scaffolds such as polymers and dendrimers, and their binding abilities with specific lectins or cell surface receptors are intensively studied for mimics of biological systems. It is known that polyrotaxanes may serve as scaffolds for polyvalent ligands [80, 81].

In order to obtain multivalent carbohydrate ligands, the α-CD based oligorotaxanes have been prepared employing click "chemistry". Oligorotaxanes **74–77** containing up to five α-CD rings have been prepared for use as multivalent lectin inhibitors. Their ability to inhibit the binding of *Arachis hypogaea* agglutinin to asialofetuin was assessed by ELLA (enzyme linked lectin assays). Lactose was chosen for experiments due to its affinity for various galactose binding proteins such as peanut lectin [82].

The preparation of multivalent species with different α-CD ratios involves reactions of pseudorotaxane **78**. The synthesis proceeds either by capping **78** with *N*-propargyl lactosylamide **79** to give **74** or by assembling two molecules of **78** by bis-propargyl spacers **80** or **81** to give rotaxanes **75–77**. Both capping and assembling reactions occured by "click chemistry", i.e. Huisgen azide-alkyne 1,3-dipolar cycloaddition. It should be noted that lactosyl group serves here as a biological recognition element and as a stopper.
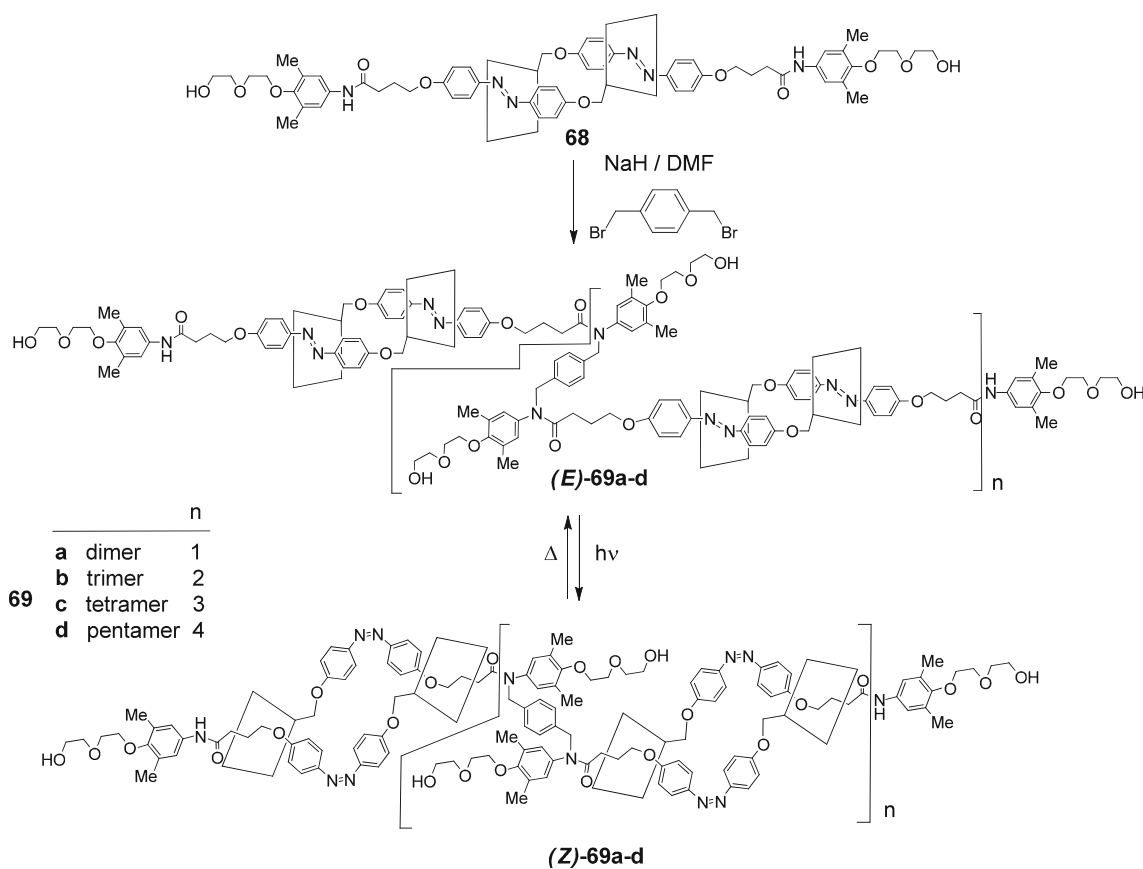
Scheme 16 Synthesis of molecular muscles **69a–69d**
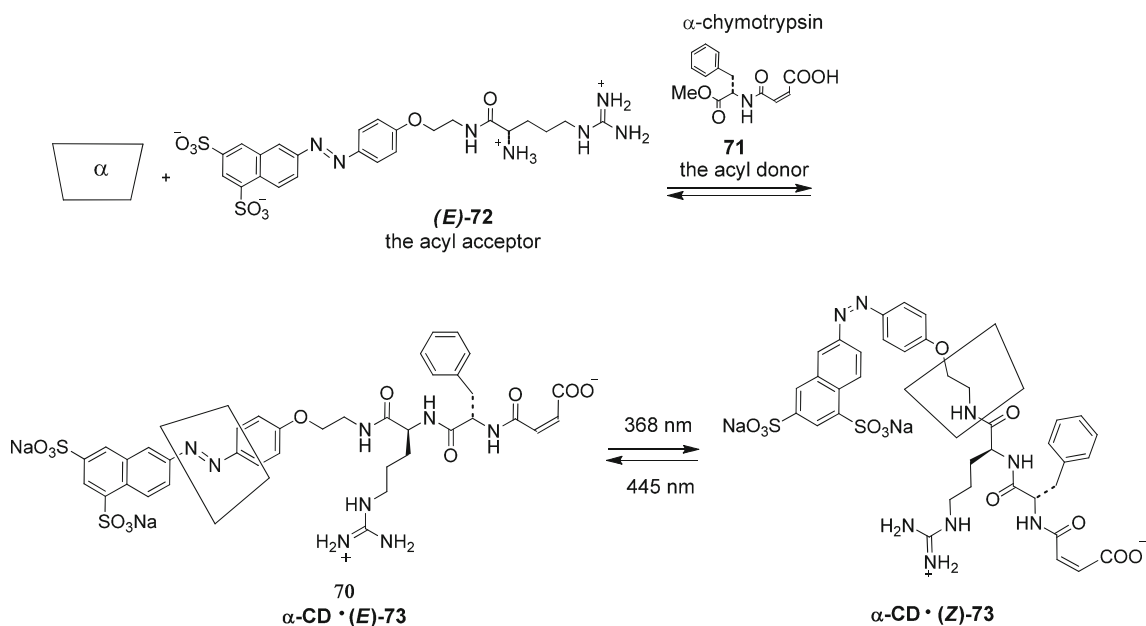
Scheme 17 Synthesis and photoisomerization of rotaxane **70**

The process begins with two click reactions of propargyl β-lactosylamide **79**: with azido-α-CD **82** the monolactosyl-α-CD **83** is obtained, and with diazide **84** lactosyldecane azide **85** is formed. Encapsulation of **83** with **85** yielded pseudorotaxane **78** which is a starting material for synthesis of rotaxane **74** and rotaxanes **75–77** [83]. *Synthesis*
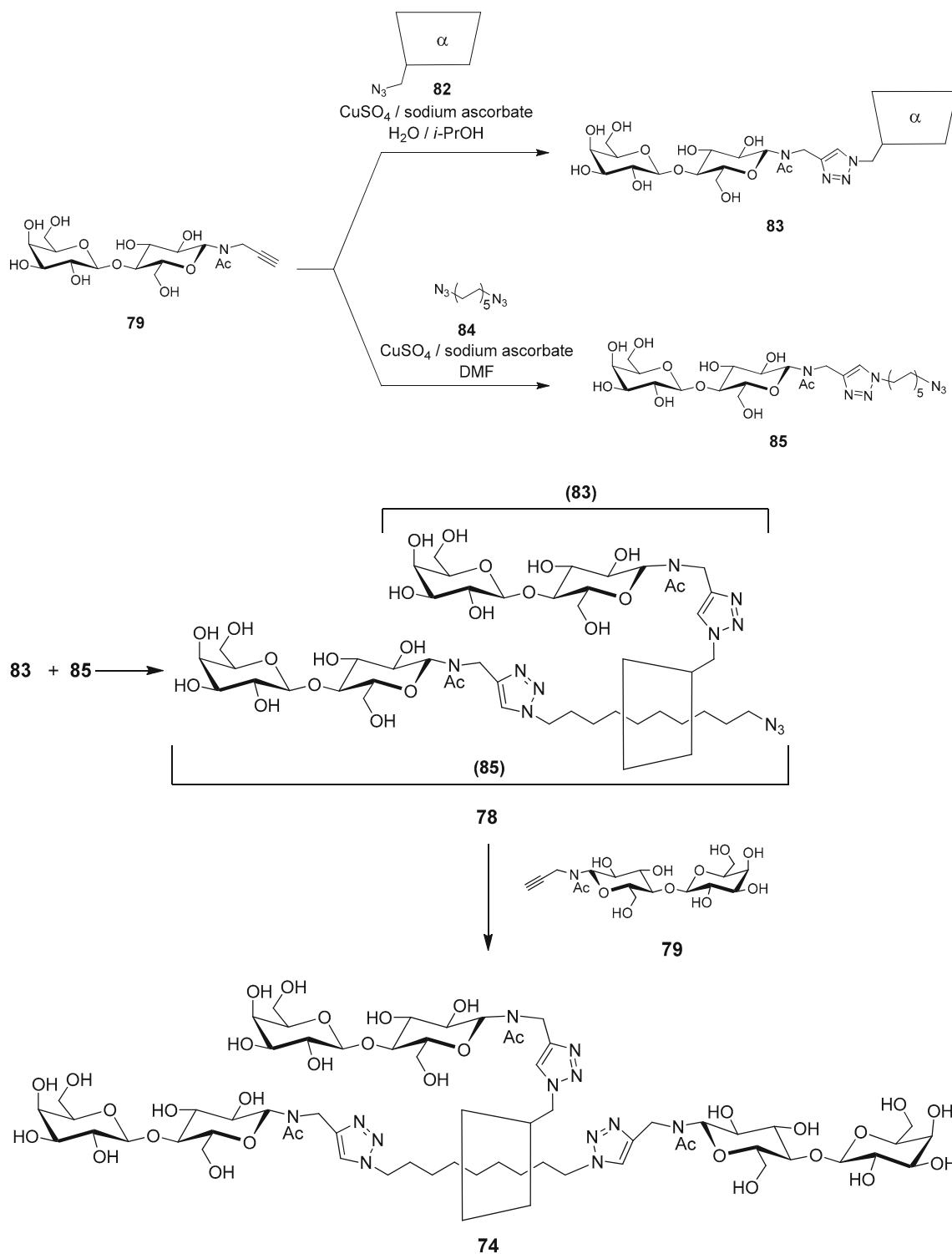
Scheme 18 Syntheses of monolactosyl-α-CD 83 and of lactosyldecane azide 85 along with the synthesis of rotaxane 74

of rotaxane 74 is performed by capping pseudorotaxane 78 with *N*-propargyl lactosylamide 79 (Scheme 18).

Synthesis of rotaxanes 75–77 involves assembling of two molecules of 78 by bis-propargyl spacers 80 and 81,

obtained from corresponding diols, also using click reactions. The treatment of 78 with 80 afforded rotaxane 75, whereas the reaction of 78 with 81 and 83 (three equivalents of 83) gave rotaxane 76, and the same procedure, but
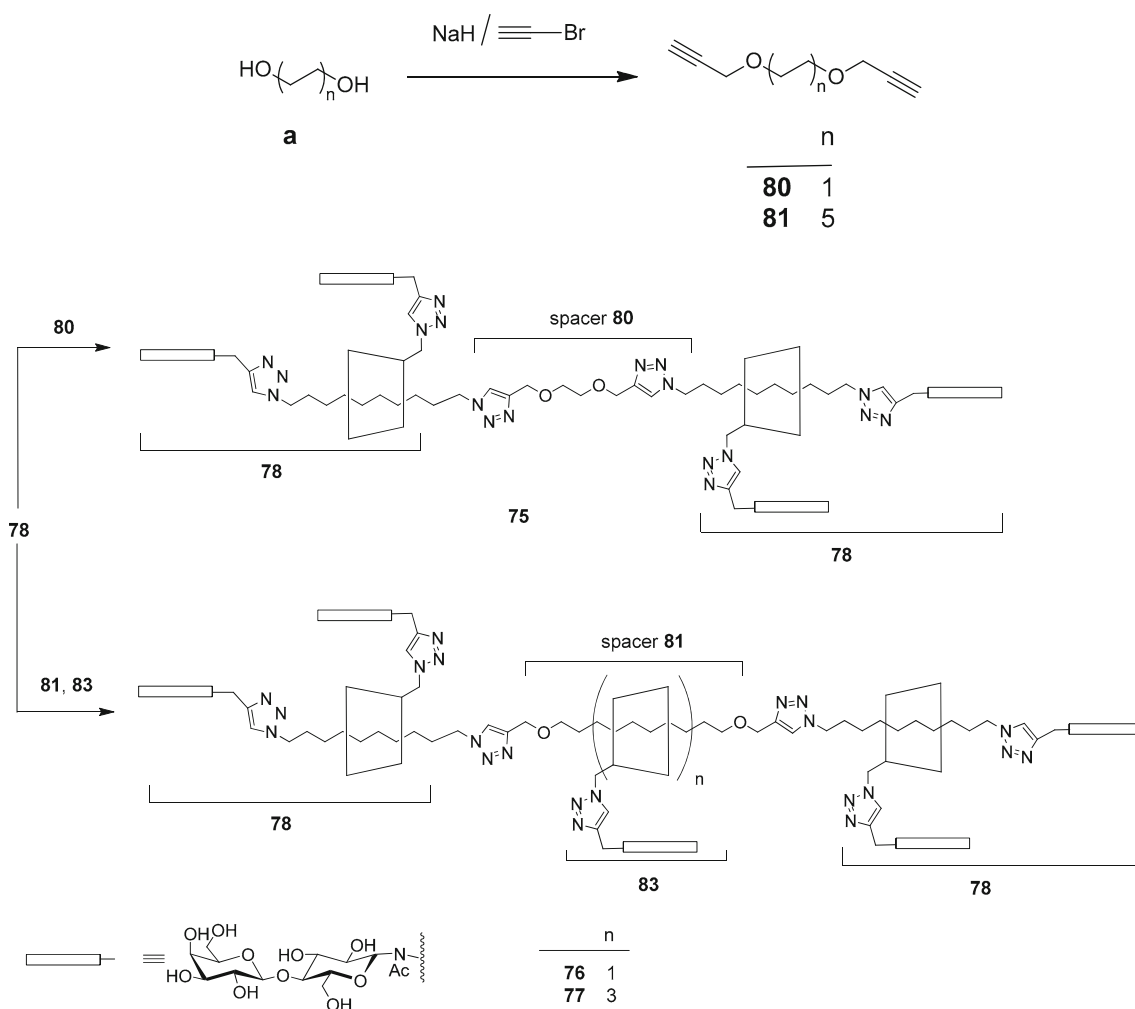
Scheme 19 Syntheses of rotaxanes **75–77**

using fifteen equivalents of **83** yielded rotaxane **77** (Scheme 19).

It was found that rotaxanes **74–77** inhibited PNA/lectin/ asialofetuin interactions in a valency-dependent manner, however no significant synergic effect was observed; this behavior presumably results from insufficient mobility of CD rings.

Conclusion

Cyclodextrin-based rotaxanes are today intensively studied [84–93], an attention being focused on their possible applications in the design of molecular devices and sensors so for analytical chemistry, as in biological investigations and research concerning environmental protection. Having in view the valuable properties of CDs [94–97] and rotaxanes [98–100], as well as a rapid development of these both domains, the interesting experimental results, confirming usefulness of designed species may be expected.

Albeit, due to the large amount of reports concerning CD rotaxanes, only selected examples are described in the present review, one should hope that they could be of use for further study of this promising chemistry area.

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