



Cite this: *Chem. Commun.*, 2016, 52, 5977

Received 5th March 2016,
Accepted 29th March 2016

DOI: 10.1039/c6cc01980c

www.rsc.org/chemcomm

A bifunctional chiral [2]catenane based on 1,1'-binaphthyl-phosphates†

R. Mitra,^a M. Thiele,^a F. Octa-Smolín,^a M. C. Letzel‡^b and J. Niemeyer*^a

A novel [2]catenane was synthesised by ring-closing metathesis from a Ca-bisphosphate template. The resulting interlocked structure features two chiral 1,1'-binaphthyl-phosphates, leading to a bifunctional catenane structure. Initial binding studies point at the applicability of such mechanically interlocked bisphosphates as artificial receptors for dicationic guest molecules.

Mechanically interlocked molecules (MIMs), such as rotaxanes and catenanes, have inspired chemists for decades.¹ Since the initial observations of MIMs as mere lab curiosities, the development of template-based synthetic approaches nowadays allows for their directed synthesis in useful quantities.² This has set the stage for the use of these topologically fascinating molecules for various applications,³ e.g. as molecular shuttles,⁴ supramolecular catalysts⁵ and even as nano-sized assembly lines.⁶

The interlocked nature of rotaxanes and catenanes makes them especially suitable as artificial receptors. The combination of several subunits in a compact interlocked fashion can be used to generate a three-dimensional binding cavity, which leads to strong and specific binding of guest molecules.⁷ This has been efficiently employed by Beer for the generation of interlocked receptors for various anions, showing that size-selective binding of halides⁸ and selective binding of dianions over monocharged guests can be achieved.⁹ The use of interlocked-structures for binding of cationic guest-species has been less systematically studied. Since a pioneering study of Swager on Cu(I)-sensing by a polyrotaxane,¹⁰ interlocked sensors for some other metal ions, such as alkali-metal ions have been reported.¹¹ Yashima has recently described a chiral amidinium-carboxylate-based [2]catenane, which acts as a sensor for Zn²⁺-ions.¹²

The successful syntheses of chiral mechanically interlocked species,¹³ even structures lacking any covalent chirality,^{5a} has generated significant interest in their application as chiral host-structures. While Hiratani has reported on the stereoselective sensing of amino alcohols by chiral rotaxanes,¹⁴ we believe that the full potential of MIMs as chiral receptors has yet to be fully explored, especially taking into account the highly successful development of non-interlocked species for stereoselective supramolecular sensing.¹⁵

Along these lines, we envisaged the synthesis of a new type of chiral bifunctional [2]catenane based on 1,1'-binaphthyl-phosphoric acids. Although these chiral Brønsted-acids have been widely employed in organocatalysis,¹⁶ they have not found application in interlocked structures so far. Their integration into a [2]catenane would result in a flexible arrangement of two chiral phosphates in an interlocked molecule, possibly generating useful chiral receptors, especially for the binding of dicationic guest molecules. In this account, we would now like to present the development of a synthetic protocol for the chiral catenane (*S,S*)-**1**, which represents the first example of an interlocked structure based on 1,1'-binaphthyl-phosphates. Also, we present initial data on its use for the binding of selected chiral dicationic guest molecules.

In order to allow for the generation of the desired [2]catenane (*S,S*)-**1** in a double-cyclisation approach, we firstly synthesised the acyclic crescent-shaped BINOL-phosphate (*S*)-**7** (see Fig. 1). The precursor (*S*)-**7** is functionalised with two terminal allyl-substituents which are connected to the 3,3'-positions of the BINOL-backbone *via* phenyl-hexaethyleneglycol linkers, thus allowing the formation of the macrocyclic subunits of the catenane *via* ring-closing metathesis (RCM).

The synthesis of (*S*)-**7** was performed in a four-step sequence starting from the previously described MOM-protected diiodide (*S*)-**3**.¹⁷ Initial introduction of 4-hydroxyphenyl groups in a Suzuki-coupling to give (*S*)-**4** was followed by attachment of the *O*-allyl-hexaethyleneglycol substituents, resulting in (*S*)-**5**.

Removal of the MOM-protecting groups to give (*S*)-**6**, followed by an introduction of the phosphate-group yielded the desired

^a Institute of Organic Chemistry, Department of Chemistry, University of Duisburg-Essen, Universitätsstrasse 7, 45141 Essen, Germany. E-mail: jochen.niemeyer@uni-due.de

^b Institute of Organic Chemistry, University of Münster, Corrensstrasse 40, 48149 Münster, Germany

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6cc01980c
‡ MS/MS-experiments.



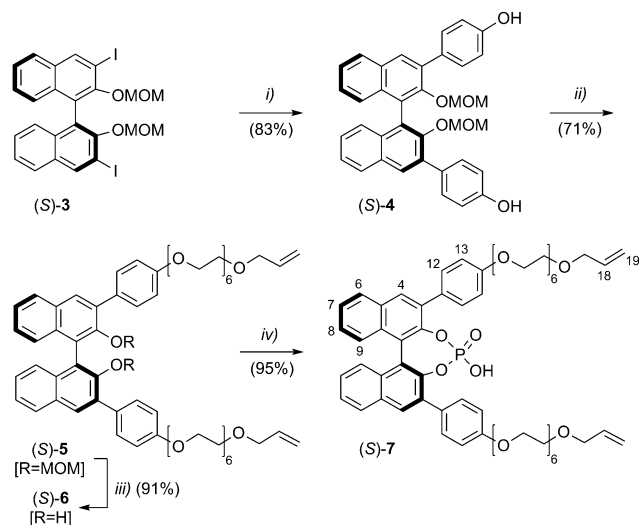


Fig. 1 Synthesis of compound (S)-7. Reagents and conditions: (i) 4-hydroxyphenyl boronic acid, Pd(PPh₃)₄, 85 °C, DME/Na₂CO₃ (2 M); (ii) O-allyl-hexaethyleneglycol-tosylate, K₂CO₃, 80 °C, CH₃CN; (iii) Amberlyst 15, 65 °C, THF/MeOH; (iv) POCl₃, pyridine, 60 °C, then H₂O.

BINOL-derivative (S)-7 in 51% overall yield. All compounds were fully characterised by standard spectroscopic and analytical techniques (see ESI†). In addition, chiral HPLC-analysis of compound (S)-6 verified its optical purity (>98% ee).

In order to construct the desired interlocked structure (S,S)-1 starting from the phosphate (S)-7 (see Fig. 2), we envisaged the use of divalent metal ions for the construction of the corresponding intertwined bisphosphate-metal(II) complexes, which would then undergo double RCM. In our hands, calcium(II) was most suitable as a templating agent, so that we decided for the calcium-bisphosphate (S,S)-8 as the precatenane-structure.

Compound (S,S)-8 could easily be obtained by reaction of (S)-7 with Ca(OMe)₂. The formation of (S,S)-8 was signalled by shifts in the ¹H-NMR (e.g. phenylene-groups: δ_H = 7.56 and 6.79 ppm for (S,S)-8, cf. δ_H = 7.61 and 6.92 ppm for (S)-7), accompanied by significant line-broadening, especially in the ¹H-NMR (see Fig. 3) and ³¹P-NMR (δ_P = 0.5 ppm (ν_{1/2} = 219 Hz) for (S,S)-8, cf. δ_P = 1.7 ppm (ν_{1/2} = 21 Hz) for (S)-7). While complete dissociation of Ca-complex (S,S)-8 was observed in protic solvents (e.g. under conditions of ESI-MS and RP-HPLC, see Fig. S21, ESI†), APCI-MS gave clear indication for the successful

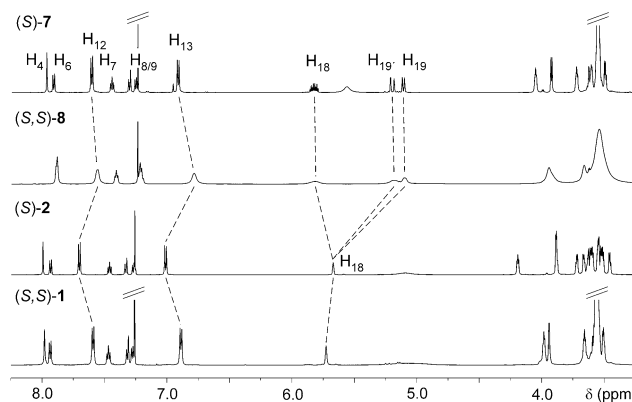


Fig. 3 ¹H-NMR-spectra of the acid (S)-7, the precatenane (S,S)-8, the macrocycle (S)-2 and the catenane (S,S)-1 [for numbering scheme see Fig. 1 and 2, all: 600 MHz, CDCl₃, 25 °C].

synthesis of (S,S)-8 (*m/z* = 2319.9234, calcd 2319.9237 for [M + H]⁺, see Fig. S23, ESI†).

For the formation of catenane (S,S)-1, the calcium salt (S,S)-8 was subjected to RCM using Grubbs-II catalyst in diluted dichloromethane solution (1.5 mM). After two days, we observed almost complete consumption of the starting materials and conversion to products of RCM, as judged by the disappearance of the allylic ¹H-resonances (δ_H = 5.82, 5.18 and 5.10 ppm for (S,S)-8) and appearance of new ¹H-NMR signals in the area of 5.72–5.64 ppm. Analysis of the reaction mixture by RP-HPLC showed the presence of two main products, which could be purified by reversed phase liquid chromatography.

The firstly eluting product was identified as the undesired non-interlocked macrocycle (S)-2 (22% yield), possibly formed by from (S,S)-8 by backfolding of the flexible ethyleneglycol linkers. (S)-2 was analysed by NMR and ESI-MS (*m/z* = 1135.44271, calcd 1135.44267 for [(S)-2 + Na]⁺, see Fig. S44, ESI†) and the assignment of the macrocyclic structure was unambiguously verified by comparison to an independently synthesised sample of (S)-2, which could be generated by RCM from the phosphate (S)-7 (see ESI†).

To our delight, the secondly eluting product could be identified as the desired interlocked catenane (S,S)-1, which we isolated in 14% yield. Positive and negative ESI-MS reveal the catenane (S,S)-1 as the corresponding mono-, di- and triply charged ions with the expected isotopic profiles and accurate

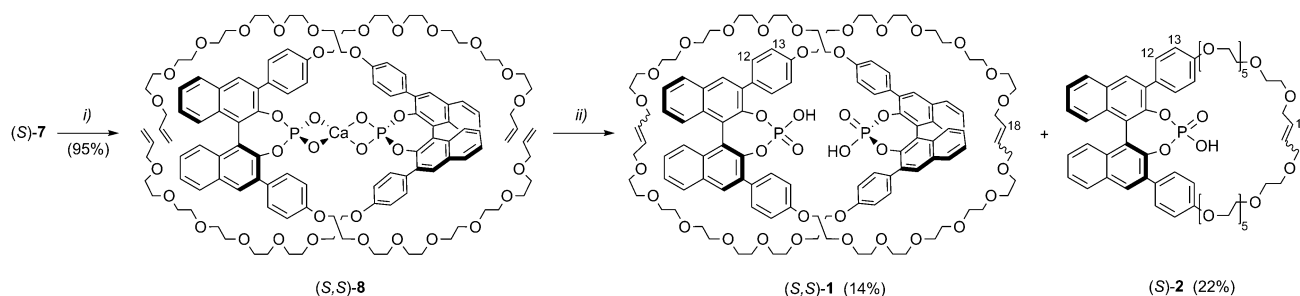


Fig. 2 Synthesis of the catenane (S,S)-1. Reagents and conditions: (i) 0.5 eq. Ca(OMe)₂, toluene; (ii) Grubbs-II catalyst, CH₂Cl₂, purification on RP-18, then washing with HCl.



masses (e.g. $m/z = 2247.89412$, calcd 2247.89612 for $[(S,S)\text{-}1 + \text{Na}]^+$, see Fig. S47–S49, ESI†), none of which were observed for the macrocycle (S)-2.

NMR-spectroscopic analysis of the macrocycle (S)-2 and the catenane (S,S)-1 (see Fig. 3) verifies the formation of chemically different species, most distinctly visible from the different chemical shifts of the phenylene-groups ($\delta = 7.68, 6.99$ ppm for (S)-2 and $\delta = 7.57, 6.87$ ppm for (S,S)-1, cf. 7.56 and 6.79 ppm for (S,S)-8). In the olefinic region, we detect major-signals at $\delta = 5.65/5.71$ ppm, together with minor additional signals at $\delta = 5.57/5.63$ ppm (each for (S)-2/(S,S)-1, see Fig. S25 and S29, ESI†), which we tentatively assign as the (Z)- and (E)-isomers of (S)-2 and the (Z,Z)- and (Z,E)-isomers of (S,S)-1, respectively (ratio major:minor = ca. 95:5 in each case). These isomers could not be separated by chromatography so that both (S,S)-1 and (S)-2 were isolated as mixtures of double-bond stereoisomers.

In order to rule out the formation of a non-interlocked [1+1]-macrocyclic (see Fig. S41, ESI†), we performed additional investigations by DOSY-NMR and MS/MS-experiments. The hydrodynamic radius of (S,S)-1 was determined as 12.5 \AA by DOSY-NMR, which clearly indicates the formation of the interlocked catenane-structure upon comparison to the corresponding calculated values (12.4 \AA for (S,S)-1, cf. 16.7 \AA for a potential [1+1] macrocycle, for details see ESI†). The interlocked structure of (S,S)-1 was also clearly proven by ESI-MS/MS-measurements. Upon collision-induced dissociation, the catenane (S,S)-1 (mass-selected at $m/z = 2248.89$ for $[(S,S)\text{-}1 + \text{Na}]^+$) shows fragmentation to give the macrocycle (S)-2 ($m/z = 1135.44322$ for $[(S)\text{-}2 + \text{Na}]^+$) and the corresponding smaller fragments.

Having established the structure of (S,S)-1 as the desired catenane, we tested its applicability as an interlocked receptor. The presence of the two $1,1'$ -binaphthyl-phosphates should allow for the strong binding of small dicationic guest molecules. We therefore performed a series of NMR-titrations in d_6 -DMSO using (S,S)-1 as a host for binding of lysine- and arginine methyl esters and *trans*-1,2-diaminocyclohexane, respectively. In order to obtain information about the stereoselectivity of binding to the chiral catenane, we used both enantiomers of all guest molecules. As a comparison, we also determined the association constants for the macrocycle (S)-2.

Upon addition of the diamine-guests (used as the bis-HCl-salts) to the phosphate hosts (S)-2 and (S,S)-1 (as the mono- or bis-tetrabutylammonium-salts),¹⁸ we observe distinct chemical shift changes for the aromatic host signals (see Fig. 4 as a representative example, also see Fig. S53–S64, ESI†). Fig. 5 shows the resulting binding isotherms for the binding of the enantiomeric arginine methyl esters to (S)-2 and (S,S)-1, as determined from the H-8 proton of the hosts (also see Fig. S67–S69, ESI†).¹⁹

The binding stoichiometry for binding of the diamines to the catenane (S,S)-1 was established to be 1:1, as determined from Job-plot analysis (see Fig. S65 and S66, ESI†). For the macrocycle (S)-2, the Job-plot analysis was less conclusive, but comparative data analysis for 1:1 and 2:1 stoichiometries indicates a 2:1 host:guest complex formation (see ESI† for details). Accordingly, we determined the association constants by analysis of the binding isotherms using 1:1 or 2:1 binding

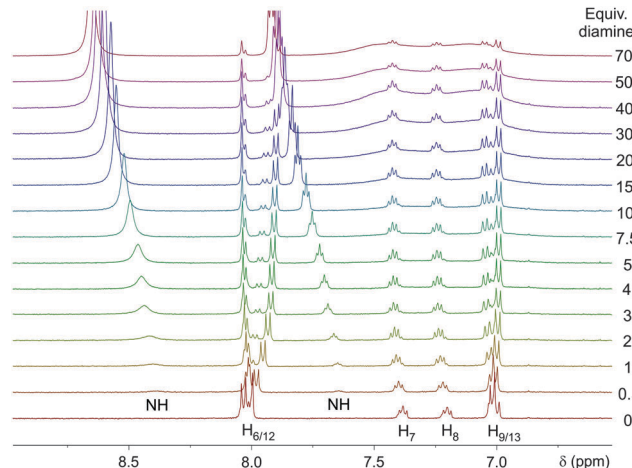


Fig. 4 Representative stacked plot (aromatic region) of the NMR-titration of (S,S)-1 (as the bis- Bu_4N^+ -salt), with 0.5 to 70 eq. of D -Arg-OMe (as the bis-HCl salt) [for numbering scheme see Fig. 1 and 2, all: 500 MHz, d_6 -DMSO, 298 K, initial concentration of (S,S)-1: 0.5 mM].

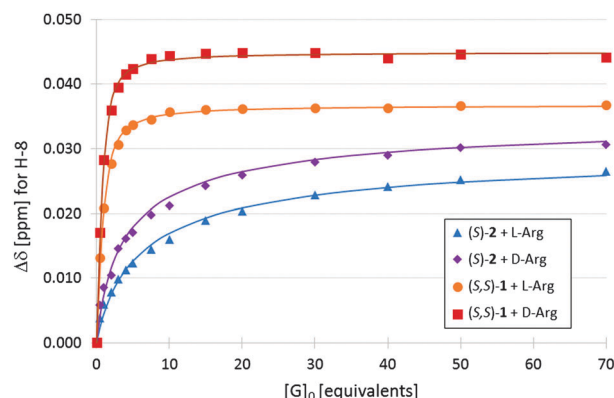


Fig. 5 Representative binding isotherms for the binding of D/L -arginine methyl esters (as the bis-HCl salts) to (S)-2 and (S,S)-1 in d_6 -DMSO (as the mono- or bis- Bu_4N^+ -salts) [initial concentration of hosts: 0.5 mM, plotted for H-8 of the hosts, data points: experimental data, lines: fitting data].

models, respectively. For easier comparison, both K_a values for the 2:1 binding process to (S)-2 were integrated into a single value (see ESI† for details).

The resulting association constants for binding of the diamines to the macrocycle (S)-2 are in the range of $570\text{--}870 \text{ M}^{-1}$, indicating a rather weak binding in DMSO-solution (see Table 1). There is little chemoselectivity between the different guest species, and only in the case of the arginine-enantiomers we observe a small degree of stereoselectivity in favour of the D -isomer ($K_{\text{fav}}/K_{\text{disfav}} = 1.3$).

For the formation of the catenane-diamine complexes however, we find significantly higher association constants of 4100 to $15\,800 \text{ M}^{-1}$, showing a stronger binding of the guests to the interlocked bisphosphate-receptor (S,S)-1 in comparison to the macrocycle (S)-2. While we observe no significant chemoselectivity between the lysine- and arginine methyl-esters, the larger association constants for the 1,2-diamino-cyclohexanes



Table 1 Association constants (M^{-1}) for $[(S)-2^-(Bu_4N^+)]$ and $[(S,S)-1^{2-}(Bu_4N^+)_2]$ with selected diamines in d_6 -DMSO

Diamine ^a	$[(S)-2^-(Bu_4N^+)]$		$[(S,S)-1^{2-}(Bu_4N^+)_2]$	
	$K_a [M^{-1}]$	K_{fav}/K_{disfav}	$K_a [M^{-1}]$	K_{fav}/K_{disfav}
L-Lys-OMe	630 ± 20	1.1	4100 ± 610	1.4
D-Lys-OMe	700 ± 30		5700 ± 730	
L-Arg-OMe	570 ± 25	1.3	5550 ± 320	1.5
D-Arg-OMe	770 ± 35		8200 ± 610	
(S,S)-DACH ^b	870 ± 170	1.0	15800 ± 2900	1.6
(R,R)-DACH ^b	840 ± 100		10050 ± 1300	

^a All diamines used as the bis-HCl-salts, all values determined by monitoring the H-8 proton of the host-molecules. ^b DACH = 1,2-diaminocyclohexane.

indicate a stronger binding of this smaller guest-molecule to the catenane-host.

More interestingly, we also observe a more significant degree of stereodiscrimination, favouring the binding of the D-amino acids and the (S,S)-enantiomer of 1,2-diaminocyclohexane, respectively. The association constants of the favoured enantiomers are 1.4 to 1.6 times higher than those of the disfavoured ones (see Table 1).

In summary, we have reported on the successful synthesis of a new type of bifunctional chiral [2]catenane based on 1,1'-binaphthyl phosphates. The homo-catenane (S,S)-1 was generated by ring-closing metathesis from a Ca-templated precatenane to generate the desired interlocked structure. Initial binding studies show a strong binding of diamines to the bifunctional catenane, alongside with slight stereospecificity induced by the chiral host structure.

Detailed studies on the variation of the catenane structure and the resulting effects on selective guest binding are currently underway in our laboratories. In addition, we believe that the bifunctional framework of the catenane (S,S)-1 will allow for its use in other applications, e.g. the formation of supramolecular polymers or in supramolecular organocatalysis.

We would like to thank Mr. Manfred Zähres for his help with the DOSY-NMRs and Mr. Martin Ehlers and Mr. Wilhelm Sicking for their help with the Macro-Model calculations. J. N. thanks Prof. Carsten Schmuck for his mentorship and the Fonds der Chemischen Industrie for funding.

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- In order to prevent chemical shift changes by proton transfer from phosphoric acid to amine, we used the respective phosphate- and ammonium-salts in the titration experiments.
- Although H-7 and H-8 only show small $\Delta\delta$ -values upon guest binding, they do not overlap with other signals over the whole titration range (as opposed to H-6/9/12/13). Analysis of $\Delta\delta$ for H-7 and H-8 gave almost identical results.

