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Chiroptical Induction with Prism[5]arene Alkoxy-Homologs

Xiaotong Liang,[a] Yanling Shen,[a] Dayang Zhou,[b] Jiecheng Ji,[a] Hongtao Wang,*[a] Ting Zhao,[a] Tadashi Mori,*[b] Wanhua Wu,[a] Cheng Yang*[a]

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The complexation of prism[5]arenes with amino acid derivatives showed association constants of up to 10^7 M^{-1}, significant CD with g_{abs} of up to 0.8×10^{-2} and CPL with g_{lum} of 2×10^{-3}. The absolute configuration-CD signal correlation was established. The CD spectra varied significantly with the substituents on prism[5]arenes.

Supramolecular chiral induction is not only interesting from a fundamental view of point but has demonstrated vast potential in such as chirality detection, asymmetric synthesis, molecular devices and chiroptical materials.[1] Supramolecular chirality transfer is particularly attractive in chirality sensing, especially for cryptochiral molecules, due to the nondestructive, fast and high-throughput advantages.[2] Various supramolecular sensors have been developed by combining reporting group(s) and a binding site together. Recently, chirality induction/sensing with macrocyclic arenes have attracted rapidly increasing attention,[3] among which pillar[n]arenes are prominent due to their excellent guest binding and chiroptical responding properties.[4] We[5] and others[6] have demonstrated that the complexation of pillar[n]arene with a chiral guest shifted the racemic equilibrium of R_p and S_p conformers and induced strong circular dichroism (CD) response. However, pillar[n]arenes are composed of hydroquinone ether subunits, showing absorption in deep ultraviolet (DUV) region and weak fluorescence in UV range. In this term, macrocyclic arenes composed by subunits of larger conjugation should offer more desirable chiral induction and sensing performance. Recently, several macrocyclic arenes comprising naphthalene[7] or anthracene[8] subunits have emerged and demonstrated excellent guest-binding properties. Gaeta and co-workers have recently reported a convenient synthesis of prism[5]arenes (Chart 1).[9] Prism[5]arenes are composed by 2,6-dialkoxynaphthalene subunits and have larger and deeper cavities than pillar[n]arenes, which are expect to have unique binding and chirality induction properties. Herein, we report the chiral binding with prism[5]arene, which exhibited binding affinity and chiroptical response superior to pillar[5]arenes.

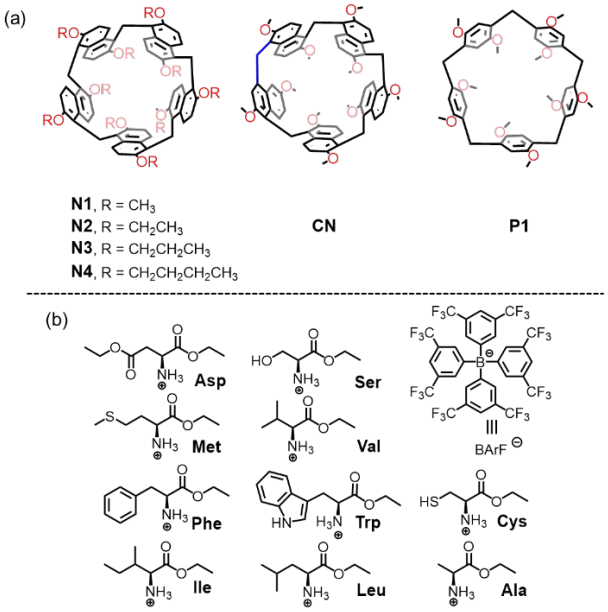

Chart 1 Chemical structures of a) prism[5]arenes, pillar[5]arene and b) the chiral guests.

Prism[5]arenes (**N1**-**N4,** Chart 1a) and 1,4-confused-prism[5]arene **CN** were synthesized[9] and were characterized by HRMS and NMR spectroscopies (Fig. S7-S18). The UV-vis spectrum of **N1** showed the S_0-S_1 (^1L_a) transition peaked at 348 nm (Fig. 1a), which is much bathochromic shifted relative to the S_0-S_1 transition of pillar[5]arene **P1** (peaked at ca. 290 nm). It emits blue-violet light peaking at 390 nm (Fig. 1b) with a moderate quantum yield Φ = 0.10 (Fig. S65 and Table S1).

[a] College of Architecture and Environment, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital, and Key Laboratory of Green Chemistry & Technology of Ministry of Education, Sichuan University, Chengdu 610064, China. E-mail: wanght@scu.edu.cn; yangchengyc@scu.edu.cn
[b] Comprehensive Analysis Center, ISIR and Department of Applied Chemistry, Osaka University, Yamada-oka, Suita 565-0871, Japan. E-mail: tmori@chem.eng.osaka-u.ac.jp

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The complexation of prism[5]arenes with a series of amino acid BArF salt (chart 1) [10] was studied by spectroscopic methods. The addition of *L*-**Ser** to a $CHCl_3$ solution of **N1** led to a bathochromic shift and a hyperchromic effect at the ^1L_a transition of **N1** (Fig. 1a), and a significant enhancement of the fluorescence intensity (Fig. 1b). Such spectroscopic changes could also be observed with other amino acids (Fig S52-S54). In particular, the Φ value of *L*-**Leu@N1** was 4.2-fold higher than the uncomplexed **N1** (Table S1), indicating that the complexation reduced the non-radiative decay, presumably owing to the fixed conformation of naphthalene subunits when binding the guest.

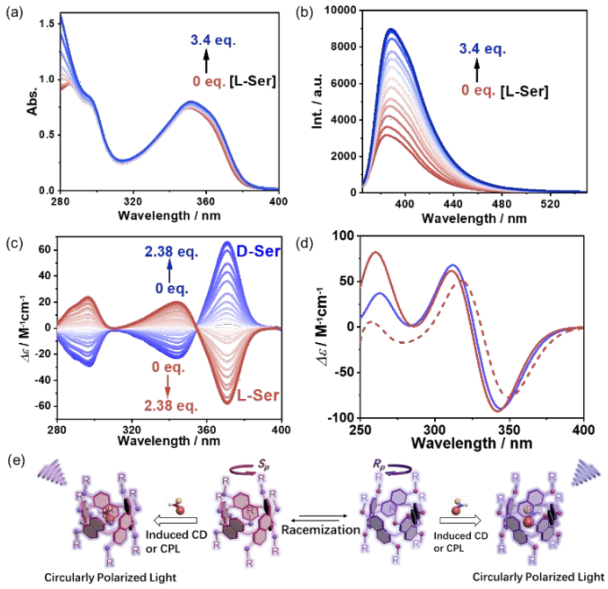

Fig. 1 (a) UV-vis, (b) fluorescence (λ_{ex} = 350 nm), and (c) CD spectral changes of 5.0×10^{-5} M **N1** upon addition of *L*-**Ser**. (d) Calculated CD spectra of *Sp* conformers of **N1** (red) and **CN** (blue). (e) Plausible mechanism diagram of chiral induction of prism[5]arene complexation with a chiral guest. All measurements were carried out in $CHCl_3$ at 25 °C.

The single crystal analysis has demonstrated prism[5]arenes to adopt all R planar chirality R_p (R_p, R_p, R_p, R_p, R_p) or all S planar chirality S_p (S_p, S_p, S_p, S_p, S_p),[9] in which all methoxyl groups are directed in the same direction to avoid the steric repulsion between them. Our attempts to enantio-separate the R_p and S_p conformers of **N1**-to-**N4** failed, demonstrating they are rapidly interconvertible through the "oxygen through the annulus" rotation.[9, 11] In the absence of a chiral binder, the R_p and S_p conformers exist as a racemic mixture. Complexing an amino acid led to a significant chiroptical response. For example, adding *L*-**Ser** to the solution of **N1** induced a negative exciton coupling CD (ECCD) signal at the ^1L_a band of naphthalene, showing a negative and a positive maximum at 371nm and 346 nm, respectively (Fig. 1c). This demonstrated a shift of the racemic equilibrium between the R_p and S_p conformers as a consequence of the chirality transfer from central chirality of the amino acid to the planar chirality of prism[5]arene. The CD intensity increased with the concentration of *L*-**Ser** (Fig. 1c), and *D*-**Ser** led to a CD spectrum that is a mirror-image of that induced by *L*-**Ser** (Fig. 1d). Large dissymmetric g-factors up to 2.7×10^{-3} was observed at 377 nm in the presence of 2.98 equiv *L*-**Ser**. The above results demonstrated that this chiroptical induction is promising for application in chirality sensing. The chiroptical induction should arise from different binding affinities of R_p and S_p conformers towards the chiral guest, and the conformational equilibrium will shift towards the conformer of stronger binding affinity (Fig 1e).

The CD spectra of prism[5]arenes were theoretically investigated at the RI-CC2/def2-SV(P)//TPSS-D4/def2-TZVP level,[12] based on the crystal structures[9a] of **N1** and **CN**. A slightly more distorted open conformer (corresponding to the *α*- and/or *β*-pseudo-polymorphic forms) turned out to be more stable and the predicted CD spectra (solid red, Fig. 1d) for the S_p enantiomer afforded intense bisignate Cotton effects at the ^1L_a band, in accord with the observed negative ECCD of the **N1** complex with *L*-**Ser** as a guest. The additional positive Cotton effect at 290 nm was also well reproduced in both excitation energy and relative intensity. Accordingly, the absolute configuration of induced prism[5]arene chirality was unambiguously confirmed. While the predicted spectral pattern (negative-positive-positive) was comparable for another conformer in which the cavity is closed in one side (based on the γ-form) (dotted red, Fig. 1d), the reproducibility was better in the open form in the (relative) intensity of the Cotton effects, implying the open (host) structure is more probable for **N1**-**N4** upon complexation. As the predicted CD spectrum was also comparable between the homologous **CN** and **N1** given the same handedness (note that the cavity structures of three forms of **CN** were essentially identical), an observed inverted induced-CD response was ascribable to the preferable formation of an oppositely enantiomeric complex in **CN**, as compared with **N1**-**N4**, with the same amino acid guests (vide infra).

It turned out that the intensity and the signs of the CD signals differ significantly among the *L*-amino acids examined. For amino acids *L*-**Ser**, *L*-**Ala**, *L*-**Asp**, *L*-**Cys**, *L*-**Leu** and *L*-**Ile**, negative ECCD with different intensities were induced at the ^1L_b band of **N1** (Fig. 2a), while *L*-**Val**, *L*-**Met**, *L*-**Phe** and *L*-**Trp**, gave positive ECCD. The varied CD signals could even differentiate small structural differences in the amino acids. For example, the complexation of **N1** with *L*-**Val** and *L*-**Leu** gave positive and negative ECCD, respectively.

Compared to chirality sensing with **P1**, the induced CD signals obtained with prism[5]arenes are generally much more significant (Fig. S20b). In particular, an intensity up to 160 mdeg was observed for the complex of *L*-**Asp** and **N1**(Fig. 2a), and the g_{abs} value of 8.0×10^{-3} obtained with *L*-**Asp@N1** is about 4-fold higher than that of *L*-**Asp@P1** (2.0×10^{-3}).[5a] To our knowledge, this is the highest g_{abs} factor obtained for the chirality sensing by macrocyclic arenes.[5a, 6a, 6b, 7a-d] Also, the g_{abs} value (2.7×10^{-3}) obtained for *L*-**Ser@N1** is 65-fold larger than the g_{abs} value (4.1×10^{-5}) of *L*-**Ser@P1**.[5a]

The chiral guest-dependent CD responses were also observed with **N2**-**N4** (Fig. 2b and S32-S37), indicating excellent sensitivity to structural changes of chiral substrates. This could be accounted for by the steric effect during the complexation: structural change in the chiral inducer should not only vary the inter-naphthalene transition angles, which will critically change

the exciton coupling CD response, as well as the binding affinity towards corresponding *Rp* and *Sp* conformers.

It is interesting to note that for a same chiral inducer, the induced CD signals vary significantly with the substituents on prism[5]arenes. For the chiral induction with *L*-**Ser** as an example, the ECCD intensity maxima decrease significantly with the alkyl chain lengths, from -57.5 mdeg for **N1** to -3.54 mdeg for **N4** (Fig. 2c). Such decrease could also be observed with other amino acids, including *L*-**Leu**, *L*-**Cys**, and *L*-**Ile** (Fig S56). On the other hand, an inversion from negative ECCD to positive ECCD was observed with *L*-**Leu** (Fig. 2d), demonstrating that the preferred chiral conformer switched from S_p for **N1** to R_p for **N4**. Longer alkyl chains should exert stronger steric and van der Waals interaction with the moiety positioning outside the cavity, thus varying both the binding affinity and stereo-preference.

For **CN**, the chiroptical induction appears to be much weaker than the symmetrical prism[5]arenes (Fig. S20a). Only *L*-**Ser**, *L*-**Ala**, *L*-**Met** and *L*-**Phe** produced CD signals, while negligible CD signals were observed with other amino acids. Compared to the induced CD of **N1**, **CN** showed inverted CD signals with *L*-**Met** and *L*-**Phe** and much-decreased CD signals with *L*-**Ala** and *L*-**Ser** (Fig. S20a and Table 1). These results indicate that the small structural difference in prism[5]arene homologs will significantly affect their chirality-sensing responses. The prism[5]arene derivatives thus provide a promising sensor array for distinguishing various amino acids.[13]

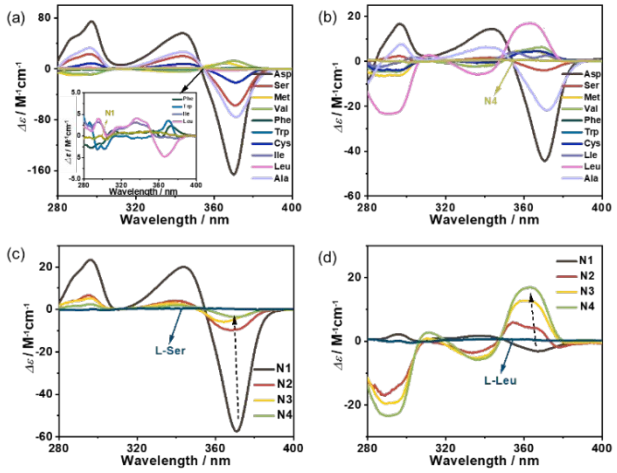

Fig. 2 CD spectra of **N1** (a) and **N4** (b) (5.0×10^{-5} M) in the presence of different chiral amino (5.0×10^{-4} M) in $CHCl_3$ at 25 °C. CD spectra of different N[5] derivatives (5.0×10^{-5} M) in the presence of *L*-**Ser** (c) and *L*-**Leu** (d) (5.0×10^{-4} M) in $CHCl_3$ at 25 °C.

The binding stoichiometries between prism[5]arenes and amino acids were determined to be 1:1 based on the continuous Job's plot analyses (Fig. S21), and the association constants (K_a) of prism[5]arene with various guests were evaluated based on the CD or fluorescence titrations (Fig. S22-S51). The K_a values fall in the range of 10^4-10^7 M^{-1} (Table 1), with up to 4.92×10^7 M^{-1} being observed for the complexation of *L*-**Ser** and **N1**. Significantly, for a certain chiral guest, the K_a values obtained with prism[5]arenes are almost an order of magnitude higher than those of **P1** (10^4-10^5),[5a, 6] demonstrating that prism[5]arenes are superior to P[5]s in terms of host-guest complexation.

Computational simulation of the complex of *L*-**Ile** and **N1** by density functional theory (DFT) calculation (Fig. S66) suggested that the ammonium is captured by the port of the prism[5]arene, while the ester part deeply enters the cavity (Fig. S66). This is in contrast to the complexation with **P1** where the amino acid primarily locates at the ports, for which the larger cavity of **N1** should be responsible. Therefore, the higher K_a values observed with prism[5]arenes should be ascribed to the deeper accommodation by the more electron-rich and larger π-plane. The simulation of *L*-**Ile@N1**$_{Sp}$ and *L*-**Ile@N1**$_{Rp}$ indicated that the binding of *L*-**Ile** to the S_p conformer was more stable, leading to a negative cotton signal, which was consistent with the CD measurements (Fig. S66). On the contrary, *L*-**Ile@N4**$_{Rp}$ has lower energy than *L*-**Ile@N4**$_{Sp}$, coinciding with the opposite CD signal (Fig. S66, Table S2 and S3).

The complexation led to upfield shifts of the all-proton peaks of the *L*-**Ile** in ^{1}H NMR spectra (Fig. S58) due to the shielding effect of prismarene. In addition, **N4** showed two sets of proton signals in the presence of *L*-**Ala** (Fig. S60) due to the formation of a pair of diastereomeric complexes of *L*-**Ala@N4**$_{Rp}$ and *L*-**Ala@N4**$_{Sp}$, showing an integral ratio of 2.25:1 (Fig. S61, S62). Larger upfield shifts of proton peaks for the complexation of *L*-**Ile** and **N4** than that of *L*-**Ile** and **N1** were observed(Fig. S58). The same was true for the complexation of *L*-**Ala** and **N1** or **N4** (Fig. S59-S63). This suggested a deeper accommodation of the amino acid in the cavity of **N4**, presumably due to the steric interaction between the long alkyl chain of **N4** that forces the guest molecules deeper into the cavity.

Table 1 Association constants and $\Delta\Delta\varepsilon$ values of CD_{max} at the ^1L_a band upon complexation of amino acid derivatives with **N1**, **CN** and **N4**[a]

Guest	N1		CN		N4	
	K_a / M^{-1}	$\Delta\Delta\varepsilon$ / $M^{-1}cm^{-1}$	K_a / M^{-1}	$\Delta\Delta\varepsilon$ / $M^{-1}cm^{-1}$	K_a / M^{-1}	$\Delta\Delta\varepsilon$ / $M^{-1}cm^{-1}$
L-Ser	4.92×10^7	-66.2	2.11×10^4	-19.8	1.81×10^6	-4.1
L-Ala	1.32×10^6	-76.7	1.77×10^4	-7.8	1.44×10^6	-21.9
L-Val	1.65×10^5	+12.2	\	+0.9	3.66×10^6	+6.4
L-Met	8.67×10^6	+9.3	2.02×10^5	-80	1.17×10^6	+5.6
L-Asp	2.09×10^4	-163.4	\	-0.3	1.00×10^4	-43.1
L-Cys	1.21×10^4	-21.7	\	-0.3	2.77×10^3	+4.7
L-Leu	3.23×10^4 [b]	-3.2	\	-0.2	1.72×10^4	+16.6
L-Lle	2.91×10^3 [b]	-0.9	\	-0.1	9.96×10^4	+4.1
L-Phe	6.42×10^5	+1.2	6.16×10^3	-5.1	3.42×10^5	+3.1
L-Trp	1.52×10^4	+2.4	\	+0.8	3.20×10^4	+5.2

[a]The CD_{max} were recorded upon complexation of 0.5 mM guest with 0.05 mM host. The association constants K_a were obtained based on the CD spectral titration. [b]K_a were estimated based on the fluorescence titrations data.

As demonstrated above, prism[5]arenes emit near ultraviolet to blue-violet region, which could be significantly enhanced upon complexation. We have revealed that supramolecular chiral assembly could be effective for producing strong circularly polarized luminescent (CPL) response,[14] and this prompted us to investigate the CPL induced by the complexation between **N1** and *D*- / *L*-**Ala**. The complexation of **N1** with *D*- and *L*-**Ala** induced CPL emission of mirror image, giving positive CPL for *L*-

Ala and negative CPL for *D*-**Ala** peaked ca. 410 nm (Fig. 3a). The luminescent asymmetry factor g_{lum} (Fig. 3b) reached a maximum of ca. 2.0 × 10^{-3}, which is in the range of chiral compounds of low molecular weight in the solution phase[15], though the chiral sensing system is composed by a non-luminescent chiral ammonium and an achiral host. This observation provides intriguing CPL-tunable supramolecular materials, which will be further explored in our future research.

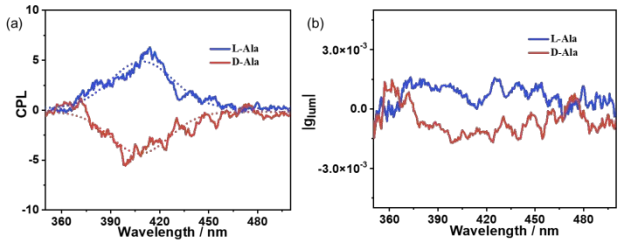

Fig. 3 CPL spectra (a) and corresponding g_{lum} factor of the complexation of **N1** (0.05 mM) with L-/D-**Ala** (0.25 mM) in $CHCl_3$ at 25 °C.

In conclusion, prism[5]arenes exhibit excellent binding ability towards amino acid derivatives, showing binding affinities usually an order of magnitude higher than P[5] due to the larger cavity and more electron-rich π-plane. The complexation with chiral ammonium salts induced intensive CD signals at the absorption band of prism[5]arenes, and g_{abs} value up to 8.0×10^{-3} was obtained, which is the highest value obtained in chirality induction with macrocyclic arenes. Based on the computational calculation, the correlation between the CD spectra and the absolute configuration of the R_p and S_p conformers of prism[5]arene was established. The signs and intensities of CD signals induced by the chiral complexation are critical functions of the chemical structures of prism[5]arenes and amino acids, thus providing a promising sensor array that could differentiate not only the absolute configuration but the chemical structure of chiral inducers. The complexation of the chiral ammonium significantly enhanced the prism[5]arene's fluorescence in the near ultraviolet to the blue-violet region and induced CPL with good dissymmetric factors. This work demonstrated that prism[5]arenes are excellent macrocyclic arenes for chirality sensing and show promising potential for application to supramolecular chiroptical materials.

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Conflicts of interest

There are no conflicts to declare.

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