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Inherently Chiral Azonia[6]helicene-Modified β-Cyclodextrin: Synthesis, Characterization, and Chirality Sensing of Underivatized Amino Acids in Water

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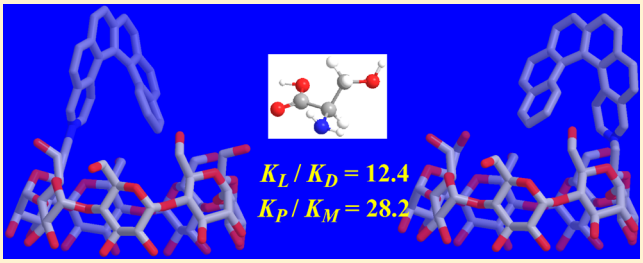
Supporting Information

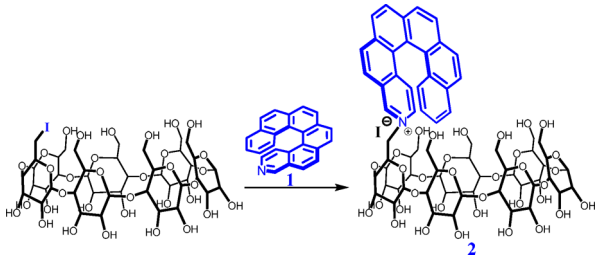
ABSTRACT: The (*P*)- and (*M*)-3-azonia[6]helicenyl β-cyclodextrins exhibit L/D selectivities of up to 12.4 and *P*/*M* preferences of up to 28.2 upon complexation with underivatized proteinogenic amino acids in aqueous solution at pH 7.3.



Chiral discrimination of proteinogenic amino acids (AAs) has long been a target of intensive studies due to their immediate relevance to the living systems and biological processes, such as enzyme activity, immunological selectivity, ion transport, and drug delivery as well as the origin of homochirality in the biosphere.[1−3] Synthetic chiral hosts that selectively bind or sense proteinogenic AAs can be used as biomimetic, pharmaceutical, and bioanalytical tools.[4] A variety of chiral hosts or binders, such as chirally coordinated metal ions,[5,6] crown ethers,[7] calixarenes,[8] binaphthol derivatives,[9] and cyclodextrins (CDs),[10−12] have been developed for discriminating D/L-AAs to exhibit significant enantioselectivities for some of the AAs but often for derivatized AAs or in pure or mixed organic media.[13−15] Thus, the efficient chiral discrimination of underivatized AAs in aqueous media still remains a challenge. A general approach to this goal is to develop a water-soluble chiral host that bears a highly enantioselective binding site. Certainly, the CD family, possessing good water-solubility and inherently chiral hydrophobic cavities for accommodating size/shape-matched organic guests, fulfils the necessary conditions and indeed constitutes the most extensively studied hosts in aqueous media.[16] However, despite the numerous CD derivatives ever examined, good enantiodifferentiation has rarely been achieved or has been limited to rather special guests, such as helical metal complexes of phenanthroline and chiral polycyclic compounds.[17−19] This may be ascribed to the smooth interior walls and conformational flexibility of the CD cavity as well as the nondirectional nature of the hydrophobic interactions derived therefrom, which jointly drive the universal but less specific complexation.[20] In this study, we constructed a dual chiral, conformationally robust CD cavity for better chiral recognition of underivatized AAs in aqueous solution by introducing an enantiomeric helicene to the primary rim of β-CD.

Inherently chiral 3-aza[6]helicene (**1**) was chosen as a readily introducible, short-tethered, and conformationally robust chiral auxiliary to improve the chiral recognition ability of native CD. Thus, 6-deoxy-6-iodo-β-CD[21] was reacted with (*P*)- and (*M*)-**1**[22] to give the corresponding diastereomeric helicene-modified CDs (*P*)- and (*M*)-**2** (Scheme 1), both of which were soluble

Scheme 1. Synthesis of 3-Azonia[6]helicene-Modified β-Cyclodextrin 2



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up to 1.2 mM in water at 25 °C, while unmodified (*P*)- and (*M*)-**1** were practically insoluble in water. Circular dichroism spectra of (*P*)- and (*M*)-**2** only slightly differed from those of protonated (*P*)- and (*M*)-3-azonia[6]helicenes (**1**·H$^+$) measured in acetonitrile[22] (Figure 1a). This result indicates that

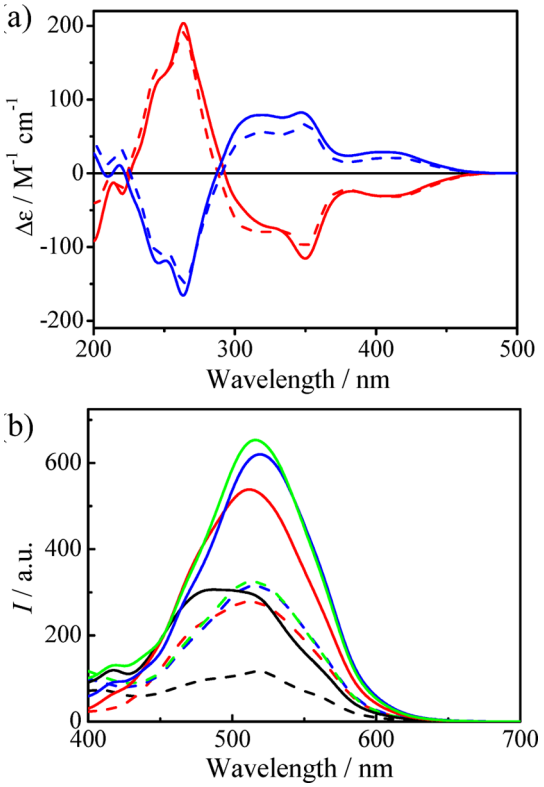

Figure 1. (a) Circular dichroism spectra of (*P*)-**2** (blue) and (*M*)-**2** (red) at 150 μM in water (solid line) and ethanol (dotted line). (b) Fluorescence spectra of 1 μM (*M*)-**2** (solid line) and (*P*)-**2** (dotted line) in ethanol (green), methanol (blue), water (red), and 1,4-dioxane (black); λ_{ex} = 380 nm.

tethering 3-azonia[6]helicene to β-CD does not appreciably alter the original chiroptical properties (and hence the structure) for which the helicene's highly rigid framework and extraordinarily large circular dichroism, compared to that induced upon (partial) inclusion into the CD cavity, would be responsible. The analogous circular dichroism spectra observed for the azonia[6]helicenes with and without a CD moiety also indicate that (*P*)- and (*M*)-**2** do not aggregate to form a supramolecular dimer or polymer but stays monomeric at least at 150 μM concentration since the main band at ca. 260 nm does not show any exciton coupling that is expected to occur for a supramolecular dimer and polymer.[23] Nevertheless, the circular dichroism spectra of (*M*)- and (*P*)-**2** are not perfectly mirror-imaged, and the cross-over points were deviated from zero, indicating that the small Cotton effect induced upon interaction with the chiral CD cavity, obeying the "sector rule",[24] is not completely negligible. In ethanol, (*P*)- and (*M*)-**2** showed appreciably different quasi-mirror-imaged circular dichroism spectra, presumably reflecting the orientational difference of the helicene moiety in the CD cavity. The absence of supramolecular aggregation was further confirmed by isothermal titration calorimetry, where no net heat (except the heat of dilution) was produced upon injection (dilution) of the host solution into water (Figures S3 and S4)[25] by differential scanning calorimetry, where no heat jump or peak was observed upon heating to 87.5 °C (Figure S5),[25] and by fluorescence spectroscopy at concentrations ranging from 0.67 to 300 μM, where all fluorescence spectra were superimposable with each other (Figure S6).[25]

The opposite helicities of azonia[6]helicene in (*P*)- and (*M*)-**2** led also to the significantly different fluorescence spectral behaviors in water, methanol, ethanol, and dioxane (Figure 1b), reflecting the microenvironment (i.e., penetration depth and hydrophobicity) felt by the helicene fluorophore.

Diastereomeric (*P*)- and (*M*)-**2** exhibited distinctly different ^{1}H NMR spectra (Figures S1 and S2).[25] As shown in Figure 2,

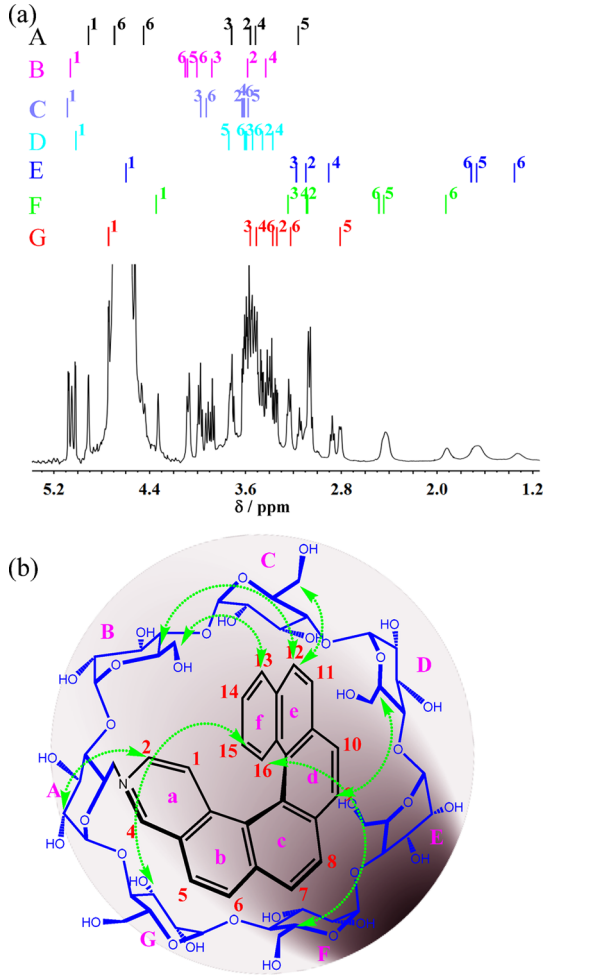

Figure 2. (a) ^{1}H NMR spectrum of (*M*)-**2** (1.0 mM) in D_2O with a full assignment of the proton signals of glucose residues A–G. (b) Orientation of the azonia[6]helicene moiety in (*M*)-**2** deduced by the NMR spectral analyses. The glucose residues under the strong shielding effect of helicene are in the dark shadow, while the protons correlated in the ROESY spectrum (Figure S22)[25] are connected by double-headed arrows.

nonanomeric glucose proton signals of (*M*)-**2** are scattered over a wide chemical shift range of δ 4.76–1.35, which is in sharp contrast to the much smaller scattering (δ 3.62–3.18) of the same protons in native β-CD.[26] Also, the anomeric protons of (*M*)-**2** are spread over a range of δ 5.13–4.38 and mutually well-separated. These spectral features allowed us to fully assign the proton signals of each glucose residue by using various 1D

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and 2D NMR techniques, such as ^{1}H and ^{13}C NMR, ^{1}H−^{1}H COSY, HSQC, HMBC, and TOCSY (Figures S11−S21).

As illustrated in Figure 2a, significant upfield shifts were observed, in particular, for the protons of E and F residues; thus, the H5 and H6 protons on the primary rim of CD showed the largest shifts of up to 1.35 ppm, relative to native β-CD, and even the H4, H2, and H1 protons located outside the CD cavity showed noticeable upfield shifts, indicating that the entire E and F residues are positioned above the helicene's π plane. The protons in A and G residues showed only small upfield shifts, as a result of a relatively weak shielding effect or, more likely, due to the balanced shielding/deshielding effects. Most of the D residue protons appeared in a narrow chemical shift range comparable to those of native β-CD, except for the H5 proton, which was slightly downfield shifted. In contrast, obvious downfield shifts were observed for the inside protons of C and B residues, which are deduced to be located near the helicene rim. The fact that the individual glucose residues experience the distinctly different shielding/deshielding effects indicates that the (*M*)-azonia[6]helicene auxiliary is firmly fixed in orientation and conformation in the CD cavity, due to its rigid framework and the short tether. As illustrated in Figure 2b, the helicene tethered to glucose A partially penetrates into the CD cavity by a hydrophobic interaction, which eventually holds the E and F residues in the helicene's shielding region and the B, C, and D residues in the deshielding region.

More precise structural information was obtained from the analysis of the ROESY cross-peaks (Figure S22). Thus, the clear correlations between the aromatic protons of helicene's e and f rings and the inside protons of CD (Figure 2b) indicate that the e and f rings are located inside the CD cavity. In contrast, the protons on the a−d rings did not show any appreciable correlations with the CD's inside protons (except for the cross-peak between H6 of D glucose and H9 of helicene's d ring). These observations reveal that the c and d rings obliquely lean over the F and E glucose residues, while the e and f rings penetrate into the CD cavity to deshield the B and C residues.

In the NMR spectrum of epimeric (*P*)-**2** (Figure S2), most of the nonanomeric protons (H2−H6) of CD appeared in a much narrower range of 3.71−3.05 ppm, suggesting shallower penetration of helicene, with some exceptions that appeared at 4.25, 2.85, and 2.56 ppm.[25] Due to the signal congestion and overlap, the full assignment was practically infeasible for (*P*)-**2**. Nevertheless, the very contrasting NMR spectral behaviors observed for (*M*)- versus (*P*)-**2** confirm the substantially different orientation and conformation of the helicene moiety in the two diastereomeric hosts. This is further supported by fluorescence spectral examinations. As shown in Figure 1b, the fluorescence spectrum of (*M*)-**2** in aqueous solution (λ_{em} = 504 nm) was stronger in intensity and shifted to shorter wavelengths compared to that of (*P*)-**2** (λ_{em} = 511 nm) obtained under comparable conditions. This result, as well as the significant solvent effects on the fluorescence spectra of both (*M*)- and (*P*)-**2** (Figure 1b), reveals the environmentally sensitive nature of the azonia[6]helicene moiety, which is rather favorable for the use of these hosts as fluorescent AA sensors in aqueous media.

Quantitative complexation behaviors of (*M*)- and (*P*)-**2** with representative proteinogenic AAs were investigated by fluorescence spectral examinations. The complexation stoichiometry was determined as 1:1 by Job plot, in which the fluorescence intensity change was maximized at the molar fraction of 0.5 (Figures S23 and S24). Then, the association constant (*K*) was determined by the nonlinear least-squares analysis of the fluorescence spectral titration data (Figure 3),

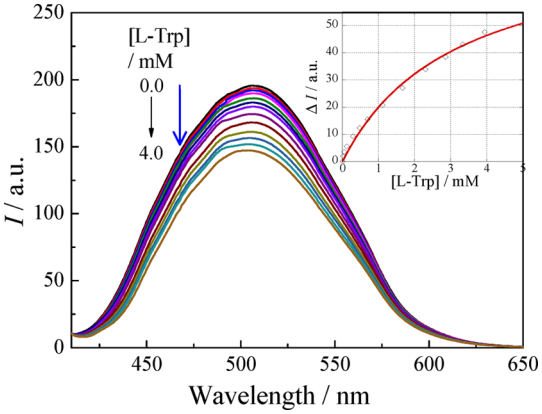

Figure 3. Fluorescence spectral changes of (*P*)-**2** (1.0 μM) upon addition of 0−4 mM L-Trp in aqueous buffer at pH 7.3 and 25 °C. Inset: Nonlinear least-squares fit, assuming a 1:1 stoichiometry, to give an association constant (*K*) of 360 ± 40 M^{-1}.

assuming the 1:1 stoichiometry. Moderate to high affinities of *K* = 270 to 12 400 M^{-1} were obtained for the AAs examined (Tables 1 and S1). These values are reasonable for the

Table 1. Association Constants (*K*) for 1:1 Complexation of L- and D-Amino Acids with (*P*)- and (*M*)-2 at 25 °C

host	guest	configuration	K^a (M^{-1})	$K_P/K_M{}^b$	$K_D/K_L{}^c$
(*P*)-**2**	Ala	L	1100	0.52	1.55
		D	1700	1.13	
	Thr	L	800	0.29	2.38
		D	1900	0.5	
	Ser	L	1100	0.65	1.55
		D	1700	1.31	
	Trp	L	360	1.12	11.7
		D	4200	15.6	
	Pro	L	2300	4.18	0.35
		D	810	0.62	
	Met	L	520	0.4	5.19
		D	2700	1.8	
	Leu	L	12400	28.2	0.081
		D	1000	0.24	
(*M*)-**2**	Ala	L	2100		0.71
		D	1500		
	Thr	L	2800		1.36
		D	3800		
	Ser	L	1700		0.76
		D	1300		
	Trp	L	320		0.84
		D	270		
	Pro	L	550		2.36
		D	1300		
	Met	L	1300		1.15
		D	1500		
	Leu	L	440		9.6
		D	4200		

[a]Determined by fluorimetric titration in aqueous buffer of pH 7.3; error in *K* <15%. [b]Relative *K* for (*P*)- versus (*M*)-**2**. [c]Relative *K* for D- versus L-amino acid.

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complexation driven by hydrophobic interaction,[16] while the electrostatic interaction of AA with the cationic azonia[6]-helicene introduced to CD does not appear to greatly contribute to the complexation, probably due to the steric hindrance and hydrophobic nature of the large aromatic moiety that may prevent the access of the carboxylate anion in AA.

Chiral discrimination of AA by (*P*)- and (*M*)-**2**, assessed by relative association constant K_D/K_L, turned out to be highly guest- and pH-dependent. In an aqueous buffer solution at pH 9.0, (*M*)-**2** consistently favored D-AA with K_D/K_L = 1.6−3.4 (Table S1),[25] while epimeric (*P*)-**2** also favored D-AAs (K_D/K_L = 2.3−2.8), except for Ser and Trp, which weakly preferred L-AA (K_L/K_D = 1.1−1.2). The D/L selectivities of >2, in particular, those (3.3−3.4) for Trp and Ser with (*M*)-**2**, are remarkably higher than those reported for acetylated Trp (0.74) and for Ser (1.06) upon complexation with amino-CDs,[11,27] suggesting the positive role played by the rigid helicene moiety in boosting the chiral discrimination ability of CD. Intriguingly, much better chiral discrimination was achieved in a buffer solution at pH 7.3, where AAs exist as zwitterions. Thus, a K_D/K_L of 11.7 was obtained for Trp with (*P*)-**2**, which is dramatically enhanced from the selectivities observed at pH 9.0 with (*P*)- and (*M*)-**2**, that is, 0.93 and 3.29, respectively. Similar remarkable pH-dependent chiral discrimination was observed for other AAs. In particular, the D/L selectivities for Leu became K_D/K_L = 9.6 for (*M*)-**2** and K_L/K_D = 12.4 for (*P*)-**2** at pH 7.3, which are also much higher than the corresponding values of 2.3 and 1.08 obtained at pH 9.0. This indicates that the ionization state of the AA critically affects the binding mode and hence the chiral discrimination ability. AAs are negatively charged (at least in part) in water at pH 9.0 but become fully zwitterionic at pH 7.3, allowing the charge-neutral zwitterionic AAs deeper penetration and more intimate stereochemical interactions in the CD cavity.

The significantly high enantioselectivities observed for aliphatic Leu and Trp at pH 7.3 prove the validity of our proposed strategy for modifying the chiral cavity. The good binding affinity and the high chiral discrimination are not attributable to the inherent hydrophobicity and chirality of the native CD cavity since underivatized and N-acetylated AAs do not appear to have appreciable affinities to native CDs[28,29] and *N*-benzyloxycarbonyl-derivatized aromatic AAs are discriminated with much lower D/L selectivities of 0.74−1.14 by native γ-CD.[29] Thus, the unprecedented D/L selectivities obtained are likely to be driven by the synergetic effects of the CD cavity and the helicene auxiliary, both of which are chiral. If the complexation of AA completely excludes the helicene moiety out of the cavity, such a high chiral discrimination could not be achieved, implicitly indicating that the complexation is complementary through the hydrophobic, electrostatic, and/or π−π stacking interactions with guest AA.

In this study, we synthesized two diastereomeric helicene-modified β-cyclodextrins, in which the (*P*)- and (*M*)-azonia-[6]helicene moieties introduced were confined in a different manner and also in conformational flexibility. The modification greatly improved the chiral discrimination ability of the β-CD cavity to achieve the L/D selectivities of up to 12.4 for underivatized proteinogenic amino acids in aqueous solution. This dual chiral approach, introducing a rigid chiral auxiliary to an inherently chiral host, is not restricted to the combination of a helicene−CD host and AA guest but is potentially applicable to other chiral supramolecular systems as a convenient yet effective general tool for enhancing the original chiral discrimination ability of a host.

EXPERIMENTAL SECTION

General Methods. All chemicals were purchased from various suppliers and used as received. The (*M*)- and (*P*)-3-aza[6]helicenes (**1**) were first prepared as a racemic mixture by the procedures reported previously[30,31] and then optically resolved by a semi-preparative chiral HPLC column eluted with a hexane−2-propanol mixture (95:5).

^{1}H and ^{13}C NMR spectra were obtained on 600 and 150 MHz instruments. Electronic absorption (UV−vis) and circular dichroism spectra were recorded on the correspondent spectrometer, respectively, in a conventional quartz cell installed in a thermostated cell holder. HRMS-FAB spectra were obtained using TOF techniques.

Syntheses of (*M*)-6-Deoxy-6-(3-azonia[6]helicenyl) β-Cyclodextrins (*M*)-2. (*M*)-3-Aza[6]helicene (**1**) (3.3 mg, 0.01 mmol) and 6-deoxy-6-iodo-β-CD (37 mg, 0.03 mmol) were dissolved in DMF (1 mL) at room temperature, and the mixture was heated to 90 °C under N_2 and stirred for 2 days at that temperature. The reaction mixture was cooled to room temperature and poured onto cool acetone (40 mL). The resulting yellow precipitates were collected by filtration and subjected to purification by reverse-phase column chromatography with the mixture solvent of ethanol and water to give (*M*)-deoxy-6-(3-azonia[6]helicenyl) β-cyclodextrin (*M*)-**2** as a light yellow solid (8.2 mg, yield 57%). The β-CD derivatives decompose when temperature increases to 200 °C. ^{1}H NMR (600 MHz, D_2O): δ 9.65 (s, 1H), 8.36 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.09−8.03 (m, 4H), 7.79−7.73 (m, 2H), 7.36 (m, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.48 (m, 1H), 5.26 (d, *J* = 3.6 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 5.20 (d, *J* = 3.6 Hz, 1H), 5.09 (d, *J* = 3.6 Hz, 1H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.82−4.70 (m, 3H), 4.51 (d, *J* = 3.7 Hz, 1H), 4.26 (d, *J* = 10.3 Hz, 2H), 4.17−4.04 (m, 4H), 3.91−3.88 (m, 2H), 3.77−3.53 (m, 18H), 3.44−3.23 (m, 6H), 3.05 (t, *J* = 9.2 Hz, 1H), 2.98 (d, *J* = 8.4 Hz, 1H), 2.65 (m, 2H), 2.11 (d, *J* = 12.4 Hz, 1H), 1.89 (m, 2H), 1.51 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (151 MHz, D_2O): δ 145.9, 135.7, 135.6, 133.3, 133.2, 133.1, 132.7, 132.2, 131.5, 129.0, 128.2, 128.0, 127.9, 127.7, 127.3, 126.7, 126.4, 125.8, 125.7, 125.1, 125.0, 124.7, 123.8, 122.7, 122.3, 102.3, 102.0, 101.7, 101.6, 101.4, 100.4, 100.2, 81.8, 81.7, 81.0, 79.7, 79.6, 78.5, 73.1, 73.0, 73.0, 72.6, 72.5, 72.4, 72.3, 72.2, 72.0, 72.0, 71.8, 71.7, 71.5, 71.0, 70.3, 61.1, 61.1, 60.6, 60.1, 59.1, 58.9, 57.5. HRMS (TOF) *m*/*z*: $[M - I]^+$ calcd for $C_{67}H_{84}NO_{34}$ 1446.4869, found 1446.4838.

Syntheses of (*P*)-6-Deoxy-6-(3-azonia[6]helicenyl) β-Cyclodextrins (*P*)-2. (*P*)-Deoxy-6-(3-azonia[6]helicenyl) β-cyclodextrin (*P*)-**2** was prepared as a light yellow solid (7.8 mg, yield 52%) by the same procedure. ^{1}H NMR (600 MHz, D_2O): δ 9.23 (s, 1H), 8.41 (s, 2H), 7.93 (s, 2H), 7.72−7.50 (m, 6H), 7.18 (s, 2H), 6.24 (m, 2H), 5.09−4.98 (m, 4H), 4.95 (s, 1H), 4.87−4.83 (m, 2H), 4.58−4.30 (m, 2H), 3.89−3.42 (m, 38H), 3.13 (m, 1H), 2.71 (m, 1H). ^{13}C NMR (151 MHz, D_2O): δ 145.9, 135.7, 135.6, 133.3, 133.2, 133.1, 132.7, 132.2, 131.5, 129.0, 128.2, 128.0, 127.9, 127.7, 127.3, 126.7, 126.4, 125.8, 125.7, 125.1, 125.0, 124.7, 123.8, 122.7, 122.3, 102.3, 102.0, 101.7, 101.6, 101.4, 100.4, 100.2, 81.8, 81.7, 81.0, 79.7, 79.6, 78.5, 73.1, 73.0, 73.0, 72.6, 72.5, 72.4, 72.3, 72.2, 72.0, 72.0, 71.8, 71.7, 71.5, 71.0, 70.3, 61.1, 61.1, 60.6, 60.1, 59.1, 58.9, 57.5. HRMS (TOF) *m*/*z*: $[M - I]^+$ calcd for $C_{67}H_{84}NO_{34}$ 1446.4869, found 1446.4839.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00130.

Physicochemical properties; UV−vis, fluorescence, HR-MS, and 1D and 2D NMR spectra of (*P*)- and (*M*)-**2**; ITC thermograms and DSC charts; Job plots and association constants (PDF)

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Notes

The authors declare no competing financial interest.

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