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The Synthesis and Anion Binding of Novel Cholic Acid-based Molecular Clefts Containing Unsymmetrically Disubstituted Urea Unit

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Abstract: A novel type of chiral molecular clefts consisting of a rigid deoxycholic acid methyl ester backbone and chiral unsymmetrically disubstituted urea side chain have been designed and synthesized. All these new receptors **3a~c** and the corresponding key intermediates **1a~c** and **2a~c** are new compounds, their structures were confirmed by ^{1}HNMR, IR, MS spectra and elemental analysis. These molecular clefts showed binding ability for halide anions.

Keywords: Molecular clefts, synthesis, cholic acid, unsymmetrically disubstituted urea.

The design and synthesis of model receptors to recognize substrates of biochemical significance to mimic biological events are of keen interest in molecular recognition research[1]. During the last decade, a lot of molecular clefts have been designed and synthesized[2]. Among the variety of molecular scaffolds， which were employed in molecular clefts, the natural rigid concave shape and inherent asymmetry of cholic acid are known as ideal building blocks for the construction of molecular clefts. In recent years, molecular clefts by using cholic acid as spacer and the various of aromatic compounds as arms have been successively reported[3~10]. However, using the unsymmetrically substituted urea as building blocks for the construction of steroidal molecular clefts, to our knowledge, is unknown. Here we report the design and synthesis of the deoxycholic acid based molecular clefts containing unsymmetrically disubstituted urea unit. A computer-aided study has been employed to elucidate the conformation of this kind of molecular clefts. The molecular clefts **3a~c** possess unique hydrophilic cavity in which two NH groups and one OH group directly towards the center of the cavity, which could form multiple hydrogen bonding with substrates in molecular recognition. We can expect that this novel type of molecular clefts possesses excellent molecular recognition property. The synthetic route is shown in **Scheme 1.**

Choosing L-amino acids methyl ester hydrochloride as the starting material, the intermediates **1a~c**, chiral unsymmetrically disubstituted ureas, have been obtained by the method of one-pot[11]. **1a~c** are reduced by $NaBH_4$ to the corresponding N-protected

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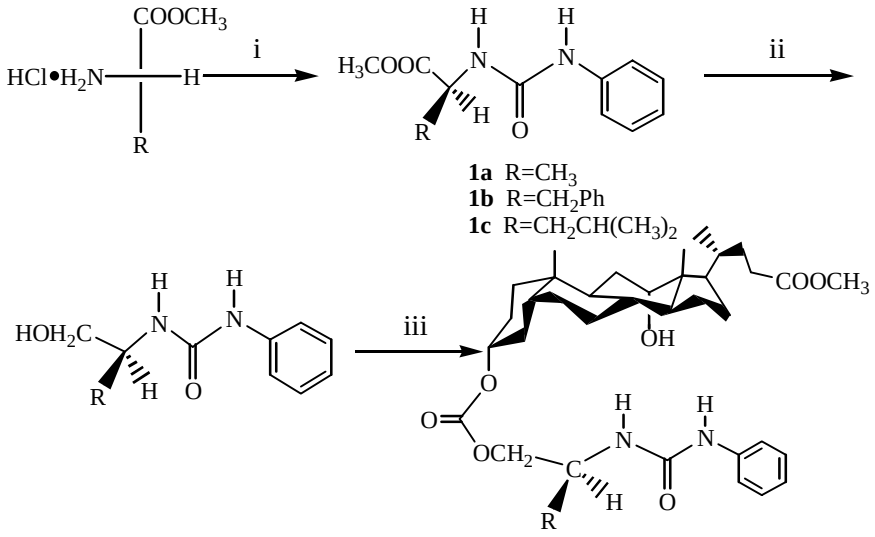
amino alcohols **2a~c**. **2a~c** are easily attached to 3α - hydroxy group of deoxycholic acid methyl ester using triphosgene to synthesize the molecular clefts **3a~c**.

Scheme 1 The preparation of chiral molecular clefts **3a~c**



2a R=CH_3
2b R=CH_2Ph
2c R=$CH_2CH(CH_3)_2$

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Reagents: i. aniline, triphosgene, DIEA, CH_2Cl_2; ii. $NaBH_4$, THF/H_2O; iii. methyl deoxycholate, triphosgene, CH_2Cl_2, pyridine.

All the L-amino acids methyl esters hydrochloride were obtained from the esterification of corresponding L-amino acids and methanol in the presence of $SOCl_2$. Deoxycholic acid was converted to methyl 3α,12α-dihydroxy-7-deoxy-5β-cholano-24-ate following a reported procedure[12].

The recognition of molecular clefts **3a~c** for anion have been investigated by UV-visible spectra titration. Using the nonlinear least squares curve-fitting method, we obtained the complexation stability constants. The preliminary results showed that all these molecular clefts possessed the ability to form complex with anion examined. The supramolecular complexes consisted of 1∶1 host and guest molecules. The stability constants of molecular cleft **3a**, for instance, is 240.7, 192.1, and 294.7 M^{-1} for Cl^-, Br^-, I^- anions respectively.. The main driving force is the multiple hydrogen bonding in molecular recognition. The details of molecular recognition of **3a~c** are under further studies.

Experimental

The melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. Infrared spectra were obtained on 1700 Perkin--Elmer FTIR. ^{1}HNMR spectra were recorded on a Varian INOVA 400 MHz spectrometer.

Mass spectra were determined on Finnegan MAT 4510 and Finnegan LCQ^{DECA} instruments. Elemental analysis were performed on a CarloErba-1106 autoanalyzer. Optical rotations were measured on a WZZ-1 polarimeter. All the solvents were used without further purification unless specified. CH_2Cl_2 was distilled from calcium hydride before use.

General procedure for preparation of N-protected amino alcohol **2a~c**

To a solution of disubsitituted urea (2 mmol) in 20 mL THF was added $NaBH_4$ (0.3 g, 8 mmol) and 10 mL H_2O at 0℃. The mixture was stirred at room temperature for 5 hours. Then 20 mL H_2O was added and extracted with ethyl acetate (20 mL×3). The extract was dried over anhydrous Na_2SO_4 and evaporated to give the product without further purification.

2a: white solid. yield 94%. $[\alpha]_D^{20}$ = -8.0 (c 0.5, EtoAc). m.p.: 125-127℃. ^{1}H NMR (DMSO-d_6, δ ppm): 8.43 (s, 1H, PhNHCO), 7.48-6.85 (m, 5H, Ar-H), 6.01 (d, 1H, J=8.0 H_Z, CONH), 4.79 (s, 1H, OH), 3.71 (m, 1H, CH), 3.40 (m, 2H, CH_2), 1.07 (d, 3H, J=6.4 Hz, CH_3). υ (KBr/cm^{-1}) 3316 (NH), 2966 (CH_3), 1632 (C=O), 1604, 1562, 1496 (C=C phenyl). *m/z*(%): 195 (M^++1, 40).

2b: white solid. yield 96%. $[\alpha]_D^{20}$ = -20.0 (c 0.5, EtoAc). m.p.: 133-134℃. ^{1}H NMR (DMSO-d_6, δ ppm): 8.46 (s, 1H, PhNHCO), 7.35-6.84 (m, 10H, Ar-H), 6.07 (d, 1H, J=8.0 H_Z, CONH), 4.87 (s, 1H, OH), 3.86 (m, 1H, CH), 3.37 (m, 2H, CH_2), 2.86 (m, 2H, $PhCH_2$). υ (KBr/cm^{-1}) 3423 (OH), 3346 (NH), 1620 (C=O), 1564, 1498 (C=C phenyl). *m/z*(%): 271 (M^++1, 60).

2c: white solid. yield 85%. $[\alpha]_D^{20}$ = -28.0 (c 0.5, EtoAc). m.p.: 88-90℃. ^{1}H NMR (DMSO-d_6, δ ppm): 8.38 (s, 1H, PhNHCO), 7.37-6.84 (m, 5H, Ar-H), 5.92 (d, 1H, J=8.8 H_Z, CONH), 4.72 (m, 1H, OH), 3.73 (m, 1H, CH), 3.14 (m, 2H, CH_2), 1.66 (m, 1H, CH), 1.37 (m, 2H, CH_2), 0.92 (d, 6H, J=6.8Hz, CH_3). υ (KBr/cm^{-1}) 3352 (OH), 3335 (NH), 2954 (CH_3), 1640 (C=O), 1600, 1578, 1546 (C=C phenyl). *m/z*(%): 237 (M^++1, 100).

General procedure for preparation of molecular cleft **3a~c**

Triphosgene (0.06 g, 0.17 mmol) and pyridine(0.1 mL) were added to a solution of methyl deoxycholate (0.2 g, 0.5 mmol) in 20 mL dry CH_2Cl_2 at room temperature. The reaction mixture was refluxed for 5 hours. Then N-protected amino alcohol (0.6 mmol) and pyridine (0.15 mL) were added to the mixture and reacted continually for 48 hours at room temperature. The solvent was removed and the residue was diluted with 50 mL ethyl acetate and washed with 1% HCl (15 mL×3), brine (15 mL×3) and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel H with dichlormethane/ethyl acetate as eluant.

3a: white solid. yield 64%. $[\alpha]_D^{20}$ = +28.0 (c 2, CH_2Cl_2). m.p.: 85-87℃. ^{1}H NMR ($CDCl_3$, δ ppm): 7.33 (s, 1H, PhNHCO), 7.31-7.05 (m, 5H, Ar-H), 6.82 (br , 1H, CONH), 4.59 (m, 1H, 12 β-H), 4.21 (m, 1H, NCH), 4.15 (m, 2H, OCH_2), 4.00 (s, 1H, 3 β-H), 3.66 (s, 3H, $COOCH_3$), 2.41 (m, 1H, CH_2-23), 2.27 (m, 1H, CH_2-23), 1.23 (d, 3H, J=6.8Hz, CH_3), 0.98 (d, 3H, J=6.0 H_Z, 21-CH_3), 0.91 (s, 3H, 19-CH_3), 0.68 (s, 3H,

18-CH_3). υ (KBr/cm^{-1}) 3550 (OH), 3370 (NH), 2934 (CH_3), 1742,1658 (C=O), 1600, 1554, 1500 (C=C phenyl). MS (FAB): *m/z*(%)= 627.52 (M^++1, 100). Anal. Calcd. for $C_{36}H_{54}N_2O_7$: C 68.98; H 8.68; N 4.47. Found: C 68.95; H 8.91; N 4.80.

3b: white solid. yield 57%. $[\alpha]_D^{20}$ = +19.5 (c 2, CH_2Cl_2). m.p.: 91-93℃. ^{1}H NMR ($CDCl_3$, δ ppm): 7.30 (s, 1H, PhNHCO), 7.29-7.06 (m, 10H, Ar-H), 6.77 (br, 1H, CONH), 4.59 (m, 1H, 12 β-H), 4.36 (m, 1H, NCH), 4.18 (m, 2H, OCH_2), 4.00 (s, 1H, 3 β-H), 3.66 (s, 3H, $COOCH_3$), 2.95 (m, 2H, $PhCH_2$), 2.41 (m, 1H, CH_2-23), 2.27 (m, 1H, CH_2-23), 0.98 (d, 3H, J=6.4 H_Z, 21-CH_3), 0.91 (s, 3H, 19-CH_3), 0.68 (s, 3H, 18-CH_3). υ (KBr/cm^{-1}) 3550 (OH), 3358 (NH), 2938 (CH_3), 1742,1662 (C=O), 1600, 1554, 1498 (C=C phenyl). MS (FAB): *m/z*(%)= 703.00 (M^++1, 100). Anal. Calcd. for $C_{42}H_{58}N_2O_7$: C 71.77; H 8.32; N 3.99. Found: C 71.55; H 8.49; N 4.14.

3c: white solid. yield 59%. $[\alpha]_D^{20}$ = +22.0 (c 2, CH_2Cl_2). m.p.: 84-86℃. ^{1}H NMR ($CDCl_3$, δ ppm): 7.36 (s, 1H, PhNHCO), 7.34-7.02 (m, 5H, Ar-H), 5.19 (br, 1H, CONH), 4.58 (m, 1H, 12 β-H), 4.18 (m, 2H, OCH_2), 4.11 (m, 1H, NCH), 3.96 (s, 1H, 3 β-H), 3.66 (s, 3H, $COOCH_3$), 2.42 (m, 1H, CH_2-23), 2.28 (m, 1H, CH_2-23), 0.99 (d, 3H, J=6.8 H_Z, 21-CH_3), 0.93 (d, 6H, J=6.8Hz, CH_3),0.90 (s, 3H, 19-CH_3), 0.68 (s, 3H, 18-CH_3). υ (KBr/cm^{-1}) 3550 (OH), 3364(NH), 2958 (CH_3), 1740,1667 (C=O), 1600, 1554, 1500 (C=C phenyl). MS (FAB): *m/z*(%)=669.32 (M^++1, 100). Anal. Calcd. for $C_{39}H_{60}N_2O_7$: C 70.03; H 9.04; N 4.19. Found: C 69.78; H 9.06; N 4.31.

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