Communication

Interaction and Interfacial Molecular Recognition of Calix[4]arene Derivatives Bearing Nucleobases for Complementary Nucleoside

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The *p-tert*-butyl calix[4]arene derivatives 1a with uracils and 1b with adenines at the lower rim were synthesized. The Interaction between 1a and 1b in $CDCl_3$ solution was demonstrated by ^1H NMR spectra. The interfacial molecular recognitions of 1a and 1b for the complementary nucleosides in aqueous subphases were investigated by Langmuir-Blodgett technique.

Keywords calixarene, molecular recognition, hydrogen bonding, nucleoside, Langmuir-Blodgett film

Introduction

Calixarenes, as a versatile class of macrocyclic host compounds, have attracted more and more attention,[1-3] not only because they can form host-guest complexes and act as an enzyme mimic, but also because they can be widely used as the platforms of molecule construction for molecular recognition.[4-7] Unlike the molecular recognition in the biological system, most of artificial receptors are effective only in nonaqueous media due to strong hydrogen bonding of the receptor or substrate with water.[8] For example, monomeric nucleic acids can not form complementary pairs in water.[9] Fortunately, the organized molecular monolayers assembled by the Langmuir-Blodgett technique can provide a unique environment resembling biological membrane systems for molecular recognition of water-soluble biomolecules in aqueous media via interfacial intermolecular interaction.[8] Some examples on interfacial recognition of typical amphiphiles for biomolecules have been reported.[10-12] Recently, we introduced two alkyl guanidinium groups into the lower rim of *p-tert*-butyl calix[4]arene molecule.[13] With the coexistence of hydrophobic *tert*-butyl groups at the upper rim and hydrophilic guanidinium groups at the lower rim of calix[4]arene, it can form stable monolayers at the air-water interface and bind complementary nucleotide efficiently from aqueous subphase.[14] Encouraged by these results, we synthesized new amphiphilic calix[4]arene derivatives with nucleobases at the lower rim and studied their interaction and the interfacial molecular recognition for nucleosides. This study may also allow us to shed light on recognition processes in biological systems and to develop novel film materials of accumulating, storing and reproducing information.

Synthesis of calix[4]arene derivatives with nucleobases at the lower rim

The synthesis of calix[4]arene derivatives with nucleobase at the upper rim have been reported and their self-assemble through complementary hydrogen bonding was demonstrated by Huang *et al*.[15] The synthesis of calix[4] nucleoside has also been achieved by the condensation of calix[4]arenediamine and thyminine nucleoside carboxylic acid.[16] However, the artificial receptors at the lower rim with nucleobases in calix[4]arene molecule have never been reported. Here we report the introduction of nucleobase groups into the lower rim of *p-tert*-butyl calix[4]-arene (Scheme 1). The compounds **1a** and **1b** were obtained via a three step synthesis, in which *p*-tetra-*tert*-butyl calix[4]arene was selectively *O*-alkylated with bromoacetonitrile, reduced with $LiAlH_4$,[17] and then condensed with uracilo-*N*-acetic acid (**3a**),[18] or adenino-*N*-propionic acid **3b**[19] in the presence of the condensing agent CDI (1, 1′-carbonyldiimidazole) in DMF, respectively. The purification of the products was achieved by flash chromatography on silica gel column, followed by crystallization from ethyl acetate/petroleum in 60%—70% yields. The spectroscopic data and elemental analysis were in agreement with the structure of the products.[20] In ^1H NMR spectra, the peaks of protons of $ArCH_2Ar$ appeared as doublet at δ 3.25—3.40 (Hexo) and δ 3.99—4.24 (Hendo). Obviously, they are consistent with the cone conformation.[21,22]

Iteraction between calix[4]arene derivatives bearing nucleobases

Calix[4]arene derivatives **1a** or **1b** tended to undergo self-association in solution, which was evidenced by

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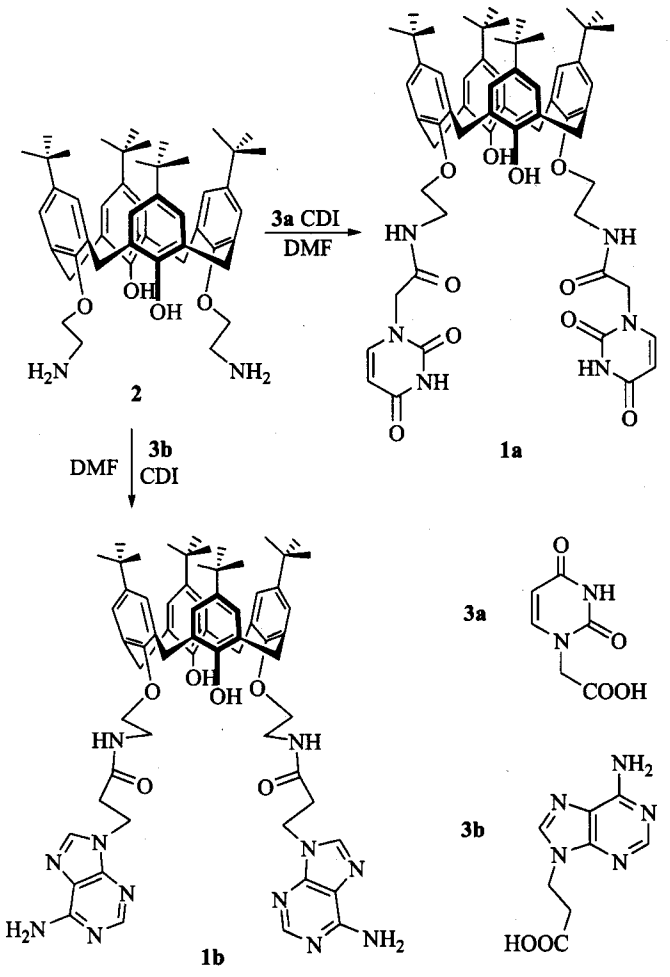
Scheme 1 Synthesis of calix[4]arene derivatives with nucleobases at the lower rim



^{1}H NMR spectra. When the concentration of **1a** or **1b** increased from 2.0 mmol/L to 10.0 mmol/L in $CDCl_3$, the chemical shifts of the uracil imido-H of **1a** and the amino protons of the adenine of **1b** shifted downfield pronouncedly. For example, when the concentration of **1a** is 2.0, 5.0 and 10.0 mmol/L, the signal of the uracil imido-H of **1a** appears at δ 9.25, 9.60 and 9.88, respectively (Fig. 1 (a), (b) and (c), peak a). This shows that hydrogen bonds are formed between the uracil imido-H and carbonyl group of other uracil. It is also notable that the signal of CH = CH hydrogens of the uracil shifts upfield when the concentration of **1a** increases (Fig. 1, peak b: 2.0 mmol/L, δ 8.34; 5.0 mmol/L, δ 8.22; 10.0 mmol/L, δ 7.92). The remarkable upfield shifts suggest that there is a π-π stacking interaction among the uracil rings.[23-25]

Fig. 2 shows partial ^{1}H NMR spectra of **1b** (5.0 mmol/L), **1a** (5.0 mmol/L), the mixture of **1a** (5.0 mmol/L) with **1b** (5.0 mmol/L) in $CDCl_3$ solution, respectively. We can find from Fig. 2(c) that both the signals of the uracil imido-H (peak a) of **1a** and the amino protons (peak b) of the adenine moiety of **1b** move downfield, with $\Delta\delta$ being 1.82 and 0.47, while the proton signals of the rest of the molecules **1a** and **1b** remain almost constant. It is clear that hydrogen bonding of A-U base

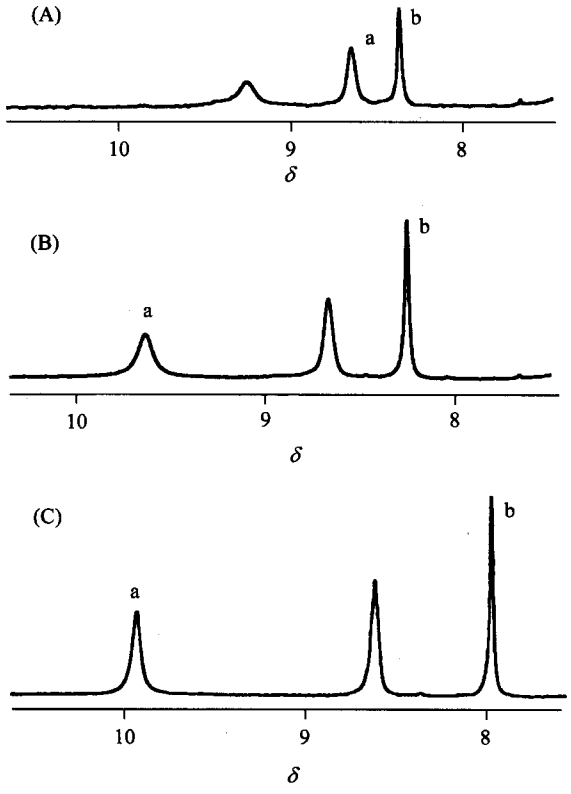


Fig. 1 Partial ^{1}H NMR spectra of **1a**: (A) 2.0 mmol/L; (B) 5.0 mmol/L; (C) 10.0 mmol/L (in $CDCl_3$, Bruker WP 300 MHz).

pairing between **1a** and **1b** is formed just as in nucleic acid.

Molecular recognition of calix[4]arene derivatives with nucleobases for complementary nucleoside at the air-water interface

With the coexistence of hydrophobic *tert*-butyl groups at the upper rim and hydrophilic nucleobases at the lower rim of calix[4]arene, **1a** and **1b** can form stable monolayers at the air-water interface. Fig. 3 shows surface pressure-area isotherms (π-*A* isotherms) of the monolayers of **1a** on the subphase of pure water and aqueous solution of the adenosine with the concentrations of 1.0 mmol/L and 5.0 mmol/L.[26] On pure water, the monolayer of **1a** gives a limiting molecular area of 1.50 nm^2, so **1a** molecules may also adopt *cone* or *pinched-cone* conformation at the air-water interface.[14,27-28] On the subphase of 1.0 mmol/L adenosine solution, the limiting molecular area (1.52 nm^2) and collapse pressure (46 mN/m) are a little more increased than that on the pure water (1.50 nm^2 and 44 mN/m). On the subphase of 5.0 mmol/L adenosine solution, π-*A* isotherm is much more expanded than that on pure water, giving a limiting molecular area of 1.75 nm^2 and a higher collapse pressure of 50 mN/m. It indicates that adenosine in the subphase can interact effectively with headgroup uracils of **1a** molecules through the hydrogen bonding of complementary base pairs. Therefore, monolayer

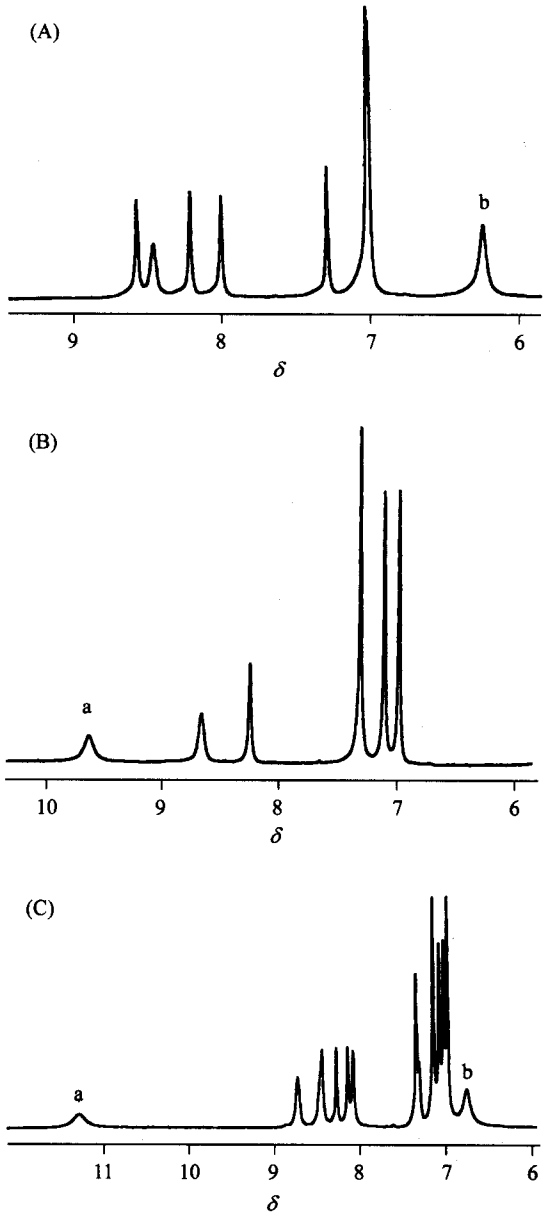


Fig. 2 Partial ^{1}H NMR spectra of (A) **1b** (5.0 mmol/L); (B) **1a** (5.0 mmol/L); (C) **1a** (5.0 mmol/L) + **1b** (5.0 mmol/L) (in $CDCl_3$, Bruker WP 300 MHz).

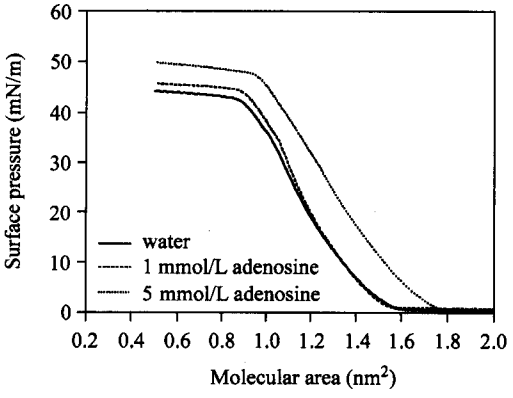


Fig. 3 π-A isotherms of the monolayers of **1a** on the surfaces of pure water, 1.0 and 5.0 mmol/L adenosine aqueous solution.

becomes more stable and a higher collapse pressure can be observed. Moreover, with the concentration of adenosine increasing in aqueous subphase, the limiting molecular area and collapse pressure of **1a** increases and rises prominently, because of the more full molecular recognition between the monolayer of **1a** and the complementary nucleobase adenosine in the subphase. Similar phenomena were also observed from π-A isotherms for the **1b** monolayers on the subphase of pure water and aqueous solution of the corresponding complementary nucleosides uridine or thymidine.

In UV spectra of 40-layer LB films of **1a** deposited on quartz substrates from the subphase of pure water and 5.0 mmol/L adenosine solution, absorption intensities of the bands of the latter increase evidently compared with that of the former, and the absorption maximum also shows a shift to 267 nm compared with that of headgroup uridine (270 nm) and the aqueous adenosine solution (260 nm). Obviously, it can be ascribed to the overlap of the similar bands of the headgroup usacil of **1a** and the adenosine derived from the subphase. In the FT-IR spectra of 40-layer LB films of **1a** deposited on CaF_2 substrates from the surface of pure water and 5.0 mmol/L adenosine solution, the diversity of spectral features can be clearly observed. Especially, the broad band of the 3500—3000 cm^{-1} region in the latter LB films can be observed, which is due to the multiple hydrogen bonding between the uracil moiety in the headgroup of **1a** and adenosine derived from the subphase. Similar spectral features are also observed from UV and FT-IR spectra of 40-layer LB films of **1b** deposited from the surface of pure water and 5.0 mmol/L complementary nucleoside uridine or thymidine subphase solution. Therefore, all UV and FT-IR spectral features demonstrate that the complementary nucleosides in the subphase can be bound by *p-tert*-butyl calix[4]arene nucleobase derivatives through hydrogen binding of the nucleobase pairing and incorporated into the LB films.

In summary, the amphiphilic calix[4]arene derivatives with nucleobases at the lower rim were synthesized in good yields by the condensation of calix[4]arene diamine **2** with uracilo-*N*-acetic acid and adenino-*N*-propionic acid in the presence of CDI in DMF. The interaction between **1a** with uracils and **1b** with adenines in $CDCl_3$ solution was demonstrated by ^{1}H NMR spectra. The interfacial molecular recognition of the amphiphilic calix[4]arene derivatives with nucleobase for the complementary nucleosides in the subphase was studied by Langmuir-Blodgett technique. The results indicate that the amphiphilic calix[4]arene derivatives can form stable monolayer at the air-water interface. The complementary nucleosides in the subphases are efficiently bound to the monolayers through base pairing recognition and they can be well transferred onto solid substrates along with the monolayers.

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20 **1a**: M.p. 220—223 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.60 (s, 2H, 2 × CONHCO), 8.63 (s, 2H, 2 × CONH), 7.63 (s, 2H, 2 × OH), 7.25 (d, J = 8.0 Hz, 2H, CH = CH), 7.23 (s, 4H, 2 × HOAr**H**), 6.95 (s, 4H, 2 × ROAr**H**), 5.65 (d, J = 8.0 Hz, 2H, CH = CH), 4.48 (s, 4H, 2 × $COCH_2N$), 4.24 (d, J = 12.9 Hz, 4H, 4 × *endo*-Ar**C**H_2Ar), 4.11—4.17 (m, 4H, 2 × OCH_2CH_2NH), 3.76—4.09 (m, 4H, 2 × OCH_2CH_2NH), 3.40 (d, J = 12.9 Hz, 4H, 4 × *exo*-ArCH_2Ar), 1.27 (s, 18H, 2 × ROAr-*t*-C_4H_9), 1.06 (s, 18H, 2 × HOAr-*t*-C_4H_9); ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 167.2 (CONH), 164.6, 151.9 (uracile CONH), 149.8, 149.1, 148.4, 145.7, 143.4, 135.3, 132.9, 128.2, 126.4, 126.0, 121.9, 102.8 (aromatic C), 77.8 (OCH_2CH_2), 75.3 (NCH_2CO), 51.1 ($NHCH_2CH_2$), 40.0, 34.5, 34.3, 32.3, 31.9, 31.4 [C (CH_3)$_3$, ArCH_2Ar]; MS (ESIMS) m/z: 1037.8 ([M − H]$^-$, calcd 1037.5). Anal. calcd for $C_{60}H_{74}N_6O_{10}$: C 69.33, H 7.18, N 8.09; found C 69.59, H 7.26, N 7.88.

2b: M.p. 240—242 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.67 (s, 2H, 2 × CONH), 8.48 (s, 2H, 2 × OH), 8.19 (s, 2H, adenine H), 7.96 (s, 2H, adenine H), 7.00 (s, 8H, ArH), 5.93 (s, 4H, 2 × NH_2), 4.57 (s, 4H, 2 × $COCH_2CH_2N$), 3.99 (d, J = 12.6 Hz, 4H, 4 × *endo*-ArCH_2Ar), 3.84 (4H, 2 × OCH_2CH_2NH), 3.44 (4H, 2 × OCH_2CH_2NH), 3.25 (d, J = 12.6 Hz, 4H, 4 × *exo*-ArCH_2-Ar), 2.88 (4H, 2 × $COCH_2CH_2N$), 1.24 (s, 18H, 2 × ROAr-*t*-C_4H_9); 1.15 (s, 18H, 2 × HOAr-*t*-C_4H_9); ^{13}C NMR (d_6-DMSO, 300 MHz) δ: 170.6 (CONH), 156.7, 153.2, 150.2, 149.9, 148.3, 142.7, 141.8, 134.0, 128.4, 126.6, 126.3, 119.5 (aromatic C), 75.6 (OCH_2CH_2), 58.3 (OCH_2CH_2N), 36.1, 34.9, 34.5, 32.2, 31.9, 31.7, 31.5 [$COCH_2CH_2N$, C(CH_3)$_3$, ArCH_2Ar]; MS (ESMS) m/z: 1111.3 ([M − H]$^-$, calcd 1111.6). Anal. calcd for $C_{64}H_{80}N_{12}O_6$: C 69.04, H 7.24, N 15.10; found C 69.26, H 7.31, N 15.46.

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26 Surface pressure-area isotherms (π-A isotherms) were determined on KSV 5000 (mini trough). The temperature was kept at (20 ± 0.2) ℃. Monolayers were formed by spreading 25 μL chloroform solution (5×10^{-4} mol/L) of receptor **1a** or **1b** onto the surface of deionized water (purified by Milli-Q system, > 18 MΩ, pH *ca.* 5.6) and the aqueous subphases containing different nucleosides, respectively. 30 min was given for the evaporation of the spreading solvent and the interaction between nucleoside and receptor. The π-A isotherms were measured three times at a barrier speed of 4 mm/min and were found reproducible.

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