Synthesis of novel macrocyclic host tetraazaparacyclophane derivatives

BAI Yinjuan, SU Yuchan，LI Jianli, YANG Bingqin & SHI Zhen

Department of Chemistry, Northwest University, Xi'an 710069, China
Correspondence should be addressed to Bai Yinjuan (email: yinjuanb@nwu.edu.cn)

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Abstract Seven macrocyclic host tetraazaparacyclophanes with different hydrophobic cavity sizes were synthesized from dibromoalkanes and 4,4'-methylendianilin. Three of the tetraazacyclophanes were modified on the four nitrogen atoms by using ferrocenoyl chloride, so a new kind of enzyme model was obtained by introducing the side arms of ferrocenoyl group. And four of the tetraazacyclophanes with straight chains were also synthesized through the reaction of 1,8,22,29-tetraaza[8.1.8.1] paracyclophane with bromoalkane and alkanecarbonyl bromide. Ten of them have not ever been reported in literature. The structures were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analysis.

Keywords: tetraazaparacyclophane, host-guest chemistry, host molecule, synthesis.

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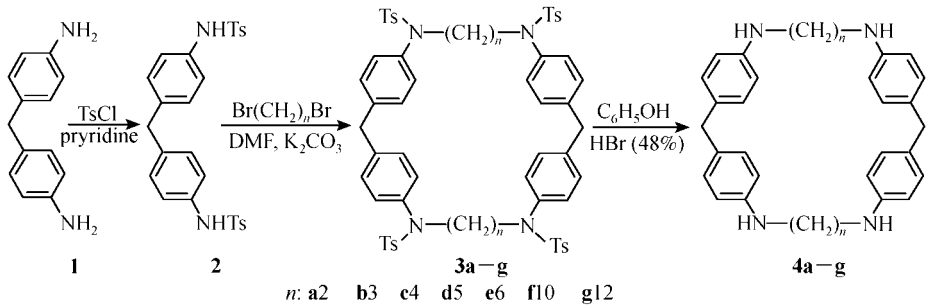
In recent years, much attention has been focused on artificial receptors capable of performing molecular recognition to mimic specific molecular functions performed by naturally occurring receptors[1,2]. Cyclophanes are a special class of compounds found in the studies of host-guest chemistry[3]. They have long been targeted for chemical synthesis. A variation of cyclophane's structure cause by adjusting the macroring's size or introducing active groups makes it easy to prepare modified macrocyclic host molecules for very specific interaction with certain guest molecules, providing ideal model for enzyme-like catalysis, as well as molecular hosts having promising properties[4,5]. Various artificial receptors such as octopus-type and cage-type cyclophanes have been developed by appropriate modifications of simple cyclophanes[6,7].

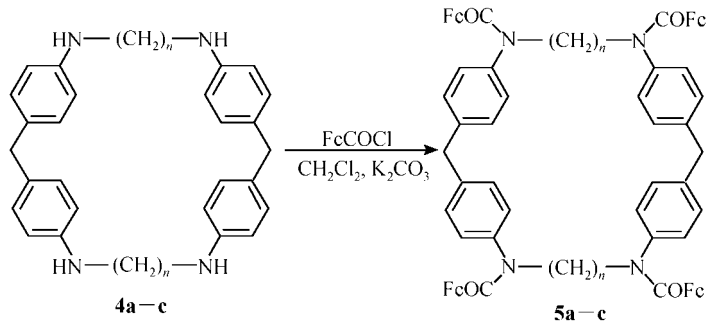
Tetraazaparacyclophanes play an important role in cyclophanes, which are also host compounds in host-guest chemistry[8,9]. Molecular recognition based on host-guest complexes is a fundamental chemical process, controlling many significant biological reactions involved in enzyme, antibody, carrier, channel, acceptor, etc. In the recent decades, host molecules that can hold with specific guest become the base of host-guest chemistry. The structure of tetraazaparacyclophane is a ring with benzene rings connected by nitrogen-containing carbon bridges. It has a well-defined hydrophobic cavity. In addition, the benzene rings are fixed at an angle and "face" conformation, which enables the formation of an inclusion cavity. As an artificial enzyme, tetraazaparacyclophane can be optimized by changing the shape and size of the hydrophobic cavity or being attached with active groups to form new host compounds. Seven of the tetraazacyclophanes with different hydrophobic cavity size were synthesized from 4,4'-diaminodiphenylmethane by protection, cyclization and deprotection (Scheme 1).



Scheme 1

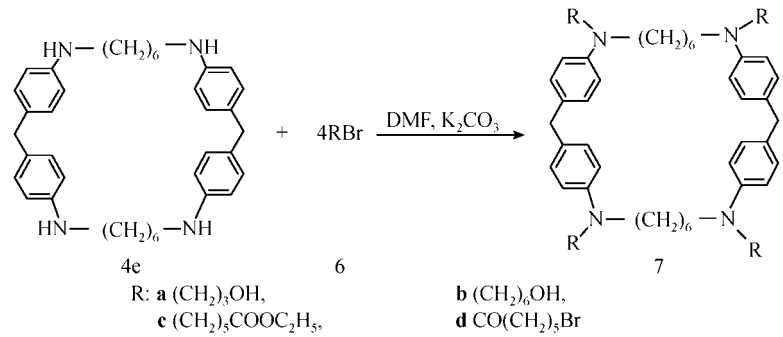
4,4’-Diaminodiphenylmethane **1** was tosylated to give the ditosylate **2**. The tetratosylates **3a**—**g** were obtained by cyclization between **2** and dibromoalkanes in the presence of K_2CO_3 in DMF under a high dilution condition. Detosylation of **3a**—**g** with 48% aqueous HBr and phenol gave **4a**—**g**. Among these compounds, **4a, 4f** and **4g** have not been reported in literature[8,10,11].

To improve molecular recognition ability of cyclophanes, we synthesized a novel kind of tetraazaparacyclophanes: tetraferrocenoyltetraazaparacyclophanes bearing ferrocenoyl branches which might enlarge the depth of the hyrophobic cavity and made it like an octopus. These cyclophanes might have the ability to perform the induced-fit molecular recognition toward certain guest and may be utilized as a multifunctional receptor model, and hence would be more promising. The cyclophanes **5a**—**c** were synthesized by the reaction sequences shown in scheme 2.



Scheme 2

1,8,22,29-Tetraaza[8.1.8.1]paracyclophane (**4e**) is a very useful cyclophane with a suitable hydrophobic cavity. It was modified with bromoalkane and alkanecarbonyl bromide, and four of the tetraazacyclophanes with straight chain on the nitrogens were obtained (Scheme 3).



Scheme 3

1 Experimental

1.1 Apparatus and reagents

Melting points were determined on a Model X-4 melting point apparatus and uncorrected; NMR spectra were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard on a VARIAN INOVA-400 spectrometer; IR spectra were recorded on a Bruker Equinox-55 spectrophotometer on a KBr matrix; Elemental analyses were performed with a PE-2400 analyzer; mass spectra were determined by an AXIMA-CFR plus Maldi-Tof mass spectrometer. All chemicals were of reagent grade.

1.2 Synthesis of N,N'-bis(4-tolylsulfonyl)-4,4'-methylendianilin (**2**)

In a 2 L 3-necked round bottom flask equipped with a magnetic stirring bar, a refluxing condenser and a dropping funnel 100.0 g of 4,4'-methylendianilin were placed with 500 mL dry pryridine. While the mixture was stirred and colded to 0℃, a solution of 190 g of 4-toluenesulfonyl chloride in 500 mL dry pryridine was added within 1 h. After stirring at room temperature overnight, the solution was poured into 2 L ice-colded 20% hydrochloric acid. The precipitate was filtered, washed with dilute hydrochloric acid, neutralized with water, and dried at 80℃. Recrystallization from ethanol furnished 200 g of slightly yellow crystals, mp 212-4℃.

1.3 Synthesis of **3a**—**3g**

50 g of the tosylanilide **2** were dissolved in 500 mL dimethyl formamide and added dropwise to a 4 L dimethyl formamide solution of 0.1 mol dibromide alkane, which was placed together with 55.3 g potassium carbonate in a flask equipped with a large magnetic stirring bar. The mixture was stirred at room temperature; after 3 days the solvent was removed down to 750 mL at the round evaporater. 1 L water was slowly added to the solution. The precipitate was filtered, washed with water before neutral reaction, and dried overnight in an oven at 80℃. The crystallization product was detosylated without further purification.

1.4 Synthesis of **4a**—**4g**

A 1-L round bottom flask was equipped with a large magnetic stirring bar and a reflux codenser. 0.04 mol raw material **3** from the cyclization, 480 mL hydrobromic acid and 96 g phenol were heated at reflux for 4.5 h, while stirring. After cooling, the lower layer of the resulting two layers containing the aqueous acid, was removed in a large separate funnel. The organic phase was transferred into an Erlenmeyer flash and stirred 5—6 times with 600 mL potions of ether containing 10—20% acetone, until the ether phase became colorless. The residue was stirred overnight at room temperature with 2 L concentrated aqueous potassium hydroxide; the precipitate was filtered, and washed with 250 mL saturated potassium hydroxide solution. The residue was heated to reflux while stirring in 500 mL ethylacetate for 2 h. After filtering off the remaining solid polymeric material, the filtrate was concentrated at the rotary evaporator down to 50 mL. The solution together with the resulting precipitate was chromatographed on a silica gel column with ethylacetate-petroleum ether (2:1). Colorless needles were obtained. **4a**: white solid，mp 277—278℃; ^{1}H NMR ($CDCl_3$) δ: 6.84 (d, J = 8.4 Hz, 8H), 6.43 (d, J = 8.8 Hz, 8H), 3.77 (s, 4H), 3.33 (br, 8H). **4b**: white solid, mp 218—221℃; ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.87 (d, J = 8.4 Hz, 8H), 6.44 (d, J = 8.4 Hz, 8H), 3.73 (s, 4H), 3.23 (t, J = 6.4 Hz, 8H), 1.85 (m, 4H). **4c**: white solid, mp 186—187℃(182.5-184℃[2]). ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.94 (d, J = 8.0 Hz, 8H); 6.53 (d, J = 8.0 Hz, 8H); 3.74 (s, 4H), 3.13 (t, J = 6.6Hz, 8H), 1.71 (t, J = 6.6Hz, 8H); ^{13}C NMR (400 MHz $CDCl_3$) δ: 146.08, 131.15, 129.52, 113.11, 43.61, 40.06, 29.70,; IR (KBr) ν: 3316, 2929, 1614, 1516, 1314, 1179, 815, 754, 595 cm^{-1}. **4d**: white solid, mp178—180℃; ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.95 (d, J = 8.0 Hz, 8H); 6.49 (d, J = 8.0 Hz, 8H); 3.74 (s, 4H), 3.11 (t, J = 7.0Hz, 8H), 1.60 (m, 8H), 1.43(m, 4H); ^{13}C NMR (400 MHz $CDCl_3$) δ: 146.13, 130.76, 129.54, 112.76, 43.83, 40.06, 29.05, 24.27. **4e**: white solid, mp 159—160℃[11]. ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.92 (d, J = 8.0 Hz, 8H); 6.48 (d, J = 8.0 Hz, 8H); 3.74 (s, 4H), 3.19 (t, J = 6.3 Hz, 8H), 1.58 (m, 8H),

1.39 (m, 8H); ^{13}C NMR (400 MHz $CDCl_3$) δ: 146.5, 130.8, 129.5, 112.9, 43.9, 40.1, 29.1, 26.4. IR (KBr) ν: 3420, 3030, 1620, 1512, 800 cm^{-1}. **4f**: white solid, mp125—133℃; ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.93(d, J = 8.2 Hz, 8H), 6.53 (d, J = 8.2 Hz, 8H), 3.75 (s, 4H), 3.21(t, J = 6.6 Hz, 8H), 1.07 (br, 32H). ^{13}C NMR (400 MHz $CDCl_3$) δ: 146.38, 130.86, 129.52, 114.42, 44.18, 40.65, 31.22, 29.48, 29.17, 26.88; IR (KBr) ν: 3331, 2912, 2849, 1614, 1519, 1458, 1321, 1269, 807 cm^{-1}. **4g**: white solid, mp144—146℃; ^{1}H NMR (400 MHz $CDCl_3$) δ: 6.93(d, J = 8.0 Hz, 8H); 6.54 (d, J = 8.0 Hz, 8H); 3.73 (s, 4H), 3.18 (t, J = 6.6 Hz, 8H), 1.17(m, 40H); ^{13}C NMR (400 MHz $CDCl_3$) δ: 146.13, 131.35, 129.41, 113.52, 43.76, 40.05, 29.96, 29.23, 28.98, 28.63, 26.05; IR (KBr) ν: 3347, 2921, 2850, 1613, 1511, 1455, 1322, 1250, 842, 807 cm^{-1}.

1.5 Synthesis of **5a**—**c**

4 mmol ferrocenoyl chloride in 30 mL dichloromethane was added dropwise to a solution of 1 mmol **4** and 1.0 g potassium carbonate in 30 mL dichloromethane. The mixture was stirred at refluxing temperature for 48 h. Then potassium carbonate was filtered and the solvent was removed by vacuum distillation. The residual was separated on silica gel column using ethyl acetate-petroleum ether (2:1) as elute. **5a**: orange crystal, mp 256—258℃, 21 %; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 6.94 (d, 8H, J = 7.6), 6.80 (d, 8H, J = 7.6), 4.18 (s, 20H), 4.13 (s, ,8H), 4.11(s, 8H), 4.01(s, 4H), 3.98 (s, 8H); ^{13}C NMR(400 MHz, $CDCl_3$) δ: 170.12, 141.63, 139.66, 129.67, 128.58, 76.43, 71.38, 69.86, 69.70, 49.33, 40.43,; IR (KBr)v: 3089, 2923, 1628, 1510, 1452, 1387, 1286, 1171, 1102, 817, 755, 485 cm^{-1}. Anal. Calcd for $C_{74}H_{64}Fe_4N_4O_4$: C 68.54, H 4.97, N 4.32; found. C 68.39, H 5.15, N 4.12; MS: 1297.76(Calcd 1296.23).**5b**: orange crystal, mp 235—237℃, 42 %; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.00(d, 8H, J = 7.4), 6.84(d, 8H, J = 7.4), 4.13(s, 20H), 4.11(br,12H), 3.94(br,16H), 1.81(s, 4H); ^{13}C NMR(400 MHz, CDCl3) δ: 170.01, 140.99, 139.54, 129.78, 128.83, 75.96, 71.29, 69.79, 60.34, 48.05, 40.54, 24.91; IR (KBr) v: 3087, 2923, 1626, 1509, 1449, 1390, 1289, 1167, 1104, 816, 755, 489 cm^{-1}; Anal. Calcd for $C_{76}H_{68}Fe_4N_4O_4$: C 68.90, H 5.17, N 4.23; found. C 69.01, H 5.33, N 4.10. MS: 1326.11 (Calcd 1324.26). **5c**: orange crystal mp 199— 201℃, 56 %; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.13(d, 8H, J = 8.0), 7.01(d, 8H, J = 8.0), 4.13 (s, 20H), 4.11(s, 8H), 3.98 (s, 4H), 3.97(s, 8H), 3.78(m, 8H), 1.61(m, 8H); ^{13}CNMR(400 MHz, $CDCl_3$) δ: 169.72, 141.50, 139.97, 129.79, 128.63, 76.74, 76.15, 71.37, 69.81, 50.46, 41.02, 25.02; IR (KBr) v: 3089, 2925, 1625, 1509, 1452, 1389, 1299, 1164, 1103, 819, 753, 492 cm^{-1}; Anal. Calcd for $C_{78}H_{72}Fe_4N_4O_4$: C 69.25, H 5.36, N, 4.14; found C 68.97, H 5.14, N 4.10; MS: 1354.85(Calcd 1352.30).

1.6 Synthesis of **7a**—**7d**

A mixture of 0.5 g (0.9 mmol) **4e**, 7.2 mmol **6** and 0.7 g (5.4 mmol) ethyldiisopropanylamine in 50 mL DMF was stirred at 80—90℃ for 24 h. The solvent and unreacted bromide were removed under vacuum condition. 80 mL chloroform was added, washed with water, and dried with sodium sulfate. The impure products **7** were purified by silica gel column chromatography (petroleum ether-EtOAc, 5:1). **7d** was synthesized in chloroform. **6** was added dropwise below 0℃. The reaction was performed at room temperature for 4 h. **7a**: brown oil, 19.7 %; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 6.99 (d, J = 8.5, 8H), 6.53 (d, J = 8.5, 8H), 3.77(s, 4H), 3.71 (br, 8H), 3.34 (br, 8H), 3.19 (br, 8H), 1.82—1.78(m, 8H), 1.51(m, 8H), 1.30(m, 8H); ^{13}C NMR(400 MHz, $CDCl_3$) δ: 147.7, 131.2, 130.6, 114.4, 60.9, 52.4, 40.9, 31.3, 27.9, 27.7. **7b**: brown solid , mp 70—72℃, 46.3 %; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 6.99 (d, J = 8.5, 8H), 6.54 (d, J = 8.5, 8H), 3.76 (s, 4H), 3.62 (t, J = 6.5, 8H), 3.22—3.17(m, 16H), 1.60—1.52(m, 24H),1.38 — 1.31(m, 24H); ^{13}C NMR(400 MHz, $CDCl_3$) δ: 146.4, 129.6, 126.0, 112.2, 62.8, 51.2, 39.7, 32.8, 27.3, 27.2, 27.1, 27.0, 25.7. **7c**: brown oil, 43.8%; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 6.98 (d, J = 8.8, 8H), 6.53 (d, J = 8.8, 8H), 4.18—4.09 (m, 8H), 3.76 (s, 4H), 3.22 — 3.08 (m, 16H), 2.33 — 2.28 (m, 8H), 1.71—1.63 (m, 16H), 1.58—1.53(m, 16H), 1.43—1.41(m, 8H), 1.35 — 1.31(m, 12H); ^{13}C NMR(400 MHz, $CDCl_3$) δ: 173.5, 146.2, 129.6, 128.9, 112.0, 63.6, 60.1, 51.2, 50.9, 39.6, 34.2, 28.1, 27.2, 26.9, 24.8;

IR (KBr)ν: 2935, 2861, 1733, 1613, 1517, 1369, 1179, 800, 737cm^{-1}. **7d**: white solid, mp 103－105℃, 61.2%; ^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.22 (d, J = 8.1, 8H), 7.05 (d, J = 8.1, 8H), 4.04 (s, 4H), 3.61 (t, J = 6.8, 8H), 3.34 (t, J = 6.8, 8H), 2.00 (t, J = 8.0, 8H), 1.80－1.73(m, 8H), 1.65－1.51(m, 8H), 1.45(m, 8H), 1.36－1.31(m, 8H), 1.29－1.24 (m, 8H); ^{13}C NMR(400 MHz, $CDCl_3$) δ: 172.4, 141.0, 140.2, 130.2, 128.4, 49.3, 40.9, 34.1, 33.7, 32.5, 27.8, 27.7, 26.6, 24.5; IR (KBr)ν: 2930, 2856, 1654, 1508, 1406, 1268, 833, 728 cm^{-1}.

2 Results and discussion

Macrocycle synthesis reactions carried out at high dilution favour cyclization over polymerization and can produce high yields of macrocyclic products. Tetraazaparacyclophanes were synthesized using high dilution techniques. At high concentration polymerization reactions dominate. The probability of a molecule meeting a second molecule decreases as the concentration decreases; therefore, the more dilute the solution, the better the ratio of macrocycle to polymer.

The high dilution method is used in the synthesis of macrocyclic compounds. High dilution reactions involve milligrams or tens of milligrams of reactants in solvent volumes of the order of litres. In a typical high dilution synthesis, solutions of each component are slowly added dropwise to a large volume of solvent, keeping the concentration of the intermediate low. The reactions of tosylanilide 2 with dibromide alkanes were performed in a large volume of DMF, and the solution of tosylanilide 2 was added dropwise to a solution of dibromide alkanes in a large volume of DMF.

The tetraazacyclophanes containing four active groups on nitrogens were designed and synthesized as a novel type of octopus-type cyclophane. The branches enlarge the depth of the hyrophobic cavity. ^{1}H NMR shows that the chemical shifts of branched tetraazacyclophane's methylenedibenzene unit move to the down field according to the tetraazacyclophanes, and the density of electric cloud is decreased.

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