Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Characterization of Tetraazaparacyclophane Disulfone

Ya-Ting Yang [a], Bing-Qin Yang [a], Min Li [a], Wei Ning [a] & Zhen-Huan Lu [a]
[a] Shannxi Key Laboratory of Physical Inorganic Chemistry, Department of Chemistry, Northwest University, Xi'an, Shannxi, China
Published online: 27 Feb 2008.

To cite this article: YaTing Yang , BingQin Yang , Min Li , Wei Ning & ZhenHuan Lu (2008) Synthesis and Characterization of Tetraazaparacyclophane Disulfone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:4, 530-536, DOI: 10.1080/00397910701796733

To link to this article: http://dx.doi.org/10.1080/00397910701796733

Synthetic Communications®, 38: 530–536, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701796733

Synthesis and Characterization of Tetraazaparacyclophane Disulfone

Ya-Ting Yang, Bing-Qin Yang, Min Li, Wei Ning, and Zhen-Huan Lu

Shannxi Key Laboratory of Physical Inorganic Chemistry, Department of Chemistry, Northwest University, Xi'an, Shannxi, China

Abstract: 1,6,20,25-Tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **D** was synthesized under high dilution (concentration: 6.91×10^{-3} mol L) by the cyclization between tetramethylene dibromide and N,N′-di-*p*-tosylaminodiphenylsulfone **B**, which was prepared using N,N′-diaminodiphenyl sulfone and *p*-toluenesulfonyl as raw materials. 1,6,20,25-Tetra-sulfoferrocene-1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **E** was prepared by modifying **D** with the bioactive unit ferrocene. The structures were confirmed by IR, ^{1}H NMR, and elemental analysis.

Keywords: diphenylsulfone, ferrocene, tetraazaparacyclophane, very dilute condition

The imitation of enzyme catalysis is a challenging research field that inspires great interest from chemists, especially biochemists. Organic cyclophane has particular properties and functions in catalysis, macromolecular receptors, electrical conductors, molecular recognition, molecular machines and devices, and molecular rotors.[1–9] Because of their unique structure, cyclophanes continue to interest synthetic chemists, and several catalytic applications employing cyclophane architecture have been recently reported.[10–15] The topic of cyclophanes with cavities of varying sizes as molecular hosts has been active recently.[16]

Received in China February 12, 2007
Address correspondence to B.-Q. Yang, Shannxi Key Laboratory of Physical Inorganic Chemistry, Department of Chemistry, Northwest University, Xi'an, Shannxi 710069, China. E-mail: yangbq@nwu.edu.cn

Macrocycles containing electrochemically active subunits are of interest because of their ability both to sense bound guest species and control the coordination environment of the host.[17,18] Ferrocene is a typical complement that has electrochemical activity and biochemical activity. The derivatives of ferrocene and cyclophane contain two aromatic rings and have similar properties, such as adequate rigidity, steric bulkiness, and stability. Furthermore, planar chirality is introduced when there are two substituents on the same ring in ferrocene or one substituent on any benzene ring in cyclophane.[19] All these properties make both ferrocene and cyclophane promising scaffolds of choice for designing chiral ligands, especially those with planar chirality.[20–24]

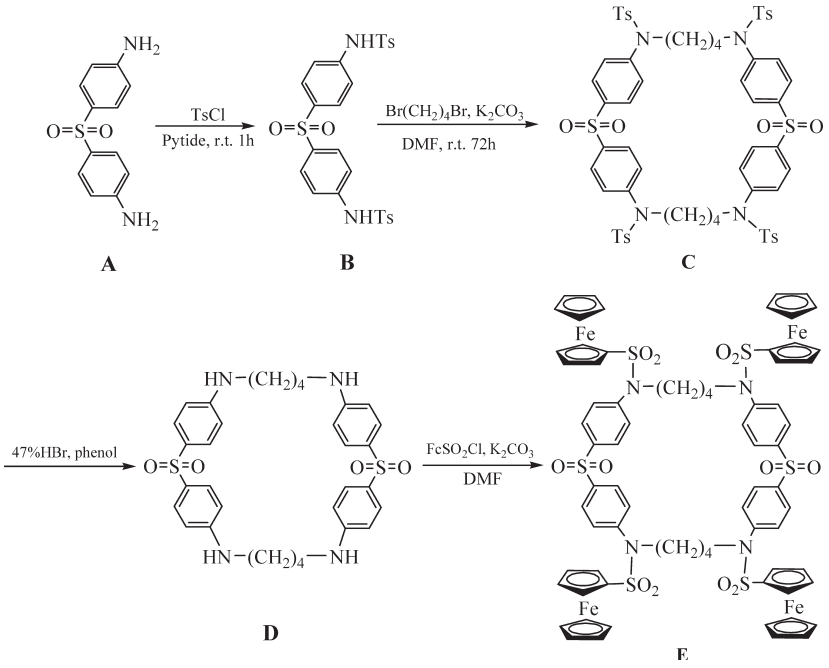
Motivated by the unique properties of ferrocene and cyclophanes, we became interested in the synthesis of a novel cyclophane with the subunits of ferrocene. Since the synthesis of 1,6,20,25-tetraaza[6.1.6.1]paracyclophane was reported in 1985 by Odashima,[25] cyclophane compounds had drawn thousands of scientists' attention. They not only researched the synthesis and modification of 1,6,20,25-tetraaza[6.1.6.1]paracyclophane(CP_{44})[26–28] but also synthesized novel 1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **C**. When the tetraparacyclophane is modified by ferrocene, the bioactive unit in the cyclophane and bridge atom can form a catalytic active center with coordinated inclusion and multicoordination, which helps imitate the recognition and catalysis that enzyme does to substrates. 1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **E** was prepared by modifying N,N′-diaminodiphenyl sulfone with *p*-toluenesulfonyl, the purity and structure of which was determined by IR, ^{1}H NMR, and elemental analysis. The synthesis procedure is shown in Scheme 1.

RESULTS AND DISCUSSION

Synthesis of N,N′-Di-*p*-tosylaminodiphenyl Sulfone B

According to the literature, during the preparation of N,N′-di-*p*-tosylaminodiphenyl sulfone **B**, when the reaction was finished, the resulting residue was put into small pieces of ice in concentrated hydrochloric acid and acidified. A viscolloid was usually obtained after it stayed overnight rather than a solid. By recrystallizing the viscolloid with a mixture of acetone and ethanol, occasionally a slight solid could be obtained, but mostly there was only oil. After several experiments, we found that the liquid can be solidified after 24 h by steeping in ethanol. Stirring of the solidified products in ethanol continued for 12 h, gave a white dusty solid, whose melting point conformed to the literature.

In conclusion, the synthesis of cyclophane compound relies on template synthesis and high dilution. It is always hard to prepare cyclocompounds because it polymerizes easily, has low yield, and gives many by-products



Scheme 1.

during the reaction. High dilution is needed to prevent polymerization. Template effects refers to coordination between cyclophane and metal ion, which can change electron condition and gain some space configuration. The reaction makes use of the template effect of the metal ion to accelerate cyclization. Metal ions in cyclization are the template agent. There are three kinds of template reactions: kinematic template reaction, thermodynamic template reaction, and equilibrated template reaction. Proper metal ion is the key to a template reaction. If the diameter of the metal ion is too long or short to the pore diameter of cyclophane, a template reaction cannot happen readily.

Our group obtained the target product under very dilute conditions in the dark. However, it is viscolloid because polymerization exists, and cyclization cannot enhance the yield very much.

EXPERIMENTAL

All glassware was dried in an oven for at least 3 h at 120°C prior to use. Solvent for general use (N,N′-dimethylformamide (DMF)) was of AR grade and was distilled after classical reagents, dried over $MgSO_4$, and filtered. ^1H

NMR spectra were recorded on Varian Inova (UVA) spectrometer. All chemical shifts are reported in parts per million (ppm) and are referenced to tetramethylsilane (TMS) utilizing residual ^1H signals of the deuterated solvents as an internal standard. Coupling constants (J) are reported in hertz (Hz). Elemental analyses were carried out with a Varrio ELIII CHNOS analyzer. Infrared spectra were recorded on a Bruker-55 spectrometer. Melting points was determined with XT-4 hot stage.

General Procedure

Synthesis of 1,4-Dibromobutane[29]

Concentrated sulfuric acid (46 mL) and tetrahydrofuran (39 mL) were added dropwise to 112 mL of stirred 47% HBr with the temperature less than 20°C. The mixture was heated to reflux for 6 h after the addition was finished. After the solution was cooled to room temperature, it was transferred to a separatory funnel, the organic phase was collected, and the water phase was disposed. The organic phase was extracted with additional water twice and then washed with a saturated solution of $NaHCO_3$ until the pH was 7. The organic phase was dried over anhydrous $MgSO_4$ overnight and distilled under reduced pressure. The distillate was collected, and diopter was measured as 1.5205. (Lit.[29]: $n_D^{20} = 1.5185$).

Synthesis of N,N′-Di-*p*-tosylaminodiphenyl Sulfone **B**[25]

To a well-mixed solution of N,N′-diaminodiphenyl sulfone **A** (4.87 g, 0.019 mol) in 15 mL of pyridine, *p*-toluenesulfonyl (6 g of 15 mL pyridine, 0.04 mol) was added dropwise over a period of 1 h. The mixture was stirred at 100°C for 0.5 h. The resulting residue was put into small pieces of ice in concentrated hydrochloric acid and was acidified overnight. The precipitated solid was filtered, washed with water, dissolved in NH_4OH, and then filtered. The filtrate was acidified with AcOH to pH 7 to give N,N′-di-*p*-tosylaminodiphenyl sulfone **B** as a white solid. Mp 250–251°C (lit.[25] 251–252°C). ^1H NMR (CD_3COCD_3, δ): 7.807–7.751 (m, 8H, aromatic), 7.391–7.327 (m, 8H, aromatic), 2.356 (s, 6H, CH_3); IR (KBr): ν (NH) 3236 cm^{-1}, ν (-CH_2,-CH_3) 2920–2853 cm^{-1}, ν (C═C) 1593 cm^{-1}, 1495 cm^{-1}, ν (SO_2) 1158 cm^{-1}.

Synthesis of N,N′,N″,N‴-Tetra-*p*-toluene-1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **C**

To a mixture of 9.4 g of K_2CO_3 in 2500 mL of dry DMF, a solution of **B** (10 g) in 100 mL of DMF and 1,4-dibromobutare (3.4 g) was added dropwise. The mixture was stirred at room temperature until the reaction was finished and

then was filtered. The medium was evaporated under reduced pressure to about 70 mL. Water was added, and the mixture was filtered under reduced pressure. The filter cake was washed with water until it became colorless. Column chromatography on silica gel ($CH_3COCH_3/CHCl_3$ 1:8) afforded N,N′,N″,N‴-tetra-*p*-toluene-1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **C** as a white solid. ^{1}H NMR ($CDCl_3$, δ): 1.266 [d, $J = 7.2$ Hz, 8H, 4(CH_2)], 2.421 [s, 12H, 4(Ph-CH_3)], 3.627 [s, 8H, 4(N-CH_2)], 7.105 (d, $J = 8.0$ Hz, 8H, aromatic), 7.252 (d, $J = 8.4$ Hz, 8H, aromatic), 7.416 (d, $J = 8.4$ Hz, 8H, aromatic), 7.803 (d, $J = 8.8$ Hz, 8H, aromatic); IR (KBr): ν (-CH_2, -CH_3) 2923 cm^{-1}–2853 cm^{-1}, ν (C═C), 1590 cm^{-1}, 1492 cm^{-1}, ν (SO_2) 1157 cm^{-1}; MALDI-TOP MS $m/z = 1244.9$ $[M + Na]^+$. Anal. calcd. for $C_{61}H_{60}N_4O_{12}S_6$: C, 59.14; H, 5.12; N, 4.61. Found: C, 59.00; H, 4.95; N, 4.59.

Synthesis of 1,6,20,25-Tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **D**

A mixture of **C** (11 g) and phenol (22 g) in 48% HBr (110 mL) was stirred vigorously under reflux for 5 h. The mixture was cooled, and the aqueous layer was collected. After washing by 15% acetone in sulfuric ether and alkalinization by KOH to pH 7, the aqueous layer was filtered under reduced pressure. The filter cake was extracted by chloroform, and the organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography on silica gel ($CH_3OH/CHCl_3$ 1:30) afforded 1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **D** as a white solid. Mp 240–241°C. ^{1}H NMR ($CDCl_3$, δ): 7.70 [d, $J = 9.2$ Hz, 8H, aromatic, 4(H2 and H6)], 6.60 [d, $J = 8.4$ Hz, 8H, aromatic, 4(H3 and H5)], 3.30–3.28 [m, 8H, 4(N-CH_2)], 2.02–2.01 [m, 8H, 4(CH_2)]; IR (KBr): ν (NH) 3367 cm^{-1}, ν (═C-H) 3080 cm^{-1}, ν (CH_2) 2923 cm^{-1}, ν (C-N) 1629 cm^{-1}, ν (C═C) 1594 cm^{-1}. Anal. calcd. for $C_{32}H_{36}N_4O_4S_2$: C, 63.42; H, 5.86; N, 9.31. Found: C, 63.55; H, 6.00; N, 9.26.

Synthesis of 1,6,20,25-Tetra-sulfoferrocene-1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **E**

A mixture of **D** (0.2 g, 0.33 mmol), ferrocenesulfonyl chloride (0.8 g, 2.6 mmol), and K_2CO_3 (0.3 g) in dry DMF (25 mL) was stirred at room temperature for 72 h and then filtered under reduced pressure. After evaporation of the filtrate, column chromatography on silica gel (AcOEt/petroleumether 1:1) afforded 1,6,20,25-tetra-sulfoferrocene-1,6,20,25-tetraaza[6.1.6.1]paracyclophane-13,32-disulfone **E** as a brown solid. Mp 226–227°C. ^{1}H NMR ($CDCl_3$, δ): 7.75 [d, $J = 9.2$ Hz, 8H, aromatic, 4(H2 and H6)], 6.80 [d, $J = 8.8$ Hz, 8H, aromatic, 4(H3 and H5)], 4.43–4.25 (m, 36H, Cp), 3.40–3.33 [m, 8H, 4(N-CH_2)], 1.72–1.51 [m, 8H, 4(CH_2)]; IR (KBr): ν (Fc-H) 3109 cm^{-1}, ν (CH_2) 2928 cm^{-1}, ν (═C-N) 1632 cm^{-1}, ν (C═C)

1601 cm^{-1}. Anal. calcd. for $C_{72}Fe_4H_{68}N_4O_{12}S_6$: C, 60.25; H, 4.42; N, 3.85. Found: C, 60.19; H, 4.77; N, 3.90.

ACKNOWLEDGMENTS

The authors thank the Chinese National Natural Science Foundation (No. 20572085) and Shannxi Science Foundation (No. 2005B20) for financial support.

REFERENCES

1. Perumal, R. A.; Rasheed, M. A. Synthesis, characterization and ion transportation studies of some novel cyclophane amides. *Tetrahedron* **2005**, *61*, 5351–5362.
2. Kakkar, A. K. Nano-organometallics: heterogenizing homogeneous catalysts via thin film methodology. *Chem. Rev.* **2002**, *102*, 3579–3587.
3. Yoshioka, N.; Yajima, S.; Kimura, K. Silver ion sensing using coordinate aromatic neutral carriers for soft metal ions. *Bunseke Kagaku* **2003**, *52*, 689–694.
4. Fish, R. H.; Jaouen, G. Bioorganometallic chemistry: structural diversity of organometallic complexes with bioligands and molecular recognition studies of several supramolecular hosts with biomolecules, alkali-metal ions, and organometallic pharmaceuticals. *Organometallics* **2003**, *22*, 2166–2177.
5. Rathhore, R.; Chebny, V. J.; Abdelwahed, S. H. A versatile and conformationally adaptable fluorene-based receptor for efficient binding of silver cation. *J. Am. Chem. Soc.* **2005**, *127*, 8012–8013.
6. Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. Artificial molecular rotors. *Chem. Rev.* **2005**, *105*, 1281–1376.
7. Hirata, O.; Takeuchi, M.; Shinkai, S. Allosteric binding of anionic guests to a bicyclic host which imitates the action of a 'turnstile.' *Chem. Commun.* **2005**, 3805–3807.
8. Alfonso, I.; Burguete, M. I.; Luis, S. V. A Hydrogen-bonding-modulated molecular rotor: environmental effect in the conformational stability of peptidomimetic macrocyclic cyclophanes. *J. Org. Chem.* **2006**, *71*, 2242–2250.
9. Kanazawa, H.; Higuchi, M.; Yamamato, K. An electric cyclophane: cavity control based on the rotation of a paraphenylene by redox switching. *J. Am. Chem. Soc.* **2005**, *127*, 16404–16405.
10. Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. A new planar chiral bisphosphine ligand for asymmetric catalysis: highly enantioselective hydrogenations under mild conditions. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208.
11. Zanotti-Gerosa, A.; Malan, C.; Herzberg, D. Phosphonites based on the paracyclophane backbone: new ligands for highly selective rhodium-catalyzed asymmetric hydrogenation. *Org. Lett.* **2001**, *3*, 3687–3690.
12. Gibson, S. E.; Knight, J. D. [2.2]Paracyclophane derivatives in asymmetric catalysis. *Org. Biomol. Chem.* **2003**, *1*, 1256–1269.
13. Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. Asymmetric addition of aryl boron reagents to enones with rhodium dicyclophane imidazolium carbene catalysis. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871–5874.

14. Hua, J.; Lin, W. Chiral metallacyclophanes: self-assembly, characterization, and application in asymmetric catalysis. *Org. Lett.* **2004**, *6*, 861–864.
15. Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M. B. Bis-paracyclophane *N*-heterocyclic carbene–ruthenium catalyzed asymmetric ketone hydrosilylation. *Tetrahedron Lett.* **2005**, *46*, 3241–3244.
16. Pìa, E.; Toba, R.; Chas, M.; Peinador, C.; Quintela, J. M. Synthesis of new viologen macrocycles with intramolecular charge transfer. *Tetrahedron Lett.* **2006**, 1953–1956.
17. Boulas, P. L.; Gomez-Kaifer, M.; Echegoyen, L. Electrochemistry of supramolecular systems. *Angew. Chem., Int. Ed.* **1998**, *37*, 216–247.
18. Allgeier, A. M.; Mirkin, C. A. Ligand design for electrochemically controlling stoichiometric and catalytic reactivity of transition metals. *Angew. Chem., Int. Ed.* **1998**, *37*, 894–908.
19. Eliel, E. L.; Wilen, S. H. *Stereochemistry Organic Chemistry*; Wiley: New York, 1994.
20. Richards, C. J.; Locke, A. J. Recent advances in the generation of non-racemic ferrocene derivatives and their application to asymmetric synthesis. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407.
21. Colacot, T. J. A concise update on the applications of chiral ferrocenyl phosphines in homogeneous catalysis leading to organic synthesis. *Chem. Rev.* **2003**, *103*, 3101–3118.
22. Sutcliffe, O. B.; Bryce, M. R. Planar chiral 2-ferrocenyloxazolines and 1,1′-bis(oxazolinyl) ferrocenes syntheses and applications in asymmetric catalysis. *Tetrahedron: Asymmetry* **2003**, *14*, 2297–2325.
23. Blaser, H. U.; Spindler, F. Enantioselective catalysis for agrochemicals: the case history of the DUAL-MAGNUM herbicide. *Chimia* **1997**, *51*, 297–299.
24. Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. Asymmetric catalysis with chiral ferrocene ligands. *Acc. Chem. Res.* **2003**, *36*, 659.
25. Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. Biomimetic studies using artificial systems, 3: design, synthesis, and inclusion complex forming ability of a novel water-soluble paracyclophane possessing diphenylmethane skeletons. *J. Org. Chem.* **1985**, *50*, 4478–4484.
26. Shi, Z. Synthesis of tetraazaparacyclophane. *J. Northwest University* **1993**, *23*, 517–520.
27. Yang, B. Q.; Zhu, A. L.; Lu, J. Supramolecular recognition of tetraazaparacyclophane for benzimidazole derivatives: progress in macrocyclic and supramolecular chemistry. **2004**, *8*, 166–167.
28. Zhu, A. L.; Yang, B. Q.; Zhang, J. Modification, molecular recognition of tatraazaparacyclophane CP_{44} and synthesis of nitrogen heterocycle ferrocene sulfanilic amide. *Org. Chem.* **2005**, *25*, 339–341.
29. Liu, Y.; You, C. C. Molecular recognition studies on supramolecular systems—The binding ability and molecular selectivity of bridged bis(cyclodextrin)s with model substrates. *Chem. Res. Chin. Univ.* **2001**, *22* (4), 591.