SYNTHESIS OF (AZA)$_n$[3^n]CYCLOPHANES AS HOST MOLECULES[1)]

Hiroyuki TAKEMURA, Masahiko SUENAGA, Kiyoshi SAKAI,
Hisao KAWACHI, Teruo SHINMYOZU, Yuji MIYAHARA,
and Takahiko INAZU*
Department of Chemistry, Faculty of Science,
Kyushu University 33, Hakozaki, Higashi-ku, Fukuoka 812

ABSTRACT: (Aza)$_n$[3^n]cyclophanes were synthesized by the coupling reaction of p-toluenesulfonamide and bis(halomethyl) derivatives in the presence of a base (K_2CO_3, NaH etc.) using DMF, dioxane etc. as a solvent, in acceptable yields. Tetraaza macrocyclic compound (the dimer in Fig. 1) obtained by the coupling of 2,11-diaza[3.3]metacyclophane with 1,3-bis(bromomethyl)benzene gave a 1:1 adduct with benzene.

1. INTRODUCTION

Because of the possibility of forming inclusion compounds and intramolecular charge-transfer complexes, macrocyclic compounds furnished with an empty space of an appropriate size at the center of their molecules are of particular interest as artificial inclusion hosts.

In the hope of obtaining such inclusion compounds of cyclophanes with small organic molecules, cyclophanes with four or more benzene rings, such as [2.1.1.1.1]paracyclophane[2)], [2.1.1.1]paracyclophane[3)], [2.1.1.1.2.1.1.1]paracyclophane[3)], [3.3.3.3]paracyclophane[4)] and [1.1.1.1]paracyclophane[5)], have been synthesized but all attempts to obtain inclusion compounds have resulted in failure. As a result of several preliminary experiments[6)], we assumed that hetero atoms as constituents of the host molecule might play an important role for the formation of inclusion compounds. In order to vary cavity size and the number of hetero atoms, we have synthesized three azaparacyclophanes with different lengths of bridges containing different numbers of nitrogen atoms[13)].

In the case of N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza-[3.3.3.3]paracyclophane, Me_4N_4[3^4]PC[14)], we have reported 1:1 adducts with benzene or dioxane molecule[13,15,16)]. This tetraaza[3.3.3.3]-

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paracyclophane may be one of the most extensively studied compounds as an artificial host molecule thus far[17].

For the synthesis of this compound, we had adopted an amide-formation method in the critical ring-closing step. This aza-paracyclophane had been prepared by the condensation of terephthaloyl chloride and 1,4-bis(N-methylaminomethyl)benzene and subsequent reduction with lithium aluminum hydride or diborane[4] in THF. But this cyclization step was somewhat tedious and troublesome and lithium aluminum hydride reduction of the cyclic tetraamide to the cyclic tetramine was not suitable for large scale preparation.

For the purpose of obtaining $Me_4N_4[3^4]PC$ with ease, we have examined another synthetic route to azacyclophanes.

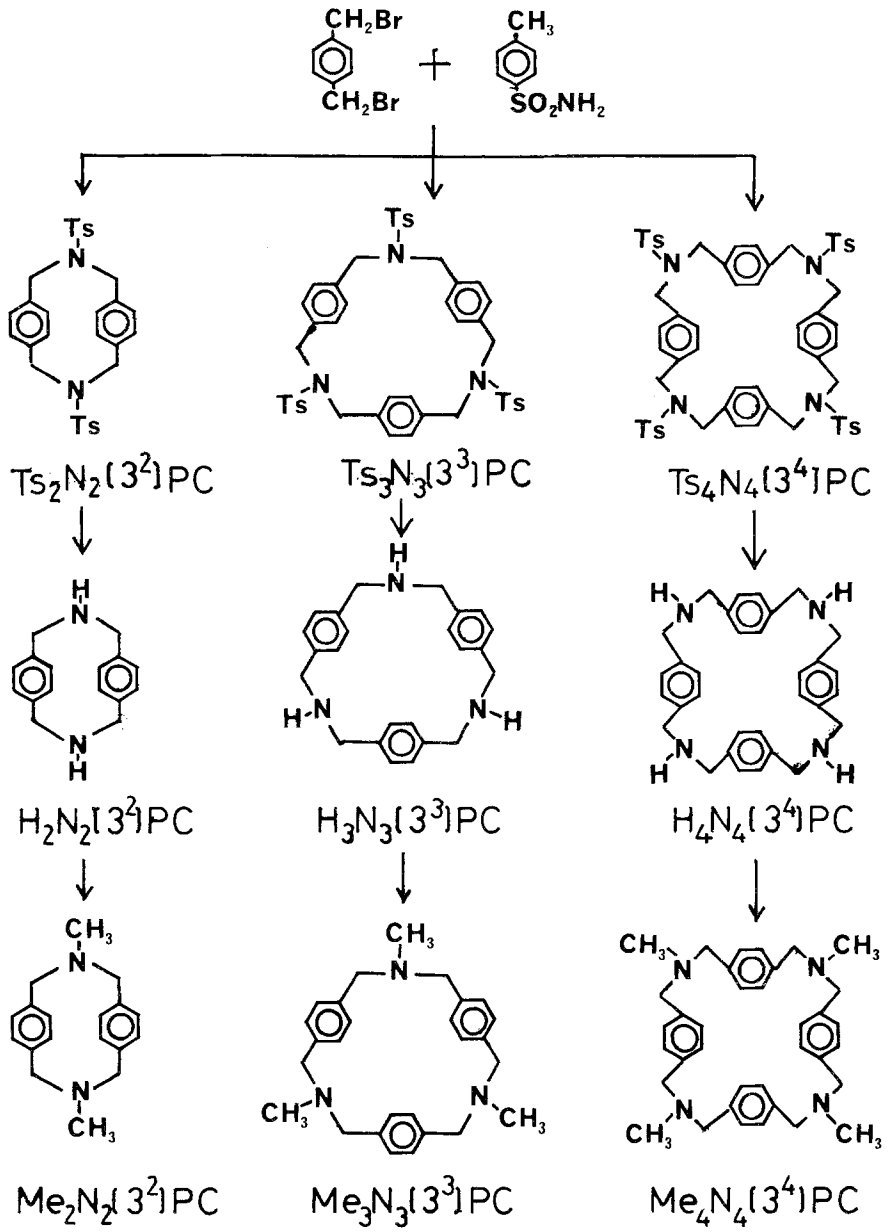
2. RESULTS AND DISCUSSION

In order to develop a simple and general method for the synthesis of $(aza)_n[3^n]$cyclophane, (n=2,3,4...), we have adopted the coupling reaction between p-toluenesulfonamide and appropriate bis(halomethyl) compounds, followed by removal of tosyl groups. The coupling reactions were carried out in the presence of a base (K_2CO_3, NaH or Na) using DMF, dioxane or C_2H_5OH as a solvent. Yields were acceptable for further studies. The removal of tosyl protective groups was performed under several reaction conditions with ease in good yields.

The reaction condition (Na/isoamyl alcohol) was applicable for many cyclophanes, but in case of $(aza)_n[3^n]$paracyclophanes, the excellent results were obtained under reaction condition (Na/liquid ammonia). As an example of alkylation, methylation by the Eschweiler-Clarke modification of the Leuckart reaction was adopted. The methylation of the cyclic amines was carried out without difficulty by only refluxing the mixture of the amine, 37% formalin and 95% formic acid.

One of the advantages of this procedure over conventional synthetic methods of azacyclophanes (cyclic amide formation) resides in its brevity and simplicity. In addition, the results obtained reveal this procedure to be an efficient diaza[3.3]cyclophane synthetic method, and an acceptable approach for the synthesis of triaza[3.3.3]cyclophanes and tetraaza[3.3.3.3]cyclophanes as host molecules of inclusion compounds. This synthetic method has been successfully applied to other cyclophane systems, such as 2,11-diaza[3.3](2,6)-, 2,11,20-triaza[3.3.3](2,6)- and 2,11,20,29-tetraaza[3.3.3.3](2,6)pyridinophane, syn- and anti-2,13-diaza[3.3](1,4)naphthalenophane, 2,13,24-triaza[3.3.3](1,4)- and 2,13,24,35-tetraaza[3.3.3.3](1,4)naphthalenophane.

3. EXPERIMENTAL


CH2Br
CH2Br
CH3
SO2NH2
Ts2N2[3^2]PC
Ts3N3[3^3]PC
Ts4N4[3^4]PC
H2N2[3^2]PC
H3N3[3^3]PC
H4N4[3^4]PC
Me2N2[3^2]PC
Me3N3[3^3]PC
Me4N4[3^4]PC

Scheme 1

3.1. Synthesis

As an example of a one-step cyclization,[18,19] synthesis of $Ts_n(aza)_n[3^n]$paracyclophane(n=2,3,4) are described.

Synthesis of $Ts_n(aza)_n[3^n]$paracyclophane (n=2,3,4)[20]:

To a stirred suspension of NaH (50%, 9 g, 187.5 mmol) in DMF (360 ml) was added a mixture of 1,4-bis(bromomethyl)benzene (23.8 g, 90.4 mmol) and p-toluenesulfonamide (15.2 g, 90.4 mmol) in DMF (350 ml) over a period of 5 h under nitrogen atmosphere, the temperature being kept at 50 °C. After additional stirring and heating for 5 h, the still hot reaction mixture was filtered, and water, then dil HCl were added to the yellow filtrate to give 22.5 g of a white precipitate. Separation by column chromatography (Wako-gel C-300, $CH_2Cl_2/CH_3COOC_2H_5$=40:1) afforded $Ts_2N_2[3^2]$PC(1.43 g, 5.8%), $Ts_3N_3[3^3]$PC(5.66 g, 22.9%) and $Ts_4N_4[3^4]$PC (2.99 g, 12.1%). Separation of $Ts_3N_3[3^3]$PC and $Ts_4N_4[3^4]$PC was easily done by recrystallization from dioxane.

$Ts_2N_2[3^2]$PC; white plates from dioxane, mp 322.1-322.6°C(dec). MS(m/z)M^+ 546(calcd 546). Anal. Found: C, 65.78; H, 5.55; N, 5.11%. Calcd for $C_{30}H_{30}N_2O_4S_2$: C, 65.91; H, 5.53; N, 5.12%. NMR($CDCl_3$, δ) 4.31s(CH_2), 6.90s(arom). $Ts_3N_3[3^3]$PC; white crystals from dioxane, mp 300 °C(dec). Anal. Found: C, 65.86; H, 5.73; N, 5.00%. Calcd for $C_{45}H_{45}N_3O_6S_3$: C, 65.91; H, 5.53; N, 5.12%. NMR($CDCl_3$, δ) 4.13s(CH_2), 6.94s(arom). $Ts_4N_4[3^4]$PC; white crystals from dioxane, mp 320 °C(dec). Anal. Found: C, 65.79; H, 5.62; N, 5.08%. Calcd for $C_{60}H_{60}N_4O_8S_4$: C, 65.91; H, 5.53; N, 5.12%. NMR($CDCl_3$, δ) 4.10s(CH_2), 6.80s(arom).

3.2. Removal of protective groups

2,11,20,29-Tetraaza[3.3.3.3]paracyclophane ($H_4N_4[3^4]$PC)[21]:

To the suspension of 624.5 mg of $Ts_4N_4[3^4]$PC in 150 ml of liquid ammonia was added 1.1 g of sodium with stirring under nitrogen atmosphere. The reaction mixture turned dark violet immediately. After the mixture was stirred for 6 h, excess ammonium chloride was added, and the ammonia was evaporated. To the residue, water was added and the mixture was extracted with benzene. After the usual work-up, 240 mg of pale yellow crystals was obtained (quantitative). NMR($CDCl_3$, δ) 1.63s(N-H), 3.70s(CH_2), 7.07s(arom). The tetramine ($H_4N_4[3^4]$PC) or triamine ($H_3N_3[3^3]$PC) thus obtained were used in the following alkylation reaction without further purification.

2,11-Diaza[3.3]paracyclophane ($H_2N_2[3^2]$PC):

Colorless plates from benzene (96.3% yield), mp 227.2-234.0°C(dec); MS(m/z)M^+ 238(calcd 238). Anal. Found: C, 80.72; H, 7.61; N, 11.56%. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75%. NMR($CDCl_3$, δ) 1.74s(N-H), 3.88s(CH_2), 6.78s(arom). IR(KBr disk) ν_{N-H} 3280 cm^{-1}.

2,11,20-Triaza[3.3.3]paracyclophane (H_3N_3[3^3]PC):

White crystals (99.3% yield). NMR($CDCl_3$, δ) 1.71bs(N-H), 3.72s(CH_2), 6.84s(arom).

3.3. Alkylation of cyclic amines

N,N',N'',N'''-Tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (Me_4N_4[3^4]PC); Methylation of the tetramine by the Eschweiler-Clarke modification of the Leuckart reaction:

A mixture of crude tetramine(H_4N_4[3^4]PC, 104.7 mg), 95% formic acid (10 ml), and 37% formalin (5 ml) was stirred at reflux for 20 h. To this mixture was added conc HCl (2.5 ml) while hot. After the solution was refluxed additional 19 h and allowed to cool, the solution was neutralized with dil NaOH solution, and extracted with benzene. After the usual work-up, crude product (pale yellow powder, 126.9 mg) was recrystallized from ethanol to afford white needles (55 mg, 47.0%), mp 195.5-197°C(lit.[13], 196-198.5°C); MS(m/z)M^+ 532 (calcd 532). Anal. Found: C, 80.95; H, 8.36; N, 10.46%. Calcd for $C_{36}H_{44}N_4$: C, 81.16; H, 8.32; N, 10.52%. NMR($CDCl_3$, δ) 2.33s(N-CH_3), 3.33s(CH_2), 7.24s(arom).

N,N'-Dimethyl-2,11-diaza[3.3]paracyclophane (Me_2N_2[3^2]PC):

White prisms from methanol (97.1% yield), mp 140-143°C; MS(m/z)M^+ 266(calcd 266). Anal. Found: C, 80.90; H, 8.27; N, 10.52%. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52%. NMR($CDCl_3$, δ) 2.60s(N-CH_3), 3.55bs(CH_2), 6.81s(arom).

N,N',N''-Trimethyl-2,11,20-triaza[3.3.3]paracyclophane (Me_3N_3[3^3]PC):

White needles from ethanol(60.7% yield), mp 119.5-120.5°C; MS(m/z)M^+ 399(calcd 399). Anal. Found: C, 81.00; H, 8.38, N, 10.43%. Calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.32; N, 10.52%. NMR($CDCl_3$, δ) 2.44s(N-CH_3), 3.28s(CH_2), 6.92s(arom).

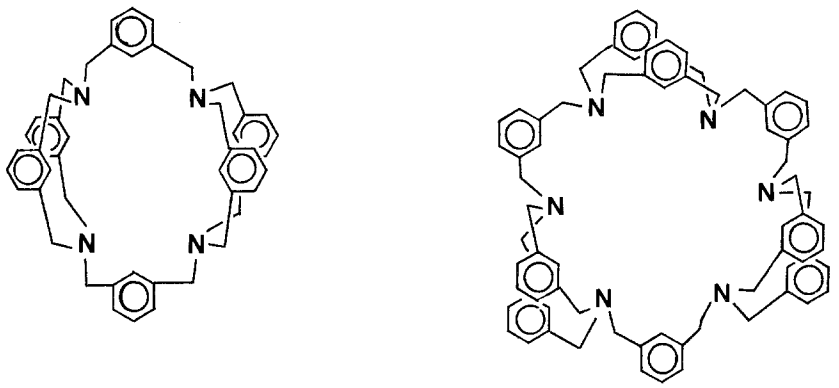
Addenda

The coupling reaction between 2,11-diaza[3.3]metacyclophane[22] and 1,3-bis(bromomethyl)benzene in the presence of NaH in dioxane or toluene gave the dimer and the trimer in Fig. 1.

The dimer, colorless powder (31.7% yield), mp 293.7-294.7°C(corr). MS(m/z)M^+ 680(calcd 680). Anal. Found: C, 84.47; H, 7.13; N, 8.14%. Calcd for $C_{48}H_{48}N_4$: C, 84.67; H, 7.10; N, 8.23%. Recrystallization of

the dimer from n-hexane-benzene mixture afforded colorless prisms of 1:1 adduct containing only benzene molecules selectively. Anal. Found: C, 85.31; H, 7.13; N, 7.52%. Calcd for $C_{48}H_{48}N_4+C_6H_6$: C, 85.45; H, 7.17; N, 7.38%.

The trimer, colorless needles from benzene (9.0%), mp 287.5-289.1°C (corr). MS(m/z)M^+ 1020(calcd 1020). Anal. Found: C, 84.57; H, 7.06; N, 8.26%. Calcd for $C_{72}H_{72}N_6$: C, 84.67; H, 7.10; N, 8.23%.



Dimer **Trimer**

Fig. 1

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References and Notes

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4) Unpublished result.
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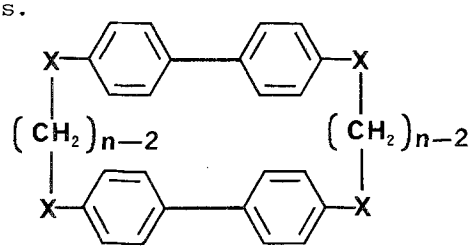
6) Unpublished results. In order to confirm the role of hetero atoms in the formation of inclusion compounds, formerly we have examined the Stetter-type compounds[7] (1,n,n+13,n+18-tetrahetera[n.0.n.0]-paracyclophanes, X=NH(Stetter compounds), $NCOCH_3$, NC_2H_5, O, S, CH_2) in Fig. 2 whether or not small organic molecules are included in the cavity of the molecules. At that time, the Stetter adducts had been considered as intramolecular inclusion compounds.[8,9]

The results thus obtained are summerized in Table 1.

Table 1.

with benzene	NH[10]	$NCOCH_3$[4]	NC_2H_5[4]	O[11]	S[4]	CH_2[12]
n=4	-[a]	-	-	-	x	-
5	x[b]	x	-	x	-	-
6	2:1[c]	x	1:1	1:1	x	x
7	x	x	-	x	-	-
with dioxane						
n=4	-	-	-	-	x	-
5	x	x	-	-	-	-
6	1:1	x	1:1	-	x	-
7	x	x	-	-	-	-

a) not examined. b) adduct was not isolated in crystalline state. c) isolated in crystalline state. cyclophane:solvent by elemental analyses.



X = NH, $NCOCH_3$, NC_2H_5, O, S, CH_2

Fig.2

7) H. Stetter and E.-E. Roos, Chem. Ber., **88**, 1390 (1955).
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10) n=4,5,6. Stetter and Roos[7]; n=7. synthesized by us.
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2546 (1971). N,N'-dimethyl-2,18-diaza[3.1.3.1]paracyclophane, N,N'-dimethyl-2,19-diaza[3.2.3.2]paracyclophane, and N,N',N'',N'''-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane.

14) Azacyclophanes are abbreviated as follows; 2,11-diaza[3.3]-paracyclophane as diaza[3^2]paracyclophane or $H_2N_2[3^2]$PC. Similar abbreviations are used throughout this paper.

15) In case of [3.3.3.3]paracyclophane itself as a parent compound, we could not isolate any adducts. To be published.

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17) a) I. Tabushi and K. Yamamura, Top. Curr. Chem., **113**, 145. ed. by F. Vögtle, Springer-Verlag, Berlin Heidelberg, 1983.
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18) Recently, Newkome et al. obtained N,N'-ditosyl-2,17-diaza[3.3]-(2,9)bipyridylophane by the coupling reaction p-toluenesulfonamide and 2,9-bis(bromomethyl)bipyridyl. G. R. Newkome, S. Pappalardo, V. K. Gupta, and F. R. Fronczek, J. Org. Chem., **48**, 4848 (1983).

19) Stepwise synthesis; Several diaza[3^2]- or triaza[3^3]cyclophanes were synthesized by the coupling reaction between N,N'-di(aryl-sulfonylaminomethyl) compound dialkali salts and bis(halomethyl) compounds so far.
a) N,N'-ditosyl-2,11-diaza[3.3]metacyclophane, F. Vögtle and P. Neumann, Tetrahedron Lett., 115 (1970); b) N,N',N''-tritosyl-2,11,20-triaza[3.3.3](1,3,5)cyclophane, F. Vögtle and P. Neumann, J. Chem. Soc., Chem. Commun., 1464 (1970); c) N,N'-ditosyl-2,11-diaza[3.3]paracyclo(9,10)anthracenophane and N,N'-ditosyl-2,11-diaza[3.3]anthracenophane, M. Usui, T. Nishiwaki, K. Anda, and M. Hida, Chem. Lett., 1516(1984).

20) The coupling reactions could also be carried out under following conditions(Na/C_2H_5OH, NaH/dioxane, K_2CO_3/DMF).

21) The removal of tosyl groups could also be carried out under following conditions ($Na/$isoamyl alcohol, H_2SO_4, CF_3SO_3H, HBr/CH_3COOH, 5% Na-Hg/dioxane-CH_3OH, $LiAlH_4$).

22) a) syn-$Ts_2N_2[3^2]$MC: lit.[19a]; one-step synthesis, NaH/dioxane (14-23%), K_2CO_3/DMF(6.2%); stepwise synthesis, Na/n-BuOH(44%).
b) syn-$H_2N_2[3^2]$MC, colorless needles from n-hexane, mp 117.5-118.5°C. MS(m/z)M^+ 240(calcd 240). Na/isoamyl alcohol(66.5-94%); 5% Na-Hg/dioxane(62.3%). Anal. Found: C, 80.54; H, 7.69; N, 11.64%. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76%.
c) syn-$Me_2N_2[3^2]$MC, colorless prisms from n-hexane, mp 98.5-99.5°C. HCOOH/HCHO(53%). Anal. Found: C, 81.09; H, 8.33; N, 10.50%. Calcd for $C_{18}H_{22}N_2$: C, 81.15; H, 8.32; N, 10.51%.