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Synthesis of a New Pyridinophane Macrocycle with Carbamate Functionality via Novel CO_2 Insertion Reaction

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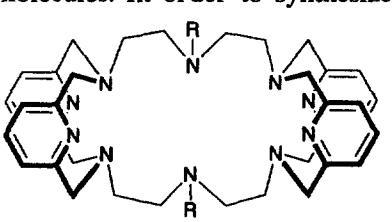
Abstract

The coupling reaction of 2,11-diaza[3.3](2,6)pyridinophane **3** and N-tosyl-diethanolamine ditosylate **4** in the presence of M_2CO_3 (M = Cs^+, K^+) in DMF afforded a novel macrocycle **2** with a carbamate moiety, whose structure was confirmed by an X-ray structural analysis.

Recent advances in host-guest chemistry demand more and more sophisticated artificial host molecules. In order to synthesize such molecules, synthetic methods for preparing the host molecule or their intermediates are of primary importance Previously, we reported the synthesis and inclusion properties of the pyridinophane-linked macrocycles where the lone pairs of the nitrogen atoms are directed toward the center of the cavity.[1] In our study along this line, we designed the synthesis of a new macrocycle **1a** with ten lone pairs of nitrogen atoms in its framework. The conventional coupling reaction[2] between 2,11-diaza[3.3](2,6)pyridinophane **3**[3] and the tosylate **4** in the presence of Cs_2CO_3 in CH_3CN failed to give the desired **1b** but resulted in decomposition of the tosylate **4**. Replacement of the solvent by DMF under similar conditions afforded an unexpected product **2** (33 %), in which CO_2 was inserted between the nitrogen atom of the amine and the carbon atom bearing the O-tosyl group (Scheme 1). Replacement of Cs_2CO_3 by K_2CO_3 similarly afforded the same product **2** (29 %), and 2,11-diaza[3.3]metacyclophane underwent a similar reaction to give a



1a; R = CH_3
1b; R = Ts

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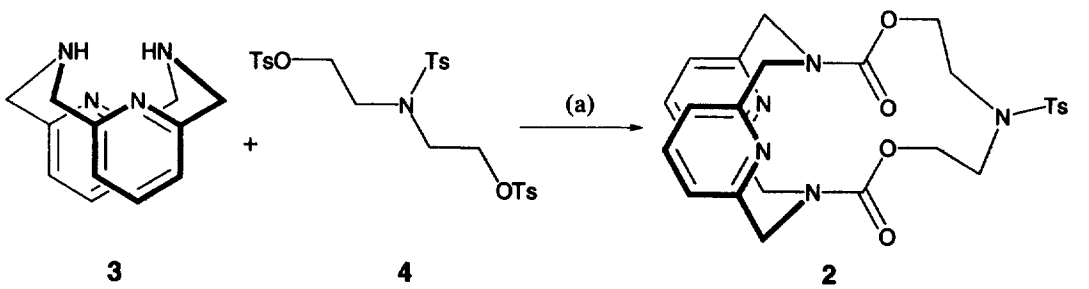

Scheme 1. Synthesis of **2**. (a) Cs_2CO_3, DMF, 4 days, under N_2, 60 °C

benzene analog of **2** (13 %).

The detailed experimental procedure is as follows: To a stirred suspension of Cs_2CO_3 (16.5 g, 50.6 mmol) in DMF (900 ml) at 60 °C were dropwise simultaneously added a DMF (750 ml) solution of **3** (1.70 g, 7.07 mmol) and a DMF (750 ml) solution of **4** (4.08 g, 7.07 mmol) over a period of 6 h under a nitrogen atmosphere. After additional stirring at 60 °C for 4 days, the solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The combined extracts were washed with water, dried with $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from EtOH to give **2** (1.29 g, 33%) as a white solid.[4] The crystals suitable for the X-ray structural analysis were obtained by the recrystallization from CH_2Cl_2/MeOH.[5]

The ORTEP drawing of **2** (Figure 1a) clearly shows that it contains two CO_2 moieties in

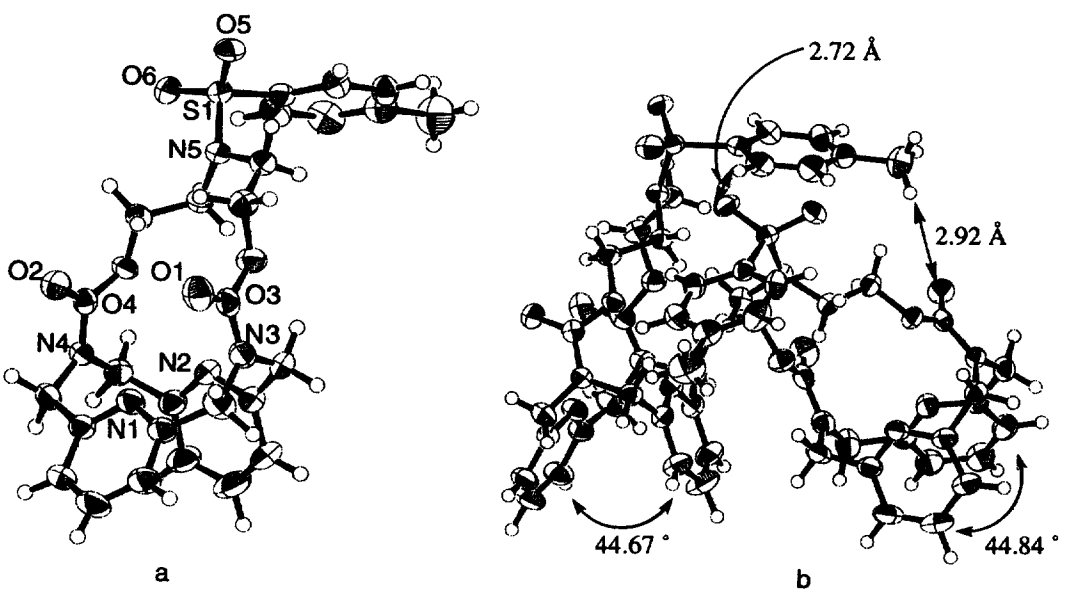

Figure 1. The result of X-ray crystal structural analysis (a) ORTEP drawing of **2**, (b) dimer structure of **2**

the carbamate functionality. The macrocycle **2** has a unique conformation in which two carbonyl groups are located in the same direction. MM3 calculations showed that this conformation was more stable than the other isomer with an anti-parallel arrangement of the carbonyl groups.[8] The dihedral angles between the two pyridine rings in **2** (44.7 and 44.8 °) are larger than those of the [3.3](2,6)pyridinophane (34 °)[9] and *N,N*-dimethyl-2,11-diaza[3.3]-(2,6)pyridinophane (17 °).[10] Interestingly, two molecules form a unique dimeric structure via weak intermolecular hydrogen bonds between one of the oxygen atoms of the sulfonyl group and a benzene proton of the other molecule (2.72 Å), as well as a carbonyl oxygen atom and a methyl proton (2.92 Å) (Figure 1b). This dimer formation was also observed in the FAB mass spectrum [m/z 552.3 (M^++1, 100%), 1103.5 ($2M^+$+1, 1%)] in *m*-nitrobenzylalcohol.

The CO_2 insertion reaction may be explained by the initial formation of a carbamic acid salt by the reaction of the secondary amine **2** and Cs_2CO_3. The resultant Cs cation is effectively stabilized by the solvation of DMF molecules, and the highly activated carbamate anion reacts with tosylate **3** to give **4**. A prototype of this reaction was first reported by Y. Hori *et al.* who found that carbamate salts are formed by the absorption of CO_2 using DBU and secondary amines.[11] The carbamate reacts with an alkylating agent to give the dialkyl carbamate in good yield. Recently, Rossi *et al.* reported a synthetic method for carbamate esters from amines and tetraethylammonium hydrogen carbonate in CH_3CN.[12] Our method is especially useful for the synthesis of macrocycles with a carbamate functionality, and wide range of application is expected. Further modification of the reaction conditions and applications of this reaction, as well as a study of the inclusion behavior of **2** and its derivatives as proton cryptates are in progress.

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4. Selected spectroscopic data and elemental analysis for **2**: mp 278-280 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H, -CH_3), 3.31, 3.53, 3.87, 4.67 (m, 8H, -OCH_2CH_2N-), 3.76, 5.52 (dd, J = 15 Hz, 4H, -CH_2-Py), 3.86, 5.24 (dd, J = 15 Hz, 4H, -N-CH_2-Py), 6.72 and 6.74 (d, J = 8 Hz, 4H, Py), 7.23 and 7.27 (t, J = 8 Hz, 2H, Py),

7.26 and 7.65 (dd, J = 8 Hz, 4H, Ts); ^{13}C NMR ($CDCl_3$) δ 21.5 (-CH_3), 47.7 and 63.9 (-OCH_2CH_2N-), 53.2 and 54.1 (-N-CH_2-Py), 120.0 and 120.6 (Py), 126.9, 129.8, 137.6, and 143.3 (Ts), 135.6, 135.8, (Py), 156.3 and 156.4 (Py), 156.6 (CO). FAB Mass m/z 552.3 (M^++1), 1103.5 ($2M^+$+1). IR (KBr) 1711 cm^{-1} (C=O). Anal. Calcd for $C_{27}H_{29}N_5O_6S$: C, 58.79; H, 5.30; N, 12.70%. Found: C, 58.51; H, 5.24; N, 12.57 %.

5. X-ray crystal data for **2**($C_{27}H_{29}N_5O_6S$) : T = 288 K, Mo-Kα (Rigaku RAXIS-IV imaging plate area detector, λ = 0.71070 Å), crystal dimensions 0.20 x 0.40 x 0.30 mm^3 (colorless prism), a = 12.493(8), b = 17.699(6), c = 12.344(3) Å, α = 89.97(3) °, β = 107.03(3) °, γ = 89.91(5) °, triclinic, space group P-1(no.2), Z = 4, μ_{Mo} = 1.77 cm^{-1}, Mr = 551.62, V = 2609.91(9) $Å^3$, anode power 50 kV x 150 mA, crystal-to-detector 110mm, 0.100mm pixel mode. ρ_{calk} = 1.404 g/cm^3, $2\theta_{max}$ = 55.1 °, F(000) = 1160. Indexing was performed from 3 oscillations which were exposed for 4 minutes. A total of 31, 5.00 ° oscillation images were collected, each being exposed for 10 minutes. Of the 8557 reflections collected, 6784 were unique. 8000 independent reflections with I > 3σ(I). The structure was solved by the direct method and refined on *SHELX 86*[6]. Data were corrected for Lorentz-polarizations. The data / parameter ratio was 7.25. R = 0.039, R_w = 0.041, GOF = 0.69, max / min residual density +0.18 / -0.27e$Å^{-3}$. Crystallographic data (excluding structure factor) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No.CCDC-103058. Copies of the data can be obtained free of charge upon request to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-33603; e-mail: deposit@ccdc.cam.ac.uk).
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