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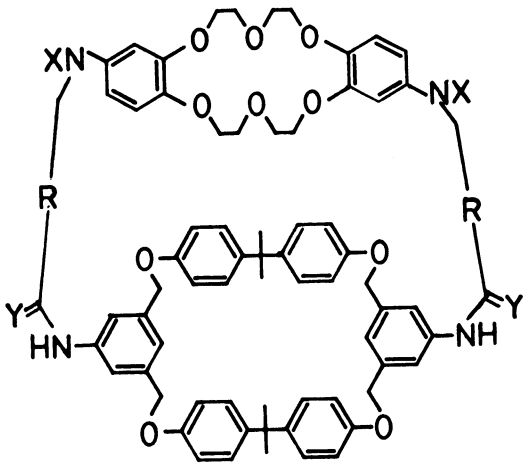
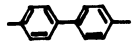
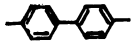
SYNTHESIS AND AMMONIUM CRYPTATE OF DISSYMMETRIC CYLINDRICAL MACROTRICYCLE CONTAINING CROWN ETHER AND CYCLOPHANE UNITS[1)]

Kazuhiko SAIGO,* Ru-Jang LIN, Masataka KUBO, Akira YOUDA, and Masaki HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

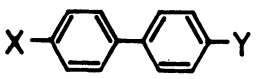
A new type of dissymmetric macrotricyclic cryptand, which contains dibenzo-18-crown-6 and cyclophane sub-units as substrate selective binding sites, was synthesized. The cryptand formed inclusion complex with 4-phenylbutylammonium picrate. Complex formation was ascertained by ^{1}H NMR spectroscopy in a $CDCl_3/CD_3OD$ (4/1) solution.

Macropolycyclic cryptands, capable of substrate inclusion, have been designed and their molecular recognition has been demonstrated towards various kinds of spherical, tetrahedral, and linear substrates (inorganic, organic, and biological cations or anions).[2)] But, dissymmetric cryptands which consist of crown ether, cyclophane, and bridge units have not been well characterized except for speleands reported by Lehn and his coworkers.[3)] On the other hand, it is well-known that crown ether and cyclophane have abilities to form inclusion complexes with primary alkylammonium salts[4)] and aromatic compounds,[5)] respectively. This suggests that dissymmetric cylindrical macrotricycle would provide the cavity of an appropriate size to accommodate organic guest molecules and would form highly recognized inclusion complexes with guests having ammonium and aromatic groups. According to this idea Hamilton and his coworker have recently reported the synthesis and the complexation of a dissymmetric macrotricycle.[6)] Independently we also synthesized and studied the complexation ability of a new type of rigid dissymmetric macrotricycle (**1a**)[1)] which consists of benzo-18-crown-6 and a cyclophane.[7)]



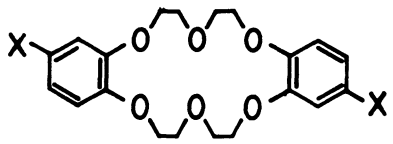
1 a, R =  ; X = H; Y = H_2
b, R =  ; X = Ts; Y = O

The macrotricycle **1a** was synthesized by stepwise condensation of sub-units prepared individually. The preparation of the sub-units and the condensation steps are described as follows: (i) Synthesis of bridge sub-unit: To enable the cavity to be held firmly, the rigid 4,4'-bisbenzyl sub-unit was chosen. 4-Methylbiphenyl (**2a**) was converted into bridge sub-unit (**2e**)[8] by Friedel-Crafts acetylation,[9] Baeyer-Villiger oxidation, esterification, and bromination with N-bromosuccinimide, successively (total yield, 46%). (ii) Synthesis of crown ether sub-unit: As the crown sub-unit, dibenzo-18-crown-6 was used. To introduce a function which is reactive with the bridge sub-unit (**2e**), a series of reactions, i.e., nitration,[10] reduction with hydrazine-Pd/C, and N-tosylation, were carried out successively to give crown ether sub-unit (**3d**)[11] in 30% total yield. (iii) Condensation of the crown ether and the bridge sub-units: The reaction of **3d** with **2e** in DMF in the presence of K_2CO_3 gave **3e** in 56% yield (mp 218-219 °C). The crude acid **3f**, obtained as a white powder by hydrolysis of **3e** (4 M NaOH/in EtOH), was converted to the corresponding diacid chloride (**3g**)[12] by treating with $SOCl_2$ in benzene (two steps, quantitative yield). (iv) Synthesis of cyclophane sub-unit: Cyclophane (**4a**), obtained by the method reported previously,[7] was quantitatively reduced with hydrazine-Pd/C to diamine (**4b**).[13] (v) Synthesis of macrotricycle: Condensation of **4b** with **3g** under high dilution conditions afforded macrotricyclic tetramide (**1b**) in 13% yield after purification by column chromotography over alumina. Subsequently, reduction of **1b** with $LiAlH_4$ in THF gave macrotricycle **1a**.[14]



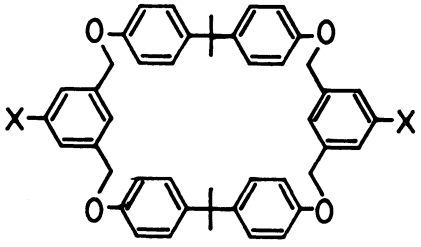
2

a, X = CH_3; Y = H
b, X = CH_3; Y = $COCH_3$
c, X = CH_3; Y = COOH
d, X = CH_3; Y = COOEt
e, X = CH_2Br; Y = COOEt



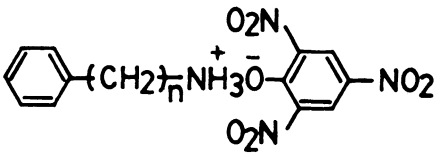
3

a, X = H
b, X = NO_2
c, X = NH_2
d, X = TsNH
e, X = $TsNCH_2$–C$_6$H$_4$–COOEt
f, X = $TsNCH_2$–C$_6$H$_4$–COOH
g, X = $TsNCH_2$–C$_6$H$_4$–COCl



4

a, X = NO_2
b, X = NH_2



5

The initial study was concerned with the complex formation with 4-phenylbutylammonium picrate (5, n = 4). Complex formation was ascertained by ^{1}H NMR spectroscopy in $CDCl_3/CD_3OD$ (4/1). Addition of 1.2 equimolar amount of **5** to a solution of **1a** in $CDCl_3/CD_3OD$ (4/1) gave **1a-5** complex. The methylene signals of **5** in **1a-5** complex shift upfield by 0.34 (α-), 0.27 (β-), 0.38 (γ-), and 0.28 (δ-) with respect to free **5** as shown in Fig. 1. It is noteworthy that β- and γ-methylene signals shift upfield and split into two multiplets. This may be attributed to a shielding effect of the biphenyl groups in the bridge sub-units. Moreover, the phenyl proton signals of **5** also shift upfield by 0.19 (o-), 0.07 (m-), and 0.04 ppm (p-). Thus, the changes of the chemical shifts of the guest protons would be taken as indication of the inclusion of the substrate molecule **5** in the central cavity of the macrotricycle **1a**, as observed for the diammonium cryptate of cylindrical coreceptors.[2,15] The changes of the chemical shifts of the host protons also support the proposed geometry of the complex. The signals of biphenyl and methylene groups in the bridge sub-units shift upfield by 0.03-0.05 and 0.04 ppm, respectively. But, the proton signals of the cyclophane sub-unit are scarcely influenced upon complexation. This might be due to the rather long distance between the cyclophane sub-unit and the guest molecule **5**. The changes of chemical shifts of the protons in **1a** and **5** are smaller than those in the hitherto known complexes of symmetrical cylindrical macropolycycles with diammonium salt.[2,15] We considered that the smaller changes of chemical shifts would result from the large internal cavity to interact weakly each other.

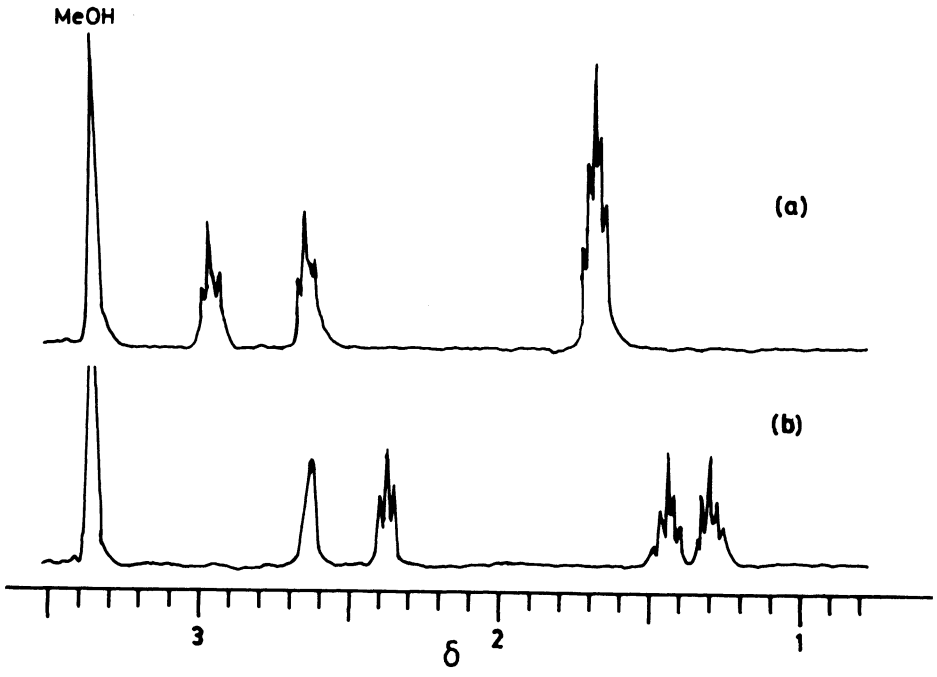


Fig. 1. Part of the 400 MHz ^{1}H NMR spectrum of 4-phenylbutylammonium picrate (ca. 1 w/v%) in $CDCl_3/CD_3OD$ (4/1): (a) before complexation; (b) after complexation.

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8) Mp 85-86 °C; IR (KBr) 1700, 1600, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.42 (3H, t), 4.45 (4H, q), 7.62 (6H, m), 8.14 (2H, d).
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11) Mp 232 °C; IR (KBr) 3450, 1520, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.30 (6H, s), 3.85 (16H, m), 6.64 (6H, m), 7.42 (8H, dd), 9.83 (2H, s).
12) Mp 217-218 °C (decomp); IR (KBr) 1600, 1520, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.42 (6H, s), 3.88 (16H, m), 4.72 (4H, s), 6.60 (6H, m), 7.30-8.10 (24H, m).
13) Mp 262-263 °C (decomp); IR (KBr) 3450, 1610, 1510 cm^{-1}; ^1H NMR (DMSO-d_6, 90 MHz) δ 1.53 (12H, s), 3.32 (4H, br. s), 4.86 (8H, s), 6.50-7.16 (22H, m).
14) Mp 263-265 °C (decomp); IR (KBr) 3450, 1510 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$ = 4/1, 400 MHz) δ 1.56 (12H, s), 3.89 (8H, m), 4.04 (8H, m), 4.34 (8H,d), 4.95 (8H, s), 6.13 (2H, dd), 6.24 (2H, d), 6.58 (4H, s), 6.68 (2H, m), 6.73 (8H, d), 7.01 (8H, d), 7.36-7.53 (16H, m).
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