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A NEW MOLECULAR RECEPTOR BASED ON THIOPHENE CONGENER OF TRÖGER'S BASE: SELECTIVE BINDING WITH ALIPHATIC AND AROMATIC DICARBOXYLIC ACIDS

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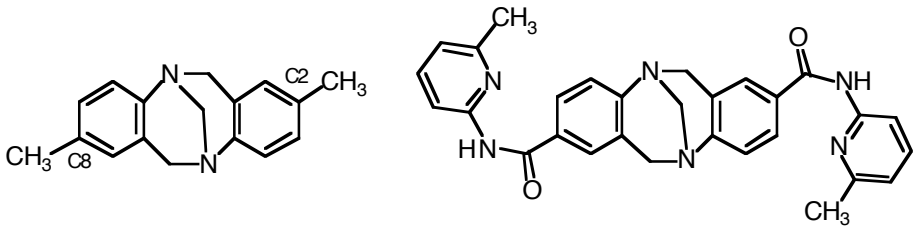
Abstract – A new molecular receptor bearing pyridylamino groups was prepared with a thiophene congener of Tröger's base as a spacer, and was found to exhibit selective binding toward aliphatic and aromatic dicarboxylic acids, primarily depending on the length of the carbon chain.

INTRODUCTION

The chemistry of synthetic receptors for a variety of guest molecules has received much attention.[1-3] Recently, Tröger's base (**1**) and its analogues were utilized as a basic skeleton to construct molecular receptors, due to their rigid structures and concave space with *ca*. 90° dihedral angle between the two aromatic rings.[4] For example, Goswami *et al*. recently reported the synthesis of Tröger's base analogue (**2**) bearing pyridylamide groups, which exhibited selective recognition of dicarboxylic acids.[5] On the other hand, the syntheses of Tröger's base analogues generally require the aniline derivatives with electron-donating groups as starting substrates, and introduction of a variety of functional groups into the Tröger's base skeleton, including electron-withdrawing ones, has been restricted.[4] We recently reported the synthesis of 5*H*,10*H*-4,9-methanodithieno[3,2-*b*:3′,2′-*f*][1,5]diazocine (**3**), the first thiophene congener of the Tröger's base, which opened up a facile and selective introduction of a variety of functional groups by intermediacy of its dianion.[6] Independently, Wärmark *et al*. also described the synthesis of substituted Tröger's bases by a bromine–lithium exchange reaction[7] as well as Sonogashira coupling.[8] We wish to describe here the synthesis of a new molecular receptor with a thiophene congener of Tröger's base bearing pyridylamino groups, which exhibits the selective recognition of

‡ University Postdoctoral Fellow (1986–1988, the Ohio State University) with Prof. Leo A. Paquette, to whom this paper is dedicated on his 70th birthday.



1 **2**

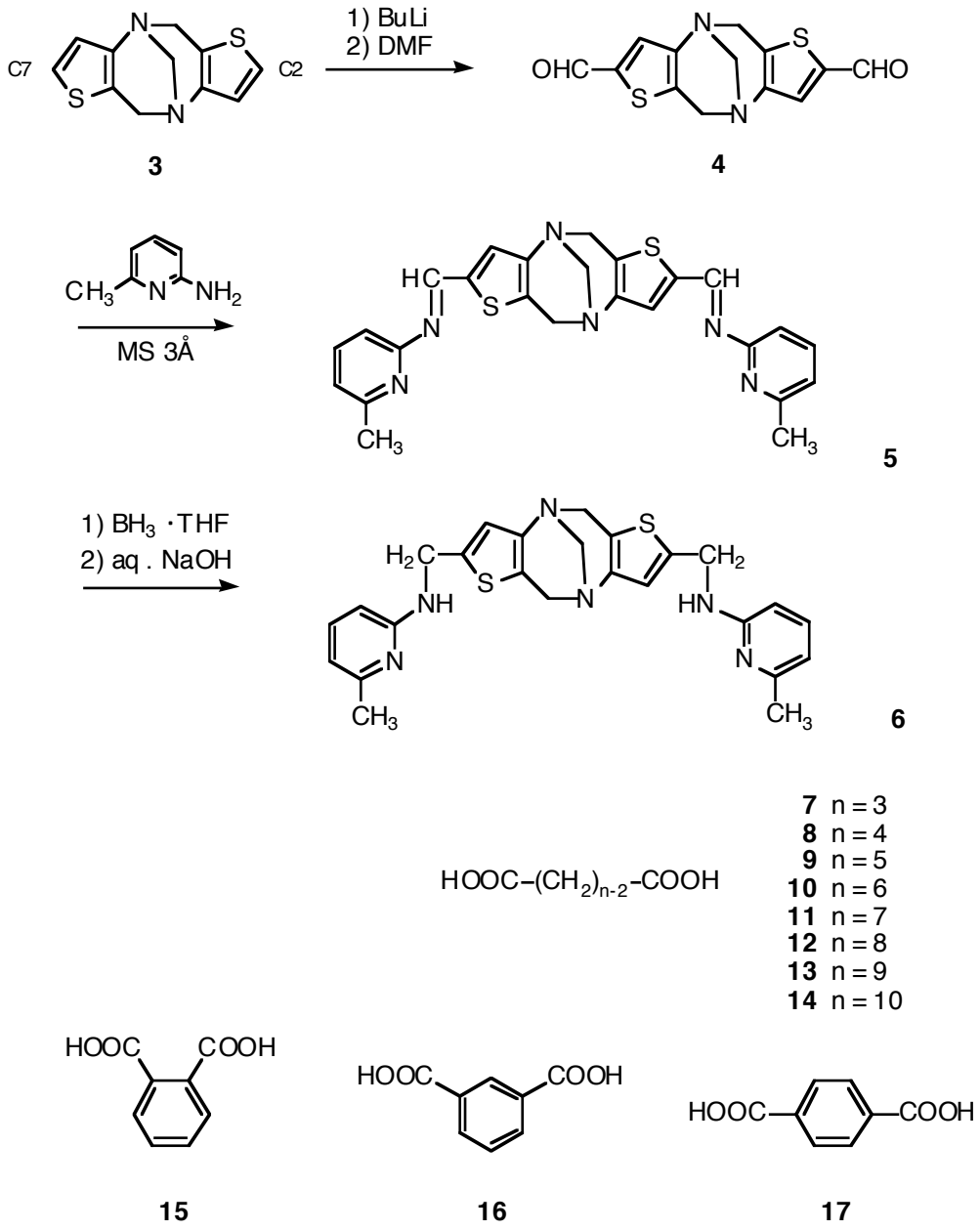
Figure 1. Tröger's base and an example of molecular receptors.

and aromatic dicarboxylic acids.

RESULTS AND DISCUSSION

The synthesis of a new molecular receptor, the bis(6-methylpyridin-2-yl)aminomethyl derivative (**6**), was performed starting from the dicarbaldehyde (**4**), which was prepared by the reaction of **3** with butyllithium and subsequent treatment with DMF.[5] The dicarbaldehyde (**4**) reacted with 2-amino-6-methylpyridine in the presence of molecular sieves 3Å to give the imine (**5**), while the reaction was incomplete in the absence of the molecular sieves. Attempts to purify the imine (**5**) by recrystallization resulted in partial decomposition, thus the imine (**5**) was used for the next step without further purification. Treatment of **5** with a boran-THF complex underwent the reduction of the C–N double bonds, and **6** was obtained in 39% overall yield from **4**.

Recognition of the aliphatic and aromatic dicarboxylic acids (**7**–**17**) with the receptor (**6**) was investigated by the NMR spectral titration. When a $CDCl_3$ solution of a dicarboxylic acid was successively added into the solution of **6** in $CDCl_3$ containing 0.5% DMSO-d_6, the chemical shift changes induced by the complexation were clearly observed for the 3´-H of the pyridine ring. The resulting titration curves (□□ vs. C_{guest}/C_{host}) were analyzed using Foster–Fyfe plot[9] (□□/C_{guest} vs. □□) to determine stoichiometry and association constants. All the dicarboxylic acids except for malonic acid (**7**) and phthalic acid (**15**) were suggested to form the complexes with a 1:1 receptor:dicarboxylic acid stoichiometry. On the contrary, the titration curves for malonic acid (**7**) and phthalic acid (**15**) suggested a 1:2 receptor:dicarboxylic acid stoichiometry. All the association constants obtained were listed in Table 1, along with the terminal H–H atomic distances of the dicarboxylic acids calculated by the PM3-MNDO method.[10] Calculations were performed on the dicarboxylic acids with all-*anti* configuration. Relationship between the association constants and the calculated terminal H–H atomic distances was shown in Figure 1. The size and topological nature of the dicarboxylic acids clearly effects on the selectivity of the recognition with **6**. As observed for the complexation with aliphatic dicarboxylic acids,



Scheme 1

the association constant was lowest for succinic acid (**8**) and successively increased toward adipic acid (**10**). Association constant values again decrease for dicarboxylic acids with longer chains. The results described above suggested that the cavity of Tröger's base analogue (**6**) selectively fitted with the dicarboxylic acids, the length of which are *ca.* 9–10 Å. However, sebacic acid (**14**) again exhibited a large value of K_a, and this outcome would be explained in terms of its conformational flexibility to form an appropriate binding. For the aromatic dicarboxylic acids, the association constant of terephthalic acid (**17**) was larger than that of isophthalic acid (**16**), while phthalic acid (**15**) did not form 1:1 complex with **6**. Compared to the aliphatic dicarboxylic acids with a similar molecular size, the aromatic dicarboxylic

acids seem to exhibit stronger complexation, probably due to a reflection of their rigid structures and less conformational freedom.

Previously, the molecular receptor (**2**) was reported to show the largest association constant for suberic acid (**12**),[5] which is two carbons longer than the results observed for **6**. The reason would be ascribed to smaller concave space of **6** compared to **2**. The X-Ray crystallographic analysis[11] of **3** revealed that the dihedral (hinge) angle between two thiophene ring (100.7°) is slightly larger than those of the Tröger's base (**1**) (92.8° and 97.4°).[12] However, the atomic distance between C2 and C7 of **3** is 6.690(3) Å,[12] the value of which is rather smaller than the corresponding atomic distance between C2 and C8 (7.29 Å by PM3 calculations) of the Tröger's base (**1**). The difference of these would attribute to the selective binding for smaller molecules with **6**.

Table 1. Association Constants of Receptor (**6**) with Dicarboxylic Acids

dicarboxylic acid	n	K_a (l/mol)[a]	K_a (l^2/mol^2)[b]	H–H distance (Å)[c]
malonic acid (**7**)	3	—	1.9×10^5	6.34
succinic acid (**8**)	4	4.4×10	—	7.58
glutaric acid (**9**)	5	2.5×10^2	—	8.83
adipic acid (**10**)	6	3.6×10^2	—	10.08
pimeric acid (**11**)	7	1.6×10^2	—	11.33
suberic acid (**12**)	8	2.1×10^2	—	12.59
azelaic acid (**13**)	9	1.3×10^2	—	13.84
sebacic acid (**14**)	10	3.9×10^2	—	15.10
phthalic acid (**15**)	—	—	7.0×10^4	6.68
isophthalic acid (**16**)	—	3.9×10^2	—	8.73
terephthalic acid (**17**)	—	6.6×10^2	—	9.15

[a] Association constant for a 1:1 complex of **6** and the dicarboxylic acid.
[b] Association constant for a 1:2 complex of **6** and the dicarboxylic acid.
[c] Calculated by PM3-MNDO method for all-*anti* configuration.

In conclusion, we were able to construct a novel Tröger's base congener with pyridinylamino units as a binding site, which selectively bound with dicarboxylic acids primarily depending on their chain lengths, while the freedom of conformation also seemed to effect the association constants.

EXPERIMENTAL

General Remarks: All mps were determined with a Yanagimoto hot-stage apparatus. IR spectra were obtained with a JEOL Diamond-20 spectrophotometer. NMR spectra were recorded with a JEOL JNM-LA400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer using TMS as internal standard. Assignments of the ^{1}H and ^{13}C signals are based on DEPT, H-H COSY, and C-H COSY measurements. MS spectra were measured with a Shimadzu GCMS-QP1000EX spectrometer operating in the electron impact mode (70

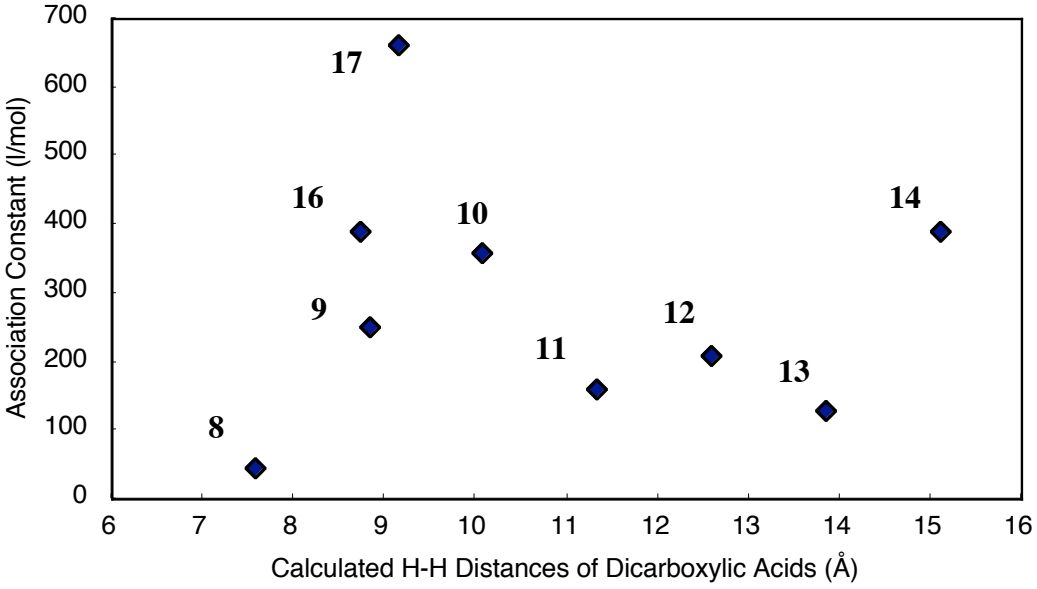


Figure 2. Relationship between Association Constants K_a (*l*/mol) and Terminal H-H Atomic Distances (Å) of Dicarboxylic Acids Calculated by PM3-MNDO method

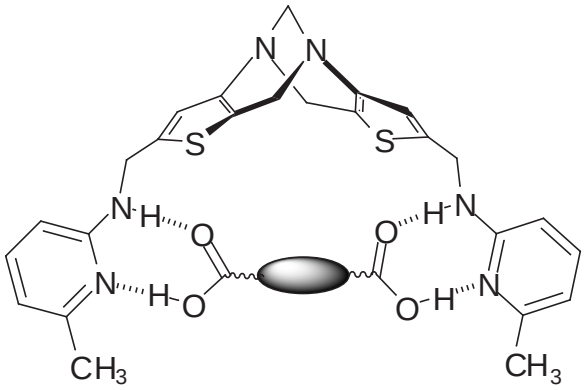


Figure 3. A Plausible Model for Complexation of the Receptor (**6**) and Dicarboxylic Acids

eV). Elemental analyses were performed with a Perkin-Elmer Model 240 apparatus. Solvents were dried and purified by standards methods. Yields are based on the isolated products with sufficient purity.

2,7-Bis[(6-methylpyridn-2-yl)aminomethyl]-5*H*,10*H*-4,9-methanodithieno[3,2-*b*;3´,2´-*f*][1,5]diazocine (6). A solution of the dicarbaldehyde[6] (**4**) (58 mg, 0.2 mmol) in toluene (15 mL) and 2-amino-6-

methylpyridine (108 mg, 2 mmol) was refluxed in the presence of molecular sieves 3 Å (4 g) for 2 h. Insoluble materials were removed by filtration, and the filtrate was concentrated. Hexane was added to the residue and the resulting solid was collected by suction to give the crude imine (**5**) (60 mg, *ca.* 64%) as a yellow solid: mp 223–224 °C; ^{1}H NMR ($CDCl_3$) =2.54 (6H, s, CH_3), 4.18 (2H, d, J = 17 Hz, 5-H_n and 10-H_n), 4.27 (2H, s, 11-H), 4.62 (2H, d, J = 17 Hz, 5-H_x and 10-H_x), 7.01 (2H, d, J = 8 Hz, 3´-H or 5´-H), 7.03 (2H, d, J = 8 Hz, 5´-H or 3´-H), 7.32 (2H, s, 3-H and 8-H), 7.59 (2H, t, J = 8 Hz, 4´-H), 9.17 (2H, s, CH=N); ^{13}C NMR ($CDCl_3$) =24.4 (CH_3), 54.2 (C-5 and C-10), 67.7 (C-11), 116.7, 121.4, 129.4, 129.7, 138.2, 139.7, 146.1, 154.5, 157.8, 159.8; IR (KBr) 3037, 2945, 2916, 2846, 1606, 1589, 1554, 1537, 1469, 1446, 1433, 1402, 1362, 1319, 1303, 1230, 1205, 1149, 1140, 1105 cm^{-1}; MS *m/z* (rel intensity) 470 (53, M^+), 378 (34, M – $CH_3C_5H_3N$), 93 (100, $CH_3C_5H_3N$).

The crude imine (**5**) (60 mg) was dissolved in THF (3 mL) and the solution was cooled with an ice-bath. To a solution was added BH_3·THF (0.9 M, 0.27 mL, 0.24 mmol) and the mixture was stirred at room temperature for 1.5 h. After removal of the solvent under vacuum, 10% aqueous NaOH solution (10 mL) was added to the residue and the mixture was refluxed for 1 h. The mixture was extracted with dichloromethane (20 mL x 3), and the combined organic phases were washed with brine prior to drying over Na_2SO_4. After removal of the solvent, methanol was added to the residue. The resulting solid was collected by suction to give **6** (37 mg, 0.078 mmol, 39% from **4**) as colorless rods: mp 185–186 °C (from methanol); ^{1}H NMR ($CDCl_3$) =2.38 (6H, s, CH_3), 3.98 (2H, d, J = 16 Hz, 5-H_n and 10-H_n), 4.16 (2H, s, 11-H), 4.44 (2H, d, J = 16 Hz, 5-H_x and 10-H_x), 4.54 (4H, m, -CH_2NH-), 4.83 (2H, br s, NH), 6.22 (2H, d, J = 8 Hz, 3´-H), 6.48 (2H, d, J = 8 Hz, 5´-H), 6.89 (2H, s, 3-H and 8-H), 7.32 (2H, t, J = 8 Hz, 4´-H); ^{13}C NMR ($CDCl_3$) =24.2 (CH_3), 41.8 (-CH_2NH-), 53.4 (C-5 and C-10), 67.9 (C-11), 103.7 (C-2´), 112.3 (C-5´), 121.3 (C-3 and C-8), 122.2, 138.0 (C-4´), 140.0, 144.6, 156.9, 157.6; IR (KBr) 3248 (NH), 3059, 2949, 2916, 2848, 1599, 1510, 1504, 1466, 1394, 1356, 1329, 1319, 1230, 1149, 1045 cm^{-1}; MS *m/z* (rel intensity) 474 (48, M^+), 366 (100, M – $CH_3C_5H_3N$ – NH_2), 93 (70, $CH_3C_5H_3N$). Anal. Calcd for $C_{25}H_{26}N_6S_2$: C, 63.26; H, 5.52; N, 17.71. Found: C, 63.39; H, 5.30; N, 17.47.

NMR Titration. A 2.5 x 10^{-3} M solution of **6** (0.5 mg, 0.001 mmol) in $CDCl_3$ (0.4 mL) was taken in an NMR tube. A 1.0 x 10^{-1} M solution of a dicarboxylic acid (0.01 mmol) in $CDCl_3$ (0.1 mL) containing DMSO-d_6 (2.0 x 10^{-3} mL) was prepared to provide a homogeneous solution. The temperature of the NMR probe was set at 298 K. An initial NMR spectrum was taken, and the initial chemical shift of the 3´-H protons was determined. A small amount of the solution of the dicarboxylic acid was added successively. The molar ratio of the dicarboxylic acid vs. **6** was determined by the integration of the NMR spectra. Such addition was continued until no further change in the chemical shift was observed.

The change in the chemical shift values (□□) was calculated by subtracting the chemical shift at each titration point from the chemical shift value of the pure host. Thus, a titration curve of □□ vs. C_{guest}/C_{host} was plotted, and Foster–Fyfe analysis[9] (□□/C_{guest} vs. □□) of the titration data gave the association constant (K_a) of a 1:1 complex.

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