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New Ditopic Receptors for Alkylammonium Ion Complexation

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Abstract. New receptor molecules have been synthesized in which α,α′-bis-(4-hydroxyphenyl)-1,4-diisopropylbenzene is linked to 1,10-diaza-18-crown-6, 1,10-diaza-21-crown-7 or 1,13-diaza-24-crown-8 units by ethylene or 1,4-butylene bridges. Binding abilities of the new receptors and the model compound *N,N*-didecyl-1,10-diaza-18-crown-6 toward alkali metal cations and alkylammonium ions were assessed by picrate extraction. Spectral evidence for inclusion of alkylammonium ions within the receptor cavity was obtained by ^{1}H NMR spectroscopy. From a ^{1}H NMR titration experiment conducted in $CDCl_3$–CD_3OD (9:1), a relatively strong inclusion complex ($K_a \sim 900\ M^{-1}$) of the receptor having a 1,10-diaza-18-crown-6 subunit and ethylene spacers with propylammonium picrate was observed.

Key words. Ditopic receptors, picrate extraction, NMR titration, inclusion complex.

1. Introduction

During the past three decades, a wide variety of macrocyclic receptor molecules which exhibit selectivity in binding of ionic [1] and molecular [2] species has been synthesized. Among numerous cyclic molecular receptors with more than one recognition site, ditopic receptors [3] derived in part from a cyclophane and in part from a crown ether deserve special attention due to their potential for enhanced binding specificity toward ions such as alkylammonium ions which have lipophilic 'tails' and polar 'heads'. Speleand **1** in which a cyclotriveratrylene moiety is capped with a triazacrown ether was reported by Lehn and coworkers to form both internal and external complexes with methylammonium ion [4]. Ditopic receptor **2**, which may be considered as a hybrid between a cyclophane and a crown ether, was noted by Hamilton and coworkers to bind various alkylammonium ions [5]. Saigo and coworkers prepared receptor **3**, a cylindrical macrotricyclic compound which has cyclophane and crown ether subunits, and observed selective complexation of ω-phenylalkylammonium ions [6]. Macrotricycles of cylindrical topology comprised of two diazacrown ethers connected via aromatic subunits and capable of complexing diammonium ion species have been described by Lehn [7] and Sutherland [8] and their coworkers.

We now report the synthesis of four bicyclic receptors **4a–d** which are based on the relatively unexplored bisphenol **5** as a hydrophobic subunit and assessment of their complexation behavior toward alkali metal and alkylammonium cations.

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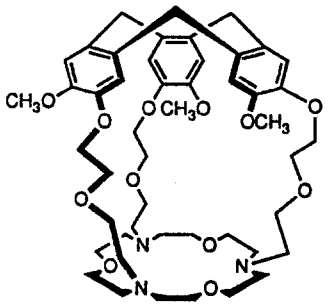

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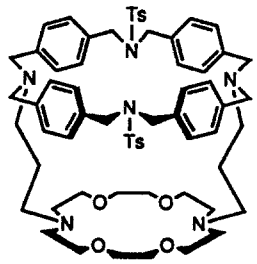

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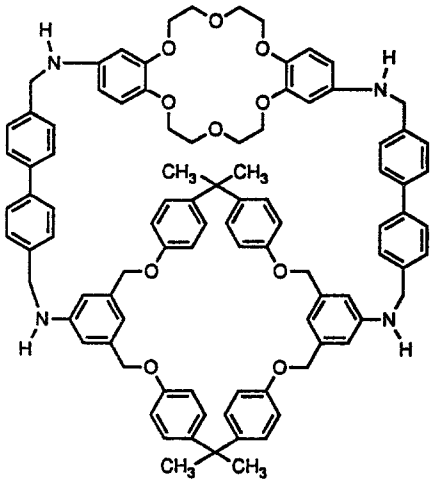

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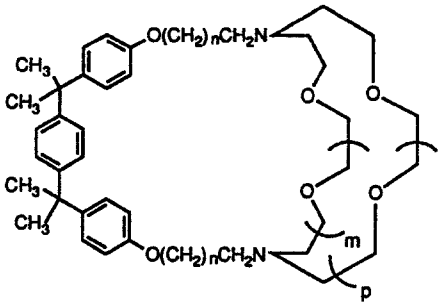
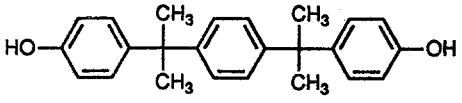


	n	m	p
4a	1	1	1
4b	1	1	2
4c	1	2	2
4d	3	1	1



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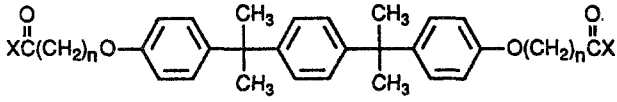
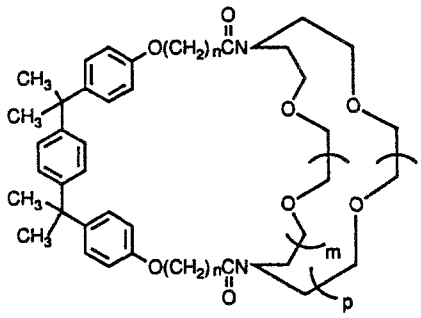
2. Experimental

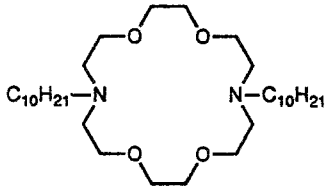
Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 267 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 300 MHz and Varian Gemini 200 MHz instruments and chemical shifts are reported in parts per million (δ) downfield from TMS. Combustion analysis was performed by Galbraith Laboratories.



	n	X
6a	1	OMe
6b	3	OEt
7a	1	OH
7b	3	OH
8a	1	Cl
8b	3	Cl



	n	m	p
9a	1	1	1
9b	1	1	2
9c	1	2	2
9d	3	1	1



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2.1. MATERIALS

Unless specified otherwise, reagent grade reactants and solvents were used as received from chemical suppliers. Acetone was stored over anhydrous K_2CO_3. Tetrahydrofuran was distilled before use from sodium benzophenone ketyl. Benzene and toluene were dried over molecular sieves (4-A). Bisphenol **5** [9], 1,13-diaza-24-

crown-8 [10], *N,N'*-didecyl-1,10-diaza-18-crown-6 (**10**) [11] and the alkali metal picrates [12] were prepared according to literature procedures. The ^1H and ^{13}C NMR spectra of bisphenol **5** are not given in Ref. [9]. For **5**: ^1H NMR [$CDCl_3 + CD_3S(O)CD_3$ (one drop)] δ 1.50 (*s*, 12H), 6.63 (*d*, 4H), 6.94 (*d*, 4H), 6.94 (*s*, 4H), 8.36 (*br s*, 2H); ^{13}C NMR [$CDCl_3 + CD_3S(O)CD_3$ (one drop)] δ 30.87 (CH_3), 41.63 (C), 114.77, 126.04, 127.62, 141.55, 147.85, 154.61 (Ar).

2.2. SYNTHESIS OF DITOPIC RECEPTORS AND PRECURSORS

*Preparation of Diesters **6a** and **6b***

A mixture of anhydrous K_2CO_3 (33.50 g, 0.24 mol), the appropriate bromoester (0.24 mol) and bisphenol **5** (28.00 g, 0.081 mol) in dry acetone (150 mL) was heated under argon for 48 h. The solvent was evaporated *in vacuo*, CH_2Cl_2 (250 mL) was added to the residue and the inorganic salts were filtered. The solvent was evaporated *in vacuo* to afford the diester which was recrystallized from MeOH.

*Diester **6a***

Yield 88%; white crystals with mp 132–134°C; IR (nujol) 1762, 1742 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (*s*, 12H), 3.71 (*s*, 6H), 4.55 (*s*, 4H), 6.95 (*ABq*, 8H), 7.08 (*s*, 4H). *Anal. Calcd.* for $C_{30}H_{34}O_6$: C, 73.45; H, 7.41. *Found*: C, 73.28; H, 7.50.

*Diester **6d***

Yield 83%; white solid with mp 64–65°C; IR (deposit on NaCl plate from THF solution) 1737 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (*t*, 6H), 1.62 (*s*, 12H), 2.08 (pentet, 4H), 2.49 (*t*, 4H), 3.96 (*t*, 4H), 4.13 (*q*, 4H), 6.97 (*ABq*, 8H), 7.09 (*s*, 4H). *Anal. Calcd.* for $C_{36}H_{46}O_6$: C, 75.23; H, 8.07. *Found*: C, 75.40; H, 8.03.

*Preparation of Diacids **7a** and **7b***

Concentrated HCl (50 mL) and water (10 mL) were added to a solution of the diester (4.08 mmol) in dioxane (100 mL). The mixture was stirred at room temperature for 48 h. The precipitate was filtered, washed repeatedly with water and air dried to give the pure diacid.

*Diacid **7a***

Yield 95%; white solid with mp 217–219°C; IR (nujol) 3100–2500 (COOH), 1743, 1712 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.58 (*s*, 12H), 4.60 (*s*, 4H), 6.97 (*ABq*, 8H), 7.10 (*s*, 4H). *Anal. Calcd.* for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. *Found*: C, 72.65; H, 6.62.

*Diacid **7b***

Yield 91%; white solid with mp 217–218°C; IR (deposit on NaCl plate from THF solution) 3300–2500 (COOH), 1692 (C=O) cm^{-1}; ^1H NMR ($CD_3S(O)CD_3$) δ

1.57 (*s*, 12H), 1.93 (pentet, 4H), 2.38 (*t*, 4H), 3.93 (*t*, 4H), 6.96 (*ABq*, 8H), 7.08 (*s*, 4H). *Anal. Calcd.* for $C_{32}H_{38}O_6$: C, 74.11; H, 7.39. *Found*: C, 74.35; H, 7.38.

Preparation of Diacid Chlorides ***8a*** *and* ***8b***

To a mixture of the diacid (4.21 mmol) and thionyl chloride (1.3 mL) in $CHCl_3$ (10 mL) was added a drop of DMF and the mixture was refluxed for 5 h. The solvent and other volatile components were evaporated *in vacuo*. Benzene was added to the residue and evaporated *in vacuo*. A second portion of benzene was added and evaporated *in vacuo* to give the acid chloride which was used without further purification.

Diacid Chloride ***8a***

Yield 100%; a white solid with mp 87–89°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1810 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (*s*, 12H), 4.83 (*s*, 4H), 6.95 (*ABq*, 8H), 7.09 (*s*, 4H).

Diacid Chloride ***8b***

Yield 100%; a white solid with mp 81–82°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1798 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (*s*, 12H), 2.14 (pentet, 4H), 3.11 (*t*, 4H), 3.97 (*t*, 4H), 6.77 (*d*, 4H), 7.05–7.20 (*m*, 8H).

Preparation of Bicyclic Diamides ***9a–d***

Solution A (45 mL) was prepared by dissolving the acid chloride (3.00 mmol) in toluene. Triethylamine (0.90 mL) and the diazacrown ether (3.00 mmol) were dissolved in toluene to make 45 mL of solution B. Solutions A and B were simultaneously added during a 7h period to 150 mL of vigorously stirred toluene at 0°C under argon. The reaction mixture was stirred overnight at room temperature, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$–EtOH as eluent to give the pure diamide.

Bicyclic Diamide ***9a***

Yield 72%; a white solid with mp 187–188°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1650 cm^{-1} (C=O), 1120 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (*s*, 12H), 3.20–3.80 (*m*, 24H), 4.68 (*s*, 4H), 6.65–7.25 (*m*, 12H); MS 688.65 (M^+). *Anal. Calcd.* for $C_{40}H_{52}N_2O_8$: C, 69.74; H, 7.61. *Found*: C, 69.55; H, 7.51.

Bicyclic Diamide ***9b***

Yield 52%, a white foam; IR (deposit on NaCl plate from $CDCl_3$ solution) 1665 cm^{-1} (C=O), 1120 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (*s*, 12H), 3.20–3.80 (*m*, 28H), 4.69 (*br s*, 4H), 6.65–7.25 (*m*, 12H); MS 732.70 (M^+). *Anal. Calcd.* for $C_{42}H_{56}N_2O_9$: C, 68.83; H, 7.70. *Found*: C, 68.77; H, 7.87.

Bicyclic Diamide ***9c***

Yield 22%, a white glass; IR (deposit on NaCl plate from $CDCl_3$ solution) 1665 cm^{-1} (C=O), 1120 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (*s*, 12H), 3.20–3.75 (*m*, 32H), 4.75 (*s*, 4H), 6.82 (*d*, 4H), 6.90–7.15 (*m*, 8H); MS 776.40 (M^+). *Anal. Calcd.* for $C_{44}H_{60}N_2O_{10}$: C, 68.02; H, 7.78. *Found*: C, 67.68; H, 8.15.

Bicyclic Diamide ***9d***

Yield 73%, a white solid with mp 175.5–177.5°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1638 cm^{-1} (C=O), 1119 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (*s*, 12H), 2.00–2.20 (*m*, 4H), 2.51 (*t*, 4H), 3.40–3.75 (*m*, 24H), 3.85–4.00 (*m*, 4H), 6.71 (*d*, 4H), 7.00–7.15 (*m*, 8H); MS 744.40 (M^+). *Anal. Calcd.* for $C_{44}H_{60}N_2O_8$: C, 70.94; H, 8.12. *Found*: C, 70.73; H, 8.23.

Preparation of Bicyclic Receptors ***4a–d***

Borane-dimethyl sulfide (3.3 mL, 33 mmol) was added to a solution of the amide (2.0 mmol) in dry THF (30 mL) and the mixture was refluxed for 6 h. Water was added and the suspension was evaporated to dryness *in vacuo*. THF (50 mL) and 6N HCl (100 mL) were added to the residue and the mixture was stirred overnight at room temperature. The mixture was evaporated to dryness *in vacuo* and the residue was treated with 100 mL of 5% aqueous LiOH and extracted repeatedly with $CHCl_3$. The combined extracts were evaporated *in vacuo* and the residue was chromatographed on alumina with $CHCl_3$-EtOH as eluent to give the pure diamine.

Receptor ***4a***

Yield 80%, white crystals with mp 111–113°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1125 (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (*s*, 12H), 2.75–2.95 (*m*, 12H), 3.45–3.60 (*m*, 16H), 4.02 (*t*, 4H), 6.87 (*ABq*, 8H), 7.07 (*s*, 4H). ^{13}C NMR ($CDCl_3$) δ 30.42 (CH_3), 41.92 (C), 55.00, 55.06 (CH_2N), 66.90, 70.59, 71.04 (CH_2O), 114.60, 126.62, 128.09, 143.76, 148.57, 157.03 (Ar); MS 660.65 (M^+). *Anal. Calcd.* for $C_{40}H_{56}N_2O_6 \cdot 0.5\,H_2O$: C, 71.72; H, 8.58. *Found*: C, 71.41; H, 8.57.

Receptor ***4b***

Yield 97%, a colorless viscous oil; IR (neat) 1120 cm^{-1} (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (*s*, 12H), 2.73–2.98 (*m*, 12H), 3.45–3.63 (*m*, 20H), 4.01 (*t*, 4H), 6.89 (*ABq*, 8H), 7.07 (*s*, 4H). ^{13}C NMR ($CDCl_3$) δ 30.52 (CH_3), 41.93 (C), 54.85, 54.96, 55.37 (CH_2N), 70.63, 70.96, 71.23 (CH_2O), 114.50, 126.62, 128.12, 143.68, 148.56, 157.04 (Ar); MS 704.70 (M^+). *Anal. Calcd.* for $C_{42}H_{60}N_2O_7 \cdot 0.5\,H_2O$: C, 70.66; H, 8.61. *Found*: C, 70.47; H, 8.54.

Receptor ***4c***

Yield 76%, white crystals with mp 94–96°C; IR (deposit on NaCl plate from $CDCl_3$ solution) 1120 cm^{-1} (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (*s*, 12H), 2.80 (*t*, 8H), 2.91 (*t*, 4H), 3.47–3.62 (*m*, 24H), 3.99 (*t*, 4H), 6.90 (*ABq*, 8H), 7.07 (*s*, 4H). ^{13}C NMR ($CDCl_3$) δ 30.69 (CH_3), 41.96 (C), 55.09, 55.33 (CH_2N), 67.07, 70.67, 71.00, 71.16 (CH_2O), 114.42, 126.63, 128.15, 143.53, 148.55, 157.14 (Ar); MS 748.70 (M^+). *Anal. Calcd.* for $C_{44}H_{64}N_2O_8 \cdot 0.5\,H_2O$: C, 69.72; H, 8.64. *Found*: C, 70.02; H, 8.51.

Receptor ***4d***

Yield 100%, a syrup; IR (neat) 1122 cm^{-1} (C—O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (*m*, 12H), 1.50–1.80 (*m*, 8H), 2.51 (*t*, 4H), 2.72 (*t*, 8H), 3.45–3.60 (*m*, 16H), 3.92 (*t*, 4H), 6.73 (*d*, 4H), 7.00–7.15 (*m*, 8H). ^{13}C NMR ($CDCl_3$) δ 23.94, 27.23 (CH_2); 30.84 (CH_3), 42.01 (C), 54.27, 55.67 (CH_2N), 67.83, 70.32, 71.07 (CH_2O), 114.26, 126.62, 128.18, 143.25, 148.61, 157.40 (Ar); MS 716.60 (M^+). *Anal. Calcd.* for $C_{44}H_{64}N_2O_6$: C, 73.71; H, 9.00. *Found*: C, 73.60; H, 9.04.

2.3. SYNTHESIS OF ALKYLAMMONIUM PICRATES

Alkylammonium picrates were prepared by adding the alkylamine to a saturated solution of picric acid in distilled, deionized water. The precipitate which formed during the addition was filtered and recrystallized from distilled, deionized water and dried *in vacuo* at room temperature to give the alkylammonium picrate as a yellow solid.

2.4. EXTRACTION OF ALKALI METAL AND ALKYLAMMONIUM PICRATES INTO DEUTERIOCHLOROFORM

Solutions of **4a–d** and **10** (5.0 mM) were prepared in ethanol-free deuteriochloroform. By use of the reported extraction procedure [12–14], extractions were conducted by adding 0.50 mL of a 5.0 mM receptor solution in deuteriochloroform to 0.50 mL of 5.0 mM alkali metal or alkylammonium picrate solution in a stoppered centrifuge tube and agitating the mixture for 1 min. Five identical samples were run concurrently. The mixture was centrifuged for 10 min to assure complete separation of the layers. Precisely measured aliquots were removed from each layer with microsyringes and diluted in acetonitrile. UV-visible spectra of these solutions were measured in the region of 300–500 nm. The absorbance at the absorption maximum (375 nm) was measured and compared with that for a known concentration of alkali metal or alkylammonium picrate. The percent extraction was calculated from the absorbance values. For the alkylammonium picrate system, extractions were also performed in the same fashion but with no receptor in the deuteriochloroform phase. The percent extraction calculated in the absence of receptor (a few percent) was subtracted from the percent extraction calculated in

the presence of receptor to give corrected values for the receptor-induced percent extraction.

2.5. ^{1}H NMR TITRATION EXPERIMENT

A procedure described by Saigo and coworkers [6] was adapted. Receptor **4a** (0.3966 g) was dissolved in $CDCl_3$–CD_3OD (9:1, v/v) and diluted to 10.00 mL to give a 50 mM stock solution. A 220 mM stock solution of propylammonium picrate was prepared by dissolving 0.6342 g of the picrate in $CDCl_3$–CD_3OH (9:1, v/v) and diluting to 10.00 mL. To 10 NMR tubes containing 25.0 μl portions of the stock solution of the picrate were added 0.00, 30.0, 50.0, 70.0, 90.0, 110.0, 150.0, 170.0, and 190.0 portions of the stock solution of **4a**. Every sample was diluted to 600 μl with the solvent and ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz instrument. The differences in chemical shifts of the picrate methyl protons in the presence and in the absence of the receptor were plotted against the concentration of the receptor to give a titration curve (Figure 1). A linear curve-fitting HOSTEST II program was used to analyze the results and calculate the association constant. This program was written by Professor Craig S. Wilcox of the University of Pittsburgh.

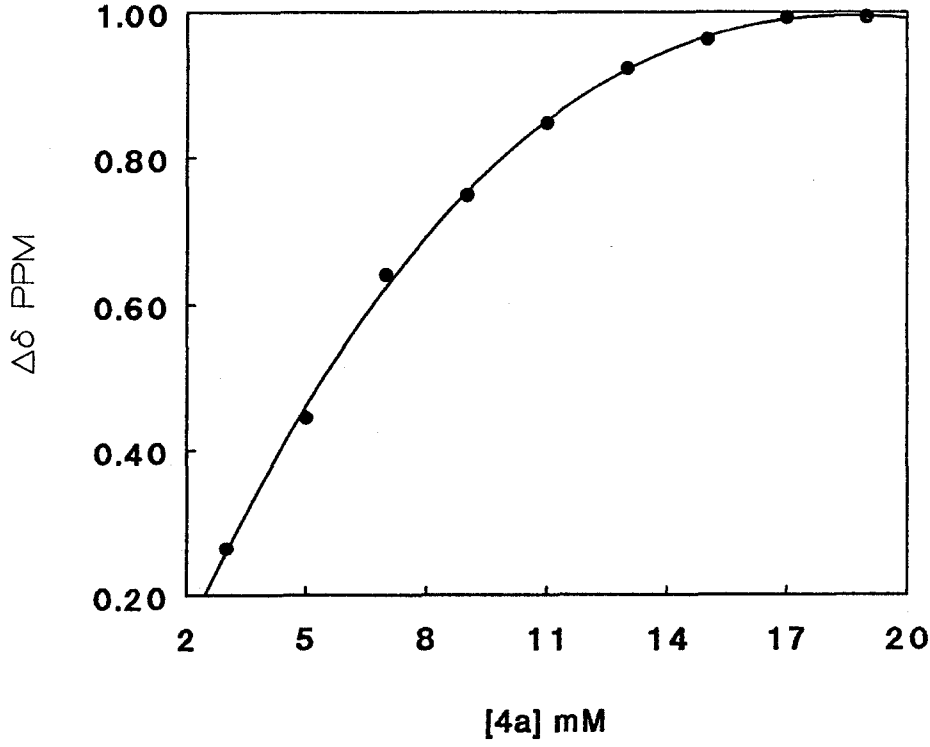

Fig. 1. ^{1}H NMR titration curve for the change of chemical shift ($\Delta\delta$) for methyl protons in propylammonium picrate (9.17 mM) in $CDCl_3$–CD_3OD (9:1) vs. the concentration of **4a**. The curved line is calculated by the HOSTEST II program.

3. Results and Discussion

3.1. SYNTHESIS OF DITOPIC RECEPTORS

Preparation of bisphenol **5**, the building block for the synthesis of receptors **4a–d**, is described in the patent literature [9]. Reaction of **5** with methyl bromoacetate or ethyl 4-bromobutanoate and K_2CO_3 in acetone produced diesters **6a** (88%) and **6b** (83%), respectively, which upon acidic hydrolysis gave diacids **7a** (95%) and **7b** (91%). The diacids were converted quantitatively into the corresponding diacid chlorides **8a** and **8b** by reaction with thionyl chloride. Cyclization of **8a** with 1,10-diaza-18-crown-6, 1,10-diaza-21-crown-7, and 1,13-diaza-24-crown-8 [10] in toluene under high dilution conditions afforded macrobicyclic diamides **9a–d** in yields of 72, 52 and 22%, respectively. Similarly macrobicyclic diamide **9d** was obtained in 73% yield from diacid chloride **8b** and 1,10-diaza-18-crown-6. Reduction of **9a–d** with $Me_2S{\cdot}BH_3$ followed by successive treatment with 6N HCl and 5% aqueous LiOH provided receptors **4a–d** in yields of 80, 97, 76 and 100%, respectively.

Intermediate diesters **6a** and **6b**, diacids **7a** and **7b** and macrobicyclic diamides **9a–d** were characterized by IR and ^{1}H NMR spectra and combustion analysis. For the intermediate diacid chlorides **8a** and **8b**, structural verification was based upon IR and ^{1}H NMR spectra only. Macrobicyclic receptors **4a–d** were fully characterized by IR, ^{1}H NMR and ^{13}C NMR, and mass spectra and combustion analysis.

3.2. COMPLEXATION OF ALKALI METAL PICRATES

Binding abilities of receptors **4a–c** and of the monocyclic model compound *N,N*-didecyl-1,10-diaza-18-crown-6 [11] (**10**) toward alkali metal cations were assessed by a picrate extraction method. Aqueous solutions of Li^+, Na^+, K^+, Rb^+ and Cs^+ picrates were extracted with deuteriochloroform solutions of **4a–c** and **10**. Data for the percent of alkali metal picrate extracted are presented in Table I.

For the monocyclic model compound **10**, the efficiencies for alkali metal picrate extractions were $K^+ \gg Rb^+ > Na^+$, $Cs^+ > Li^+$. Most efficient extraction of K^+ is anticipated for the diaza-18-crown-6 macrocycle on the basis of crown ether cavity-cation size complementarity. Receptor **4a**, which has the same 1,10-diaza-18-crown-6 unit as **10**, also exhibits the same extraction selectivity order, but with a

Table I. Alkali metal picrate extractions for monocyclic model compound **10** and bicyclic receptors **4a–c** into deuteriochloroform at 22–23°C

M^+ of M^+Pic^-	Percent extraction (%)[a] for			
	10	**4a**	**4b**	**4c**
Li^+	15.4	8.3	9.0	6.0
Na^+	18.2	11.2	8.8	6.2
K^+	43.1	33.7	12.3	8.0
Rb^+	22.0	15.3	12.1	10.2
Cs^+	17.6	12.4	12.5	6.9

[a]Standard deviation from the stated average value was $\pm 1.0\%$ or less.

uniformly lower extraction efficiency for each alkali metal picrate. Decreased flexibility of the diazacrown ether ring and/or reduced solvation of the macrocycle-bound cation due to enhanced hydrophobicity on one side of the diazacrown ether ring in **4a** may be responsible. For macrobicyclic receptors **4b** and **4c**, the pronounced selectivity for K^+ extraction noted with **4a** and **10** is lost due to the expanded ring sizes of the diazocrown ether units.

3.3. COMPLEXATION OF ALKYLAMMONIUM PICRATES

The alkylammonium ion-binding abilities of receptors **4a–d** and model monocyclic compound **10** were compared by extracting aqueous solutions of methyl, ethyl, propyl, butyl and *tert*-butyl picrates with deuteriochloroform solutions of the macrocyclic or macrobicyclic compounds. Due to non-negligible solubilities of the alkylamonium picrates in the organic phase, extractions were also performed without complexing agent in the deuteriochloroform phase. The percent extraction of each alkylammonium picrate in the absence of receptor was subtracted from that obtained in the presence of receptor to give corrected percent extraction values for the macrocycle- or macrobicycle-induced extraction. The percent extraction data are given in Table II.

For the model macrocyclic compound **10**, the influence of alkyl group variation in the alkylammonium picrate upon extraction efficiency is Pr > Et > Bu > Me, *t*-Bu. For receptor **4a** which has the same 1,10-diaza-18-crown-6 subunit as **10**, the extraction efficiency ordering is the same. Although the percent extraction values for ethyl- and propylammonium picrate are nearly the same for **4a** and **10**, the percent extraction values for methyl-, butyl- and *tert*-butylammonium picrates are markedly lower with **4a** than for **10**. The latter pattern is similar to the differences in alkali metal ion extraction efficiency for bicyclic receptor **4a** compared with monocyclic **10** (*vide supra*). Thus the extraction of ethyl- and propylammonium picrates by **4a** is considerably more efficient than would be expected based upon results of the alkali metal picrate extractions. This is consistent with inclusion of these two alkylammonium ion species within the receptor cavity.

Table II. Alkylammonium picrate extractions for monocyclic model compound **10** and bicyclic receptors **4a–d** into deuteriochloroform at 22–23°C

R of $RNH_3^+ Pic^-$	Percent extraction (%)[a] for				
	10	**4a**	**4b**	**4c**	**4d**
methyl	31.2	11.5	9.8	5.8	34.1[c]
ethyl	84.8[c]	81.3[c]	83.6[c]	81.6[c]	84.5[c]
propyl	92.6[c]	91.3[c]	90.8[c]	90.8[c]	93.0[c]
butyl	60.3	35.5	19.0	15.7	60.9[c]
tert-butyl	30.8	10.9	10.5	6.3	32.3[c]

[a]Values are corrected for alkylammonium picrate extraction into the organic phase in the absence of receptor.
[b]Standard deviation from the stated average value was ±2.0% or less.
[c]Based on aqueous phase readings only.

Examination of CPK space-filling models reveals that when the alkyl 'tail' and ammonium ion 'head' of the alkylammonium ion are directed toward the hydrophobic and the diazacrown ether subunits in **4a**, respectively, both ethyl- and propylammonium ions are well accommodated within the cavity. On the other hand, butyl- and *tert*-butylammonium ions are too large to fit entirely within the cavity of **4a**. The small methylammonium ion fits loosely within the cavity, but the methyl group of the diazacrown ether-complexed ammonium ion does not project into the hydrophobic pocket of the receptor.

Ring size expansion of the diazacrown ether subunit in going from **4a** to **4b** to **4c** further diminishes the efficiencies for methyl-, butyl- and *tert*-butylammonium picrate extraction. However the extraction efficiencies for ethyl- and propylammonium picrates are the same for receptors **4a–c**. These results are consistent with inclusion of ethyl- and propylammonium ions within the cavities of all three receptors.

Receptor **4d** has the same hydrophobic and diazacrown ether subunits as does receptor **4a**, but with 1,4-butylene spaces rather than ethylene groups. This structural modification elongates the cavity in **4d** compared with **4a**. Compared with **4a** the efficiencies for extraction of ethyl- and propylammonium picrates by **4d** were essentially the same. However, extraction efficiencies for methyl-, butyl- and *tert*-butylammonium picrates were markedly increased with **4d**. It is interesting to note that the efficiencies for extraction of the five alkylammonium picrates by elongated bicyclic receptor **4d** and those obtained with monocyclic model compound **10** are the same within experimental error. This indicates that receptor **4d** has sufficient flexibility and a large enough cavity to offer no obstruction to alkylammonium ion complexation by the diazocrown ether subunit. However in **4d** the elongated cavity places the hydrophobic subunit too far away from the diazacrown ether subunit to allow for simultaneous association with both the liphophilic tails and polar heads of the alkylammonium ions so no enhancement of alkylammonium ion extraction is seen for **4d** compared with **10**.

Interactions of bicyclic receptors **4a** and **4d** and monocyclic model compound **10** with alkylammonium ions were also probed by ^{1}H NMR spectroscopy. The ^{1}H NMR chemical shifts of methyl-, ethyl-, propyl-, isopropyl-, butyl-, *tert*-butyl- and pentylammonium picrates in $CDCl_3$–CD_3OD (9:1) in the absence and presence of equimolar monocyclic model compound **10** and bicyclic receptors **4a** and **4d** are recorded in Table III. When compared with the chemical shifts for the free alkylammonium picrates in $CDCl_3$–CD_3OD (9:1), the presence of one equivalent of model compound **10** has no significant effect. On the other hand the presence of one equivalent of receptor **4a** induces a very pronounced change in chemical shift for the methyl group protons of the propylammonium ion from 0.91 δ to -0.07 δ. The chemical shift for the methylene hydrogens on C2 also moves upfield by approximately 0.5 ppm in the presence of **4a**. These changes together with a smaller (approximately 0.1 ppm) downfield shift for the singlet assigned to protons of the central benzene ring of **4a** demonstrates formation of the inclusion complex.

The data also indicate formation of an inclusion complex between **4a** and ethylammonium ion, but the upfield change in chemical shift for the methyl proton on C2 is only 0.5 ppm. In agreement with this observation, examination of CPK space-filling models indicates that the methyl group of this ammonium ion would

Table III. ^{1}H NMR chemical shifts for alkylammonium picrates in $CDCl_3$–CD_3OD (9:1) at 22–23°C in the absence and presence of equimolar monocyclic model compound **10** and bicyclic receptors **4a** and **4d**

R of $RNH_3^+Pic^-$	Hydrogens on	Chemical shift (δ)			
		Free	with **10**	with **4a**	with **4d**
methyl	C1	2.52	2.38	2.23	2.27
ethyl	C2	1.22	1.16	0.73	1.11
	C1	2.95	2.81	~2.7	2.72
propyl	C3	0.91	0.90	−0.07	0.80
	C2	1.63	1.50	1.06	1.45
	C1	2.86	2.68	2.42	~2.5
isopropyl	C2	1.22	1.14	0.92	1.11
	C1	3.38	3.19	3.19	3.14
butyl	C4	0.85	0.86	0.40–0.65	0.65
	C3	1.31	1.20–1.55		1.17
	C2	1.55		1.15	~1.5
	C1	2.87	2.70	2.53	~2.5
tert-butyl	C2	1.28	1.23	1.23	1.19
pentyl	C5	0.79	0.82	0.65	0.61
	C4	1.23			1.12
	C3		1.20–1.60	0.93	
	C2	1.57		1.15	~1.45
	C1	2.89	2.69	2.50	~2.5

not penetrate the hydrophobic pocket of the receptor to the same extent as does the methyl group of the propylammonium ion.

To provide a quantitative evaluation of association between receptor **4a** and propylammonium picrate in $CDCl_3$–CD_3OD (9:1), a ^{1}H NMR titration experiment [6] was conducted in which the concentration of propylammonium picrate was kept constant and the concentration of receptor **4a** was varied. The difference in chemical shift for the methyl protons of the ammonium salt in the absence and presence of varying amounts of **4a** (Figure 1) were evaluated with the HOSTEST II program to give an association constant of 900 M^{-1}. This value is similar in magnitude to those obtained by Saigo and coworkers [6] for complexation of ω-phenylalkylammonium picrates by tricyclic receptor **3** in $CDCl_3$–CD_3OD (4:1).

4. Conclusion

New ditopic receptors **4a–d** have been synthesized and their binding of alkali metal and alkylammonium ions has been assessed by the picrate extraction method. NMR evidence is obtained for strong association of propylammonium ion and **4a** by inclusion of the guest within the cavity of the receptor.

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