JOC*Article*

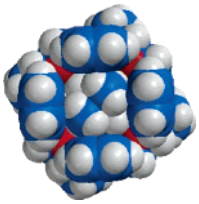
Synthesis and Complexation Properties of "Zorbarene": A New Naphthalene Ring-Based Molecular Receptor

Anh Huu Tran, David O. Miller, and Paris E. Georghiou*

Department of Chemistry, Memorial University of Newfoundland, Newfoundland and Labrador, NL, Canada, A1B 3X7

parisg@mun.ca

Received September 3, 2004

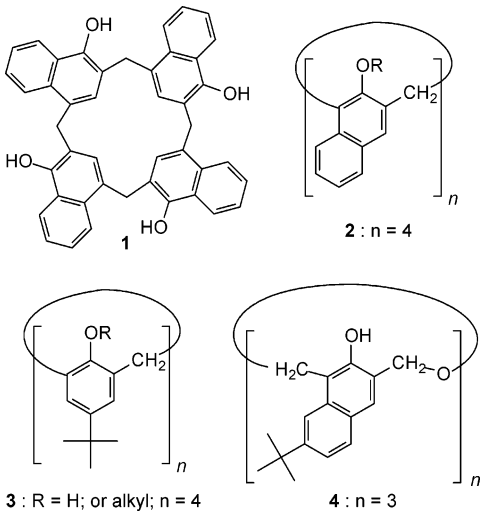


The syntheses of the first 2,3-dialkoxy-substituted naphthalene ring-based macrocycles which have calixarene-like structures are reported. The complexation properties of these octahomotetraoxaisocalix[4]naphthalenes were investigated. These new members of the calixnaphthalene family did not demonstrate any appreciable complexation with C_{60} or C_{70} under the conditions studied, but did so with the tetramethylammonium cation, showing relatively strong association constants suggesting among other considerations that stronger cation-π interactions versus $\pi-\pi$ interactions are operative with these hosts. An X-ray crystal structure of the octa-*O*-ethoxy derivative revealed a structure having a "flattened partial-cone" conformation in which two acetonitrile guest molecules are trapped.

Introduction

Macrocyclic molecular receptors which are formed by cyclic arrays having naphthalene ring-containing units are of interest since they can form deep, electron-rich cavities. Furthermore, as Glass et al.[1] have also recently shown, the fluorescence properties of a naphthalene core can allow for the sensitive detection of complexes formed between guest molecules and such naphthalene ring-based receptors. Our own particular interest has been in designing new receptors which could be effective hosts for electron-deficient guest molecules such as C_{60}. Calixnaphthalenes, e.g., **1**[2] and **2**,[3] are a group of such compounds whose macrocycles are formed by naphthol rings linked via their meta positions by $-CH_2-$ groups. As such, they may therefore also be considered to be examples of "[1$_n$]metacyclonaphthaleneophanes" by analogy with calixarenes **3**.[4,5]

We previously reported that the C_3-symmetrical hexahomotrioxacalix[3]naphthalene **4**,[6] in which the $-CH_2-$ bridges which link the aromatic rings are replaced by $-CH_2OCH_2-$ groups, formed supramolecular complexes with C_{60} in solution and also yielded a stable solid 2:1 host:guest complex with C_{60}.[7] We were therefore interested in determining whether a receptor having larger, more electron-rich cavities would demonstrate any enhanced affinity for C_{60} or other electron-deficient guests.



In this paper we report the synthesis and some properties of the tetra-*O*-methyl, -ethyl, -*n*-propyl, and

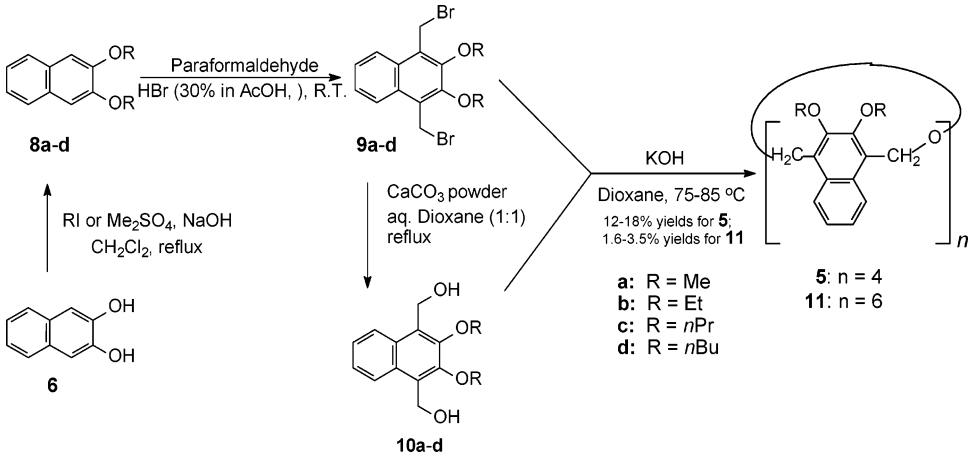
(1) For other examples of naphthalene-ring based macrocycles see: (a) Shorthill, B. J.; Avetta, C. T.; Glass, T. E. *J. Am. Chem. Soc.* **2004**, *126*, 12732. (b) Shorthill, B. J.; Granucci, R. G.; Powell, D. R.; Glass, T. E. *J. Org. Chem.* **2002**, *67*, 904.

(2) Structure **1** is one of four regioisomers of 1-naphthol-based calix[4]naphthalenes which were reported in 1993. See: (a) Georghiou, P. E.; Li, Z. *Tetrahedron Lett.* **1993**, *34*, 2887. (b) The synthesis of the newest member of the calixnaphthalene family was reported recently: Chowdhury, S.; Georghiou, P. E. *J. Org. Chem.* **2002**, *67*, 6808.

(3) Andreetti, G. D.; Böhmer, V.; Jordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023.

10.1021/jo0484427 CCC: $30.25
Published on Web 01/19/2005

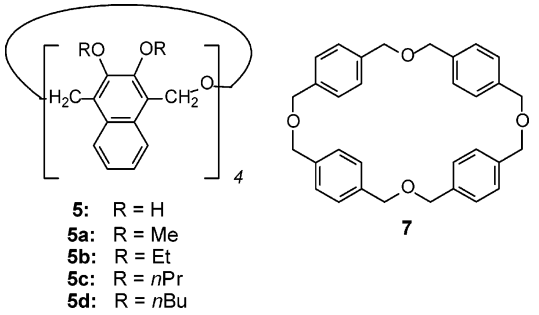
SCHEME 1



-*n*-butyl ethers (**5a**−**d**, respectively) of a new 2,3-dihydroxynaphthalene-based molecular receptor, **5**.[8] Also reported is the single-crystal X-ray crystallographic structure derived for **5b** that reveals a "*flattened partial-cone*" conformation in which two acetonitrile guest molecules are accommodated. While **5a** and **5b** did not form complexes with either C_{60} or C_{70}, they instead were found to be efficient hosts of the tetramethylammonium (TMA) ion.

Results and Discussion

Design and Synthesis. CPK molecular models and molecular modeling[9] suggested that a molecule such as **5** could be an attractive candidate receptor for C_{60}. In **5** four 2,3-dihydroxynaphthalene (**6**) units are linked in a para fashion by $-CH_2OCH_2-$ groups and its resulting cavity dimensions suggested that guests such as C_{60}- and/or C_{70}-fullerenes could be adequately accommodated. Since these compounds are linked via the 1,4 positions on the naphthalene rings and do have calixarene-like structures,[10] they could be considered as members of a new class of "octahomotetraoxaisocalix[4]naphthalenes",[11] and also as "tetraoxa[3.3.3.3]para(2,3-dihydroxy)naphthaleneophanes" by analogy with the corresponding benzenoid paracyclophane (**7**) recently described by Roelens' group.[12]



Molecular modeling "docking" simulations[9] between, e.g., C_{60} and compounds **5a**−**d** supported our hypothesis that structures generated using *cone* or *partial cone* conformers of **5a**−**d** could form attractive energy-minimized host:C_{60} complexes. The molecular modeling observations also suggested that although the host molecules were conformationally flexible, $\pi-\pi$ van der Waals interactions between the electron-rich naphthalene rings and the electron-poor fullerenes could result in a conformational reorganization of these structures to adopt conformations which permitted complex formation. The syntheses of these compounds were therefore undertaken.

Syntheses of **5a**−**d** were accomplished as outlined in Scheme 1 via the common precursors, the di-*O*-alkylated derivatives **8a**−**d**, which were easily produced by base-mediated alkylation of **6**. Preliminary experiments revealed that bromomethylation of **6** itself only afforded intractable resinous products, hence necessitating the use of ethers, **8a**−**d**. At first, the larger homologous alkyl ethers (octa-*n*-pentyl- and octa-*n*-hexyl-) were chosen but their subsequent reaction products proved to be difficult to purify and characterize. Double bromomethylation[13] of each of **8a**−**d** easily afforded the corresponding bis-bromomethylated naphthyl ethers **9a**−**d**, which, when

(4) Calixarenes are considered to be members of the class of [1$_n$]-metacyclophanes. For a recent comprehensive review of calixarenes, see: Gutsche, C. D. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001.

(5) Mandolini, L.; Ungaro, R., Eds. *Calixarenes in Action*; Imperial College Press: London, England, 2000.

(6) Ashram, M.; Mizyed, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 1473.

(7) Mizyed, S.; Ashram, M.; Miller, D. O.; Georghiou, P. E. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1916.

(8) A preliminary account of this work was presented at "Calix 2003", the 7th International Conference on Calixarenes, Vancouver, B.C., Canada, August 19−25, 2003.

(9) Molecular modeling was conducted using Spartan Pro V1.1 Molecular Modeling Software from Wavefunction Inc.: Irvine, CA. PM3 calculations were conducted on the optimized geometry of the host and/or complexes which were obtained through molecular mechanics (MMFF94) conformational searches.

(10) Calixnaphthalenes and these new homooxa homologues adopt conformations which are similar to those that are typically found for the calixarenes (see ref 1).

(11) The name "isocalixnaphthalenes" for these *1,4-* or para-linked compounds was suggested to us by Professor C. David Gutsche, the originator of the name "calixarenes". Personal communication, October 21, 2004.

(12) Sarri, P.; Venturi, F.; Cuda, F.; Roelens, S. *J. Org. Chem.* **2004**, *69*, 3654. We thank the referees for alerting us to this contribution, which was published after we had completed (ref 8) much of the complexation work that is described in this paper.

(13) (a) van der Made, A. W.; van der Made, R. H. *J. Org. Chem.* **1993**, *58*, 1262. (b) Li, Z. Ph.D. Dissertation, Memorial University of Newfoundland, 1996, p 165.

hydrolyzed with $CaCO_3$ in aqueous dioxane, led to the respective bishydroxymethyl analogues **10a**−**d**. Molecular models suggested that steric hindrance resulting from the alkoxy groups on the naphthalene rings would impede any cross-ether coupling between compounds **9a**−**d** and **10a**−**d**, respectively, which could result in the formation of the corresponding [3.3]-para(2,3-dialkoxy)-naphthaleneophanes. This was found to be the case as none of these products were detected under the conditions employed.

The most difficult experimental conditions to determine were those required for forming the macrocyclic ethers. Nevertheless, after considerable experimentation, optimal conditions were found that were based upon Masci's methodogy.[14] Macrocycles **5a**−**d** were obtained in 12−18% isolated yields, respectively. In addition, along with **5a** and **5d** the corresponding dodecahomohexaoxaisocalix[6]naphthalenes (or "hexaoxa[3.3.3.3.3.3]paranaphthaleneophanes"), **11a** and **11d**, respectively, were also isolated, albeit in low yields, 3.5% and 1.6% respectively, which for now precluded further detailed structural analyses. None of the corresponding compounds **11b** or **11c** were detected by TLC analysis of the crude reaction products.

Characterization 5a−**d.** All of the new macrocylic compounds had relatively simple ^{1}H NMR spectra (ambient temperature) which indicated that they were highly symmetrical. Fast conformational equilibration in solution at ambient temperature was obvious from the fact that all of the signals were sharp, and that the bridging methylene groups appeared as singlets. A VT-^{1}H NMR experiment conducted on **5b**, for example, down to 223 K, revealed broadening of all of the signals, but no coalescence temperature could be observed since the samples precipitated out of solution at the lower temperatures. Furthermore, it was not possible either to gain any insight into the conformations of any of compounds **5a**−**d** at the lower temperatures.

When the chemical shifts of the alkoxy protons in the spectra of **5a**−**d** were compared with those of their respective precursors, only in the cases of **5a** and **5b** were there any significant differences. The position of the CH_3 signal of the methoxy groups in **5a** at δ 3.81 is shifted upfield from the positions of the corresponding signals in the precursors **8a**, **9a**, and **10a** which are all at approximately δ 4.00. The positions of the $-CH_2-$ and the CH_3- groups of the ethoxy groups in **5b** at δ 4.03 and 1.41, respectively, are shifted upfield from the corresponding signals of the precursors **8b**, **9b,** and **10b**, which appear at approximately δ 4.22 and 1.54 respectively, indicating a shielding effect from the naphthyl rings. By way of contrast, the changes in the corresponding chemical shifts in **5c** and **5d** relative to their precursors were less than ~0.10 ppm.

Although crystals were obtained from **5a** and **5b**, only those from **5b** successfully resulted in an X-ray crystal structure (Figure 1). The structure reveals a "*flattened partial-cone*" conformation, in which three naphthalene subunits (**A**, **B**, and **C**)[15a] are in a tripodal arrangement. The fourth ring (**D**), which is nearly orthogonal to the *distal* (**B**) naphthyl subunit, has its two ethoxy substituents directed *exo* to the partial cavity, or enclosure defined by the other three naphthyl subunits. The structure therefore contains two "partial cavities", one defined by the half that contains the ethoxy groups of rings **A**, **B**, and **C** and the other by the unsubstituted rings of these naphthyl groups. Two acetonitrile guest molecules are contained within this latter enclosure. The methyl groups of each acetonitrile guest are oriented inward toward the aromatic rings, and their nitrogen atoms directed away.[16] These findings are consistent with other well-known π-methyl interactions which have been seen between calixarenes and other methyl group-containing guests such as toluene, acetonitrile,[17] and tetramethylammonium salts. A search for the lowest conformer (using MMFF94 prior to geometry optimization with PM3) conducted on **5b** after the X-ray structure was revealed showed that the *flattened pinched cone* conformation is indeed the lowest energy conformer. A similar molecular modeling conducted on the 2:1 acetonitrile:**5b** complex is also in agreement with the X-ray structure, and is of lower energy than a corresponding 2:1 complex in which **5b** was preorganized and locked into a *cone* conformation.

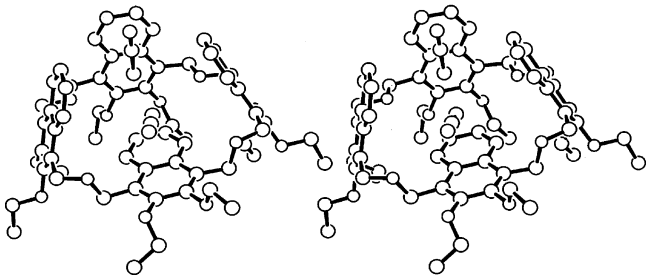


FIGURE 1. X-ray stereoview of **5b** showing its *flattened partial cone* conformation. Two acetonitrile guest molecules are contained within the partial enclosure defined by three naphthyl subunits which are in a tripodal arrangement.[15,16]

Solution Complexation Studies of 5a and 5b. The macrcrocycles which were targeted had been predicted on the basis of their molecular architecture and molecular modeling determinations to be potentially efficient hosts for C_{60} and/or C_{70}. However, when complexation determinations in toluene solution were conducted with either

(14) (a) Masci, B. *Tetrahedron* **1995**, *51*, 5459. (b) Masci, B.; Finelli, M.; Varrone, M. *Chem. Eur. J.* **1998**, *4*, 2018. (c) Masci, B. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2001. (d) Masci, B. *J. Org. Chem*. **2001**, *66*, 1497. (e) Masci, B. *Tetrahedron* **2001**, *57*, 2841.

(15) (a) On the basis of the numbering used for the C atoms in the X-ray determination and in the PLUTO plot (see Supporting Information) the naphthyl subunits designated as **A** to **D** contain carbon atoms C2−C11; C14−C23; C26−C35; and C38−C47, respectively. (b) The angle subtended by the plane of the naphthyl **D** subunit and the plane of the distal naphthyl **B** subunit is 84.7°. (c) The acetonitrile guest molecule that is oriented *parallel* to naphthyl subunit **B** contains atoms C67−C68 and N2; the other acetonitrile contains atoms C65−C66 and N1.

(16) Amusingly, the structure generated by the X-ray crystallography can be imagined to resemble a ring of four anthropomorphic dancers. We propose calling this molecule a "Zorbarene" in honour of the dance-loving "Zorba" character created by the Greek writer Nikos Kazantzakis (1883−1957) in the widely acclaimed and popular book "Zorba the Greek" originally published in 1952. For an account of the origins of various names coined by organic chemists see: Nickon, A.; Silversmith, E. F. *Organic Chemistry. The Name Game*; Pergamon Books, Inc.: Oxford, U.K., 1987.

(17) See: Gutsche, C. D. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: Oxford, U.K., 1991; Vol. 4.

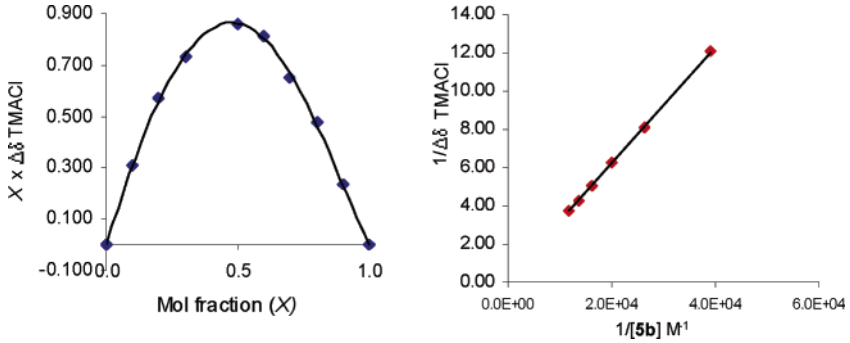


FIGURE 2. Job plot (left) and Benesi−Hildebrand (right) plot for **5b** and TMACl.

UV−vis or ^{1}H NMR spectroscopic analysis, it was unequivocal that no such complexation occurred. This finding was in contrast to the results previously seen with **4** under similar conditions.[7] It is possible that the supramolecular complexation with these new receptors may be inhibited by both an entropic effect due to the greater flexibility of the larger, 28-membered annulus and the consequential lack of preorganization of these macrocyles. Another factor may be the lack of a complementary symmetry element[18] between the host and these particular fullerene guest molecules.

Quaternary ammonium salts have been employed as guests in host−guest studies involving cyclophanes in lipophilic solvents, thus demonstrating the importance of cation−π interactions.[19] Masci et al. conducted an extensive study on the fine-tuning of the cavity sizes[14] of a series of homooxacalix[4]arenes using various tetraalkylammonium picrate salts as guest probes, in organic solvents. Arduini et al.[20] also described the use of TMACl and other TMA salts for binding studies with their particular para-substituted calix[4]arene host molecules. We therefore undertook a compexation study with **5a** and **5b**, both of which could be obtained in crystalline form. More recently, Roelens' group[12] reported a complexation study with various TMA salts, including TMACl, with the related receptor **7**.

Since stability or association constants (K_{ASSOC}) can be determined on relatively small amounts of compounds with ^{1}H NMR spectroscopy[21] this was the method of choice used in this study. The method of continuous variations (Job's plot)[22] was used to determine the stoichiometry of complexation between TMACl and **5a** or **5b**, which was found to be 1:1 under the conditions examined, in both cases (Figure 2). The Job Plots indicated that the largest chemical shifts induced for the receptors **5a** and **5b** ($\Delta\delta_{max}$ = 0.37 and 0.48 ppm, respectively) were for their aromatic signals, as compared with those for their $-CH_2-$ groups of the bridging $-CH_2-OCH_2-$ groups ($\Delta\delta_{max}$ = 0.029−0.026 ppm, respectively), or those for the alkoxy groups (e.g., $\Delta\delta_{max}$ = 0.03 ppm for **5a**). In contrast, the largest chemical shifts induced for the methyl groups of the TMA cation with **5a** and **5b** were 1.97 and 3.09 ppm, respectively. The K_{ASSOC} values which were determined from the subsequent titration experiments were therefore based upon measurements of the $\Delta\delta$ values for the methyl groups of the TMA cation.

TABLE 1. K_{Assoc} Values (M^{-1}) for TMACl Complexes with 5a and 5b in $CDCl_3$ at 298 K[a]

complex	method	run 1 (r^2)	run 2 (r^2)	average
5a: TMACl	B−H	1227 (1.00)	1319 (0.99)	1274 ± 65
	F−F	1247 (0.99)	1136 (0.96)	1192 ± 79
5b: TMACl	B−H	636 (1.00)	724 (0.99)	680 ± 62
	F−F	689 (0.96)	607 (0.93)	648 ± 58

[a] Note: method B−H is the Benesi−Hildebrand double reciprocal treatment, and method F−F is the Foster−Fyfe *x*-reciprocal treatment; r^2 values are the correlation coefficients obtained from the linear regression analyses of the respective plots. The actual data are provided in the Supporting Information.

To determine K_{ASSOC} values, titration experiments were conducted by adding aliquots of **5a** or **5b**, respectively, to saturated ($\sim 10^{-3}$ M) solutions of TMACl in $CDCl_3$. The [guest]:[host] ratios used in all cases were $\gg$10:1. The changes in the chemical shift of the TMA methyl signal were determined and K_{ASSOC} values were calculated by using both the Benesi−Hildebrand and Foster−Fyfe treatments.[21] The results are summarized in Table 1. The chemical shift changes which were induced for the methyl groups of the added TMACl were all to higher fields, thereby demonstrating the shielding effect due to the naphthyl rings. Also noticeable were the line broadening of the TMACl methyl signals upon the addition of the host molecules, although this did not preclude accurate determination of the mean position of the observed signals for the K_{ASSOC} determinations. Furthermore, the NMR spectra obtained from the complexation solutions were very simple, suggesting the formation of both symmetrical and rapidly interconverting complexes.

The K_{ASSOC} values obtained for **5a** were almost double those for **5b**. A possible explanation for these significantly different values is that the greater steric requirements of the ethoxy groups may limit the extent of preorganization of the macrocyclic hosts that must occur in solution in order to permit the TMA cation to enter the cavity. Another factor could be the additional entropic effects which need to be overcome due to the additional degrees of freedom which the ethoxy groups possess, compared with the methoxy groups. Thus, although no complexation was observed between these new host molecules and C_{60}- or C_{70}-fullerene the smaller, more polar quaternary ammonium salt, TMACl, afforded larger stability

(18) (a) Atwood, J. L.; Barbour, L. J.; Nichols, P. J.; Raston, C. L.; Sandoval, C. A. *Chem. Eur. J.* **1999**, *5*, 990. (b) Steed, J. W.; Junk, P. C.; Atwood, J. L.; Barens, M. J.; Raston, C. L.; Purkhalter, R. S. *J. Am. Chem. Soc*. **1994**, *116*, 10346.

(19) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303 and references therein.

(20) Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *J. Org. Chem.* **2001**, *66*, 8302.

(21) Fielding, L. *Tetrahedron* **2000**, *56*, 6151.

(22) Job, P. *Ann. Chim.* **1928**, *9*, 113.

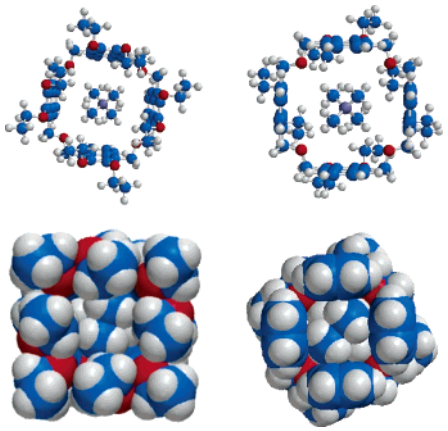


FIGURE 3. Computer-generated PM3 model of the complex between **5b** and the TMA cation. Top left and bottom left: Ball-and-stick and space-filling representations, respectively, of the complex as viewed from the face in which the ethoxy groups can be seen. Top right and bottom right: Ball-and-stick and space-filling representations, respectively, of the complex as viewed from the opposite face, looking into the cavity defined by the four naphthyl groups.[9]

constant values than those obtained by Masci[14] for the analogous tetramethoxy octahomotetraoxacalix[4]arenes with TMA picrate. Furthermore, the association constant values which were obtained with **5a** and **5b** are respectively approximately 7- and 4-fold larger when compared with the value of 165 M^{-1} that Roelens' group reported for the TMACl complex with their unfunctionalized benzenoid tetraoxaparacyclophane **7**. Figure 3 shows the computed model of the **5b**:TMA complex and indicates a very good fit existing between the TMA cation and the host, even when compared with the computed model of Roelens' TMA:**7** complex.[12] Furthermore, in this **5b**:TMA complex, the receptor is in a symmetrical *cone* conformation and is energetically preferred in this case over a *flattened pinched cone* conformation. The TMA cation can also be seen to be embedded in the lower half of the receptor, closest to the unsubstituted B-rings of the naphthyl groups.

Conclusions

A series of new 2,3-dialkoxy-substituted naphthalene-based previously unreported cavity-containing molecular receptors have been synthesized, and some of their complexation properties have been determined. The syntheses of the octamethoxy and octa-*n*-butoxy macrocyclic compounds **5a** and **5d** were accompanied by small amounts of the corresponding higher hexaoxa homolgues, **11a** and **11d**, respectively, but their complexation properties have not yet been determined. The ^{1}H NMR spectra of all of the macrocycles obtained showed clearly that they were highly symmetrical and conformationally flexible. However, suitable crystals of **5b** for single-crystal X-ray crystallography were obtained and the structure revealed it to be in a *flattened partial cone* conformation. The X-ray structure also revealed it to contain two acetonitrile guests, both situated within the same enclosure generated by three naphthalene rings which are in a tripodal arrangement.

Although CPK models and molecular modeling suggested that these new receptors had the potential to be suitable hosts for the electron-deficient neutral guest molecules, C_{60}- and C_{70}-fullerenes, solution complexation experiments did not demonstrate any such complexation. With TMACl, however, relatively large stability constant values were observed indicating that cation$-\pi$ interactions may be more effective than the $\pi-\pi$ interactions which are only possible in the case of the host$-$fullerene complexations. A further contributing factor could also be the importance of the symmetry complementarity between the hosts and the tetrahedral TMA cation. Further research on developing these new macrocycles is underway in our laboratory.

Experimental Section

2,3-Dimethoxynaphthalene (8a). To a stirred solution of **6** (19.2 g, 119 mmol) in aqueous 10% NaOH (98.0 mL, 260 mmol) was added Adogen (0.50 mL) and CH_2Cl_2 (300 mL). Dimethyl sulfate (25.0 mL, 264 mmol) was added at 0 °C over 1 h with use of a syringe pump. The reaction mixture was stirred for a further 9 h. Additional aqueous 6 M KOH (60 mL) was added and the mixture was heated at reflux for another hour. The CH_2Cl_2 layer was then separated and washed with aqueous saturated NH_4Cl (2 × 50 mL), brine (2 × 50 mL), and distilled water (2 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the light yellow residue was crystallized from MeOH$-$$H_2O$ to afford **8a** (16.56 g, 74% yield) as colorless prisms: mp 119$-$120 °C (lit.[23] mp 115$-$116 °C, crystallized from $CH_2Cl_2$$-$pentane). ^{1}H NMR (300 MHz) δ 4.00 (s, 6H), 7.11 (s, 2H), 7.34 (m, 2H), 7.68 (m, 2H); ^{13}C NMR δ 56.0, 106.5, 124.4, 126.4, 129.3, 149.6.

2,3-Diethoxynaphthalene (8b). To a stirred solution of **6** (6.54 g, 40.8 mmol) in aqueous 10% NaOH (34 mL, 90 mmol) was added Adogen (2 mL) and CH_2Cl_2 (150 mL). Ethyl iodide (9.06 mL, 120 mmol) was added over 1 h with use of a syringe pump. The reaction mixture was stirred and heated at reflux for 3 d. The CH_2Cl_2 layer was separated, washed with aqueous 10% K_2CO_3 (1 × 50 mL), aqueous saturated NH_4Cl (2 × 50 mL), brine (2 × 50 mL), and distilled water (2 × 50 mL), dried over anhydrous $MgSO_4$, and filtered. After the solvent was evaporated, the yellow residue was crystallized from MeOH$-$$H_2O$ to afford **8b** in 75% yield as colorless prisms (MeOH$-$$H_2O$): mp 96$-$97 °C (lit.[23] mp 96 °C, crystallized from $CH_2Cl_2$$-$pentane). ^{1}H NMR (300 MHz) δ 1.53 (t, J = 12 Hz, 6H), 4.22 (q, J = 12 Hz, 4H), 7.12 (s, 2H), 7.30 (m, 2H), 7.65 (m, 2H); ^{13}C NMR δ 14.6,. 64.1, 107.4, 123.9, 126.1, 129.1, 148.9.

2,3-Di-*n*-propoxynaphthalene (8c). By using the general procedure for **8a**, **8c** was obtained in 70% yield as colorless prisms (MeOH$-$$H_2O$): mp 75$-$76 °C; ^{1}H NMR δ 1.09 (t, 6H), 1.93 (m, 4H), 4.07 (t, J = 7 Hz, 4H), 7.11 (s, 2H), 7.30 (m, 2H), 7.65 (m, 2H); ^{13}C NMR δ 10.7, 22.6, 70.5, 108.1, 124.1, 126.4, 129.4, 149.6; MS (m/z) 244 (M^+, 25), 202, 160 (100), 114, 77, 41.

2,3-Di-*n*-butoxynaphthalene (8d). By using the general procedure for **8a**, **8d** was obtained in 73% yield as colorless prisms (MeOH$-$$H_2O$): mp 59$-$60 °C (lit. mp 56$-$57 °C, crystallized from $CH_2Cl_2$$-$pentane); ^{1}H NMR (500 MHz) δ 1.00 (t, J = 7 Hz, 6H), 1.56 (m, 4H), 1.88 (m, 4H), 4.11 (t, J = 6 Hz, 4H), 7.11 (s, 2H), 7.30 (m, 2H), 7.65 (m, 2H); ^{13}C NMR δ 14.1, 19.5, 31.3, 68.7, 108.1, 124.1, 126.4, 129.4, 149.6.

1,4-Bis(bromomethyl)-2,3-dimethoxynaphthalene (9a). To a mixture of **8a** (1.57 g, 8.3 mmol) and 95% paraformaldehyde (1.53 g, 48 mmol) in glacial acetic acid (70 mL) was added a solution of HBr in glacial acetic acid (30 wt %, 9.6 mL, 48 mmol of HBr). After being stirred at room temperature for 5 d, the reaction mixture was poured into cold water (200 mL), and the resulting precipitate was filtered and then dissolved

(23) Simonet, J.; Patillon, H.; Belloncle, C.; Simonet-Gueguen, N.; Cauliez, P. *Synth. Met.* **1995**, *75*, 103.

in EtOAc (200 mL). The organic layer was washed with distilled water (2 × 50 mL), aqueous 5% $NaHCO_3$ (2 × 50 mL) and distilled water until the washings were neutral to pH paper, dried over $MgSO_4$, and filtered. The solvent was evaporated and the crude product was purified by column chromatography eluting with hexane to afford **9a** in 78% (2.33 g) yield, as light yellow fine needles (acetone−hexane): mp 189 °C dec; ^{1}H NMR (300 MHz) δ 4.04 (s, 6H), 5.03 (s, 4H), 7.57 (m, 2H), 8.08 (m, 2H); ^{13}C NMR δ 24.1, 61.1, 124.2, 126.4, 127.4, 129.4, 150.7.

1,4-Bis(bromomethyl)-2,3-diethoxynaphthalene (9b). By using the general procedure used for **9a**, **9b** was obtained in 75% yield from **8b** as light yellow fine needles (acetone−hexane): mp 150 °C dec; ^{1}H NMR (300 MHz) δ 1.50 (t, J = 12 Hz, 6H), 4.23 (m, 4H), 5.05 (s, 4H), 7.58 (m, 2H), 8.07 (m, 2H); ^{13}C NMR δ 16.1, 24.5, 69.6, 124.3, 126.2, 127.4, 129.3, 150.1.

1,4-Bis(bromomethyl)-2,3-di-*n*-propoxynaphthalene (9c). By using the general procedure used for **9a**, **9c** was obtained in 75% yield from **8c** after column chromatography as a white powder: mp 113 °C dec; ^{1}H NMR (500 MHz) δ 1.12 (t, J = 7 Hz, 6H), 1.92 (m, 4H), 4.12 (t, J = 6 Hz, 4H), 5.04 (s, 4H), 7.57 (m, 2H), 8.07 (m, 2H); ^{13}C NMR δ 10.7, 23.9, 24.5, 75.6, 124.3, 126.2, 127.3, 129.4, 150.3.

1,4-Bis(bromomethyl)-2,3-di-*n*-butoxynaphthalene (9d). By using the general procedure used for **9a**, **9d** was obtained in 62.0% yield from **8d** after column chromatography as a white powder: mp 93−94 °C dec; ^{1}H NMR (500 MHz) δ 1.03 (t, J = 7 Hz, 6H), 1.57 (m, 4H), 1.87 (m, 4H), 4.15 (t, 4H), 5.03 (s, 4H), 7.57 (m, 2H), 8.06 (m, 2H); ^{13}C NMR δ 14.2, 19.5, 24.5, 32.7, 73.9, 124.3, 126.2, 127.3, 129.4, 150.3.

1,4-Bis(hydroxymethyl)-2,3-dimethoxynaphthalene (10a). To a stirred mixture of **9a** (3.70 g, 9.89 mmol) and $CaCO_3$ (15.7 g, 157 mmol) was added aqueous 50% dioxane (200 mL) and the mixture was heated at reflux for 3 d. After the solvent was evaporated, the residue was dissolved in aqueous 6 M HCl (25 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was washed with distilled water, dried over $MgSO_4$, and filtered. The solvent was evaporated to afford a colorless solid (2.40 g), which was purified by chromatography (4:6 hexane: ethyl acetate) to afford **10a** in 75.0% (1.86 g) yield as a colorless powder: mp 180−1 °C; ^{1}H NMR (300 MHz) δ 1.88 (t, J = 10 Hz, 2H) 3.98 (s, 6H), 5.19 (d, J = 9.5 Hz, 4H), 7.54 (m, 2H), 8.16 (m, 2H); ^{13}C NMR δ 56.4, 62.0, 124.4, 126.1, 129.1, 130.2, 150.7; GC-MS 248 (M^+,80), 201 (95), 186 (30), 128 (70), 115 (100), 77, 31.

1,4-Bis(hydroxymethyl)-2,3-diethoxynaphthalene (10b). By using the general procedure used for **10a**, **10b** was obtained in 71.9% yield after chromatography (3:7 hexanes−ethyl acetate) as a colorless powder: mp 173−4 °C. ^{1}H NMR (300 MHz) δ 1.44 (t, J = 11.5 Hz, 6H), 1.98 (t, J = 9.5 Hz, 2H), 4.16 (m, 4H), 5.19 (d, J = 9.5 Hz, 4H), 7.51 (m, 2H), 8.15 (m, 2H); ^{13}C NMR δ 16.0, 56.6, 70.5, 124.5, 125.9, 129.3, 130.2, 149.8; GCMS 276 (M^+, 30), 201(25), 186 (60), 128 (70), 115 (100), 77.

1,4-Bis(hydroxymethyl)-2,3-di-*n*-propoxynaphthalene (10c). By using the general procedure used for **10a**, **10c** was obtained in 71.3% yield from **9c** after chromatography (2:8 hexanes−ethyl acetate) as a colorless powder: mp 155−156 °C; ^{1}H NMR (500 MHz) δ 1.09 (t, J = 8 Hz, 6H), 1.86 (m, 4H), 1.96(t, 2H), 4.03 (t, J = 7 Hz, 4H), 5.17 (d, J = 6 Hz, 4H), 7.50 (m, 2H), 8.14 (m, 2H); ^{13}C NMR δ 10.7, 23.8, 56.6, 76.6, 124.4, 125.9, 129.2, 130.2, 150.0; MS 304 (M^+, 60), 215 (10), 186 (100), 128 (40), 115 (40), 77, 41.

1,4-Bis(hydroxymethyl)-2,3-di-*n*-butoxynaphthalene (10d). By using the general procedure used for **10a**, **10d** was obtained in 71.8% yield from **9d** after chromatography (2:8 hexanes−ethyl acetate) as a colorless powder: mp 160 °C; ^{1}H NMR (500 MHz) δ 1.01 (t, 6H), 1.57 (m, 8H, overlap with HOD exchange signal), 1.84 (m, 4H), 1.91 (t, 2H), 4.08 (t, J = 7 Hz, 4H), 5.17 (d, J = 6 Hz, 4H), 7.50 (m, 2H), 8.14 (m, 2H); ^{13}C NMR 14.1, 19.5, 32.6, 56.5, 74.9, 124.4, 125.8, 129.2, 130.2, 150.0; GCMS 332 (M^+, 30), 202 (10), 186 (100), 156, 115, 57, 41.

Synthesis of 5a. To a stirred suspension of powered 85% KOH (1.12 g, 20.0 mmol) in dioxane (20 mL) preheated to 75−85 °C was added a solution of **9a** (748 mg, 2.00 mmol) and **10a** (496 mg, 2.00 mmol) in dioxane (40 mL) over 2.5 h with use of a syringe pump. The mixture was heated at 75−85 °C with stirring for another 16 h. After the dioxane was evaporated water (30 mL) was added and the residue was neutralized with aqueous 3 M HCl, extracted with $CHCl_3$ (2 × 50 mL), and dried over $MgSO_4$. After the solvent was evaporated, the crude product was purified by PLC (3:7 ethyl acetate−hexane) to afford 169 mg of **5a** in 18% yield from **9a** and **10a** as colorless fine needles (MeCN−MeOH): mp 152−6 °C; ^{1}H NMR (500 MHz) δ 3.80 (s, 6H), 5.05 (s, 4H), 6.76 (m, 2H), 7.41 (m, 2H); ^{13}C NMR δ 62.0, 62.6, 124.2, 125.3, 126.9, 130.4, 150.9; +MALDI-TOF MS (m/z) 959.0 (M + K^+, 32%), 943.2 (M + Na^+, 100%); and **11a** as a colorless semisolid (32 mg, 3.5%); ^{1}H NMR (500 MHz) δ 3.87 (s, 6H), 5.06 (s, 4H), 7.14 (m, 2H), 7.86 (m, 2H); ^{13}C NMR δ 62.0, 63.2, 125.0, 125.5, 126.6, 130.7, 151.2; +MALDI-TOF MS (m/z) 1419.8 (M + K^+, 23%), 1403.8 (M + Na^+,100%).

Synthesis of 5b. By using the general procedure used for **5a**, **5b** was obtained in 15% yield from **9b** after PLC (1.5:8.5 ethyl acetate−hexane) and **10b** as colorless fine needles (MeCN−MeOH): mp 120−124 °C; ^{1}H NMR (300 MHz) δ 1.40 (t, J = 12 Hz, 6H), 4.05 (m, 4H), 5.05 (s, 4H), 6.69 (m, 2H), 7.32 (m, 2H); ^{13}C NMR δ 16.0, 62.8, 70.4, 124.1, 125.2, 127.1, 130.4, 150.1; +MALDI-TOF MS (m/z) 1072.2 (M + K^+, 100%), 1056.2 (M + Na^+, 33%).

X-ray Crystal Structure of 5b. A colorless fragment crystal (acetonitrile−methanol), mp 120−124 °C, of $H_{77.25}N_{1.75}O_{12}C_{67.50}$ having approximate dimensions of 0.50 × 0.45 × 0.41 mm^3 was mounted on a glass fiber. Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell, space group $Pna2_1$ (no. 33), with dimensions a = 17.2682(7) Å, b = 14.3146(5) Å, c = 25.106(1) Å, V = 6205.9(4) Å^3. For Z = 4 and fw = 1105.11, the calculated density is 1.18 g/cm^3. Intensity data were made at 193 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) and a sealed tube source radiation to $2\theta_{max}$ = 52.8°; 44 279 reflections converged to a final R_{int} = 0.026 for 12658 unique relections; 10 993 observations with $I > 2.00\sigma(I)$. Final R1 and wR2 values were 0.044 and 0.129, respectively, and GoF indicator = 1.03.[24]

Synthesis of 5c. By using the general procedure used for **5a**, **5c** was obtained in 15% yield after PLC (1.25:8.75 ethyl acetate−hexane) from **9c** and **10c** as a colorless powder: mp 98−103 °C. ^{1}H NMR (500 MHz) δ 1.07 (t, J = 7 Hz, 6H), 1.86 (m, 4H), 3.95 (t, 4H), 5.05 (s, 4H), 6.65 (m, 2H), 7.31 (m, 2H); ^{13}C NMR δ 10.9, 23.7, 62.8, 76.6, 124.1, 125.1, 127.0, 130.4, 150.3; +MALDI-TOF MS (m/z) 1183.8 (M + K^+, 27%), 1167.8 (M + Na^+, 100%).

Synthesis of 5d. By using the general procedure used for **5a**, **5d** was obtained in 12% yield from **9d** and **10d** as a colorless powder, after PLC (1:9 ethyl acetate:hexane), mp 160−2 °C; ^{1}H NMR (500 MHz) δ 0.99 (t, 6H), 1.55 (m, 5H, overlap with HOD exchange signal), 1.81 (m, 4H), 3.98 (t, 4H), 5.04 (s, 4H), 6.64 (m, 2H), 7.29 (m,2H); ^{13}C NMR δ 14.2, 19.6, 32.7, 62.8, 74.9, 124.1, 125.1, 127.0, 130.4, 150.3; +MALDI-TOF MS (m/z) 1296.8 (M + K^+, 100%), 1280.8 (M + Na^+, 96%); and **11d** (1.6%): ^{1}H NMR δ 0.99 (t, 6H), 1.55 (m, 5H, overlap with HOD exchange signal), 1.81 (m, 4H), 4.03 (t, 4H), 5.05 (s, 4H), 7.08 (m, 2H), 7.82 (m, 2H); ^{13}C NMR δ 14.2, 19.6, 32.7, 63.6, 74.9, 125.1, 125.3, 126.7, 130.7, 150.6; +MALDI-TOF MS (m/z) 1908 M + Na^+ (25%).

(24) Atomic coordinates for the structure of **5b** have been deposited with the Cambridge Crystallographic Data Centre. These are available upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EK, U.K.

Job Plot Determinations. Job plot (method of continuous variations) determinations were conducted by varying the mole fractions of TMACl and **5a** or **5b**, using solutions which were ca. 8.94×10^{-4} M in $CDCl_3$ solution. After mixing, each of the respective solutions (total combined final volumes = 1.00 mL) in a series of nine NMR tubes was sonicated for approx 10 min and then allowed to stand overnight. NMR measurements were recorded at 298 K and 500 MHz, using a 16 K data table, for a 10.0 ppm sweep width having a digital resolution of 0.321 Hz. Job plots were produced by plotting the mole fractions of TMACl against the mole fractions of either **5a** or **5b**, multiplied by the $\Delta\delta$ determined for each set of chemical shifts present for both the host and guest molecules. In all cases the plots clearly revealed maxima at 0.5 indicating the formation of 1:1 complexes.

Association Constant Determinations. The association (stability) constants for the complexation in $CDCl_3$ between **5a** and **5b** with TMACl were determined by ^{1}H NMR spectroscopy. Changes in the chemical shift ($1/\Delta\delta$) of the methyl signal of TMACl as a function of 1/[**5a**] or [1/**5b**] were determined, and K_{ASSOC} values were determined by using the Benesi−Hildebrand treatment or the Foster−Fyle treatment, by plotting $\Delta\delta/$[**5a**] or $\Delta\delta/$[**5b**] versus $\Delta\delta$. In a typical experiment, aliquots ranging from 20 to 80 μL of approximately 10^{-3} M stock solutions of either **5a** (1.22×10^{-3} M) or **5b** (1.30×10^{-3} M) were added to a series of individual NMR tubes which each contained 1.00 mL of a saturatured solution of TMACl (ca. 8.94×10^{-4} M). The resulting solutions were sonicated for ca. 10 min, were left overnight before NMR measurements were recorded at 298 K and 500 MHz, as before.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Council of Canada and Memorial University of Newfoundland. We thank Dr. Michael Ferguson, University of Alberta for the X-ray data collection. We also acknowledge Ms. Erin Dodd, Memorial University of Newfoundland for her contributions to the preliminary work in this area.

Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectra of compounds **5a**−**d**, **8a**−**d**, **9a**−**d**, **10a**−**d**, **11c**, and **11d**; a PLUTO figure for **5b** showing the numbering system employed for the X-ray structure determination, as well as figures showing the orientation of the acetonitrile guest molecules relative to the planes of naphthyl subunits **B** and **D**; and the Job plots, and the data used for K_{ASSOC} determinations for the complexation of TMACl with **5a** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0484427