J. Org. Chem. **1996,** *61,* 4282–4288

Lower Rim–Upper Rim Hydrogen-Bonded Adducts of Calix[4]arenes

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Received February 14, 1996[⊗]

An upper-rim-substituted calix[4]arene tetracarboxylic acid forms hydrogen-bonded duplexes with lower-rim-substituted tetra(4-pyridyl)- and tetra(3-pyridyl)calix[4]arenes in chloroform. The formation of these adducts was studied by extraction experiments. The association constants determined *via* ^{1}H NMR dilution experiments in $CDCl_3$ are 7.6×10^3 and 1.3×10^3 M^{-1} for the 4-pyridyl and the 3-pyridyl derivative, respectively. IR studies in the solid state and in solution indicate that the interaction is based on hydrogen bonding and that the degree of proton transfer is negligible. VPO measurements support the formation of 1:1 adducts.

Introduction

In recent years there has been an increased interest in the construction of noncovalently bonded aggregates.[1–4] Since material characteristics are determined by the structure and organization of the individual components, a careful study of molecular self-organization and self-assembly should provide information about how molecular functionalities are translated into macroscopic functions. The relatively small size (of many) of the assemblies of well-defined shape, size, and dimensionality may lead to novel properties.[5] The resulting materials may find application in the fields of nonlinear optics, electronics, photonics, and information storage and processing.

Calix[4]arenes[6] have proved to be very useful building blocks in the synthesis of receptors for cations,[7] anions,[8] and neutral molecules.[9] The cyclic skeleton provides substantial preorganization, and this, in combination with the many possibilities of selective functionalization, makes it possible to tune the molecule toward the desired application.

The preorganization of functional units not only plays a very important role in molecular recognition but is also of premier importance in the self-assembly of larger structures.[10] In other words, the specific positioning of moieties that are able to interact on an associative basis is part of the information that is needed in the self-assembly process.

Even though calix[4]arenes seem to meet the prerequisites needed for a molecule to be of any interest in the construction of well-defined aggregates, very little effort has been devoted to the behavior of calix[4]arenes in noncovalent aggregation processes.[11]

The first hydrogen-bonded aggregates of calix[4]arenes were described only a few years ago by our group.[12] A calix[4]arene fixed in the cone conformation substituted with a self-complementary pyridone moiety dimerizes in chloroform with a dimerization constant of 100 M^{-1}, comparable to that of simple pyridones.[13,14] However, attaching a second pyridone moiety to the calix[4]arene did not give rise to well-defined dimers; instead, a mixture of oligomers was obtained. The second example was described by Shinkai *et al.*[15] A hydrogen-bonded duplex was formed through the interaction between a calix[4]arene with four carboxyl groups and a calix[4]-arene with four stilbazole moieties. Recently, Pochini *et al.* described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acids.[16] In these three cases described above, all hydrogen-bonding groups are located at the upper rim.[17]

In this paper we describe the first well-defined hydrogen-bonded aggregates in which a calix[4]arene substi-

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1996.

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(14) All association constants given are in chloroform at 298 K unless stated otherwise.

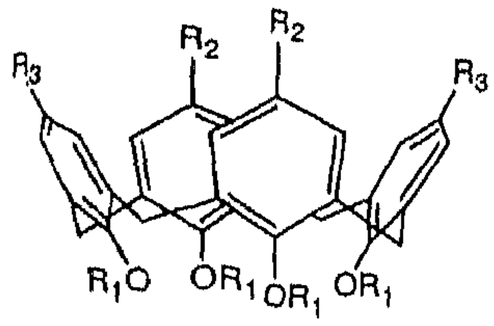
(15) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255.

(16) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454.

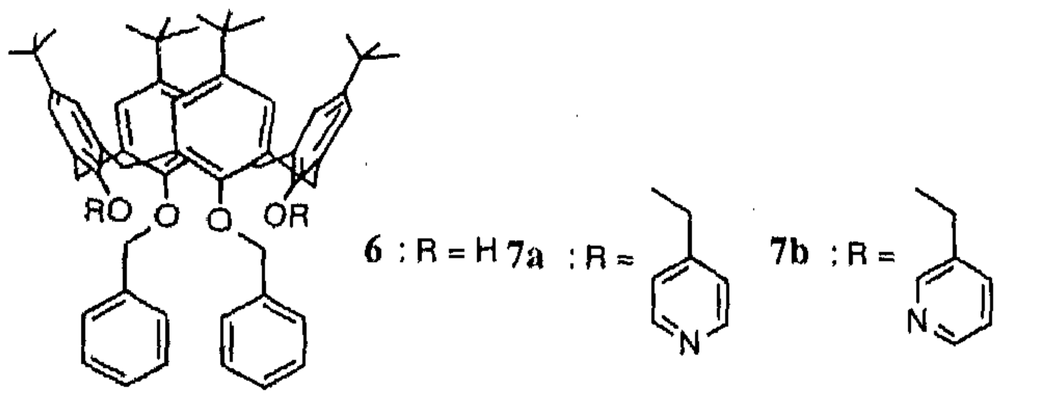
(17) Recently Shinkai *et al.* reported the formation of hydrogen-bonded complexes/structures comprising calix[4]arenes substituted with diaminopyridine moieties at the lower rim and simple barbituric acid derivatives: Lhotak, P.; Shinkai, S. *Tetrahedron Lett.* **1995**, *36*, 4829.

S0022-3263(96)00308-8 CCC: $12.00

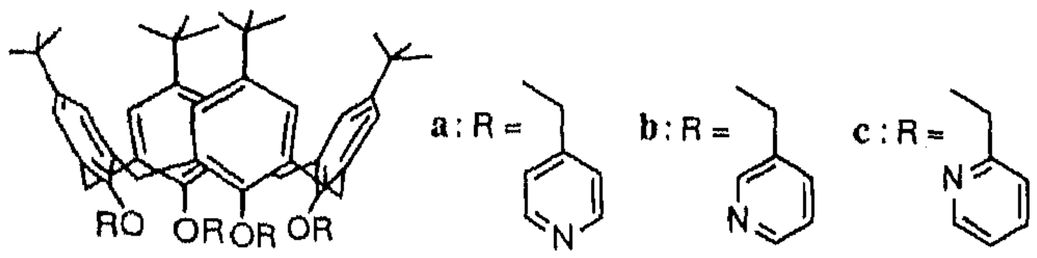
Chart 1



1 : R_1 = EtOEt, R_2 = H, R_3 = CHO
2 : R_1 = EtOEt, R_2 = H, R_3 = COOH
3 : R_1 = C_8H_{17}, R_2 = R_3 = H
4 : R_1 = C_8H_{17}, R_2 = R_3 = CHO
5 : R_1 = C_8H_{17}, R_2 = R_3 = COOH



6 : R = H **7a** : R = **7b** : R =



a : R = **b** : R = **c** : R =

8a-c

tuted with hydrogen-bonding groups at the upper rim interacts with calix[4]arenes substituted with complementary hydrogen-bonding groups at the lower rim. The hydrogen bonding interaction used is that between carboxylic acids and pyridines, the effectiveness of which in supramolecular chemistry has been described by several groups.[18]

Results and Discussion

Synthesis. To investigate the interaction between upper rim- and lower rim-substituted calix[4]arenes compounds **2**, **5**, **7a,b**, and **8a–c** were synthesized (Chart 1). These compounds make it possible to compare the 2-fold functionalized calix[4]arene derivatives (**2** and **7a,b**) with the 4-fold functionalized derivatives **5** and **8a–c**. This is expected to provide information about the strength and stoichiometry of the interaction, while the different points of attachment of the pyridine moieties should give insight in geometrical aspects and the nature of the interaction.

Calix[4]arenedicarboxylic acid **2** was prepared in 61% yield by oxidation of diformylcalix[4]arene **1**[19] with sodium chlorite and sulfamic acid.[20] Calix[4]arene-tetracarboxylic acid **5** was synthesized starting from tetrakis(octyloxy)calix[4]arene **3**. Exhaustive formylation of **3**, using α,α-dichloromethyl methyl ether and titanium tetrachloride, afforded tetraformyl derivative **4** in 56% yield, which was oxidized using sodium chlorite and sulfamic acid to give tetracarboxylic acid **5** in 87% yield.[21]

The dipyridylcalix[4]arenes **7a** and **7b** were synthesized in 32% and 66% yield, respectively, by reaction of bis(benzyloxy)calix[4]arene **6** with a large excess (10 equiv) of the HCl salt of the corresponding picolyl chlorides under strongly basic conditions (NaH, 25 equiv) in DMF, similar to the procedure described by Pappalardo *et al.* for the preparation of tetrapyridylcalix[4]-arene **8c**.[22] The easily accessible bis(benzyloxy)calix[4]-arene **6**[23] was used in order to avoid undesirable interactions of the pyridine nitrogens with the phenolic hydrogens and to allow for a good comparison with the tetrapyridylcalix[4]arenes **8a–c**. The latter were synthesized according to the procedure of Pappalardo *et al.*[22] The yields were 53% and 71% for **8a** and **8b**, respectively. The structure of the synthesized compounds was determined by ^{1}H NMR, ^{13}C NMR, FAB-MS, and elemental analyses.

^{1}H NMR Studies. In order to investigate the interactions between dicarboxylic acid **2** and dipyridyls **7a** and **7b**, equimolar amounts of **2** and the corresponding dipyridyl derivative were mixed in $CDCl_3$ at a concentration of 5 mM. In the ^{1}H NMR spectra of these mixtures no changes were observed compared with the ^{1}H NMR spectra of the free compounds. From this it was concluded that the interaction between the dipyridyls **7a,b** and dicarboxylic acid **2** is too weak to compete effectively with the dimerization of **2**.[24] Similarly, no changes were observed in the spectra of equimolar mixtures of dicarboxylic acid **2** and tetrapyridyls **8a–c**. Also, in this case strong dimerization most probably prevents the hydrogen-bonded interaction of **2** with **8a–c**.

Contrary to the above, the mixtures of tetracarboxylic acid **5** and tetrapyridyls **8a–c** show much more interesting behavior. The solubility of **5** in chloroform is very low, even though the lower rim is substituted with four octyl chains. However, after a 1:1 mixture of **5** was warmed with tetra(4-pyridyl) **8a**, a clear solution was obtained, even at concentrations higher than 0.02 M, and this solubilization is accompanied by downfield shifts of the aromatic protons of **8a**. When less than 1 equiv of **8a** was added, ^{1}H NMR analysis of the obtained suspensions showed that the amount of carboxylic acid which had dissolved is equal to that of the amount of **8a** added. The results of this extraction series are depicted in Figure 1. These results strongly suggest the formation of a 1:1 complex of tetracarboxylic acid **5** and tetra(4-pyridyl) **8a** (Chart 2, **9a**).

Virtually identical results were obtained for mixtures of **5** and tetra(3-pyridyl) **8b** (Figure 2). Again, upfield

(18) This interaction has been used in the design of receptors for amines by Rebek *et al.*: Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426. The interaction is also used to stabilize liquid crystallinity in polymers or to introduce ferroelectricity. See, for instance: Wilson, L. M. *Macromol.* **1994**, *27*, 6683. Kumar, U.; Fréchet, J. M. J.; Kato, T.; Ujiie, S.; Timura, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1531. The same interaction was used by Shinkai *et al.* in the construction of the upper rim hydrogen-bonded calix[4]arene duplexes mentioned above. Further, interesting solid state structures were obtained by mixing isophthalic acids with pyrimidine or pyrazine: Valiyaveetil, S.; Enkelmann, V.; Müllen, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2097.

(19) (a) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936. (b) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, *60*, 1448.

(20) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

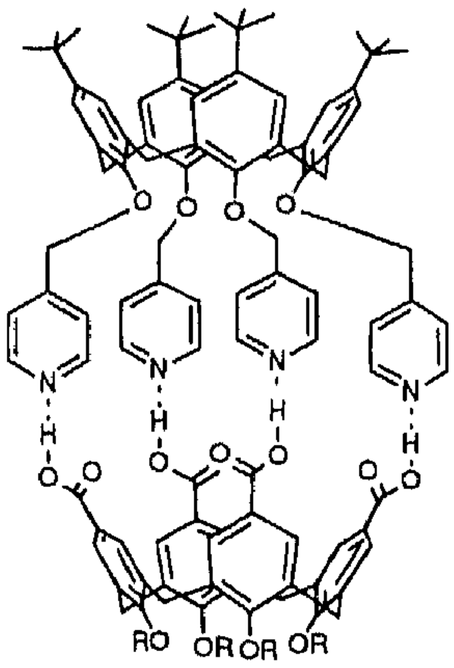
(21) The route *via* the tetraformyl derivative has the advantage over the procedure described by Regen *et al.* of being clean and producing the tetracarboxylic acid in good yield after very simple purification, especially on a larger scale. Conner, M.; Janout, V.; Regen, S. L. *J. Org. Chem.* **1992**, *57*, 3744.

(22) Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallager, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.

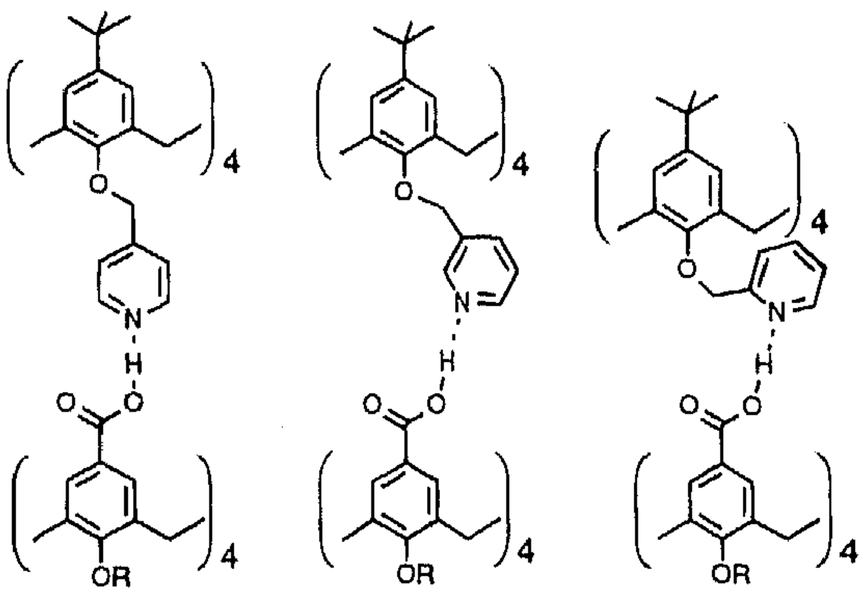
(23) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.

(24) Dicarboxylic acid **2** is quite soluble in chloroform and is assumed to be present as a strongly hydrogen-bonded dimer in apolar solvents like chloroform, since such behavior was established recently for a closely related compound: (a) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454.

Chart 2



9a



9a **9b** **9c**

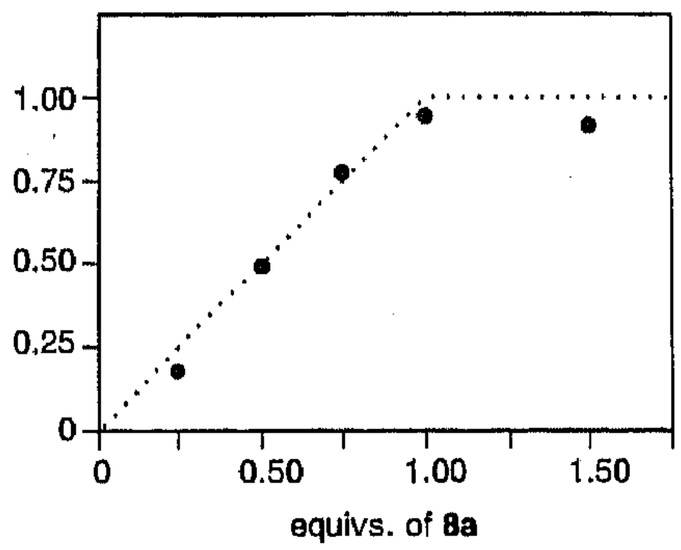


Figure 1. Extraction of **5** in $CDCl_3$ by **8a**: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex.

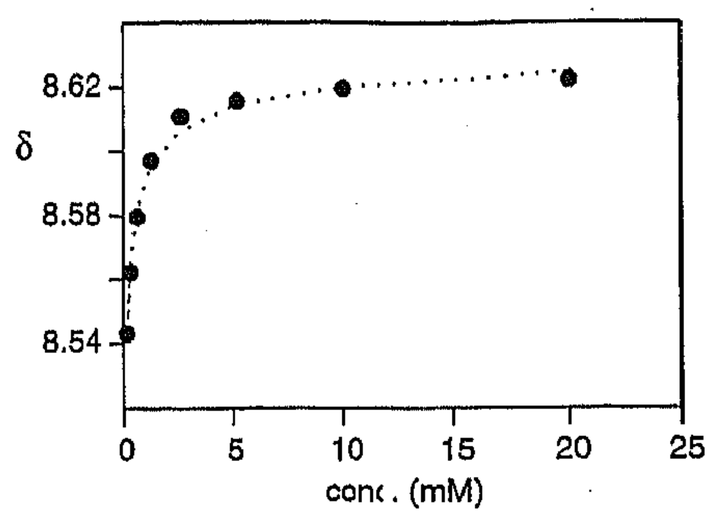


Figure 3. Dilution of 1:1 complex of **5** and **8a**: ● = measured; ··· = calculated for $K = 7.6 \times 10^{-3}$ M^{-1}.

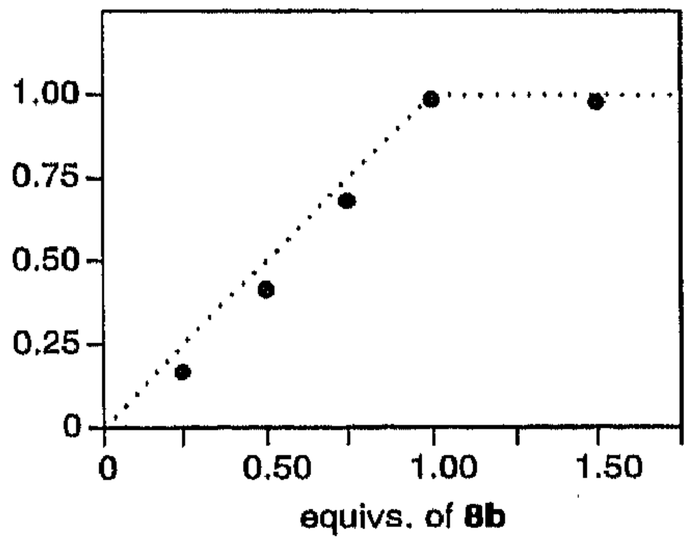


Figure 2. Extraction of **5** in $CDCl_3$ by **8b**: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex.

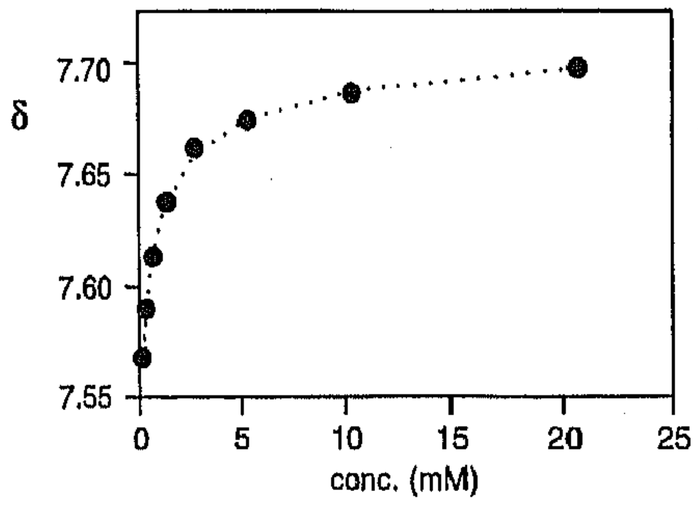


Figure 4. Dilution of 1:1 complex of **5** and **8b**: ● = measured; ··· = calculated for $K = 1.3 \times 10^{-3}$ M^{-1}.

shifts for the aromatic protons of **8b** are observed in the ^1H NMR spectra, and an extraction series indicates the formation of a 1:1 adduct.

When more than 1 equiv of tetrapyridyl **8a** (or **8b**) was added, the downfield shifts of the aromatic protons of the tetrapyridyl **8a** (or **8b**) decreased as the concentration of tetrapyridyl increased. A decrease in the changes of these shifts is also observed when a 1:1 solution of the tetracarboxylic acid **5** and the tetrapyridyl are diluted. The results of these dilution experiments are depicted in Figures 3 and 4. The hyperbolical shape of the curves in Figures 3 and 4 indicates that the interaction between the tetracarboxylic acid **5** and the tetrapyridyls **8a** and **8b** is of an associative nature and is not the result of simple proton transfer from acid to base.[25] Proton transfer was also not expected based on the estimated pK_a's of the components.[26,27]

When the data of Figures 3 and 4 are treated as dilution curves for 1:1 association of the molecules, complexation constants of 7.6×10^3 and 1.3×10^3 M^{-1} for the association of tetracarboxylic acid **5** with tetrapyridyls **8a** and **8b**, respectively, can be calculated by the method of Hormann and Dreux.[28,29] The somewhat stronger interaction of **5** with tetra(4-pyridyl) **8a** as

(25) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH Publishers: Weinheim, 1991.

(26) Investigations on solid state mixtures of pyridine and chloroacetic acids using IR spectroscopy[a] and ^{35}Cl NMR spectroscopy[b] indicated that the degree of proton transfer is strongly correlated with the difference in pK_a of the two components in water. For ΔpK_a's smaller than 2.0 the interaction is mainly of the neutral hydrogen bond type. Similar characteristics have been found for the interaction between carboxylic acids and pyridine in chloroform.[c] It was further shown that there is a critical ΔpK_a of 3.7 above which the solid state adducts are predominantly ionized and below which the adducts are predominantly unionized.[d] (a) Dega-Szafran, Z.; Grech, E.; Naskret-Barciszewska, M. Z.; Szafran, M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 250. (b) Chihara, H.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1980. (c) Barrow, G. M. *J. Am. Chem. Soc.* **1956**, *78*, 5802. (d) Johnson, S. L.; Rumon, K. A. *J. Phys. Chem.* **1965**, *69*, 74.

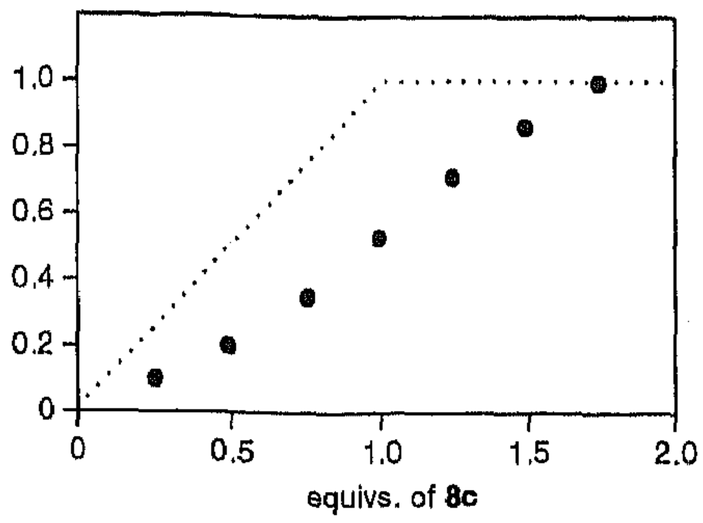


Figure 5. Extraction of **5** in $CDCl_3$ by **8c**: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex.

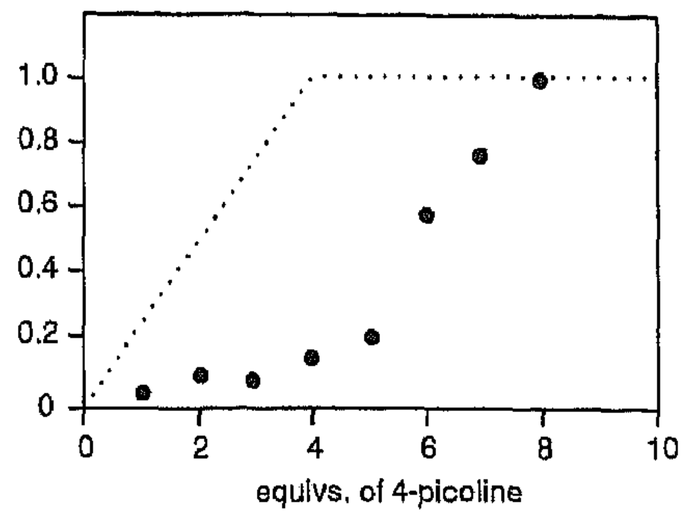


Figure 6. Extraction of **5** in $CDCl_3$ by 4-picoline: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex.

expressed by the relative magnitudes of the K values is most probably the result of the higher basicity of the 4-pyridyl derivative compared to the 3-pyridyl derivative.[27d,30]

The interaction between tetracarboxylic acid **5** and tetra(2-pyridyl) **8c** differs largely from that between **5** and tetrapyridyls **8a** or **8b**. Even after refluxing, no solutions were obtained for mixtures with less than 1.75 equiv of **8c** (Figure 5). The latter result was somewhat expected on the basis of studies of CPK molecular models of the complexes: it is not possible for all four nitrogens of tetra(2-pyridyl) **8c** to interact simultaneously with the four carboxyl groups of **5**. The CPK models indicated that tetracarboxylic acid **5** in the cone conformation can interact with tetra(4-pyridyl) **8a** and tetra(3-pyridyl) **8b** by formation of four hydrogen bonds, schematically depicted as **9a** and **9b**, respectively. In complex **9b** the rotation of the pyridine rings, which is necessary to orient the pyridine nitrogens correctly, also causes the pyridines to diverge slightly, making the molecule compatible with the cone conformation of **5**, in which the carboxylic acid groups are slightly divergent.

The inability of tetra(2-pyridyl) **8c** to solubilize 1 equiv of tetracarboxylic acid **5** together with the observation that at least 8 equiv of 4-picoline is needed to solubilize tetracarboxylic acid **5** at room temperature (Figure 6) further illustrate the cooperative nature of the interaction of the four pyridine moieties of tetra(4-pyridyl) **8a** and tetra(3-pyridyl) **8b** with tetracarboxylic acid **5**.

An important feature of the mixtures of tetracarboxylic acid **5** and all of the pyridyl compounds (including 4-picoline) is that two separate signals, at 6.7 and 8.0 ppm, are present for the aromatic protons of **5**. The two resonances have the same chemical shift as the two sharp resonances that appear upon cooling of a solution of **5** in $CDCl_2CDCl_2$ to −4 °C and are at equal distance from the singlet that is observed for these protons at 100 °C.[31,32] The two signals observed at low temperature can be associated with the tetracarboxylic acid **5** being present in the *pinched cone* conformation, in which two of the aromatic units become parallel while the other two become more divergent. This observation indicates that the interaction of the tetracarboxylic acid **5** with the tetrapyridyls **8a** and **8b** slows down the interconversion between the two equivalent pinched cone conformations. In other words, the intermolecular hydrogen bonding influences the flexibility of the calix[4]arene skeleton of the tetracarboxylic acid **5** substantially.

The observation of the pinched cone conformation of tetracarboxylic acid **5** could in principle also be explained by the formation of an *intra*molecular hydrogen bond in addition to two *inter*molecular hydrogen bonds, *i.e.* the intramolecular hydrogen bond causes the pinching of the tetracarboxylic acid **5**, while the remaining carboxyl groups are available for intermolecular association. Another possibility is that two tetracarboxylic acids adopt a pinched cone conformation and self-associate in the manner that was described by Pochini *et al.* for a corresponding calix[4]arene dicarboxylic acid[16] and that the remaining four divergent carboxyl groups interact with pyridine moieties of tetrapyridyls **8a** and **8b** in a 2:2 fashion.

In the two cases described above, only two of the four pyridine moieties of the tetrapyridyls are involved in the intermolecular interaction with the tetracarboxylic acid. However, the ratio of the components in these complexes is the same as those depicted in Chart 2, *i.e.*, 1:1. This prompted the investigation of the interaction between tetracarboxylic acid **5** and the dipyridylcalix[4]arenes **7a** and **7b**.

Extraction experiments in $CDCl_3$ showed that in the case of **7a** at least 2 equiv of the dipyridylcalix[4]arene is needed to completely solubilize tetracarboxylic acid **5**, and in the case of **7b** 3 equiv of the dipyridylcalix[4]arene is required (Figures 7 and 8, respectively). These observations further support the formation of 1:1 adducts of tetracarboxylic acid **5** and tetrapyridyls **8a** and **8b** as a result of simultaneous hydrogen bonding between the

(27) The pK_a of the calix[4]arene carboxylic acids is estimated to be slightly higher than 4.8, based on the acidities of benzoic acid, *p*-propoxybenzoic acid, and 3,5-dimethylbenzoic acid: (a) Eberson, L. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; John Wiley & Sons: London, 1969; pp 211–293. (b) Hadži, D.; Detoni, S. In *The Chemistry of Acid Derivatives, Suppl. B*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1979; pp 213–266. (c) Kortüm, G.; Vogel, W.; Andrussow, K. *Dissociation Constants of Organic Acids in Aqueous Solution*; Butterworths: London, 1961. (d) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1972. The electron-donating substituent on the pyridine ring will lead to an increase in pK_a value. Considering the pK_a values of methyl-substituted pyridines and taking into account that the ether oxygens in **7** and **8** decrease the electron-donating ability of the methyl groups, the first pK_a of compounds **7** and **8** is expected to be lower than 6.02, but higher than 5.21, being closer to the former than to the latter. These estimates result in a minimum value for ΔpK_a of 0.90 and a maximum value of 1.72. Since both of these values are < 2 it may be assumed that any interaction between these acids and bases will be of a hydrogen-bonded nature, with negligible proton transfer.

(28) Horman, I.; Dreux, B. *Helv. Chim. Acta* **1984**, *67*, 754.

(29) The possible self-association of the components has not been taken into account since in the case of tetracarboxylic acid **5** this could not be determined on account of its very low solubility in chloroform. The estimated error in the K values is about 10%.

(30) Qualitatively, the stronger interaction is also indicated by the ease of which the initial suspensions of the 1:1 mixtures become clear solutions.

(31) Conner, M.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 9670.

(32) The same studies show that at room temperature tetracarboxylic acid **5** is still present in the pinched cone conformation with C_{2v} symmetry.

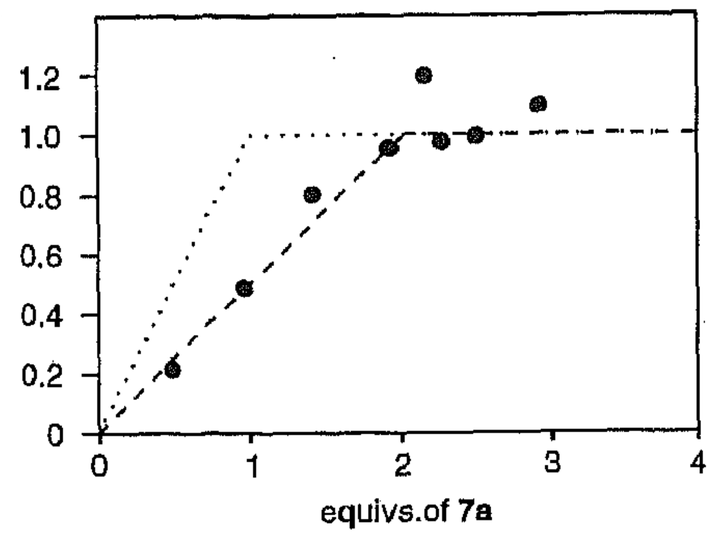


Figure 7. Extraction of **5** in $CDCl_3$ by **7a**: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex; - - - = expected for 1:2 complex.

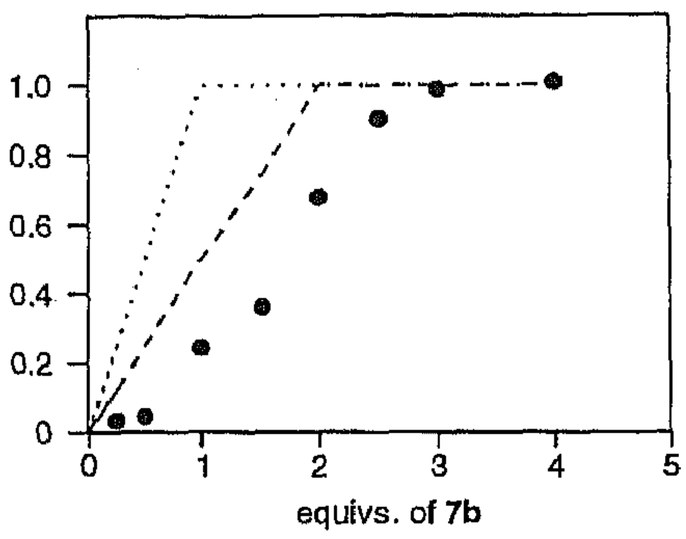


Figure 8. Extraction of **5** in $CDCl_3$ by **7b**: ● = fraction of **5** dissolved; ··· = expected for 1:1 complex; - - - = expected for 1:2 complex.

four carboxyl groups and the four pyridine moieties. These duplexes are then stabilized by two strong and two weak hydrogen bonds, strong with parallel COOH groups and weak with divergent COOH groups.

Vapor Pressure Osmometry. The association between **5** and **8a** and between **5** and **8b** were further characterized by vapor pressure osmometric measurements in chloroform. For the **5·8a** associate a molecular weight of 2004 ± 200 g/mol was determined, whereas for the **5·8b** associate a molecular weight of 2179 ± 120 g/mol was determined. Both values agree well with the expected molecular weight for a 1:1 complex, which is 2063 g/mol.

Infrared Spectroscopy. To investigate the nature of the interaction the tetracarboxylic acid **5** with the tetra(4-pyridyl) **8a** and the tetra(3-pyridyl) **8b** infrared spectroscopy was used. The interaction was studied both in the solid phase (KBr) and in solution (tetrachloroethane, 10 mM). For the former, the 1:1 mixtures of the tetracarboxylic acid **5** and the corresponding tetrapyridyl in chloroform were concentrated to dryness under reduced pressure. When the solid phase IR spectrum of the mixture of **5** and **8a** is compared to those of the free carboxylic acid and the free tetra(4-pyridyl) **8a** a broad signal of medium intensity appears around 1942 cm^{-1}. This signal has been assigned to the OH of carboxylic acids which are involved in hydrogen bonding to pyridine derivatives.[26d] Further, no change is observed for the C=O frequency of the carboxyl groups, which suggests that the carbonyls are not involved in the association process. Moreover, the fact that the carbonyl stretch is observed at 1702 cm^{-1} indicates that indeed no proton transfer occurs.[33] Similar observations were made in solution. Again, a broad signal is present at 1921 cm^{-1}, and no shifts were noticed for the carbonyl frequencies at 1700 cm^{-1}.

The results from the IR spectroscopic measurements of the interaction between the tetracarboxylic acid **5** and the tetra(3-pyridyl) **8b** are almost identical to those for the **5·8a** complex. In KBr the broad hydrogen bonding OH-signal appears at 1921 cm^{-1}, while the carbonyl frequency remains unchanged at 1702 cm^{-1}. In tetrachloroethane the broad OH signal appears at 1921 cm^{-1}, and the carbonyl stretch frequency is stable at 1699 cm^{-1}. From the above results, it can be concluded that the hydroxyl group of the tetracarboxylic acid **5** is involved in hydrogen-bonded interaction with both tetrapyridyls **8a** and **8b** and that no proton transfer occurs.

Conclusions

It has been shown by ^1H NMR and IR spectroscopy, together with VPO measurements, that the interaction between the calix[4]arenetetracarboxylic acid **5** leads to formation of well-defined hydrogen-bonded 1:1 associates with the tetra(4-pyridyl)calix[4]arene **8a** and the tetra(3-pyridyl)calix[4]arene **8b**. For geometrical reasons the formation of such an aggregate is not possible with the tetra(2-pyridyl)calix[4]arene **8c**. That the interaction involves the simultaneous formation of four hydrogen bonds was demonstrated by comparison with the dipyridyl derivatives **7a** and **7b**. No interaction was observed between the pyridylcalix[4]arenes and the dicarboxylic acid **2**, due to the strong self-association of the latter.

At first glance the results obtained for the combinations of the tetracarboxylic acid **5** and the tetra(4-pyridyl)- (**8a**) and the tetra(3-pyridyl)calix[4]arene (**8b**) are in line with those reported by Shinkai *et al.* for the association of a tetracarboxylic acid calix[4]arene and a tetrastilbazolecalix[4]arene.[15] The authors, however, did not report association constants, so no comparison can be made with the associates described in this paper with regard to the strength of the association. Furthermore, they did not observe any changes in chemical shift in the ^1H NMR spectra for either the tetracarboxyl component or the tetrastilbazole component. The main structural difference between the associate described by Shinkai *et al.* and the associates described in this paper is that the former consists of two calix[4]arenes which are both substituted at the upper rim, while the latter combine lower rim substituted tetrapyridylcalix[4]arenes with an upper rim substituted tetracarboxylcalix[4]arene. To the best of our knowledge this is the first example of a hydrogen-bonded calix[4]arene duplex that involves both the upper and the lower rim.

Experimental Section

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) using residual solvent protons as internal reference. Mass spectra were recorded using *m*-NBA as a matrix. Hexanes (refering to petroleum ether with bp 60–80 °C), CH_2Cl_2, and EtOAc were distilled from K_2CO_3. $CHCl_3$ was distilled from $CaCl_2$. DMF was dried over molecular sieves (4 Å) for at least 3 days. NaH was a 55–65% dispersion in mineral oil. Other chemicals were of reagent grade and were used without further purification. Flash column chromatography was performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh) from Merck. All reactions were carried out in an argon atmosphere unless

(33) Such proton transfer would cause a decrease of the carbonyl frequency to about 1670 cm^{-1}.

otherwise stated. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Diformyl- (**1**),[19] tetrakis(octyloxy)- (**3**),[21] bis(benzyloxy)- (**6**),[23] and tetra(2-pyridyl)calix[4]arene (**8c**)[22] were synthesized according to literature procedures.

25,26,27,28-Tetrakis(2-ethoxyethoxy)calix[4]arene-5,17-dicarboxylic Acid (2). To a solution of diformylcalix[4]arene **1** (0.25 g, 0.33 mmol) in $CHCl_3$ (10 mL) and acetone (30 mL) were added a solution of H_2NSO_3H (0.14 g, 1.4 mmol) in H_2O (1.0 mL) and a solution of $NaClO_2$ (0.12 g, 1.3 mmol) in H_2O (1.0 mL). The solution was stirred at rt for 3 h and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL), washed with 1 N HCl (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from MeOH to give the product in 61% yield: mp 273–275 °C; ^{1}H NMR δ 7.16 (d, 4 H, J = 7.4 Hz), 7.10–7.00 (m, 2 H), 6.78 (s, 4 H), 4.46 and 3.15 (ABq, 8 H, J = 13.7 Hz), 4.27 (t, 4 H, J = 6.3 Hz), 3.94 (t, 4 H, J = 4.7 Hz), 3.87 (t, 4 H, J = 6.3 Hz), 3.75 (t, 4 H, J = 4.7 Hz), 3.58, 3.51 (q, 4 H, J = 7.0 Hz), 1.23 (t, 6 H, J = 7.0 Hz), 1.16 (t, 6 H, J = 7.0 Hz); ^{13}C NMR δ 172.0, 159.2, 157.7, 136.3, 133.8, 129.8, 129.3, 123.0, 123.4, 73.9, 72.4, 69.6, 69.5, 66.6, 66.2, 30.8, 15.3, 15.2; FAB-MS *m/z* 800.0 (M^-, calcd 800.4); IR (KBr) 1697 cm^{-1} (C=O). Anal. Calcd for $C_{46}H_{56}O_{12}$: C, 68.98; H, 7.05. Found: C, 68.74; H, 6.88.

25,26,27,28-Tetrakis(1-octyloxy)calix[4]arene-5,11,17,23-tetracarboxaldehyde (4). To a solution of α,α-dichloromethyl methyl ether (1.40 mL, 15.5 mmol) in dry $CHCl_3$ (30 mL) was added freshly distilled $TiCl_4$ (2.0 mL, 18.2 mmol). After the resulting solution was cooled to −15 °C, a solution of tetrakis(octyloxy)calix[4]arene **3** (1.00 mL, 1.15 mmol) in dry $CHCl_3$ (20 mL) was added dropwise over 5 min. The reaction was stirred at −15 °C for 1 h, allowed to warm to rt, and stirred at rt for 18 h. The reaction was stirred at −15 °C for 1 h, allowed to warm to rt, and stirred at rt for 18 h. The reaction was carefully quenched with 1 N HCl (50 mL), and after the mixture was stirred for 1 h the layers were separated. The organic layer was diluted with CH_2Cl_2 (100 mL), washed with 1 N HCl (3 × 100 mL) and brine (1 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography (hexanes/EtOAc, first 90/10, later 75/25; charged as adsorbate on silica) and recrystallization from CH_2Cl_2/hexanes to give the product in 56% yield: mp 122–124 °C; ^{1}H NMR δ 9.57 (s, 4 H), 7.14 (s, 8 H), 4.48 and 3.34 (ABq, 4 H, J = 13.8 Hz), 3.95 (t, 8 H, J = 7.4 Hz), 2.00–1.75 (m, 8 H), 1.50–1.15 (m, 40 H), 0.88 (t, 12 H, J = 7.6 Hz); ^{13}C NMR δ 191.3, 161.9, 135.6, 131.4, 130.2, 75.7, 31.9, 30.9, 30.3, 29.8, 29.5, 26.2, 22.7, 14.1; FAB-MS *m/z* 986.0 ([M + H]$^+$, calcd 985.6); IR 1688 cm^{-1} (C=O). Anal. Calcd for $C_{64}H_{88}O_8$: C, 78.01; H, 9.00. Found: C, 77.99; H, 9.03.

25,26,27,28-Tetrakis(1-octyloxy)calix[4]arene-5,11,17,23-tetracarboxylic Acid (5). To a solution of **4** (0.63 g, 0.64 mmol) in $CHCl_3$ (30 mL) and acetone (90 mL) were added a solution of H_2NSO_3H (0.55 g, 5.6 mmol) in H_2O (3.0 mL) and a solution of $NaClO_2$ (0.46 g, 5.1 mmol) in H_2O (3.0 mL). The solution was stirred at rt for 18 h and quenched with 2 N HCl (50 mL), and the organic solvents were evaporated under reduced pressure. The white precipitate was filtered off, rinsed thoroughly with H_2O, and dried in *vacuo* over P_2O_5 to give **5** in 87% yield as a white solid: mp 330 °C dec; FAB-MS *m/z* 1072.4 ([M + Na]$^+$, calcd 1071.6); IR (KBr) 1694 cm^{-1} (C=O). Anal. Calcd for $C_{64}H_{88}O_{12}$: C, 73.25; H, 8.45. Found: C, 73.28; H, 8.46. For the ^{1}H and ^{13}C NMR spectra see ref 21.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-bis(benzyloxy)-26,28-bis[(4-pyridylmethyl)oxy]calix[4]arene (7a). 5,11,17,23-Tetra-*tert*-butylbis(benzyloxy)calix[4]arene (**6**) (0.41 g, 0.50 mmol) was added to a suspension of NaH (1.00 g, 25 mmol, 60% in oil, washed with hexanes) in dry DMF (20 mL). After the suspension was warmed for 30 min to 50 °C the mixture was allowed to cool to rt, whereupon 4-picolyl chloride hydrochloride (0.82 g, 5.0 mmol) was added in portions over 15 min. The reaction was stirred for 18 h at 60 °C and then quenched with MeOH (2 mL) and subsequently concentrated to dryness using an oil pump. The residue was taken up in CH_2Cl_2/H_2O (50 mL/25 mL), and after separation the organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 25 mL). After the organic layer was dried over Na_2SO_4 the solvent was removed by evaporation under reduced pressure. The residue was triturated with MeOH and recrystallized from CH_2Cl_2/hexanes to give **7a** in 32% yield: mp 247–249 °C; ^{1}H NMR δ 8.34 (AB, 4 H, J = 5.9 Hz), 7.35–7.15 (m, 14 H), 6.96, 6.60 (s, 8 H), 4.95 (s, 4 H), 4.73 (s, 4 H), 4.23 and 2.99 (ABq, 8 H, J = 12.7 Hz), 1.23, 0.95 (s, 18 H); ^{13}C NMR δ 152.8, 152.1, 149.5, 147.0, 145.3, 144.8, 137.7, 134.5, 132.6, 129.1, 128.3, 128.1, 125.7, 124.9, 123.6, 77.6, 74.6, 34.0, 33.8, 31.6, 31.3; FAB-MS *m/z* 1011.9 (M^+, calcd 1011.6). Anal. Calcd for $C_{70}H_{78}N_2O_4$: C, 83.13; H, 7.77; N, 2.77. Found: C, 83.17; H, 7.79; N, 2.51.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,27-bis(benzyloxy)-26,28-bis[(3-pyridylmethyl)oxy]calix[4]arene (7b) was synthesized following the same procedure as in the synthesis of **7a**, using 3-picolyl chloride hydrochloride: yield 66%; mp 237–239 °C; ^{1}H NMR δ 8.54 (m, 4 H), 7.59 (d, 2 H), 7.25–7.20 (m, 10 H), 7.05–6.95 (m, 2 H), 6.91, 6.52 (s, 4 H), 4.94 (s, 4 H), 4.71 (s, 4 H), 4.08 and 2.86 (ABq, 8 H), 1.21, 0.90 (s, 18 H); ^{13}C NMR δ 152.4, 152.0, 150.8, 148.9, 145.3, 144.6, 137.7, 137.3, 134.9, 133.6, 132.6, 129.5, 128.2, 127.9, 125.5, 124.7, 122.9, 77.4, 73.3, 34.0, 33.7, 31.6, 31.3, 31.3; FAB-MS *m/z* 1011.8 (M^+, calcd 1011.6). Anal. Calcd for $C_{70}H_{78}N_2O_4$: C, 83.13; H, 7.77; N, 2.77. Found: C, 82.84; H, 7.75; N, 2.63.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrakis[(4-pyridylmethyl)oxy]calix[4]arene (8a). *p-tert*-Butylcalix[4]arene (0.74 g, 1.0 mmol) was added to a suspension of NaH (2.00 g, 50 mmol, 60% in oil, washed with hexanes) in dry DMF (25 mL). After the suspension was warmed for 30 min to 50 °C the mixture was allowd to cool to rt, whereupon 4-picolyl chloride hydrochloride (3.28 g, 20.0 mmol) was added in portions over 15 min. The reaction was stirred for 18 h at 60 °C and then quenched with MeOH (2 mL). After the mixture was cooled to rt, it was poured into H_2O (200 mL) and stirred overnight. The precipitate was filtered off, taken up in CH_2Cl_2 (100 mL), and washed with brine (2 × 50 mL). After the organic layer was dried over $MgSO_4$, the solvent was removed by evaporation under reduced pressure. Recrystallization from CH_2Cl_2/hexanes gave **8a** as a white crystalline material in 53% yield: mp 255–257 °C; ^{1}H NMR δ 8.64 and 7.21 (AB, 8 H), 6.78 (s, 8 H), 4.85 (s, 8 H), 4.12 and 2.95 (ABq, 8 H, J = 12.7 Hz), 1.08 (s, 36 H); ^{13}C NMR δ 152.0, 149.7, 146.3, 145.6, 133.4, 125.5, 123.4, 75.3, 33.9, 31.4, 31.1; FAB-MS *m/z* 1014.3 ([M + H]$^+$, calcd 1013.6). Anal. Calcd for $C_{68}H_{76}N_4O_4 \cdot 0.5\ H_2O$: C, 79.89; H, 7.59; N, 5.48. Found: C, 79.95; H, 7.59; N, 5.48.

5,11,17,23-Tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrakis[(3-pyridylmethyl)oxy]calix[4]arene (8b) was synthesized following the same procedure as described for **8a**, using 3-picolyl chloride hydrochloride instead of 4-picolyl chloride hydrochloride: yield 71%; mp 258–259 °C; ^{1}H NMR δ 8.58 (s, 4 H), 8.56–8.51 (m, 4 H), 7.49 (d, 4 H, J = 7.8 Hz), 7.15–7.10 (m, 4 H), 6.73 (s, 8 H), 4.84 (s, 8 H), 3.96 and 2.80 (ABq, 8 H, J = 12.6 Hz), 1.06 (s, 36 H); ^{13}C NMR δ 151.7, 150.9, 149.2, 145.3, 136.9, 133.7, 125.2, 122.9, 74.0, 33.9, 31.4, 31.1; FAB-MS *m/z* 1014.3 ([M + H]$^+$, calcd 1013.6). Anal. Calcd for $C_{68}H_{76}N_4O_4 \cdot 0.5H_2O$: C, 79.89; H, 7.59; N, 5.48. Found: C, 79.97; H, 7.59; N, 5.43.

Extraction of Tetracarboxylic Acid 5 by Tetrapyridyls 8a and 8b in $CDCl_3$. To eight vials containing tetracarboxylic acid **5** (5.25 mg, 5 μmol) were added increasing amounts (0.14–0.5 mL) of a 10 mM solution of tetra(4-pyridyl)calix[4]arene **8a** in $CDCl_3$, and extra $CDCl_3$ was added to bring the total volume to 1.00 mL. To obtain mixtures above the 1:1 stoichiometry, increasing aliquots of the 10.0 mM solution of **8a** were added to a 1:1 5 mM solution of **5** and **8a**. The mixtures were sonicated for 15 min and heated at reflux for 5 min in the closed vials, and after the mixtures were cooled to room temperature the ^{1}H NMR spectra of the mixtures were recorded. To determine the fraction of **5** that had dissolved eq 1 was used

$$X_A = (I_A/I_P)/(A_o/P_o) \quad (1)$$

with

X_A = fraction dissolved carboxylic acid (**5**)

I_A = integral of equatorial methylene bridge protons of **5**

I_P = integral of equatorial methylene bridge protons of **8a** (or **8b**)

A_0 = total amount of **5** present in mixture

P_0 = total amount of **8a** (or **8b**) present in mixture

The fraction of dissolved carboxylic acid **5** was calculated using the integral at 3.3 ppm ($ArCH_2Ar$) for the tetracarboxylic acid and the integral at 3.0 ppm ($ArCH_2Ar$) for **8a**. For **8b** the integral at 4.9 ppm (OCH_2) was used.

Extraction of Tetracarboxylic Acid 5 by Tetra(2-pyridyl) 8c in $CDCl_3$. To seven vials containing ~4.20 mg of tetracarboxylic acid **5** were added increasing amounts (0.15, 0.30, 0.45, 0.60, 0.75, 0.90, and 1.05 mL) of a 6.68 mM solution of **8c** in $CDCl_3$, and extra $CDCl_3$ was added to bring the total volume to 1.00 mL. The closed vials were heated at reflux for 10 min and stirred at 50 °C for at least 1 h, after which the ^1H NMR spectra of the mixtures were recorded. The fraction of dissolved **5** was calculated with eq 1 using the integral at 0.86 ppm (CH_3) for the carboxylic acid and the integral at 5.0 ppm (OCH_2) for **8c**. The results were normalized for the mixture with 1.75 equiv (1.05 mL) of **8c**, since in that case a clear solution (at rt) was obtained, indicating 100% solubilization of **5**. Due to overlap the bridging methylene protons could not be used in this case.

Extraction of Tetracarboxylic Acid 5 by 4-Picoline in $CDCl_3$. To eight vials containing ~4.20 mg of **5** were added increasing amounts (0.13, 0.25, 0.37, 0.50, 0.63, 0.75, 0.87, and 1.00 mL) of a 32 mM solution of 4-picoline (dried over molecular sieves) in $CDCl_3$, and extra $CDCl_3$ was added to bring the total volume to 1.00 mL. In the closed vials the mixtures were heated at reflux for 10 min and stirred at 50 °C for at least 1 h and at rt for at least 30 min, after which the ^1H NMR spectra of the mixtures were recorded. The fraction of dissolved **5** was calculated with eq 1 using the integral at 0.9 ppm (CH_3) for the carboxylic acid and the integral at 8.4 ppm (2,6-pyH) for 4-picoline. Only the mixture containing 8 equiv of 4-picoline gave a clear solution at rt.

Extraction of Tetracarboxylic Acid 5 by Dipyridyls 7a and 7b in $CDCl_3$. To eight vials containing ~4.20 mg of tetracarboxylic acid **5** were added increasing amounts (0.06, 0.13, 0.25, 0.37, 0.51, 0.62, 0.75, and 1.00 mL) of a 16 mM solution of dipyridyl **7a** in $CDCl_3$, and extra $CDCl_3$ was added to bring the total volume to 1.00 mL. The closed vials were sonicated for 5 min, heated at reflux for 10 min, and stirred overnight at 40 °C, after which the ^1H NMR spectra of the mixtures were recorded. The fraction of dissolved **5** was calculated with eq 1 using the integral at 8.0 ppm (ArH) for the carboxylic acid and the integral at 8.4 ppm (2,6-pyH) for **7a**. For determination of the interaction between **5** and **7b** the aliquots of a 16 mM solution of **7b** were 0.13, 0.25, 0.37, 0.50, 0.55, 0.60, 0.65, and 0.75 mL. For the carboxylic acid the integral at 6.8 ppm (ArH) was used and for the dipyridyl the integral at 6.4 ppm (ArH).

Vapor Pressure Osmometry. The vapor pressure osmometric measurements were carried out in $CHCl_3$ on a Gonotec SA-70 vapor pressure osmometer, operated at 29 °C. The $CHCl_3$ was of analytical grade, and the residual ethanol was removed by passing it over an Al_2O_3 column (50 g/100 mL). The calibration standard, polystyrene, M_n = 4000, M_w/M_n = 1.05, was obtained from Polysciences, Inc. For the molecular weight determination five solutions of a 1:1 mixture of the tetracarboxylic acid **5** and the tetrapyridyl (**8a** or **8b**) of concentrations between 20 and 4 mM were measured.

Acknowledgment. Akzo Nobel International Research is kindly acknowledged for their financial support.

JO9603082