Synthesis of *C*-Alkylcalix[4]arenes. 5. Design, Synthesis, Computational Studies, and Homodimerization of Polymethylene-Bridged Resorc[4]arenes

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Treatment of tetraalcohol **1** with glutaroyl (**2a**, $n = 3$), adipoyl (**2b**, $n = 4$), and pimeloyl (**2c**, $n = 5$) dichlorides in the presence of Et_3N gave the corresponding double-spanned calix[4]resorcarenes **3a**−**c**, in which the insertion of two polymethylene bridges led to the formation of a cavity-shaped architecture resembling a basket. NMR, X-ray, and molecular dynamic studies showed that one of the two equivalent flattened-cones, which constituted the original cone conformation of **1**, had been frozen in the basket derivative. In the solid state the calixarene **3b** exists as a supramolecular dimer, in which one of the handles is inserted in the concave cavity of an adjacent molecule. A molecular modeling study revealed that the minimum absolute free energy was associated to the unsymmetrical type of dimer named AB−AC.

Introduction

Calixarenes represent an interesting family of structures that exhibit a characteristic cavity-shaped architecture and can behave as ionophores and enzyme mimics.[1] The balance between rigidity and flexibility is at the base of the host−guest interaction in molecular recognition.[2]

We have shown that ethereal BF_3 catalyzes the tetramerization of (*E*)-2,4-dimethoxycinnamic acid esters to the corresponding *C*-alkylcalix[4]resorcarenes, octamethyl octaethers.[3,4] These products are characterized by a large flexibility and thus a potential low selectivity in the interaction with ions and/or small molecules. This is particularly true for the cone conformation, which is the average C_{4v} symmetry structure resulting from a fast equilibrium between two equivalent C_{2v} flattened cone conformers.[5] By contrast, examination of CPK models of *C*-alkylcalix[4]resorcarene, octamethyl octaethers in the cone conformation with substituents linked by two polymethylene bridges revealed an increased rigidity of the molecule. Therefore, we planned the synthesis of double-spanned calix[4]resorcarenes with the aim to build potential preorganized hosts and then to compare, in future studies, their complexing ability with those of the conformationally mobile host previously synthesized.[3,4] Macrobyclic calixarenes or resorcarenes have been previously prepared bridging, by bifunctional reagents, phenolic functions or opposite aromatic rings.[6]

The calix[4]resorcarene **1**, in the flattened-cone conformation, recently synthesized by us,[4] was treated with long-chain acid chlorides of general formula $ClCO(CH_2)_n$-$COCl$. The main studies were performed with adipoyl chloride (**2b**, $n = 4$), but the results were extended to glutaroyl (**2a**, $n = 3$) and pimeloyl (**2c**, $n = 5$) chlorides.

The initial synthetic studies, employing high-dilution techniques, were patterned according to the literature.[7] However, and somewhat surprising, the product obtained was not the expected **3b**, but a series of compounds with structures that featured one to four tentacles and resembled a "globular jelly fish".

The present paper describes our studies to evaluate and determine the appropriate reaction parameters in order to obtain the desired calix[4]resorcarene **3b** and to shed light on the possible mechanism of the reaction in high dilution condition. The stereostructure of **3b**, established by NMR measurements, was confirmed by molecular modeling studies and by X-ray analysis. The last experiments revealed an interesting property of the molecule, that is, the ability to form a supramolecular dimer.

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(1) Gutsche, C. D. In *Calixarenes—Monographs in Supramolecular Chemistry*; Stoddard, J. F., Ed.; The Royal Society of Chemistry: London, 1989; Vol. 1.

(2) (a) Cram, D. J.; Artz, S. P. *J. Am. Chem. Soc.* **1984**, *106*, 2160. (b) Gibb, B. C.; Chapman, R. G.; Sherman, J. C. *J. Org. Chem.* **1996**, *61*, 1505.

(3) Botta, B.; Iacomacci, P.; Di Giovanni, C.; Delle Monache, G.; Gács-Baitz, E.; Botta, M.; Tafi, A.; Corelli, F.; Misiti, D. *J. Org. Chem.* **1992**, *57*, 3259.

(4) Botta, B.; Di Giovanni, M. C.; Delle Monache, G.; De Rosa, M. C.; Gács-Baitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, *59*, 1532.

(5) Abis, L.; Dalcanale, E.; Du Vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475.

(6) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713 and references therein.

(7) Gutsche, C. D.; See, A. K. *J. Org. Chem.* **1992**, *57*, 4527.

Table 1. Summary of Results Obtained from the Reaction of 1 with Adipoyl Dichloride 2b

		mequiv[a]		% yield			
				unreacted	products		
expt	reaction condns	base[b]	dichloride	starting material	basket	jelly fish	other
1	high dilution		8	97			
2	high dilution	4.5	2	54		18	18
3	high dilution	4.5	4	27		63	5
4	high dilution	4.5	8	12		57	18
5	normal dilution	4.5	8	17	50		24
6	normal dilution		8	15	43		30
7	normal dilution	4.5	8	14	48		25
8	normal dilution		2	30	13		45
9	high dilution	2	8	8	53		18
10	high dilution	1	8	5	70		12

[a] Relative to 1 mmol and one alcoholic function of substrate. [b] Et_3N for experiments 2–5, 9, and 10. K_2CO_3 for experiment 6. Pyridine for experiment 7. No base was used for experiments 1 and 8.

Results and Discussion

Synthesis and NMR Studies. The reaction of **1** with adipoyl chloride **2b** in high-dilution conditions gave a series of products. The ^{1}H NMR spectrum of the less polar product was characterized by a triplet ($J = 8$ Hz) signal at 3.13 ppm.

Irradiation of this signal by an INEPTL experiment revealed a heterocorrelation with the carbon resonances at ca. 212, 162, 29, and 28 ppm. The downfield signals were attributed to a cyclic ketone and to an ester carbonyl function, respectively, whereas the remaining resonances by an HETCOR measurement were related to two methylene groups. A series of decoupling experiments suggested that the signal at 3.13 ppm belonged to the methine group of a cyclopentanone ring substituted in the α position by the ester carbonyl group (see R in **4a**, Scheme 1), clearly derived by the adipoyl chain. In the FABMS spectrum of compound **4a** ($[MH]^+$ at 1217) the loss of 155 mu can be considered diagnostic for the presence of a chain containing the cyclic adipoyl residue. The compound was thus assigned the structure **4a** of a tetraacylated derivative.

On consideration of the molecular peaks in the mass spectra, which showed a regular difference of 110 mu, the other isolated compounds **4b**, **4c**, and **4d** (structures not drawn) were considered as the tri-, di-, and monoacyl derivatives, respectively.

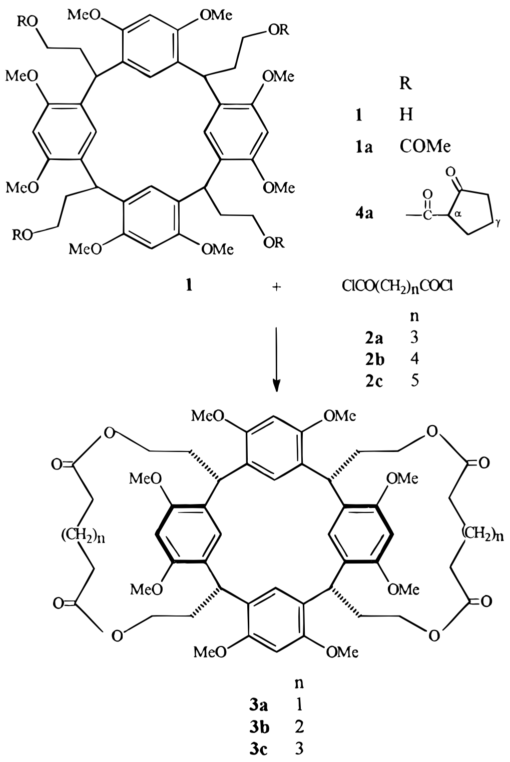
No effort was made to establish the stereochemistry at the methine group in these compounds.

Table 1 summarizes the results obtained when the alcohol **1**, the acid chloride, and triethylamine were reacted under high-dilution condition in CH_2Cl_2 as solvent. When the high dilution process was evaluated under a molar ratio of **1**/Et_3N/chloride of 1:0:32 (experiment 1 in Table 1), the starting material **1** was recovered in a quantitative manner. Experiment 1 thus showed that the base must be present, in low to moderate amounts, in order for any reaction to occur.

Experiments 2–4 (Table 1) reveal that, regardless of variations in the molar ratios of the reactants, mainly "jelly fish" products, differing in the number of acylated chains, were observed. Thus, normal dilution reactions were used (experiments 5–8 in Table 1).

The ^{1}H- and ^{13}C-NMR data of the major product, obtained from experiment 5, are reported in Table 2 together with those of the starting alcohol **1**, its tetracetyl derivative **1a**, and diethyl adipate. As Table 2 reveals, the ^{1}H- and ^{13}C-NMR spectra of the compound may be considered as the sum of the spectra of **1a** and the adipate (obviously with the exclusion in the latter ones of the signals due to the acetyl and the ethyl groups). In particular, the chemical shifts of the oxygenated methylene and the neighboring one in the ^{13}C NMR spectrum (δ 64 and 33, respectively) indicated that the alcoholic functions are all acylated, as confirmed by the integration of the relative proton signals. Moreover, the ^{13}C NMR spectrum of the product showed only one signal for both of the methylenes near the carbonyl (CH_{2e}) and the inner methylenes (CH_{2i}) of the adipate chain.

Scheme 1. General Scheme of Basket Formation 1 → 3a–c



These findings required that **1** was esterified by two adipoyl units, which link two equivalent and sequential hydroxymethylenes (e.g., the first linked to C-2 and the second to C-8 carbons). The addition of the two adipoyl bridges (110 mu each) is confirmed by the molecular peak at *m*/*z* 996 in the EIMS and *m*/*z* 997 in FABMS spectrum.

In conclusion, the product was assigned the gross structure **3b** (Scheme 1).

The distribution pattern of the remaining signals in the ^{1}H- and ^{13}C-NMR spectra of **3b** (Table 2) requires the existence of only two symmetry planes, passing through two opposite aromatic rings. As a consequence,

Table 2. ^{1}H- and ^{13}C-NMR Spectral Data[a] of Compounds 1, 1a, and 3b

	1		**1a**		**3b**	
position	δ_C	$\delta_H b$	δ_C	δ_H[b]	δ_C	δ_H[b]
1, 9, 13, 21, 3, 7, 15, 19					126.47	
	125.72		125.35		123.11	
2, 8, 14, 20	30.94	4.56 (t, 8)	31.78	4.58 (t, 7.5)	32.38	4.46 (t, 7)
4, 6, 16, 18, 10, 12, 22, 24					156.67	
	155.71		156.01		155.21	
5, 17, 11, 23					97.72	6.09 (s)
	96.75	6.33 (s)	96.63	6.29 (s)	94.99	6.49 (s)
25, 27, 26, 28					125.94	6.03 (s)
	125.46	6.69 (s)	125.46	6.67 (s)	125.72	7.33 (s)
CH_2	37.17	2.08 (q, 7)	33.61	2.18 (q, 7)	33.83	2.22
CH_2O (4, 6, 16, 18)	60.48	3.54 (t, 6.5)	63.63	4.05 (t, 7)	63.96	4.14
					56.01	3.30 (s)
OMe (10, 12, 22, 24)	56.02	3.62 (s)	56.02	3.59 (s)		
					55.94	3.92 (s)
diethyl adipate						
CO	172.70				173.40	
						2.31 (m)
CH_{2e}	33.94	2.32 (m)			34.06	
						2.26 (m)
CH_{2i}	23.97	1.66 (m)			24.53	1.70 (m)

[a] ^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz; TMS as internal standard. The signals of the acetyl group of **1a** and of the ethoxy group of diethyl adipate are not reported. [b] The signals showed the appropriate integrate intensity. Multiplicity and coupling constants are reported in parentheses.

Table 3. Homo- and Heterocorrelations in Compound 3b

selectively irradiated signal	rel protons[a]	protons correlated by DIF NOE	carbons correlated by INEPTL
7.33	H-26 H-28	H-25, H-27, H_2-14, H_2-20, H_2-2, H_2-8	$^3J_{14}$ $^3J_{16}$ $^3J_{18}$ $^3J_{20}$ $^3J_2$ $^3J_4$ $^3J_6$ $^3J_8$
6.49	H-11	10-OMe, 12-OMe	$^3J_9$ $^3J_{13}$ $^2J_{10}$ $^2J_{12}$
6.09	H-5	4-OMe, 6-OMe	
4.46	H-2	H-25, H_2-2, CH_2O_4, 4-OMe, 24-OMe	
3.92	10-OMe	H-8, H-11	
3.30	4-OMe	H-5	$^3J_4$

[a] For the signal at δ 7.33 both the protons to which the signal is attributed are listed. For the remaining signal only a representative of the relative protons is reported.

calix[4]resorcarene **3b** has C_{2v} symmetry with two parallel adipoyl bridges.

A series of INEPTL experiments and DIFNOE measurements (Table 3) allowed a complete unambiguous assignment of proton and carbon signals and gave further information on the stereochemistry of **3b**. In particular, the high-field chemical shift (δ 6.03) of the signal attributed to two internal (e.g., H-25 and H-27) aromatic protons suggests that both lie in the shielding cone of the two neighboring aromatic rings. For the same reason the signal of the equivalent methoxyl groups of these rings (i.e., those at C-4, C-6, C-16, and C-18) is shifted to high field (δ 3.30). By contrast, H-26 and H-28 as well as the C-8, C-10, C-22, and C-24 methoxyl groups, show signals (at δ 7.33 and δ 3.92) shifted downfield with respect of those in the starting **1**. The mutual NOE effect between the H_i (internal) protons excludes a saddle-like conformation, with contiguous aromatic rings forming a 180° angle. In general, it appears that the signals of aromatic and methoxyl protons in **1** are symmetrically split in **3b**.

Because the signals of the cone conformation of **1** are the average of the two equivalent flattened-cone conformations in equilibrium,[5] we may conclude that the formation of the adipoyl bridge froze one of the two conformations.

Two additional experiments, similar to experiment 5 (Table 1), were conducted in which triethylamine was replaced by potassium carbonate (experiment 6 in Table 1) and pyridine (experiment 7 in Table 1) as basic reactants. The yields were similar to those in experiment 5 (Table 1).

Since the formation of **3b** could be achieved without triethylamine (experiment 8 in Table 1), it was of interest to evaluate the yield of **3b** when a lower molar ratio of base and a high dilution process was undertaken (experiments 9 and 10 in Table 1). Indeed, the optimum conditions that afforded **3b** in 70% yield involved the molar ratio of **1**/Et_3N/chloride of 1:4:32, respectively, and high dilution conditions (experiment 10 in Table 1).

In summary, it is clear from Table 1 that a high molar ratio of triethylamine and high dilution conditions favor an internal Dieckmann-like cyclization to the five-membered cyclopentanone ring system before any reaction to provide the rigid "basket" system can occur.

The formation of the "basket" **3b** system is thus favored when lesser amounts of triethylamine are involved. Under such conditions, anion formation is suppressed and the internal Dieckmann cyclization cannot occur.

Calix[4]resorcarene (**1**) was reacted under the normal-dilution conditions of experiment 5 (Table 1) with glutaroyl (**2a**, $n = 3$) and pimeloyl (**2c**, $n = 5$) dichlorides. Double-spanned calix[4]resorcarenes **3a** (M^+ at m/z 968) and **3c** (M^+ at m/z 1024) were obtained with 28 and 38% yields, respectively. The distribution pattern of proton and carbon signals in the ^{1}H- and ^{13}C-NMR spectra of compounds **3a** and **3c** was in close agreement with that of **3b**, thus indicating that in both cases the molecule had been frozen in a flattened-cone structure.

X-ray Structure Analysis. Details of the crystallographic data of **3b** are reported in Table 4. The structure was solved by direct methods, and it has also been fully refined by routine procedures. The final *R*

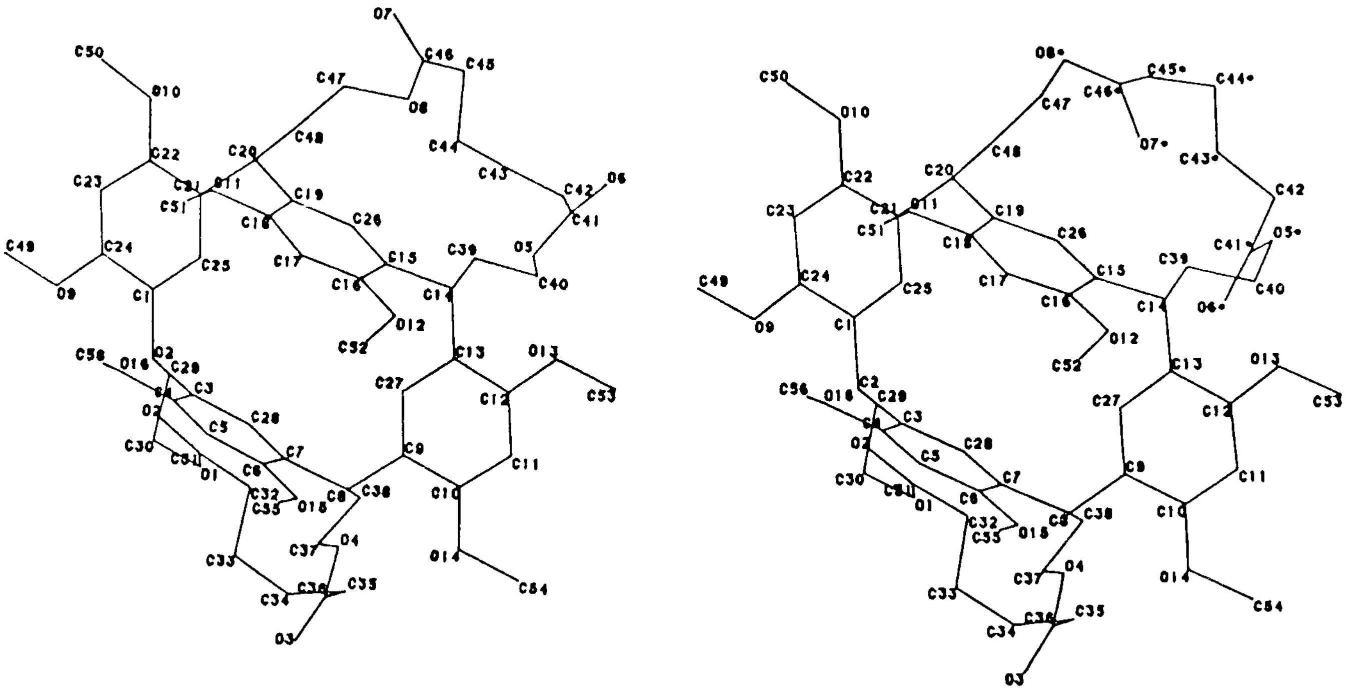


Figure 1. Molecular structure of the two statistical conformations of the basket molecule with the numbering of the atoms.

Table 4. Crystal Data for 3b

molecule	**3b**	molecule	**3b**
mol form.	$C_{56}H_{68}O_{16}$	α, deg	97.81(1)
form. wt, D	997.1	*β*, deg	99.03(1)
cryst syst	triclinic	*γ*, deg	91.77(1)
dimens, mm	0.2−0.2−0.3	*V*, Å^3	2578.4(6)
space grp	*P*-1	*d* (expt), g/cm^3	1.28
Z, molecules/cell	2	*d* (calcd), g/cm^3	1.284
a, Å	13.120(2)	radiatn, Å	Cu Kα (λ = 1.541 84, Ni filtered)
b, Å	13.616(2)	solvent	EtOH/CH_2Cl_2 1:1
c, Å	14.771(3)	*T*, °C	22

value was 0.063 for 8376 independent "observed" reflections with $I \geq 3.0\sigma(I)$.[21]

Figure 1 shows the molecular model of the calixarene **3b** with the scheme adopted for the numbering of the atoms.

Molecular Symmetry and Conformation. If the cyclic side-chain substituents of atoms C2, C8, C14, and C20 are not considered, the macrocyclic ring system can be described as having a flattened-cone conformation with an approximate C_{2v} symmetry, as shown by the values of the torsion angles around the four pairs of bonds C1−C2 and C2−C3, C7−C8 and C8−C9, C13−C14 and C14−C15, and C19−C20 and C20−C21, which have approximately the same absolute values but opposite signs.[8] The same occurs for the torsion angle around bond C7−C8, which is symmetry related to that around bond C14−C15 (with values of 17.81° and −7.51°, respectively). The observed distortions from the ideal C_{2v} symmetry are to be ascribed to crystal forces, which might to a lesser extent influence locally the conformation of the macrocyclic ring system and to a greater extent the conformation of the side chains.

In this conformation opposite benzene rings on the macrocycle are almost coplanar (small angles of 10° and 9° occur between opposite rings), while adjacent benzene rings are almost perpendicular to each other: the angles that each benzene ring forms with the adjacent rings are either 95° or 83°.

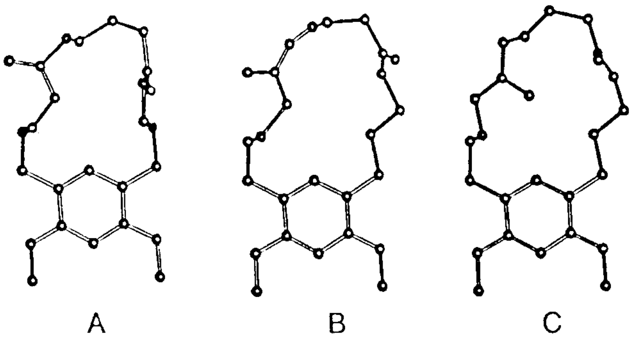


Figure 2. Lateral side chains of the basket molecule, where B and C indicate the two statistical conformations of one of the side chains, while A indicates the other nonstatistical side chain for comparison.

The angles between the plane defined by the four methine carbon atoms C2, C8, C14, and C20 and the planes of the four benzene rings are close to 90° or 0°. In all instances, the two methoxyl groups substituents of each benzene ring lie nearly on the same plane of the aryl system. However, a small deviation from the plane of the aromatic ring is observed for each methoxyl group: one is always found below and one is found above the average plane.

Some atoms in one of the two cyclic side chains of the basket show a statistic in their positions, giving rise to

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[8] Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 337.

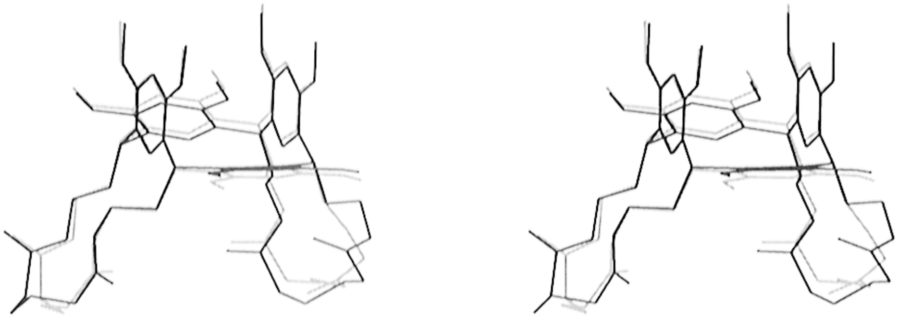

Figure 3. Stereoview of the superimposition between X-ray-determined (thick lines) and computer-generated geometries of the basket molecule (thin lines), obtained using the discontinuous method of simulated annealing and applying the modified AMBER force field.

two different conformations present in equal amounts: the occupancy factor, which has been refined, is 50% for each conformation. In Figure 2 the three observed conformations are represented. The three chains A, B, and C are nearly superimposable in the portion linked to the calixarene benzene ring. Their conformation differentiates in the orientation of the ester groups and mainly in the adipic acid moiety used for the ring closure of adjacent side chain. In particular, the two ester groups of each handle (including the statistic one) tend to be one nearly coplanar and the other nearly orthogonal to the average plane of the 17-membered handle. The polymethylene $-(CH_2)_4-$ units, being the most flexible portions of the ring, show the largest changes in the torsion angles. It is because of this flexibility that the ester groups can rotate and achieve the observed conformations. In one of these conformations one C═O group points inside the cyclic calixarene ring, whereas in the other two conformations all C═O groups point outside the ring.

Molecular Modeling Study. The structural complexity of derivative **3b** (more than 30 rotatable bonds) induced us to explore the conformational space of this compound using molecular dynamics-involving procedures.

MD calculations were performed using the AMBER[9] (All Atom) and CVFF[10] force fields, as implemented in Discover software package from Biosym Technol.[11] The results obtained with the two force fields have been compared to evaluate the reliability of their parametrization. In fact, although the AMBER force field has been generally applied to calixarenes,[12−15] its use in this study has required the addition of new parameters to model the aromatic methoxyl groups (Supporting Information).

The search has been carried out by the method of simulated annealing,[16,17] which combines high-temperature molecular dynamics simulations and subsequent energy minimizations of the collected structures. Two procedures (of simulated annealing) differing in the way the temperature was lowered during the analysis have been applied. The first method (referred to as the continuous one) consists in many subsequent slow-cooling MD runs, while the second method (the discontinuous one) is characterized by two subsequent loops, one performed at high temperature and the other one at medium temperature.

According to the continuous method, a double set of 82 fully minimized structures has been generated and compared to the X-ray-determined structure without satisfactory results. Root mean square (rms) calculations (0.99 Å by AMBER and 1.01 Å by CVFF) and energy differences ($\Delta E = 4.4$ kcal/mol by AMBER and $\Delta E = 7.8$ kcal/mol by CVFF) revealed very poor matching between the X-ray structure and the best fitting calculated one.

When the discontinuous method is applied, a quite relevant number of geometries (200) has been generated and compared to the crystallographic data. The superimposition between the X-ray-determined structure and the best-fitting computer generated one by AMBER showed extremely good matching (Figure 3). When all the carbon atoms of the four phenyl rings plus the eight methoxyl groups are compared, an rms value of 0.05 Å is obtained; this value increases to 0.67 Å when the side chains are also considered. The deviation in the calculated energy value between the two conformations appears to be insignificant ($\Delta E = 0.1$ kcal/mol). Furthermore, a perfectly symmetric global minimum geometry was found with a steric energy value 6.0 kcal/mol lower than that of the experimental conformation. By contrast, when CVFF was used, the global minimum was missed and the best rms found in the superimposition was 0.86 Å.

The Supramolecular Dimer. In the solid state one of the handles of the basket-like resorcarene inserts itself into the concave cavity of an adjacent molecule, as shown in Figure 4A.

Hydrogen-bonded dimers of calixarenes in solution[18] and in the solid state[19] have been previously reported.

Conversely, dipole−dipole, hydrophobic, and van der Waals forces are responsible for the interactions at the

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(9) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

(10) Dauber-Osguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. T. *Proteins: Struct., Funct., Genet.* **1988**, *4*, 31.

(11) Biosym Technologies, 9685 Scranton Road, San Diego, CA 92121-2777.

(12) Kollman, P. A.; Wipff, G.; Singh, U. C. *J. Am. Chem. Soc.* **1985**, *107* , 2212.

(13) Groothenuis, P. D. J.; Kollman, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 2152.

(14) Miyamoto, S.; Kollman, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 3668.

(15) Groothenuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

(16) Wong, Y.-T.; Schubert, B.; Hoffman, R. *J. Am. Chem. Soc.* **1992**, *114*, 2367.

(17) Kirkpatrick, S.; Gelatt, C. D.; Vecchi, M. P. *Science* **1983**, *220*, 671.

(18) Fukazawa, Y.; Demaya, K.; Usui, S. *Tetrahedron Lett.* **1992**, *33*, 5803.

(19) Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645.

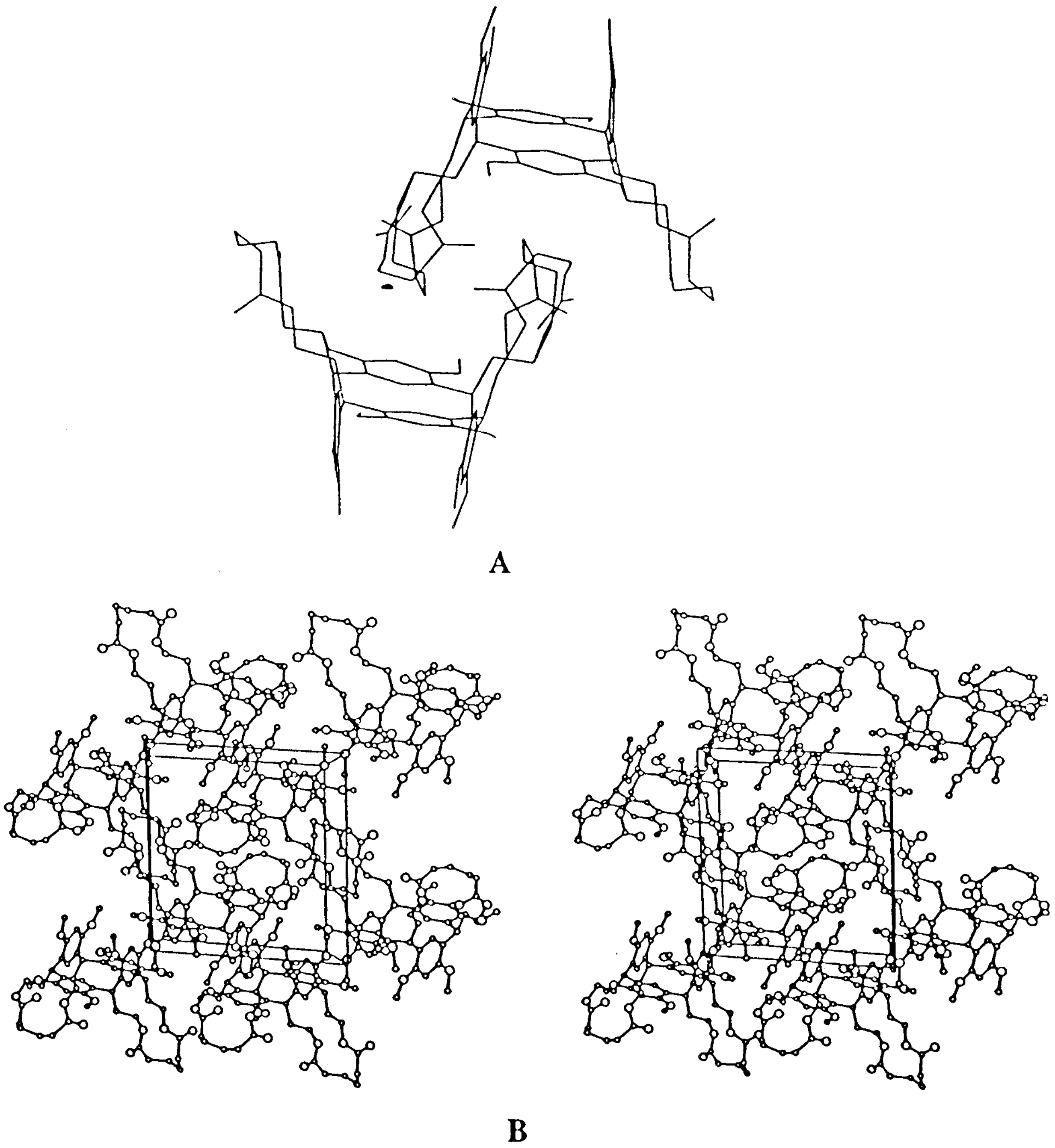

Figure 4. (A) The supramolecular dimer observed in the structure of the basket. (B) Stereoview of the mode of packing of the basket molecules projected down the *c* axis: only one of the two observed statistical conformation on one of the side chains is shown.

level of the two statistic cyclic side chains and the formation of the dimer in **3b**.

Since in each basket molecule of the supramolecular dimer one of the two cyclic side chains can assume both conformations (respectively referred to as B and C in Figure 2), three arrangements are possible: the first and the second are characterized by a center of symmetry where both molecules simultaneously share the same exact disposition of statistical atoms (couples AB—AB and AC—AC), while the third one looks as the result of a combination described by the monogram AB—AC.

To predict the most likely disposition of the few statistical atoms in the cyclic side a molecular modeling study has been performed. The energetic stability of the three combinations AB—AB, AC—AC, and AB—AC has been calculated by the absolute free energy method[20] as implemented in the Discover program.[11] The set of the corresponding energy-minimized X-ray coordinates have been chosen as the reference state for each of the three situations AB—AB, AC—AC, and AB—AC.

The absolute free energies (in kcal/mol) associated with the three types of dimers were as follows: $\underline{\text{AB}}$—$\underline{\text{AB}}$ 1045.6 ± 2.3; $\underline{\text{AC}}$—$\underline{\text{AC}}$ 961.6 ± 1.9; and $\underline{\text{AB}}$—$\underline{\text{AC}}$ 957.5 ± 1.9.

The large preference for the unsymmetrical type of dimer named AB—AC as compared to the symmetrical ones AB—AB and AC—AC supports the hypothesis that

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[20] Singh, U. C.; Brown, F. K.; Bash, B. A.; Kollman, B. A. *J. Am. Chem. Soc.* **1987**, *109*, 1607.

[21] The author has deposited atomic coordinates for **3b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

in the gas phase a considerable conformational modification of the side chains follows the recognition of the basket molecules, allowing the insertion and the best fitting of one molecule "inside" the cavity of the adjacent one.

A stereodrawing of the mode of packing of the dimers in the solid state is represented in Figure 4B.

Conclusions

The large flexibility of *C*-(2-hydroxyethyl)calix[4]-resorcarene, octamethyl octaether (**1**), has been reduced by reaction with polymethylene dichlorides **2a**−**c**, which formed a bridge between each of two contiguous alkyl side chains and established an anchored flattened-cone conformation. The reaction was shown to be dependent on the substrate−base ratio and the concentration of the reactants.

The signals in ^{1}H- and ^{13}C-NMR spectra of **3a**, **3b**, and **3c** were related to a flattened-cone conformation, with two contiguous aromatic rings forming a 90° dihedral angle. Notably, this flattened-cone structure can be considered as one of the equivalent conformers contributing to the flexible cone conformation of the starting calixarene **1**.

In the X-ray studies the most interesting result appears to be the recognition between two molecules of the basket-calixarene **3b**, caused by the insertion of one of the bridges into the cavity of an adjacent macrocycle.

The molecular dynamics approach, based on the discontinuous method of simulated annealing, gave stimulating results because of the small difference in the conformational energies found between the X-ray and the computer-generated structures.

Experimental Section

Synthesis of *C*-(2-Hydroxyethyl)calix[4]resorcarene, Octamethyl Octaether (1). The alcohol **1** was prepared by reduction with $LiAlH_4$ of the corresponding isopropyl ester, which in turn was synthesized by tetramerization with $BF_3 \cdot Et_2O$ of 2,4-dimethoxycinnamic acid isopropyl ester.[3,4]

General Procedure for High-Dilution Reactions (Experiments 1−4, 9, and 10 in Table 1). The acid chloride and the mixture of calixarene **1** and Et_3N in CH_2Cl_2 were kept in separate dropping funnels and were slowly added to solvent over a period of 60 h. The reaction was allowed to stir for a further 40 h. The entire process was conducted at room temperature under N_2 atmosphere. For example, in experiment 3 a solution of calixarene **1** (100 mg, 0.128 mmol) and Et_3N (0.32 mL, 2.3 mmol) in CH_2Cl_2 (300 mL) and a solution of the chloride **2b** (0.3 mL, 2 mmol) in CH_2Cl_2 were used. The reaction mixture was concentrated and washed with a saturated solution of $NaHCO_3$ and then with HCl (2 N). The residue of the organic layer gave on a silica gel column, eluting with $CHCl_3$ and $CHCl_3$−MeOH 99:1, a series of fractions, which in turn by extended chromatography afforded the following main products: **4a** (31 mg, 20%), **4b** (27 mg, 19%), **4c** (12 mg, 10%), and **4d** (18 mg, 14%). Physical and spectral data of compounds **4a**−**d** are given in the Supporting Information.

In experiment 9 (1 mmol of Et_3N) and experiment 10 (0.5 mmol of Et_3N) a similar workup gave compound **3b** in 53 and 70% yields, respectively.

General Procedure for Normal Dilution Reactions (Experiments 5−8 in Table 1). The starting alcohol **1** and Et_3N were initially placed in the reaction flask, to which the appropriate dichloride was added over a 2 h period, and then continuously stirred for a further 24 h. The entire process was still conducted at room temperature but not under N_2 atmosphere. For instance, in experiment 5 a solution of **1** (100 mg, 0.128 mmol) and Et_3N (0.32 mL, 2.3 mmol) in CH_2Cl_2 (100 mL) and a solution of the chloride **2b** (0.6 mL, 4.1 mmol) were used. The reaction mixture was concentrated and washed with a saturated solution of $NaHCO_3$ and then with HCl (2 N). The residue of the organic layer on a silica gel column, eluting with $CHCl_3$, gave compound **3b** (64 mg, 50%; mp 279−80 °C; ^{1}H- and ^{13}C-NMR in Table 2; EIMS $[M]^+$ 996; FAB-MS $[MH]^+$ 997). A similar procedure with chlorides **2a** and **2c** gave compounds **3a** (35 mg, 28%; mp 272−3 °C; FAB-MS $[MH]^+$ 969) and **3c** (50 mg, 38%; mp 275-6 °C; FAB-MS $[MH]^+$ 1025), respectively.

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Supporting Information Available: ^{1}H- and ^{13}C-NMR and MS spectral data of compounds **3a**−**c** (Tables 1s−3s) and **4a**−**d** (Scheme 1s and Tables 4s−6s). Details of X-ray structure analysis: positional parameters (Table 7s) and torsion angles (Table 8s). Computational details: additional parameters (Tables 9s) and electrostatic point charges for the basket molecule 3b (Figure 1s) (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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