EXPERIMENTAL AND THEORETICAL EVIDENCE OF THE BIDENTATE BINDING MODE OF DICHLOROACETAMIDO GROUPS AT THE *UPPER* RIM OF CALIX[4]ARENE HYDROGEN-BONDING ANION RECEPTORS

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Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday in acknowledgement of his contribution to the supramolecular chemistry of anions.

Calix[4]arenes in the *1,3-alternate* conformation (**1**–**3**) and bearing activated amide groups at the *upper* rim have been synthesized and their anion binding properties studied and compared with conformationally *mobile* (**4**) or *cone* (**Ib**) receptors having the same binding groups. Association constants determined in $CDCl_3$ show a stronger complexation for Y-shaped carboxylate anions and a higher efficiency for receptors (**Ib** and **3**) bearing dichloroacetamido moieties as hydrogen bonding donor groups. Molecular modeling studies performed on the *cone* derivative (**Ib**) and its *1,3-alternate* isomer (**10**) and ab initio calculations on 4-methoxyaniline derivatives (**11**–**13**) used as simplified models, reveal that the α,α-dichloroacetamido moieties bind anions in a bidentate fashion using both the N–H and the $CHCl_2$ as hydrogen bonding donor groups. This explains the higher efficiency in carboxylate binding found for **Ib** and **3** that incorporate the dichloroacetamido binding unit in their structures.

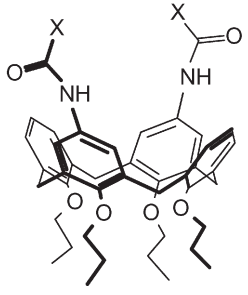
Keywords: Calixarenes; Molecular modeling; Anion recognition; α,α-Dichloroacetamides; Hydrogen bonds; Conformation analysis; Carboxylate binding.

Calix[4]arenes have been extensively used as platform for the construction of neutral hydrogen bonding receptors for anions[1–4].

(Thio)ureas are by far the most studied and the most efficient binding groups introduced onto calix[4]arenes for anion recognition. Derivatives in the *cone* conformation and having urea groups at the *lower* rim show selectivity for chloride[5] and dihydrogenphosphate[6] in $CDCl_3$, while those bear-

ing one to four thioureas at the *upper* rim bind carboxylates quite efficiently also in competing solvents like DMSO [7,8]. This high efficiency in anion binding was attributed to the ability of the *trans–trans* conformation of ureas to act as bidentate H-bonding groups and to the presence of two favourable secondary hydrogen-bonding interactions[9]. Stibor and coworkers showed that a homoditopic tetraureacalix[4]arene in the *1,3-alternate* structure shows a negative allosteric effect[10], while heteroditopic *cone* tetramide calix[4]arene-diurea[11] or *1,3-alternate* calix[4]arene-crown-diurea[12] can extract hydrophilic salts in apolar media through the simultaneous complexation of the anion and cation. More recently, glycosylthioureidocalix[4]arenes able to bind anions and interesting as potential site-specific molecular delivery systems[13], have been prepared. The NH amide groups in *C*-linked peptidocalixarenes have been employed as binding groups in a series of biomimetic synthetic receptors[14,15], which bind anions in acetone with selectivity for carboxylates and efficiency from moderate to good. In order to increase the H-bonding donor ability, activated amides[16] having electron-withdrawing groups in the acyl or amine groups have been proposed. For example, the introduction of sulfonamides[17] and pentafluorobenzamides[16,18] onto calixarenes led to new efficient anion receptors.

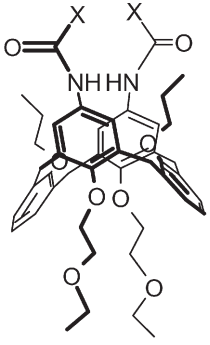
In line with these efforts, Loeb and Cameron developed 1,3-bisamidocalix[4]arenes **I** having acyl groups with different degrees of halogen substitution[19]. Interestingly, they observed a remarkable high efficiency in the binding of benzoate anion by dichloroacetamido (**Ib**), weak binding with monochloroacetamido (**Ia**) and no binding at all with the trichloroacetamido derivative (**Ic**). The benzoate selectivity was attributed to the op-



Ia X= CH_2Cl

Ib X= $CHCl_2$

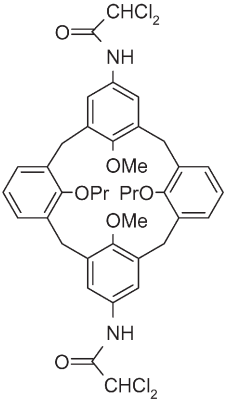
Ic X= CCl_3



1 X= CF_3

2 X= C_6F_5

3 X= $CHCl_2$



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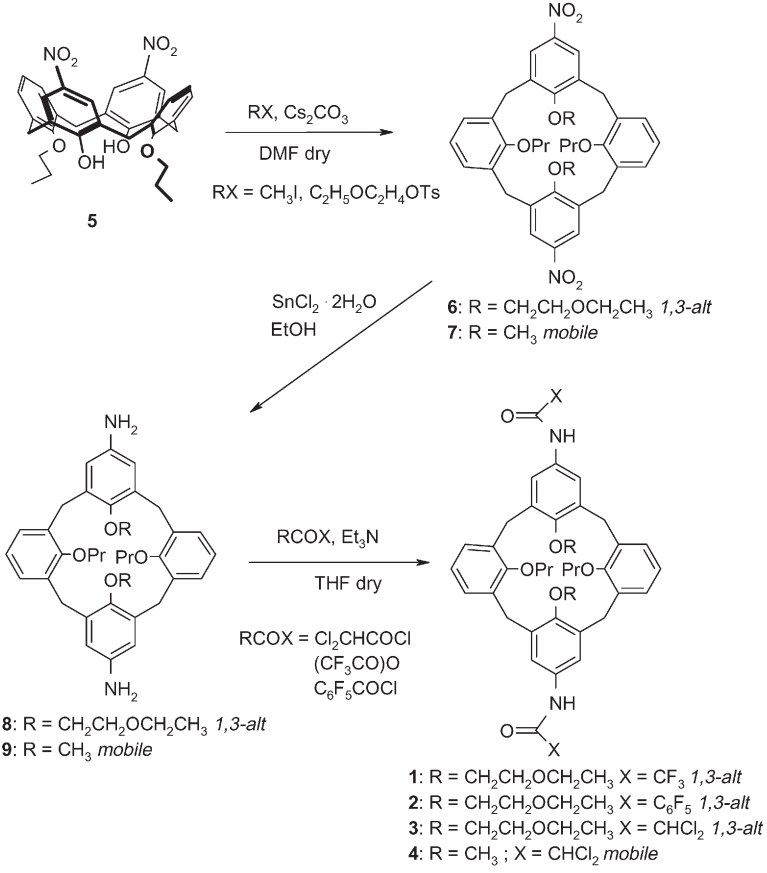
eration of π–π interaction between the aromatic rings of the guest and those of the host. In order to study in more detail the origin of the binding efficiency shown by receptors bearing dichloroacetamido groups, we synthesized the new calix[4]arene bisacetamide derivatives **1**–**3**, which differently from Loeb's compounds **I**, possess a fixed *1,3-alternate* conformation. Compound **1** has a strong electron-withdrawing group, CF_3, but with small steric hindrance compared with CCl_3. Compound **3** presents the same $-CHCl_2$ groups as **Ib** but in a different conformation. Moreover, we also synthesized a conformationally mobile derivative **4** in order to see whether carboxylate binding could induce a rearrangement in the calixarene structure to a conformation more suitable for complexation.

RESULTS

Synthesis and Conformational Properties of Ligands

Diamides **1**–**4** were obtained in 27–54% overall yields starting from 1,3-dinitrodipropoxycalix[4]arene (**5**) (Scheme 1). The first step, corresponding to the dialkylation of **5** was performed using well established procedures[20]. Because of the high insolubility of compound **5** which prevents the reaction, dry DMF was used instead of acetonitrile. First attempts to alkylate **5** with PrI resulted in the formation of the product in the *partial cone* (*paco*) conformation with the presence of only traces (<5%) of the *1,3-alternate* (*1,3-alt*) stereoisomer. On the other hand, when using 2-ethoxyethyl tosylate, compound **6** is obtained pure (58% yield) after column chromatography in the *1,3-alt* conformation as indicated by the presence of a singlet ($\delta_H \approx 3.65$) in the ^1H NMR and a triplet ($\delta_C \approx 35.0$) in the ^{13}C NMR spectra[21] for the $ArCH_2Ar$ group. Alkylation of compound **5** with MeI was first carried out using NaH in DMF at 70 °C but also after five-day conversion was very low (<10%). The use of Cs_2CO_3 (50 °C, 12 h) increased the yield to 72%. It is well known that 1,3-dimethoxy-2,4-dialkoxy derivatives of calix[4]arenes are conformationally mobile in solution[22,23], giving rise, at low temperature (–25 °C) in $CDCl_3$, to mixtures of *paco* and *cone* conformers. Surprisingly, compound **7** is already in slow exchange regime on the NMR time-scale at 27 °C and a mixture of *paco*:*cone* = 3:1, but no *1,3-alt* (<5%) was detected (see Experimental). The dinitro derivatives **6** and **7** were reduced in nearly quantitative yields (92 and 90%, respectively) with $SnCl_2 \cdot 2H_2O$ in ethanol at reflux. The diamines **8** and **9** thus obtained were reacted in dry THF and Et_3N using the proper acylating reagent to obtain compounds **1**–**4** in 51–93% yields. The presence of intermolecular H-bonds between –NHCOX

groups in solution was ruled out by dilution experiments (10^{-2}–10^{-4} mol/l) which showed no significant shifts (<0.05 ppm) for the signals of NH groups of compounds **1**, **2** and **3** resonating at δ 8.06, 7.87 and 8.09 ppm, respectively. Therefore compounds **1**–**3** are present as monomers in $CDCl_3$ and their NH groups are able to interact with anionic species. The ^1H NMR spectrum of compound **4** in $CDCl_3$ at 27 °C shows, besides the well defined signals of the *cone* conformer, broad signals that at 5 °C sharpen, revealing the presence of the *paco* conformer. At this temperature, the *cone*:*paco* ratio is 60:40 while no traces (<5%) of the *1,3-alt* conformation could be detected.



SCHEME 1

^{1}H NMR Complexation Studies

In the light of our previous results on metal ion complexation by calix[4]-crowns[24], where a strong influence of the calix[4]arene conformation was shown, both on the selectivity and on the efficiency of cation recognition, we first investigated the binding properties of the conformationally mobile dichloroacetamido calix[4]arene derivative **4** to benzoate anion, which was the most efficiently bound guest by the fixed *cone* derivative **Ib** studied by Loeb. The NH and $CHCl_2$ protons of both the *cone* and *paco* conformers of **4** underwent strong downfield shifts upon benzoate addition but no significant change of the conformer distribution was observed. From the fitting of the titration data, a $K_{assoc} \approx 100$ l/mol was evaluated which was much lower than the value of 5160 l/mol found by Loeb for the fixed *cone* analogue **Ib**. We then investigated the binding properties of ligands **1**–**3** with different tetrabutylammonium anions such as acetate, benzoate and bromide, in $CDCl_3$ solution (Table I). Interestingly, the efficiency in the binding of all these anions follows the order **1** < **2** << **3** which points to a very special role of the dichloroacetamido group in anion binding, as observed also by Loeb[19]. Ligand **3** shows a moderate selectivity for carboxylates over spherical (Br^-) and tetrahedral ($H_2PO_4^-$) anions. In particular, acetate is the best-bound carboxylate followed by benzoate, isobutyrate and lactate. Contrary

TABLE I
Association constants (K_{assoc})[a] of tetrabutylammonium anions in $CDCl_3$ at 300 K

Anion	**Ib**[b]	**1**[c]	**2**[d]	**3**			Δδ, ppm in **3**·X^-	
				average[e]	NH[f]	$CHCl_2$[g]	NH	$CHCl_2$
AcO^-	609	30	55	400	365	435	3.80	1.01
BzO^-	5160	35	110	245	220	270	3.54	1.12
Br^-	[h]	45	70	165	160	170	1.78	1.03
$H_2PO_4^-$	[h]	[i]	[i]	150	140	160	3.41	1.05
Isobutyrate	[h]	[i]	[i]	180	160	200	3.43	0.95
Lactate	[h]	[i]	[i]	100	90	110	2.57	0.72

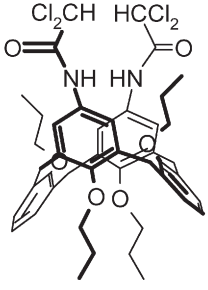
[a] Errors within 10%. [b] Ref.[19]. [c] Determined from the ArH protons. [d] Determined from the NH protons. [e] Average of the values determined from the NH and $CHCl_2$ protons. [f] Determined from the NH proton. [g] Determined from the $CHCl_2$ proton. [h] Not reported. [i] Not determined.

to what was reported for *cone* **Ib**, where a strong preference for benzoate over acetate was observed, the *1,3-alt* **3** seems to be quite sensitive to steric hindrance of the groups present in the α-position to the carboxylate: acetate < benzoate < isobutyrate < lactate.

During the ^{1}H NMR titration of **3** with anions it was observed that, besides the downfield shifts of the amide NH protons (Δδ 1.78÷3.80 ppm) attributable to strong H-bonding with the anionic guests, also the $CHCl_2$ protons experience remarkable and systematic downfield shifts (Δδ 0.72÷1.12 ppm) which were also used to calculate K_{assoc} values (Table I). These changes, which were also observed by Loeb and attributed to a perturbation of the see-saw motion between the two *pinched cone* conformers of the calix[4]arene skeleton, attracted our attention and we wanted to investigate them further, also with the help of molecular modeling.

Molecular Modeling Studies

As a first step in the modeling, we carried out a detailed study on the *N*-(chloroacetyl) (**11**), *N*-(dichloroacetyl) (**12**) and *N*-(trichloroacetyl) (**13**) derivatives of 4-methoxyanilines using the Hartree–Fock method at the 6-31G(d,p) level using Gaussian 03 [25], in order to calculate their conformational preference and their interaction energy with the simpler chloride anion. Although these calculations were performed in the gas phase, we think that they can well approximate what is taking place in solvents of low polarity such as chloroform.



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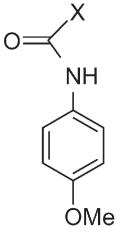

11: X= CH_2Cl

12: X= $CHCl_2$

13: X= CCl_3

The optimized geometry of ligand **12** is shown in Fig. 1a together with the molecular electrostatic potential (MEP) mapped on the molecular surface. The two hydrogen atoms of the $NHCOCHCl_2$ group are in *trans* posi-

tion. This is not surprising considering that the negative MEP on the carbonyl oxygens is coupled with the positive MEP on the H atom of the $CHCl_2$ group and, at the same time, the negative MEP on the two chloride ions is coupled with the positive MEP on to the NH hydrogen.

The optimized geometry of the chloride complex (**12**·Cl^-) is shown in Fig. 1b. The binding energy is –85.8 kJ/mol. In this case the Cl^- ion is bound through hydrogen bonds to the NH and to the nearest aromatic hydrogen, *ortho* to the NH group (Table II).

TABLE II
Selected angles[a] (in °) and distances[b] (in Å) in the complexes of ligands **11**–**13** and chloride anion

Ligand	Angle N–H···Cl^-	Distance NH···Cl^-	Angle ArC–H···Cl^-	Distance ArH···Cl^-	Angle ClC–H···Cl^-	Distance ClCH···Cl^-
trans-**12**	167.5	2.301	147.9	2.578		
cis-**12**	176.5	2.195		2.991	151.7	2.599
cis-**11**	176.9	2.211		2.997		3.163
13	167.4	2.313	148.6	2.56		

[a] Donor–H···acceptor angle. [b] H···acceptor distance.

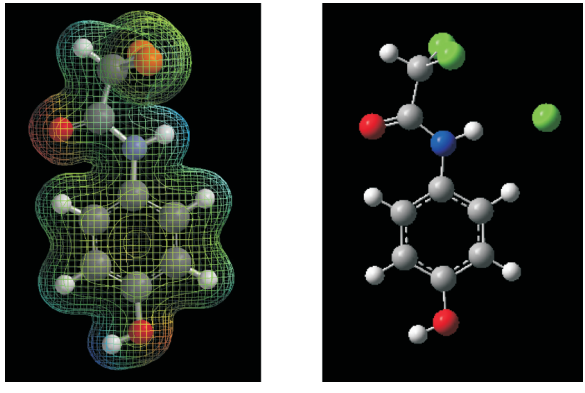

FIG. 1
Optimized geometry a of ligand **12** and molecular electrostatic potential plotted on to the molecular surface (colors from red, MEP = –80 kcal/mol, to blue, MEP = 100 kcal/mol) and b of its chloride complex in *trans* conformation

We have also examined the possible complex formation with the CCl_2H hydrogen atom in *cis* position with respect to the NH group. We scanned the potential energy as a function of the rotations of ϕ (°) of the torsion angle N–$C_{C=O}$–C–H from 0 (*trans*) to 180° (*cis*) to calculate the energy barrier for the interconversion. The energy profile (Fig. 2) shows that the *cis* conformation corresponds to a maximum which is 21.68 kJ/mol higher than the *trans* conformation.

However, although less stable, the free ligand in the *cis* conformation gives rise to a more stable complex with the chloride anion. The optimized geometry of the chloride complex of ligand **12** in *cis* conformation (Fig. 3)

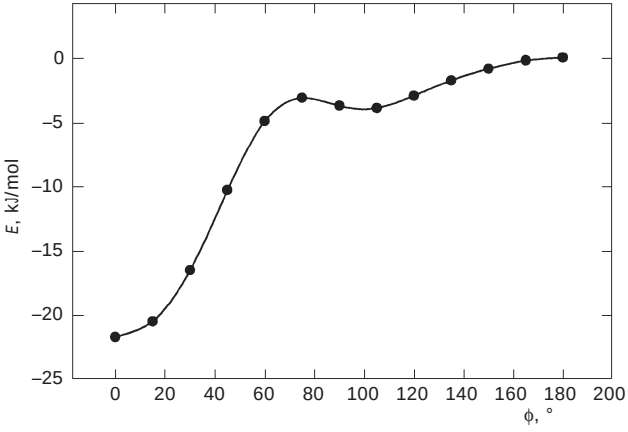

FIG. 2
Total potential energy (kJ/mol) of ligand **12** as a function of the torsion angle Φ. ϕ = 0° *trans*, ϕ = 180° *cis* conformation (relative scale with the zero fixed at maximum ϕ = 180°)

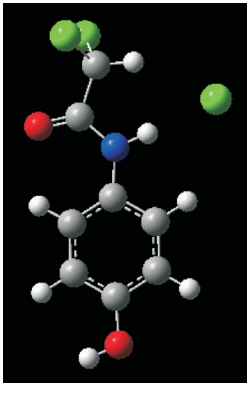

FIG. 3
Optimized geometry of the chloride complex of ligand **12** in *cis* conformation

shows a binding energy of –125.48 kJ/mol. Also considering that ligand **12** has to pay +21.68 kJ/mol for reorganizing its structure, the total energy for complex formation of *cis* isomer of **12** is –103.8 kJ/mol and thus this complex is by 18 kJ/mol more stable than the *trans* one.

This extra stabilization is due to the fact that Cl^- ion is strongly hydrogen-bonded (Table II) to both the NH and $CHCl_2$ hydrogen and, at a longer distance, with the aromatic hydrogen atom (ArH).

The case of chloride complex of ligand **11** is quite different. The most stable conformation of the free ligand (Fig. 4a) still results to be the *trans* one with the two hydrogen atoms opposite to the NH group, but, differently from **12**, only one stable chloride complex (Fig. 4b) is possible which requires the interconversion from the *trans* to the *cis* conformation of the ligand prior to complexation to bring both hydrogen atoms of the CH_2Cl towards the Cl^-.

The total binding energy (including the expense of energy for the *trans–cis* interconversion) is –111.73 kJ/mol. In this case the chloride ion is mainly hydrogen bonded to the N–H atom and a weaker hydrogen bond with the aromatic hydrogen atom (Table II) contributes to stabilize the complex.

The case of receptor **13** is the simplest one. The optimized structure of the complex (Fig. 5) shows the presence of two hydrogen bonds with the NH and aromatic hydrogen. The binding energy is –94.89 kJ/mol.

We have then investigated the binding modes of the acetate anion with the *1,3-alternate* ligand **10**, a simpler model of **3**, and compared it with the *cone* conformer **Ib** using semi-empirical methods at the PM3 level using Spartan 02 [26].

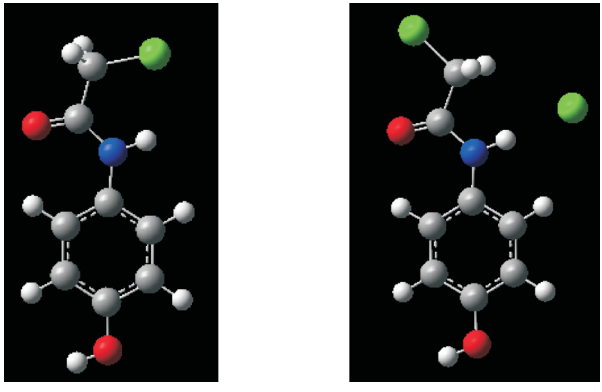

FIG. 4
Optimized geometry a of receptor **11** and b of its chloride complex

Both **10** and **Ib** bind the acetate anion through multiple hydrogen bonds involving the acetate oxygen atoms as acceptors and the NH and $CHCl_2$ hydrogen atoms as donors.

Three different acetate complexes of **10** have been calculated. Their structures are displayed in Figs 6a–6c.

In the first complex (Fig. 6a) each acetate oxygen atom acts as acceptor in a bifurcated hydrogen bond with the NH and the $CHCl_2$ donor hydrogens of the same chloroacetamido group. In the other two complexes (Figs 6b, 6c), one acetate oxygen atom acts as acceptor in a bifurcated hydrogen bond with the $CHCl_2$ hydrogen atoms of the two chloroacetamido chains. The third hydrogen bond takes place between the other acetate oxygen and the NH hydrogen of one chloroacetamide. The only difference between the two complexes lies in the different orientations of the chloroacetamido groups.

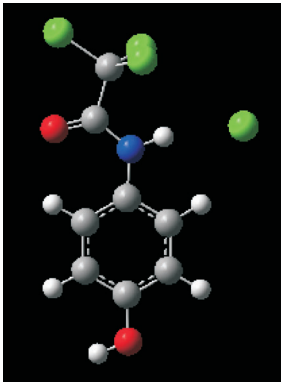

FIG. 5
Optimized structure of the chloride complex of ligand **13**

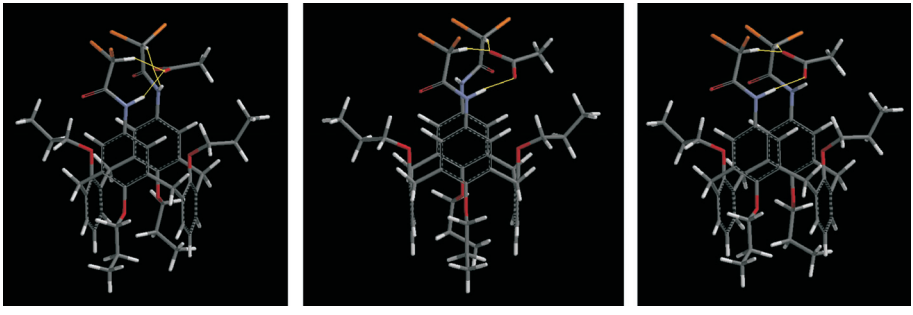

FIG. 6
Acetate complexes of receptor **10** (hydrogen bonds in yellow)

Receptor **Ib** gives two acetate complexes (Figs 7a, 7b) in which the anion is linked to the receptor through two bifurcated hydrogen bonds.

In one case (Fig. 7a), each acetate oxygen is bound to the NH and the $CHCl_2$ donor hydrogen atoms of the same chloroacetamido chain; in the other complex (Fig. 7b), each acetate oxygen links the $CHCl_2$ hydrogen atoms or the NH hydrogen atoms of the two chloroacetamido chains.

DISCUSSION

The results obtained in this work with the *1,3-alternate* calix[4]arene anion receptors containing activated amides as binding groups, confirm the previous observation on *cone* calix[4]arene derivatives[19] and indicate that compounds containing dichloroacetamido groups have a special efficiency in anion binding. Loeb and Cameron[19] attributed the higher efficiency in the benzoate anion binding of the *cone* calix[4]arene receptor **Ib** containing these groups compared with the monochloroacetamido **Ia** and trichloroacetamido derivative **Ic** to a compromise between the electron-withdrawing and steric effects of the substituents, which decrease in the order CCl_3 > $CHCl_2$ > CH_2Cl. On the basis of the experimental and theoretical results obtained in this work we are inclined to conclude that this special behavior is due to the bidentate nature of the dichloroacetamido group which interacts with the anions both through the NH and the $CHCl_2$ protons. This is clearly indicated in the results of the ab initio study on model compounds **11**–**13**, which show that, although the most stable conformation of the free

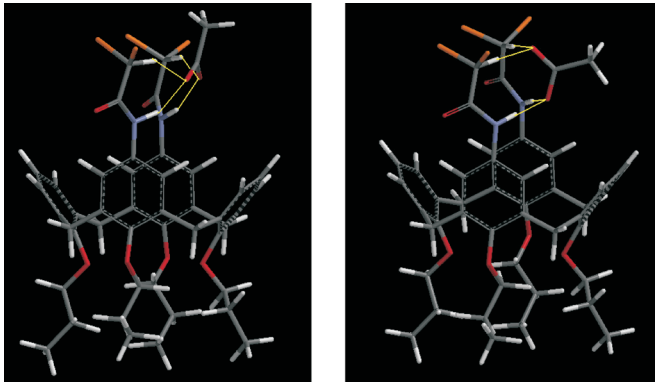

FIG. 7
Optimized structures of the acetate complexes of **Ib**

ligand **12** has the N–H and $CHCl_2$ hydrogen atoms *trans*, the most stable chloride anion complex is obtained with the *cis* conformer in which both hydrogen atoms are bound to the Cl^-.

The bidentate binding mode of the dichloroacetamido groups is also found in the optimized structures of the acetate complexes of ligands **Ib** (*cone* conformation, Fig. 6) and **10** (*1,3-alt* conformation, Fig. 7). This also explains the higher efficiency in anion binding found for compound **Ib** compared with monochloroacetamido **Ia** or trichloroacetamido derivative **Ic** [19] and for compound **3** compared with **1** and **2** (Table I), which contain activated but monodentate amide groups.

The comparison of the acetate complexes of **Ib** and **10** (Figs 8a, 8b) shows that when the receptor is in the *cone* conformation (**Ib**), the intramolecular space between the chloroacetamido chains is sufficiently small to allow the formation of two bifurcated hydrogen bonds (Fig. 8a) (the distances are: $CCl_2H\cdots HCl_2C$ 2.7 Å and NH···HN 2.8 Å). On the contrary, when the receptor is the *1,3-alt* conformer **10** (Fig. 8b), the intramolecular space between the two chloroacetamides is larger due to the steric effect exerted by the two propoxy chains (the distances are: $CCl_2H\cdots HCl_2C$ 3 Å and NH···HN 4.7 Å) and thus two bifurcated hydrogen bonds are no more allowed. This feature justifies the slightly better binding of acetate anion with the *cone* receptor **Ib** compared with the *1,3-alt* analogue **3** (Table I), similar to **10**.

In conclusion, we suppose that there is enough theoretical and experimental background to consider the dichloroacetamido ligand as a new bidentate hydrogen bonding donor group which can be incorporated onto a variety of scaffolds to build up new efficient neutral receptors for anions.

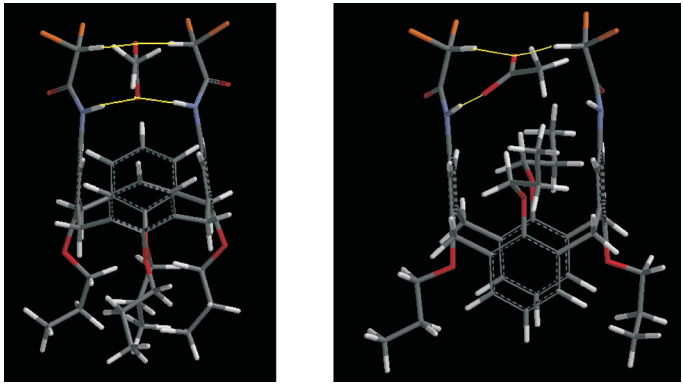

FIG. 8
Comparison of the acetate complexes a of ligand **Ib** and b of ligand **10**

EXPERIMENTAL

Most of the solvents and all reagents were obtained from commercial supplies and used without further purification. DMF employed in the synthesis was stored over 3 Å molecular sieves. All reactions were performed with efficient stirring in a nitrogen atmosphere. Melting points were obtained in a nitrogen-sealed capillary on Electrothermal Apparatus. TLC analyses were performed on precoated silica gel plates (Merck 60 F_{254}), while silica gel 60 (Merck, particle size 0.040–0.063 mm, 230–240 mesh) was used for preparative column chromatography. ^{1}H and ^{13}C NMR spectra (300 MHz and 75 MHz, respectively) were recorded on a Bruker AC300 or Bruker Avance300 spectrometers. Chemical shifts are reported as δ values in ppm and calibrated to the residual signal of the deuterated solvent, coupling constants (*J*) are given in Hz. Mass spectra were performed with Finnigan MAT SSQ 710 (CI, CH4) or ZMD Micromass Quattro LC spectrometer (ESI). Compound **5** was synthesized according to literature[20].

1,3-alternate 26,28-Bis(2-ethoxyethoxy)-5,17-dinitro-25,27-dipropoxycalix[4]arene (**6**)

Cs_2CO_3 (4.7 g, 14.4 mmol) was added to a stirred solution of dinitrodipropoxycalix[4]arene **5** (0.58 g, 0.96 mmol) in dry DMF (30 ml). After 0.5 h heating at 80 °C, 2-ethoxyethyl tosylate (3.5 g, 14.4 mmol) was added and the temperature raised to 120 °C. After 24 h the reaction mixture was quenched with 1 M HCl (60 ml) and extracted with CH_2Cl_2 (60 ml). The organic layer was washed with H_2O (2 × 40 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column by flash chromatography (SiO_2; hexane/ethyl acetate, 10:2) and compound **6** obtained as a yellow oily solid. Yield 0.41 g (58%). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): 7.92 s, 4 H (ArH); 7.08 d, 4 H, *J* = 7.5 (ArH); 6.67 t, 2 H, *J* = 7.5 (ArH); 3.92 t, 4 H, *J* = 5.1 (ArOC**H**$_2$CH$_2$O); 3.75–3.57 m, 20 H (ArOCH$_2$C**H**$_2$OC**H**$_2$, OC**H**$_2$CH$_2$CH$_3$, ArCH$_2$Ar); 1.96–1.89 m, 4 H (OCH$_2$C**H**$_2$CH$_3$); 1.29 t, 6 H, *J* = 7.2 (OCH$_2$C**H**$_3$); 1.09 t, 6 H, *J* = 7.4 (OCH$_2$CH$_2$C**H**$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 161.1 s (ArNO$_2$ *ipso*); 156.0 s (Ar *ipso*); 142.5 s (ArNO$_2$ *para*); 134.5, 132.3 s (Ar *ortho*); 130.3 d (Ar *meta*); 125.2 d (ArNO$_2$ *meta*); 122.0 d (Ar *para*); 74.6, 72.2, 69.4, 66.6 4t (OCH$_2$); 35.0 t (ArCH$_2$Ar); 23.7 t (OCH$_2$CH$_2$CH$_3$); 15.1 q (OCH$_2$CH$_3$); 10.4 q (OCH$_2$CH$_2$CH$_3$). MS (CI), *m/z* (%): 743.9 (M + 1)$^+$ 100; 742.8 (M)$^+$ 98; 671 (M – CH$_2$CH$_2$OCH$_2$CH$_3$)$^+$ 50. For $C_{42}H_{50}N_2O_{10}$ (742.87) calculated: 67.91% C, 6.78% H, 3.77% N; found: 67.86% C, 6.85% H, 3.83% N.

26,28-Dimethoxy-5,17-dinitro-25,27-dipropoxycalix[4]arene (**7**)

Compound **7** was synthesized as reported for compound **6** but using MeI as alkylating agent and heating at 50 °C for 12 h. The reaction mixture was poured in 1 M HCl (80 ml), the precipitate filtered on a Buchner and washed with H_2O (20 ml). The resulting precipitate was treated with methanol and the white solid filtered. Yield 0.43 g (72%); m.p. 191–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): *paco*:*cone* ratio = 75:25, *paco* 8.26 s, 2 H (ArH); 8.03 s, 2 H (ArH); 6.93 d, 2 H, *J* = 7.2 (ArH); 6.53 dd, 2 H, *J* = 7.2 (ArH); 6.36 d, 2 H, *J* = 7.2 (ArH); 4.08 d, 2 H, *J* = 13.8 (ArCH$_2$Ar ax); 3.92–3.84 m, 2 H (OCH**H**CH$_2$CH$_3$); 3.82 d, 2 H, *J* = 12.7 (ArCH$_2$Ar); 3.81 s, 3 H (OCH$_3$); 3.69 d, 2 H, *J* = 12.7 (ArCH$_2$Ar); 3.63–3.55 m, 2 H (OC**H**HCH$_2$CH$_3$); 3.23 d, 2 H, *J* = 13.8 (ArCH$_2$Ar eq); 3.15 s, 3 H (OCH$_3$); 1.99–1.90 m, 4 H (OCH$_2$C**H**$_2$CH$_3$); 1.10 t, 6 H, *J* = 7.2 (OCH$_2$CH$_2$C**H**$_3$); *cone* 8.10 s, 4 H (ArH); 6.32–6.28 m, 6 H (ArH); 4.41 d, 4 H, *J* = 13.4 (ArCH$_2$Ar ax); 4.04 s, 6 H (OCH$_3$); 3.72 t, 4 H, *J* = 6.8 (OC**H**$_2$CH$_2$CH$_3$); 3.33 d, 4 H, *J* = 13.4 (ArCH$_2$Ar eq); 1.99–1.90 m, 4 H (OCH$_2$C**H**$_2$CH$_3$);

1.17 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (300 MHz, $CDCl_3$, 300 K): 164.6, 163.8 s ($ArNO_2$ *ipso*); 156.0, 155.6 s (Ar *ipso*); 142.7, 142.4, 141.8 s ($ArNO_2$ *para*); 138.1, 137.9, 134.9, 132.2, 131.7, 130.8 s (Ar and $ArNO_2$ *ortho*); 129.2, 128.6, 127.8 d (Ar *meta*); 126.1, 124.3, 124.2, 122.6, 122.3 ($ArNO_2$ *meta* and Ar *para*); 77.2 t ($O\mathbf{C}H_2CH_2CH_3$ *cone*); 76.2 t ($O\mathbf{C}H_2CH_2CH_3$ *paco*); 61.2, 60.2, 59.6 q (OCH_3); 35.6 and 30.6 t ($ArCH_2Ar$ *paco*); 29.6 t ($ArCH_2Ar$ *cone*); 23.7 t ($OCH_2\mathbf{C}H_2CH_3$); 10.9 and 10.7 q ($OCH_2CH_2\mathbf{C}H_3$). MS (CI), *m/z* (%): 627 $(M + 1)^+$ 40; 626 $(M)^+$ 100; 611 $(M - CH_3)^+$ 25; 583 $(M - Pr)^+$ 20. For $C_{36}H_{38}N_2O_8$ (626.71) calculated: 68.99% C, 6.11% H, 4.47% N; found: 68.88% C, 6.05% H, 4.56% N.

1,3-alternate 5,17-Diamino-26,28-bis(2-ethoxyethoxy)-25,27-dipropoxycalix[4]arene (**8**)

A mixture of compound **6** (0.28 g, 0.38 mmol) and $SnCl_2 \cdot 2H_2O$ (0.86 g, 3.8 mmol) in EtOH (25 ml) was refluxed for 2 h. Then the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (30 ml). The organic phase was washed with a 1 M NaOH solution (40 ml) and H_2O (2 × 30 ml). The solvent was removed on a rotavapor to give pure compound **8**. Yield 0.24 g (92%); m.p. 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): 7.07 d, 4 H, *J* = 7.5 (ArH); 6.63 t, 2 H, *J* = 7.5 (ArH); 6.46 s, 4 H (ArH); 3.76 t, 4 H, *J* = 5.1 ($ArOC\mathbf{H}_2CH_2OCH_2CH_3$); 3.63–3.45 m, 20 H ($ArOCH_2C\mathbf{H}_2O\mathbf{CH}_2CH_3$, $OC\mathbf{H}_2CH_2CH_3$, $ArCH_2Ar$); 1.81–1.74 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.29 t, 6 H, *J* = 7.1 ($OCH_2C\mathbf{H}_3$); 1.04 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 156.2 s (Ar *ipso*); 145.4 s ($ArNH_2$ *ipso*); 139.9 s ($ArNH_2$ *para*); 134.4, 133.5 s (Ar *ortho*); 129.8 d (Ar *meta*); 121.7 d (Ar *para*); 117.6 d ($ArNH_2$ *meta*); 74.1, 71.3, 69.5, 66.5 t (OCH_2); 35.5 t ($ArCH_2Ar$); 23.9 t ($OCH_2\mathbf{C}H_2CH_3$); 15.3 q ($OCH_2\mathbf{C}H_3$); 10.8 q ($OCH_2CH_2\mathbf{C}H_3$). MS (CI), *m/z* (%): 683 $(M)^+$ 100. For $C_{42}H_{54}N_2O_6$ (685.91) calculated: 73.87% C, 7.97% H, 4.10% N; found: 73.95% C, 8.02% H, 4.18% N.

5,17-Diamino-26,28-dimethoxy-25,27-dipropoxycalix[4]arene (**9**)

Compound **9** was synthesized as reported for compound **8** starting from dinitrocalix[4]arene **7**. The product was crystallized from ethanol. Yield 0.19 g (90%); m.p. 229–232 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): 6.96–6.84 m (ArH); 6.69–6.30 m (ArH); 4.29 d, *J* = 12.7 ($ArCH_2Ar$ ax); 4.04–3.13 m (OCH_3, $OC\mathbf{H}_2CH_2CH_3$, $ArCH_2Ar$, NH_2); 3.03 d, *J* = 12.7 ($ArCH_2Ar$ eq); 1.94–1.85 m ($OCH_2C\mathbf{H}_2CH_3$); 1.16–1.08 m ($OCH_2CH_2C\mathbf{H}_3$). MS (CI), *m/z* (%): 567.8 $(M + 1)^+$ 40; 566.7 $(M)^+$ 100. For $C_{36}H_{42}N_2O_4$ (566.75) calculated: 76.30% C, 7.47% H, 4.94% N; found: 76.36% C, 4.53% H, 5.04% N.

Acylation of Diamines **8** and **9**. General Procedure

To a stirred solution of diamine **8** or **9** (0.3 mmol) and triethylamine (0.9 mmol) in dry THF at 0 °C was added an appropriate acylating agent (0.9 mmol). The reaction mixture was stirred at room temperature for 2–12 h, then THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 ml), washed with a 1 M NaOH solution (30 ml) and water (2 × 30 ml). The organic layer was dried over anhydrous Na_2SO_4 and CH_2Cl_2 removed on a rotavapor to yield compounds **1**–**4**.

1,3-alternate 26,28-Bis(2-ethoxyethoxy)-25,27-dipropoxy-5,17-bis(trifluoroacetamido)calix[4]-arene (**1**). Acylating agent was trifluoroacetic anhydride. Reaction time 3 h. Yield 0.24 g (93%); m.p. 217–219 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): 8.12 bs, 2 H (NH); 7.09 d, 4 H, *J* = 7.5 (ArH); 7.04 s, 4 H (ArH); 6.63 t, 2 H, *J* = 7.5 (ArH); 3.90 t, 4 H, *J* = 5.1 ($ArOC\mathbf{H}_2CH_2O$);

3.73–3.46 m, 20 H ($OC\mathbf{H}_2CH_2CH_3$, $ArOCH_2C\mathbf{H}_2OC\mathbf{H}_2$, $ArCH_2Ar$); 1.89–1.82 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.32 t, 6 H, *J* = 7.0 ($OCH_2C\mathbf{H}_3$); 1.03 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 156.2 s (Ar *ipso*); 154.9 s (ArNH *ipso*); 134.4, 132.4 s (Ar *ortho*); 130.5 d (Ar *meta*); 127.2 s (ArNH *para*); 125.1 d (ArNH *meta*); 121.3 d (Ar *para*); 116.0 q, J_{C-F} = 288 ($COCF_3$); 74.3, 71.9, 69.6, 66.6 t (OCH_2); 35.0 t ($ArCH_2Ar$); 23.9 t ($OCH_2CH_2CH_3$); 15.2 q (OCH_2CH_3); 10.3 q ($OCH_2CH_2CH_3$). IR (liquid film, cm^{-1}): ν(N–H) 3310; ν(C=O) 1717. MS (CI), *m/z* (%): 875 $(M)^+$ 100. For $C_{46}H_{52}F_6N_2O_8$ (874.93) calculated: 63.15% C, 5.99% H, 3.20% N; found: 63.21% C, 5.87% H, 3.28% N.

1,3-alternate 26,28-Bis(2-ethoxyethoxy)-5,17-bis(pentafluorobenzoylamido)-25,27-dipropoxycalix-[4]arene (**2**). Acylating agent was pentafluorobenzoyl chloride. Reaction time 12 h. Compound **2** was recrystallized from methanol. Yield 0.16 g (51%); m.p. 284–286 °C. ^1H NMR (300 MHz, $CDCl_3$, 300 K): 7.89 bs, 2 H (NH); 7.10 d, 4 H, *J* = 7.5 (ArH); 7.08 s, 4 H (ArH); 6.64 t, 2 H, *J* = 7.5 (ArH); 3.90 t, 4 H, *J* = 4.6 ($ArOC\mathbf{H}_2CH_2O$); 3.73–3.48 m, 20 H ($ArOCH_2C\mathbf{H}_2OC\mathbf{H}_2CH_3$, $ArCH_2Ar$, $ArOC\mathbf{H}_2CH_2CH_3$); 1.97–1.87 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.32 t, 6 H, *J* = 7.0 ($OCH_2C\mathbf{H}_3$); 1.10 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 156.3 s (Ar *ipso*); 154.9 s (ArNH *ipso*); 134.3, 132.5 s (Ar *ortho*); 130.4 d (Ar *meta*); 128.3 s (ArNH *para*); 126.4 d (ArNH *meta*); 121.3 d (Ar *para*); 74.2, 71.9, 69.6, 66.6 t (OCH_2); 35.1 t ($ArCH_2Ar$); 23.9 t ($OCH_2CH_2CH_3$); 15.2 q (OCH_2CH_3); 10.5 q ($OCH_2CH_2CH_3$). MS (CI), *m/z* (%): 1070 $(M)^+$ 100. IR (KBr, cm^{-1}): ν(N–H) 3320–3190; ν(C=O) 1662. For $C_{56}H_{52}F_{10}N_2O_8$ (1071.03) calculated: 62.80% C, 4.89% H, 2.62% N; found: 62.71% C, 4.95% H, 2.71% N.

1,3-alternate 5,17-Bis(dichloroacetamido)-26,28-bis(2-ethoxyethoxy)-25,27-dipropoxycalix[4]-arene (**3**). Acylating agent was dichloroacetyl chloride. Reaction time 5 h. Compound **3** was obtained after trituration in hexane. Yield 0.14 g (85%); m.p. 250–252 °C. ^1H NMR (300 MHz, $CDCl_3$, 300 K): 8.13 s, 2 H (NH); 7.10 s, 4 H (ArH); 7.09 d, 4 H, *J* = 7.4 (ArH); 6.66 t, 2 H, *J* = 7.4 (ArH); 6.09 s, 2 H ($COCHCl_2$); 3.83 t, 4 H, *J* = 5.1 ($ArOC\mathbf{H}_2CH_2O$); 3.70–3.51 m, 20 H ($ArOCH_2C\mathbf{H}_2OC\mathbf{H}_2CH_3$, $OC\mathbf{H}_2CH_2CH_3$, $ArCH_2Ar$); 1.84–1.76 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.30 t, 6 H, *J* = 7.0 ($OCH_2C\mathbf{H}_3$); 1.01 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 162.1 s (C=O); 156.3 s (Ar *ipso*); 154.4 s (ArNH *ipso*); 134.3, 132.7 s (Ar *ortho*); 130.4 d (Ar *meta*); 128.9 s (ArNH *para*); 124.3 d (ArNH *meta*); 121.4 d (Ar *para*); 73.8, 71.4, 69.5, 66.5 t (OCH_2); 67.0 d ($COCHCl_2$); 35.6 t ($ArCH_2Ar$); 23.8 t ($OCH_2CH_2CH_3$); 15.2 q (OCH_2CH_3); 10.6 q ($OCH_2CH_2CH_3$). MS (CI), *m/z* (%): 910 $(M + 8)^+$ 1; 908 $(M + 6)^+$ 5; 906 $(M + 4)^+$ 25; 904 $(M + 2)^+$ 62; 902 $(M)^+$ 100. IR (liquid film, cm^{-1}): ν(N–H) 3310; ν(C=O) 1698. For $C_{46}H_{54}Cl_4N_2O_8$ (904.76) calculated: 61.07% C, 6.02% H, 3.10% N; found: 61.01% C, 6.11% H, 3.17% N.

5,17-Bis(dichloroacetamido)-26,28-dimethoxy-25,27-dipropoxycalix[4]arene (**4**). Acylating agent was dichloroacetyl chloride. Reaction time 3 h. Compound **4** was purified by column chromatography (SiO_2; hexane/ethyl acetate, 75:25). Yield 0.20 (83%); m.p. 172–174 °C. ^1H NMR (300 MHz, $CDCl_3$, 278 K): *paco*:*cone* ratio = 40:60, *paco* 8.26 bs, 1 H (NH); 8.10 bs, 1 H (NH); 7.52 s, 2 H (ArH); 7.34 s, 2 H (ArH); 6.93 d, 2 H, *J* = 7.2 (ArH); 6.52 dd, 2 H, *J* = 7.2 (ArH); 6.41 d, 2 H, *J* = 7.2 (ArH); 6.09 s, 2 H ($COCHCl_2$); 4.06 d, 2 H, *J* = 13.6 ($ArCH_2Ar$ ax); 3.88–3.81 m, 2 H ($OC\mathbf{H}CH_2CH_3$); 3.73–3.65 m, 7 H (OCH_3 and 2 $ArCH_2Ar$); 3.60–3.51 m, 2 H ($OC\mathbf{H}CH_2CH_3$); 3.12 s, 3 H (OCH_3); 3.11 d, 2 H, *J* = 13.6 ($ArCH_2Ar$ eq); 1.95–1.86 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.09 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$); *cone*: 8.29 bs, 2 H (NH); 7.41 s, 4 H (ArH); 6.34 s, 6 H (ArH); 6.10 s, 2 H ($COCHCl_2$); 4.35 d, 4 H, *J* = 13.2 ($ArCH_2Ar$ ax); 3.92 s, 6 H (OCH_3); 3.69–3.65 m, 4 H ($OC\mathbf{H}_2CH_2CH_3$); 3.18 d, 4 H, *J* = 13.2 ($ArCH_2Ar$ eq); 1.95–1.86 m, 4 H ($OCH_2C\mathbf{H}_2CH_3$); 1.16 t, 6 H, *J* = 7.4 ($OCH_2CH_2C\mathbf{H}_3$). ^{13}C NMR (300 MHz, $CDCl_3$,

300 K): 161.5 s (C=O); 156.5, 156.2, 155.7 s (Ar *ipso*); 137.8, 132.6, 131.5, 130.5, 128.9, 128.3, 127.4, 122.5, 122.2, 121.8, 120.7 (Ar *ortho*, ArNH *para*, Ar *meta*, Ar *para*, ArNH *meta*); 75.7 t ($OCH_2CH_2CH_3$); 67.0 d ($COCHCl_2$); 60.8, 59.2 q (OCH_3); 35.8 t ($ArCH_2Ar$ *paco*); 30.7 t ($ArCH_2Ar$ *cone*); 23.8 t ($OCH_2CH_2CH_3$); 10.9 q ($OCH_2CH_2CH_3$). MS (CI), *m/z* (%): 794 $(M + 8)^+$ 4; 792 $(M + 6)^+$ 20; 790 $(M + 4)^+$ 62; 788 $(M + 2)^+$ 100; 786 $(M)^+$ 85. For $C_{40}H_{42}Cl_4N_2O_6$ (788.60) calculated: 60.92% C, 5.37% H, 3.55% N; found: 60.86% C, 5.41% H, 3.63% N.

Molecular Modeling

Ab initio calculations have been carried out at the HF/6-31G(d,p) level using Gaussian 03 [25]. The geometry of each chloride complex was obtained starting from the optimized geometry of the receptor, placing the chloride anion at 2.5 Å along the N–H direction and leaving the system free to relax without constraints. No BSSE correction has been applied. The modeling of acetate complexes of calixarenes has been performed by semiempirical methods at the PM3 level using Spartan 02 [26]. The geometry of each free ligand was first determined with the "minimum conformer" search using the molecular mechanics MMFF method. Then the obtained geometry was minimized with semiempirical methods at the PM3 level. The geometry of each acetate complex was obtained starting from the optimized geometry of the receptor, placing the acetate anion in different selected positions faced on the N–H and CCl_2H hydrogen atoms and leaving the system free to relax without constraints. All the calculations were carried out on a Pentium IV PC at 2.5 MHz.

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