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Calix[4]arenequinazolinones. Synthesis and structure

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Abstract—The synthesis of calix[4]arenes bearing two quinazolin-4-ones group at the upper rim is decribed. ^{1}H NMR spectra and quantum chemical calculations make it possible to suggest that calix[4]arenequinazolinones form three rotamers in solutions at room temperature, due to the restricted rotation of the quinazolinone fragments. The X-ray structure investigation indicates that quinazolin-4-onecalix[4]arene exists in the crystal state as the methanol 1:1 inclusion complex.

1. Introduction

Calixarenes[1] are bowl-shaped macrocyclic compounds that are easily obtained by cyclocondensation of *para*-substituted phenols and formaldehyde. They are widely used for the creation of selective metal cation extractants (including radionuclides), catalysts, medicinal remedies, sensor materials, etc. With this purpose in mind, calix[4]arenes have been functionalized by various receptor groups, which can selectively bind cations, anions, and neutral molecules. Different nitrogen containing heterocycles are often used as such receptor groups. The synthesis and properties of picolyl-,[2] bipyridyl-,[3] imidazolyl-,[4] triazolyl-,[5] tetrazolyl-,[6] pyrazolyl-,[7] and cyclopeptidocalix[4]arenes[8] have been described in the literature. It has been shown that the palladium complex of bis-pyrazolylocalix[4]arene[7] is an effective catalyst in Suzuki cross-coupling. Calixarenes bearing cyclopeptide groups[8] can selectively bind cytochrome *c* with K_{ass} 10^6 M^{-1}. Copper and zinc complexes of calix[4]arenes modified with pyridyl and imidazolyl moieties, similar to metalloenzymes, catalyze esterification and trans-esterification of phosphates.[9] Picolynamido- and picolynthioamidocalixarenes selectively extract actinides from nitric acid solutions.[10] Triazolosulfamidocalixarenes are known as anionic receptors.[5] Calixarenes possessing azoheteryl based chromophore systems are sensitive to some metal cations, changing their spectral properties on complexation.[11]

We report here the synthesis, structural investigations, and some binding properties of calix[4]arenes functionalized at the wide rim of the macrocycle with two quinazolinone groups.

2. Results and discussion

There are two approaches for grafting calixarenes with heterocyclic residues. The first, modular approach consists in attaching readily formed heterocyclic moieties to the upper or lower rim of calixarene. If the first approach is impossible for some reasons, the desired calixarene can be obtained by heterocyclization of appropriate functional groups at the calixarene rim (the second approach). Earlier we synthesized calixareneimidoylchlorides, which were easily converted via azides to calixarenetetrazoles.[6] In the current research, calixareneimidoylchlorides were used for the formation of quinazolinone groups at the upper rim of the macrocycle.

Imidoylchlorides **2a**,**b**[6] prepared via chlorination of amides **1a**,**b** with phosphorus pentachloride form calixarenequinazolinones **4a**,**b** by interacting with methyl anthranilate in refluxing benzene in the presence of equivalent amounts of triethylamine. Amidines **3a**,**b** formed as intermediates undergo cyclization under the reaction conditions, due to the intramolecular nucleophilic attack of the nitrogen atom on the carbonyl group. It should be noted that cyclization of amidines **3** to quinazolinone **4** occurred only in the presence of triethylamine hydrochloride, which acts as a catalyst in this reaction (Scheme 1).[12]

Colorless high-melting crystalline compounds **4a**,**b** were obtained in an analytically pure state by crystallization or column chromatography. Three singlets of *tert*-butyl groups at

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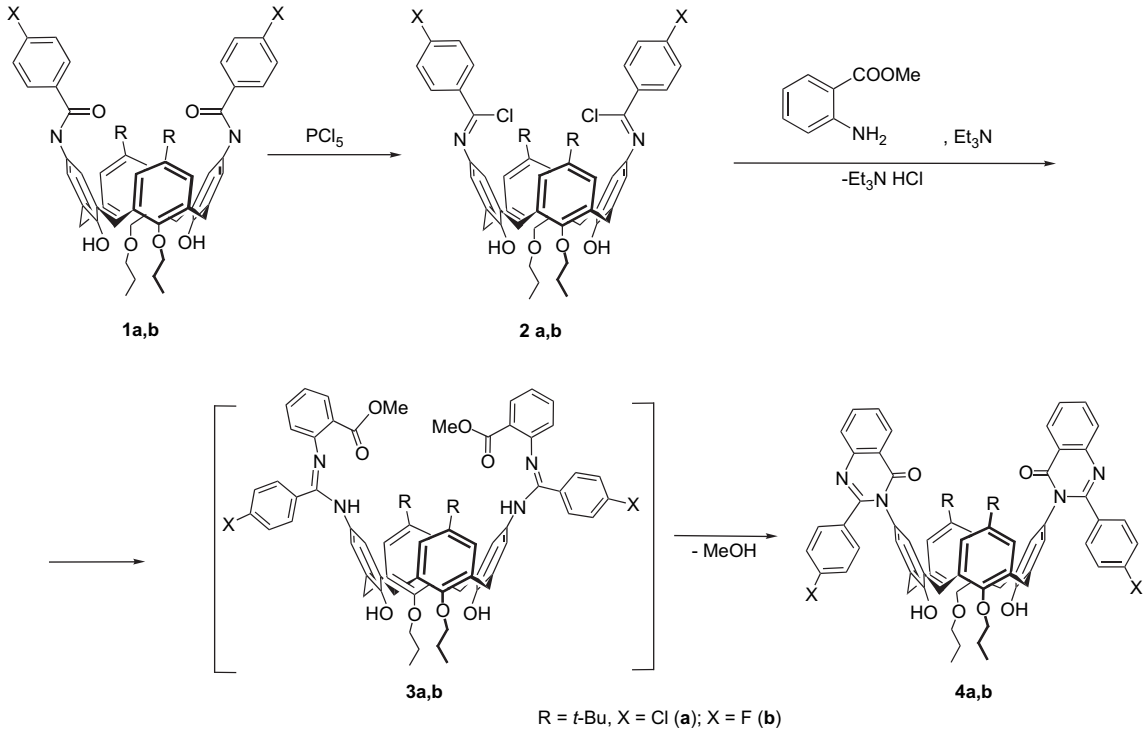

Scheme 1.

0.89 ppm, 0.96 ppm, and 1.07 ppm with different intensities are observed in the ^{1}H NMR spectra at room temperature in $CDCl_3$ and DMSO-d_6 solutions. Evidently calixarenes **4a**,**b** exist as three conformers stable within the NMR time scale (Fig. 1).

If heated, changes of the signal shape typical of dynamic processes occurred. Narrow and well-resolved signals for all protons are observed at 120 °C (Fig. 2). The singlet for *tert*-butyl groups, a pair of doublets from the equatorial and axial protons of methylene groups (AX-spin system, δ 3.30 ppm and 4.14 ppm, $^2J_{HH}$ 13.5 Hz) corresponds to the C_{2v} symmetric cone-shaped conformation of the macrocyclic skeleton of the molecule.[13]

Additional information about the nature and character of the observed dynamic processes of compound **4b** were obtained from quantum chemical calculations at the DFT (RI-BP86) approximation (see also Section 4.2.2). Two possible dynamic processes were considered for the calixarene **4b**, rotation of the heterocyclic group (RHG) and inversion of the aromatic ring (IAR). The first process, RHG, is evidently hampered not only by breaking the π,π-conjugation, but also due to the presence of the bulky *tert*-butyl groups. The second process, IAR, is typical for a calixarene system with small-size X substituents at the lower rim of the macrocycle, and hence should also be assumed in our case. We consider here three local minima in energy for the dynamic RHG process (**I**–**III**) and one minimum for the IAR process (**IV**) (Fig. 3). Their total energies (Table 1) calculated at the approximation level used for geometry optimization differ by no more than 3 kcal/mol, i.e., they are close in energy taking into account possible calculation errors inherent to the DFT approximation level. Conformer **4b-I** with carbonyl groups oriented into the macrocyclic cavity has the lowest total energy. The most energy rich conformation is **4b-III** with fluorine atoms in the cavity. Conformation **4b-II** is intermediate in energy compared to the two mentioned structures. This situation holds true for the total energy values, calculated using the optimized geometry parameters, but with the larger basis sets, TZVP.[23] It is noteworthy that the differences in the total energies are slightly increased in this case.

Analysis of the potential products of IAR shows that their total energies are significantly higher then those obtained for **4b**(**I**–**III**), and hence, even if this process occurs in solution,

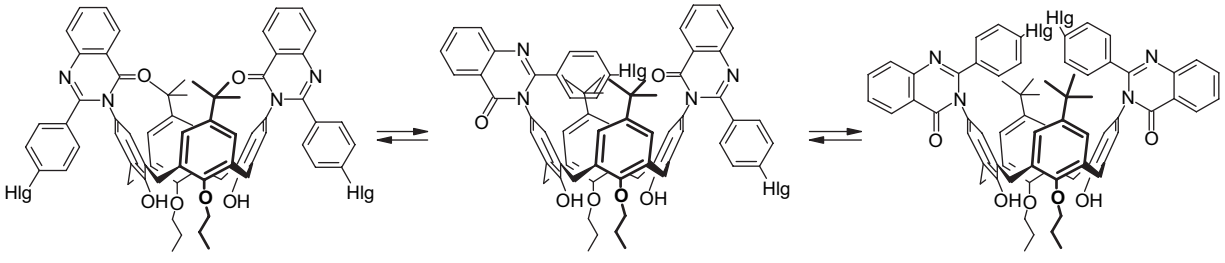

Figure 1. Interconversion of rotamers **4**.

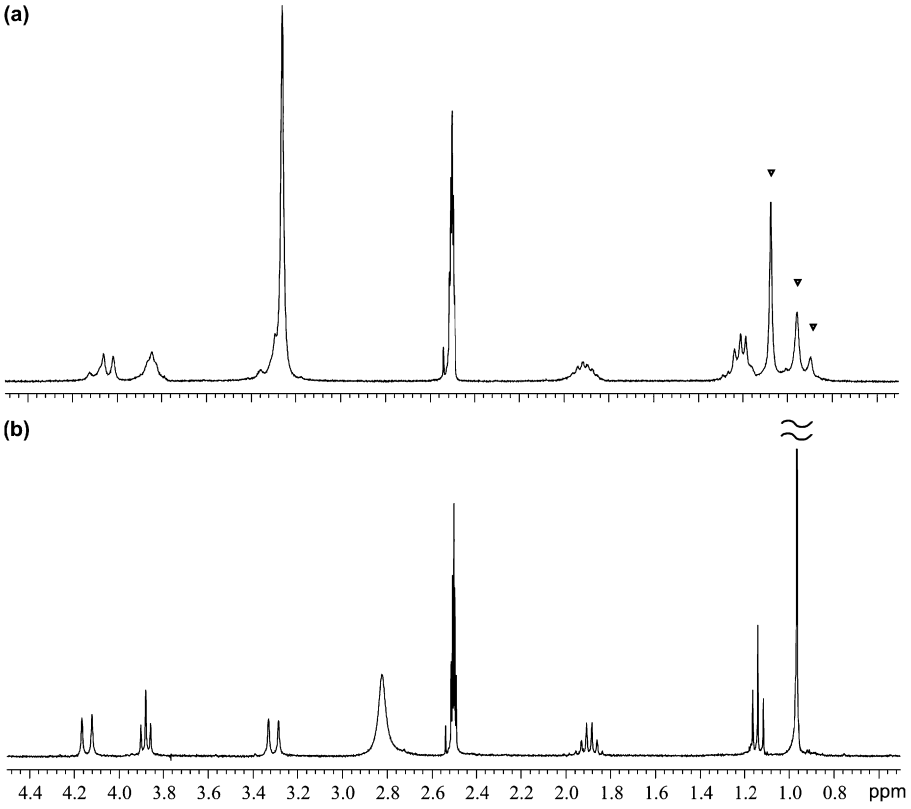

Figure 2. Sections of ^{1}H NMR spectra of **4a** in DMSO-d_6: (a) 20 °C and (b) 120 °C.

the population of the corresponding conformations is negligible, if any. Even the most favorable conformer from this series (**4b-IV**) possesses an energy 3.6–4.0 kcal/mol higher than that found for **4b-I**. The corresponding structure is also shown in Figure 3. A possible reason for the increasing total energy is the forced rupture of one or both hydrogen bonds O–H···O–Pr-*n* and the inversion of one aromatic ring through the annulus. Other products of IAR possess even higher total energies and their formation in solution is very unlikely. These structures, as well as the IAR process itself, are not considered further in the present work. Corresponding structural and quantitative data can be found in the Supplementary data.

It is known that quantum chemical calculations usually treat an isolated molecule in the gas phase or in vacuum. This situation is significantly distinguished from the conditions for the NMR experiment in solution or by the X-ray structural investigation in crystals. The solvent effects on the total energies can be taken into account (for chloroform and

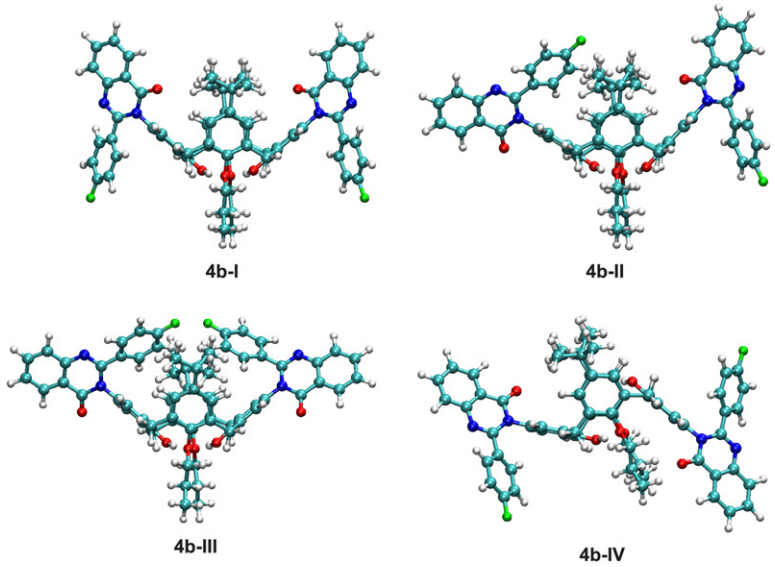

Figure 3. Optimized (RI-BP86/SV(P)) structures **4b(I–IV)**, VMD plots.

Table 1. Total and relative energies calculated for structures **4b(I–IV)**

Structure	RI-BP86/SV(P)		RI-BP86/TZVP		RI-BP86/TZVP (COSMO)	
	E, a.u.	Δ*E*, kcal/mol	*E*, a.u.	Δ*E*, kcal/mol	$CHCl_3$	DMSO
					Δ*E*, kcal/mol	Δ*E*, kcal/mol
4b-I	−3574.797276	0.00	−3578.653026	0.00	0.00	0.00
4b-II	−3574.794704	1.61	−3578.649117	2.45	−0.03	−1.23
4b-III	−3574.793695	2.25	−3578.645515	4.71	2.15	0.94
4b-IV	−3574.791548	3.59	−3578.646636	4.01	5.13	7.75

dimethylsulfoxide) using the COSMO procedure. The large size of the molecules and the insufficiently high level of approximation used for calculations do not allow us to expect a quantitative reproduction of the trends found in the NMR experiment. Besides, due to the same reasons we couldn't perform vibrational analyses for **4b** in order to ensure that we deal with the true local minima in energy and to calculate the total energy corrections by vibrations at 0 K. However, within these constraints, conformations **4b-I** and **4b-II** are similarly stable in chloroform and **4b-II** is found to be even more favored in DMSO. The latter conformation was found by the single-crystal X-ray investigation for **4a**. Additionally, in the last case, the corrected total energies for the conformations **I–III** are very close to one another and hence, these three conformations can simultaneously exist in solution.

The X-ray structure of **4a** (as 1:1 methanol host–guest complex) is shown in Figure 4. Calixarenequinazolinone **4a** has a *distorted cone* conformation for the macrocyclic skeleton. It is stabilized with intramolecular hydrogen bonds OH···OPr (2.683 Å and 2.782 Å) at the lower rim and intermolecular hydrogen bonds C═O···HOMe (2.828 Å) with the methanol guest included in the macrocycle cavity.

Due to the host–guest interaction, there is significant deviation of the crystal structure from the typical *flattened cone* conformation of 25,27-dialkoxy-26,28-dihydroxycalix[4]-arenes. Dihedral angles between the aromatic rings of the macrocycle and the plane of methylene linkers are equal to 109.18° and 116.46° for the alkylated rings and 127.97°, 138.49° for the rings bearing quinazolinone fragments. The quinazolinone fragments are differently oriented relative to the macrocycle, one of them can form a hydrogen bond C═O···H–OCH_3 with the methanol guest included in the cavity. The chlorophenyl moiety is oriented out of the cavity. The chlorophenyl substituent of another ring is directed into the cavity due to an intermolecular C–H···OH bond with methanol. Additionally an intermolecular CH···O hydrogen bond is also found between the methanol molecule and the proton at the sixth position of the quinazolinone ring of the neighboring molecule (with a distance C···O 3.400 Å). As a result, in the solid state the molecules form polymeric chains. The chains are parallel and rotated by 180° relative to one another along their axes (Fig. 5).

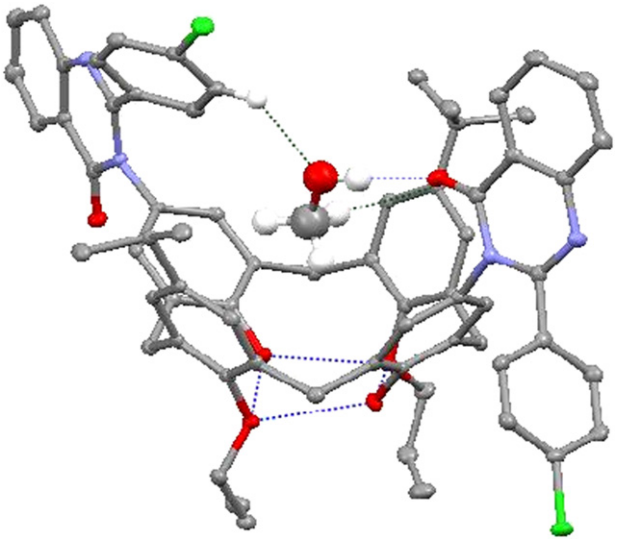

Figure 4. Intermolecular and intramolecular interactions in **4a·CH_3OH** complex.

3. Conclusions

In conclusion, we have synthesized calixarenes functionalized with quinazolinone groups that are able to stabilize host–guest complexes with proton donor molecules by formation of hydrogen bonds. Quantum chemical calculations at the DFT (RI-BP86) approximation, as well as NMR data show that calixarenequinazolinones exist in solution as three rotamers, stable at room temperature. X-ray analysis shows that quinazolinone groups promote the formation of a host–guest complex with methanol stabilized by intermolecular hydrogen bonds C═O···H–O. Taking into account the high pharmacological potential of quinazolinones (in particular, their psychotropic activity), their hybrids with calixarenes may be of interest for biomedical investigations.[14]

4. Experimental part

4.1. General

All reactions were carried out in anhydrous solvent under a dry atmosphere. IR spectra were recorded on spectrometer Specord M-80. ^{1}H NMR (299.94 MHz) and ^{19}F NMR (182.14 MHz) spectra were recorded on spectrometer 'Varian VXR-300' using, respectively, hexamethyldisiloxane and hexafluorobenzene as internal standards. Chemical shifts are given in δ scales relative to tetramethylsilane (^{1}H) and $CFCl_3$ (^{19}F). Diamide **1a** and diimidoylchloride **2a** were synthesized by known methods.[6]

4.1.1. 5,17-Di(4-fluorophenylcarboxamido)-11,23-di-*tert*-butyl-25,27-dipropoxy-26,28-dihydroxycalix[4]arene 1b. A solution of diaminocalixarene[15] (650 mg, 1 mmol) in toluene (10 ml) was added to a stirred solution of *para*-fluorobenzoylchloride (320 mg, 2.2 mmol) in toluene (10 ml).

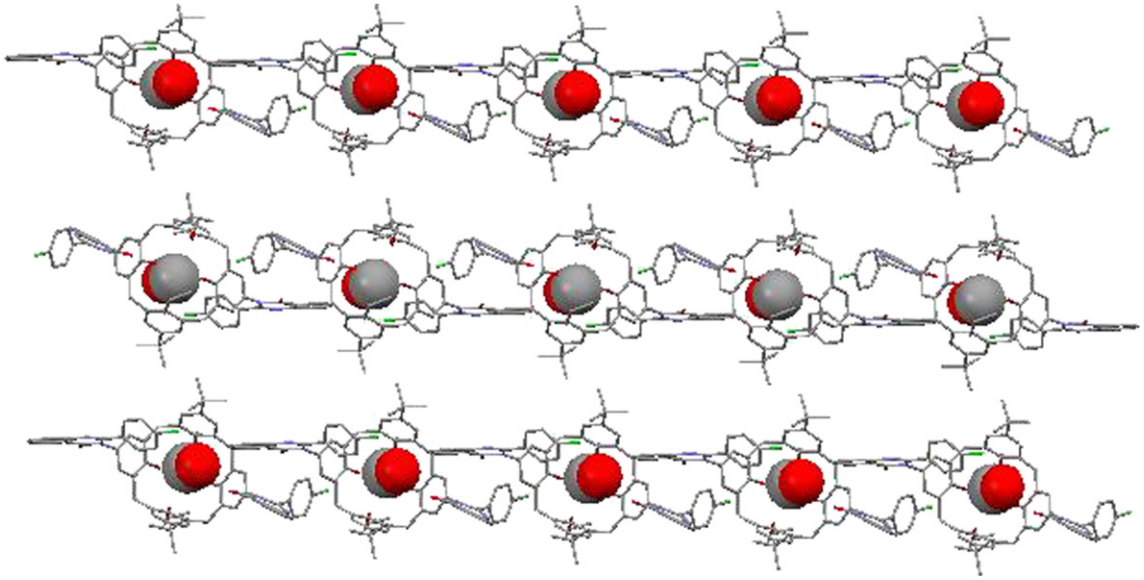

Figure 5. Crystal packing of **4a**·CH_3OH complex; chloroform molecules omitted.

The reaction mixture was stirred under reflux for 12 h. The product was filtered off from the cooled mixture and recrystallized from toluene. Yield 70%, mp 222–224 °C. Pale-rose crystals. IR (KBr) ν (cm^{-1}) 1665 (C═O), 3285 (NH, OH); ^{1}H NMR ($CDCl_3$): δ 8.25 (2H, s, OH), 7.85 (4H, m, C(O)ArH, *ortho*), 7.49 (2H, br s, NH), 7.31 and 6.96 (8H, two s, ArH), 7.15 (4H, t, J=8.5 Hz, C(O)ArH *meta*), 4.32 (4H, d, J=13.1 Hz, $ArCH_{ax}Ar$), 3.97 (4H, t, J=6.5 Hz, O–CH_2–CH_2–CH_3), 3.38 (4H, d, J=13.1 Hz, $ArCH_{eq}Ar$), 2.09 (4H, m, O–CH_2–CH_2–CH_3), 1.28 (6H, t, J=6.4 Hz, O–CH_2–CH_2–CH_3), 1.10 (18H, s, *t*-Bu). ^{13}C NMR ($(CD_3)_2S$═O, 100.60 MHz), δ ppm: 164.93, 163.60, 162.46, 149.70, 148.94, 146.91, 132.74, 129.97 (d, J=8.9 Hz), 127.95, 125.60, 121.25, 115.16 (d, J=21.4 Hz), 79.08, 78.01, 33.97, 31.08, 23.00, 10.84. ^{19}F NMR ($CDCl_3$) δ: −109.6 s. Calcd for $C_{56}H_{60}F_2N_2O_6$: C 75.14%, H 6.76%, N 3.13%. Found: C 75.19%, H 6.85%, N 3.17%.

4.1.2. 5,17-Di(1-chloro-1-(4-fluorophenyl)methylideneamino)-11,23-di-*tert*-butyl-25,27-dipropoxy-26,28-dihydroxycalix[4]arene 2b. A mixture of amidocalixarene **1b** (270 mg, 0.3 mmol) and phosphorus pentachloride (130 mg, 0.605 mmol) was refluxed in dry benzene (15 ml) for 14 h. A small amount of precipitate was filtered off. After the solvent and phosphorus oxychloride were removed in vacuo pure imidoylchloride **2b** was obtained with a yield of 85%. Yellow-brown moisture sensitive solid. ^{19}F NMR ($CDCl_3$) δ: −108.2 s. Calcd for $C_{56}H_{58}Cl_2F_2N_2O_4$: Cl 7.61%. Found: Cl 7.47%.

4.1.3. General procedure for the synthesis of calixarene-quinazolinones 4a,b. To a solution of calixareneimidoylchlorides **2a**,**b** (0.5 mmol) in benzene (10 ml) was added the solution of methyl anthranilate (1 mmol) and triethylamine (1 mmol) in benzene (10 ml) under stirring. The reaction mixture was refluxed for 15 h. The precipitate of triethylamine hydrochloride was filtered off after cooling and the solvent was evaporated in vacuum (10 mmHg, 90 °C). Compounds **4a**,**b** were purified according to the procedures mentioned below.

4.1.3.1. 5,17-(2(4-Chlorophenyl)-4-oxo-1,4-dihydro-1-quinazolinyl)-11,23-di-*tert*-butyl-26,28-dihydroxy-25,27-dipropoxycalix[4]arene 4a. Glass-like residue was dissolved in chloroform and precipitated by methanol. Precipitate was filtered off and crystallized from chloroform–methanol mixture (3:2 v/v). Colorless crystalline compound. Yield 53%, mp >360 °C. IR ($CHCl_3$) ν (cm^{-1}) 1700 (C═O), 3360 (OH); ^{1}H NMR (DMSO-d_6, 393 K) δ: 8.21 and 7.75 (4H, two m, 5,8-Quin), 7.86 and 7.57 (4H, two m, 6,7-Quin), 7.56 (4H, d, J=8.4 Hz, N–C(N)ArH, *ortho*), 7.29 (4H, d, J=8.4 Hz, N–C(N)ArH *meta*), 7.17 (2H, br s, OH), 7.09 (4H, s, *t*-Bu–Ar*H*), 6.72 (4H, br s, Quin–Ar*H*), 4.14 (4H, d, J=13.5 Hz, $ArCH_{ax}Ar$), 3.88 (4H, t, J=6.7 Hz, O–CH_2–CH_2–CH_3), 3.31 (4H, d, J=13.5 Hz, $ArCH_{eq}Ar$), 1.89 (4H, m, O–CH_2–CH_2–CH_3), 1.14 (6H, t, J=7.3 Hz, O–CH_2–CH_2–CH_3), 0.96 (18H, s, *t*-Bu). Calcd for $C_{70}H_{70}Cl_2N_4O_6$: C 74.13%, H 6.22%, N 4.94%, Cl 6.25%. Found: C 74.03%, H 6.20%, N 5.03%, Cl 6.15%.

4.1.3.2. 5,17-(2(4-Fluorophenyl)-4-oxo-1,4-dihydro-1-quinazolinyl)-11,23-di-*tert*-butyl-26,28-dihydroxy-25,27-dipropoxycalix[4]arene 4b. Solid residue was refluxed in methanol (10 ml) for 3 h and filtered off after cooling. Then, the mixture was purified by column chromatography on silica gel (L 35/100, Acros Organics) (eluent benzene–diethyl ether, 6:1 v/v). Pale-rose crystalline compound. Yield 24.5%, mp >360 °C. IR ($CHCl_3$) ν (cm^{-1}) 1710 (C═O), 3350 (OH); ^{1}H NMR ($CDBr_3$, 393 K) δ: 8.24 (2H, d, J=7.8 Hz, 5-Quin), 7.74 (2H, br s, OH), 7.53–7.42 (6H, m, N–C(N)ArH, *ortho*, 8-QuinH), 7.73 and 7.15 (4H, two m, 6,7-Quin), 6.90–6.80 (8H, m, N–C(N)ArH, *meta*, *t*-Bu–ArH), 6.57 (4H, br s, Quin–Ar*H*), 4.15 (4H, d, J=13.5 Hz, $ArCH_{ax}Ar$), 3.87 (4H, t, J=6.7 Hz, O–CH_2–CH_2–CH_3), 3.21 (4H, d, J=13.5 Hz, $ArCH_{eq}Ar$), 1.88 (4H, m, O–CH_2–CH_2–CH_3), 1.14 (6H, t, J=7.5 Hz, O–CH_2–CH_2–CH_3), 0.91 (18H, s, *t*-Bu). ^{19}F NMR ($CDBr_3$, 393 K) δ: −96.7 s. Anal. Calcd for $C_{70}H_{70}F_2N_4O_6$: C 76.34%, H 6.41%, N 5.09%. Found: C 76.79%, H 6.84%, N 5.10%.

4.2. X-ray investigation

4.2.1. Crystal data for 4a·CH$_3$OH. $C_{70}H_{70}Cl_2N_4O_6\cdot CH_3OH\cdot 3CHCl_3$ M_r=1520.31; colorless, crystal size 0.30 ×0.20 ×0.20 mm, triclinic *P*-1, *a*=13.6756(3) Å, *b*=14.4739(4) Å, *c*=20.3384(5) Å, α=92.567(1)°, β=99.879(1)°, γ=114.748(2)°, *V*=3571.1(2) Å^3, *Z*=2, ρ_{calcd}=1.414 g/cm^3; $2\theta_{max}$=52.8°. Intensity data were collected at 100(2) K on a Nonius Kappa CCD diffractometer using Mo Kα radiation (λ=0.71073 Å). Lorentz and polarization corrections were applied and diffracted data were not corrected for absorption.[16] Structure was solved and refined using SHELXS97[17] and SHELXL97,[17] respectively. Hydrogen atoms were calculated to their idealized positions and were refined as riding atoms. Three molecules of chloroform and one of methanol were presented. The final values of *R*-factors are R_1=0.040 for 10.364 reflections [$I>2\sigma$(I)] and 0.064 for all 14.473 data; final *wR* was 0.052. Residual electron density was between 0.789 and −0.812 e Å^{-3}. The crystallographic data for this structure have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 636954.

4.2.2. Details of calculations. All calculations were performed with the TURBOMOLE set of programs.[18] Structures were optimized without any symmetry restrictions. The standard split-valence SV(P) basis sets[19] and DFT BP86[20,21] functional were used for calculations in combination with the high integration accuracy (grid=5) and convergence criterion (scfconv=1×10^{-8}). For more performance, the RI (Resolution of the Identity)[22] algorithm was employed for all calculation routines. No vibration frequency calculations were made, due to the large size of the investigated structures. The single-point energy calculations were performed with the optimized structures using the TZV basis sets of triple-zeta quality suggested by Ahlrichs et al.:[23] [(11s6p)/[5s3p] for C, N, O, and F contracted as {62,111/411} and (5s)/[3s] for H with contraction {311}]. The basis sets were expanded by addition of the polarization functions (the TZVP basis sets standard within the TURBOMOLE packet). This meant the above-mentioned TZV basis sets plus one set of three p-functions for hydrogen and one set of five d-functions for the other elements. The solvent effects were taken into account using the COSMO[24] procedure implemented into the TURBOMOLE set of program. The VMD program packet[25] was used for the graphical presentation of the calculated structures.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.047.

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