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One-Step Heterylation at the Upper Rim of Calix[4]arene with 1,2,4-Triazin-5(2*H*)-ones

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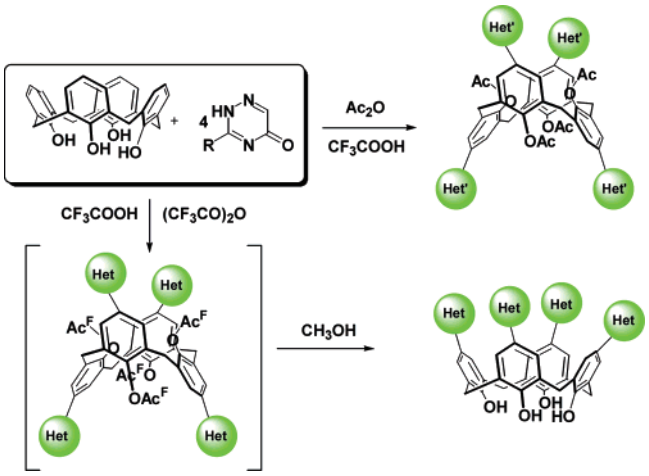

A convenient way to modify calix[4]arenes based on the direct C−C coupling reaction of their phenol moiety with 1,2,4-triazines has been advanced, and the ability of modified calixarenes to provide transport of La^{3+} and Ga^{3+} cations through organic membranes has been examined.

Calix[4]arenes are widely used to design receptors for cationic, anionic, or neutral species. To enhance their complexing abilities, a variety of chemical reactions on hydroxy groups, aromatic rings, or linking fragments have been performed. A great deal of publications describe structural modification of calixarenes through incorporation of heterocyclic fragments; however, a vast majority of these works are dedicated to functionalization of the lower rim of the calixarene.[1]

Chemical modification at the upper rim of calixarenes appears to be a promising approach because it has to enlarge a molecular cavity and to change the ability of these molecules to form complexes. Heterocyclic substituents located at the upper rim allow the receptor to interact with both polar or ionic groups and nonpolar fragments of substrates due to their inclusion into the molecular cavity of calixarene. A few examples of functionalization of calixarene rings with heterocyclic fragments have been reported in the literature; however, all of them exploit a multistep strategy to build heterocycles on the calixarene platform.[2]

In this paper, we wish to describe a new approach for heterylation at the upper rim which enables one to incorporate a heterocyclic fragment into unsubstituted calixarenes through a one-step procedure. This approach is based on direct C−C coupling of the phenol moiety of calixarene with electron-deficient 1,2,4-triazines, and it appears to be the first example of successful application of the S_N^H methodology in calixarene chemistry.[3]

We have recently elaborated a convenient method for functionalization of 1,2,4-triazin-5(2*H*)-ones with fragments of π-excessive carbo- and heterocycles. It has been shown that, being activated with acylating agents, 2-acyl-1,2,4-triazin-5(2*H*)-ones are capable of reacting with phenols to give a new C−C bond between unsubstituted carbon atoms of two aromatic rings.[4] This work exploits the same methodology to perform heterylation of calixarene rings with 1,2,4-triazin-5(2*H*)-ones.

It has been established that the C−C coupling of calixarene **1** with 1,2,4-triazinones **3** can be carried out in TFA in the presence of acylating agents, such as acetic or trifluoroacetic anhydrides. Without an organic anhydride, the reaction does not occur, as indicated by ^{1}H NMR of the reaction mixture. Indeed, an electrophilic character of protonated 1,2,4-triazin-5(2*H*)-one appears to be not sufficient to cause the reaction with calixarenes. Treatment of 1,2,4-triazin-5-ones **3** with acetic

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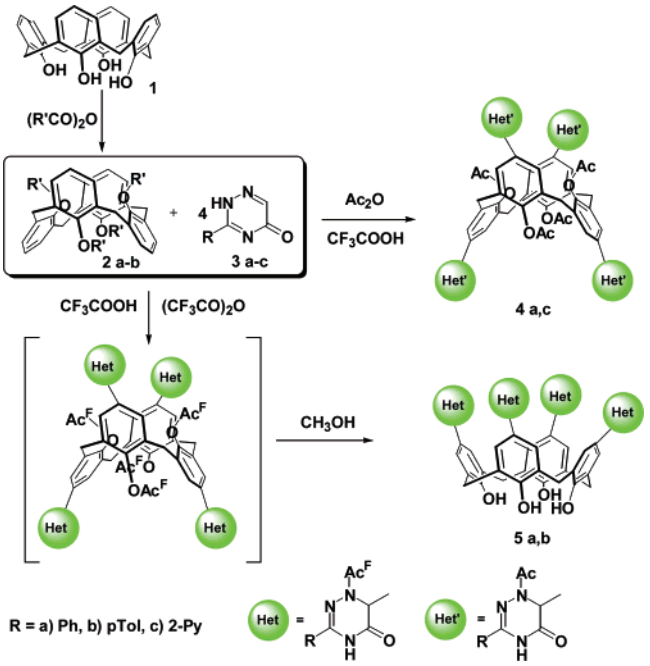
SCHEME 1



(trifluoroacetic) anhydride in TFA affords a protonated form of 2-acyl-1,2,4-triazinone.[5] Nucleophilic addition of calix[4]-arene **1** takes place at C-6 of **3** to give the corresponding σ^H-adducts. The feature of the reaction is that it is accompanied by the rearrangement of the N(2)-acyl derivatives into more stable adducts **4** and **5**, bearing the acyl group at the N(1) atom, adjacent to the reaction center (Scheme 1).

Although the parent calix[4]arene **1** exists in the *cone* conformation, chemical modifications may give four possible conformers: *cone*, *partial cone*, *1,2-* and *1,3-alternates*. Organic anhydrides acylate the hydroxy groups of calixarene and change their conformation from the cone into the 1,3-alternate to give calixarenes **2**, which can be isolated in 40 min after beginning of the reaction. The NH salts of 2-acyl-1,2,4-triazin-5-ones, which are formed in situ by dissolving triazinones in a mixture of trifluoroacetic acid and a (trifluoro)acetic anhydride, react with calixarenes **2a**,**b** to afford the relatively stable adducts **4** and **5** in good yields. The mechanism of this reaction is somewhat similar to that observed for the interaction of triazinones with benzoannelated crown ethers[4a] and involves nucleophilic addition at the unsubstituted carbon atom of the triazine ring followed by the 1,2-acylotropic rearrangement, which results in the formation of a more stable N(1)-acyl isomer. The stereochemistry of the reaction of **1** with 1,2,4-triazinones depends on the nature of an acylating agent and reaction conditions. Indeed, in the presence of acetic anhydride, the reaction results in calix[4]arenes **4a**,**c** existing in the 1,3-alternate conformation, while trifluoroacetic anhydride facilitates deacylation of all O-trifluoroacetyl groups, and recrystallization from methanol proved to give the *cone* isomers of the modified calixarenes **5a**,**b** (Scheme 1).

Behavior of 3-(2-pyridyl)-1,2,4-triazin-5-one **3c** has some differences. Like other 3-(*R*)-1,2,4-triazin-5-ones, compound **3c** reacts with calixarene **1** in the presence of acetic anhydride into

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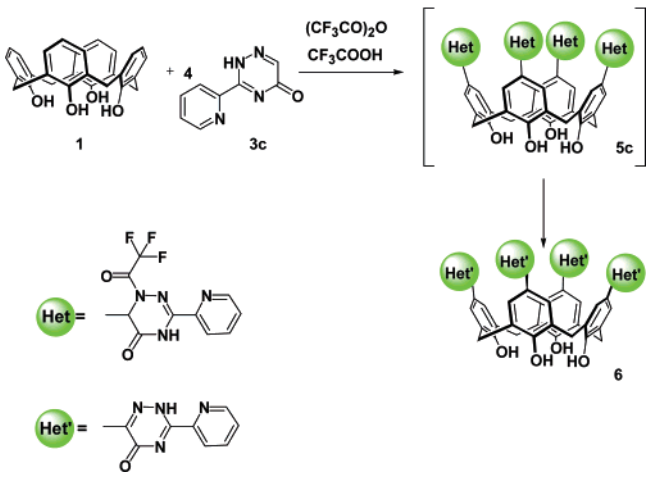
SCHEME 2



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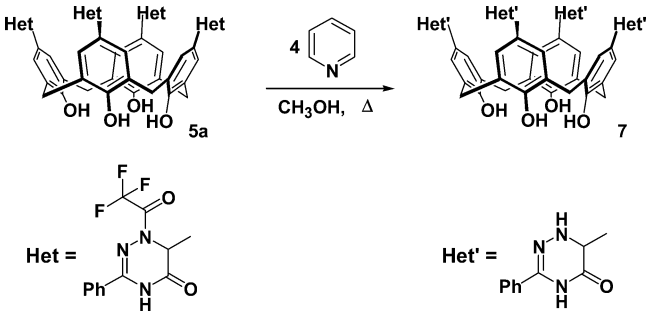

rather stable adduct **4c**. However, in the presence of trifluoroacetic anhydride, the reaction affords the S_N^H product **6**. We believe that the α-pyridyl substituent promotes elimination of the trifluoroacetyl groups, thus facilitating aromatization of the σ^H-adduct **5c** into calixarene **6** (Scheme 2).

Indeed, the reaction of 5,11,17,23-tetra[1-trifluoroacetyl-3-phenyl-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]calix[4]arene (**5a**) with 4 equiv of pyridine is accompanied by deacylation of triazinone rings and affords calixarene **7** (Scheme 3). It can, therefore, be concluded that pyridine facilitates elimination of the trifluoroacetyl groups.

In summary, a convenient one-step procedure to functionalize calix[4]arenes by using a nucleophilic attack at unsubstituted carbon C-6 of 3-substituted-1,2,4-triazin-5-ones has been advanced. Also, conformational features and their dependence on the reaction conditions have been established.

Structural elucidation of the compounds obtained has been performed by means of ^{1}H and ^{13}C NMR spectroscopy, including the NOESY and heteronuclear correlation experiments.

In the ^{1}H NMR spectra of **4** resulting from a nucleophilic addition of calix[4]arene **1** at the unsubstituted C(6) carbon atom of the triazine ring, the resonance signal of the proton attached at the sp^3-hybridized carbon is observed at 5.6−6.0 ppm. In the ^{13}C NMR spectra of **4**, the resonance signal of methylene groups is observed at 37.2 ppm, and according to the Mendoza rule, it indicates that the adduct **4** adopts the 1,3-alternate conformation. In the ^{13}C NMR spectra of **4**, the signals of C(3) of the calixarene fragment and C(9), C(10), and C(11) of the 3-phenyl substituent of the 1,2,4-triazine ring were assigned by using the ^{1}H−^{13}C HETCOR experiments. Assignment of other

signals in the ^{13}C NMR of **4a** was made on the basis of long-range $^{1}H-^{13}C$ coupling constants. Thus, the $^{13}C-^{1}H$ long-range COSY spectrum reveals correlation of C(1), C(6), C(7), C(8), and C(11) atoms with C(3)−H, C(5)−H, C(9)−H, C(10)−H, and C(9)−H protons, respectively (Figure 1 in the Supporting Information). No cross-peaks were observed in the COSY $^{1}H-^{13}C$ spectra for the C(2) carbon resonance. The quaternary C(4) carbon was identified due to spin−spin interaction with C(5)−H and absence of any geminal couplings.

The assignment of the C(10) carbon resonance was based on the $^{13}C-^{1}H$ HETCOR and $^{1}H-^{13}C$ HMBC spectra. In the $^{1}H-^{13}C$ HMBC spectrum of **4a**, the correlation of C═O carbon with protons of the acetyl group has been observed; however, the absence of cross-peaks between H(5) and C═O carbons does not allow one to differentiate O−Ac and N−Ac signals. The unequivocal assignments of *O*- and *N*-acetyl signals have been obtained by means of NOE experiments. Also, the NOE data provide an argument in favor of the 1,3-alternate conformation since, in this case, the correlation of *O*- and *N*-acetyl protons is possible. The cross-peaks of OCH_3 groups with protons of bridging methylene units enable one to distinguish the signals of *O*-acetyl and *N*-acetyl groups in the ^{1}H NMR spectra of **4a**.

Conformational analysis of **5a** was based on the data of ^{1}H, ^{19}F, and ^{13}C NMR spectra. In the ^{19}F NMR spectrum of **5a**, the only signal of the $NCOCF_3$ group was observed. In the ^{13}C NMR spectra of **5a**, the signal of bridged methylene units was registered at ∼32.1−32.7 ppm, while no signals at 37−38 ppm were observed. These data correspond to the cone conformation of **5a**. However, double sets for aromatic proton and carbon resonances of calixarene, as well as for the sp^3-carbon resonance of the triazine ring observed in ^{1}H and ^{13}C NMR of **5a**, indicate that the compound exists in solution in both C_2 and C_4 symmetrical cone conformations.[6] Another explanation of high multiplicity of signals in the ^{1}H NMR spectra is an unsymmetrical arrangement of the 1,2,4-triazine rings caused by a hindered rotation around the C(6)−C(4′) bond.

To examine conformation changes, the dynamic NMR experiments have been carried out (see Supporting Information). It has been shown that gradual heating of compound **5a** in DMSO-d_6 results in merging of signals of both aromatic protons and C(6)−H.

Transport measurements were carried out in a permeation cell, as described earlier[7] (effective membrane area is 4.909 cm^2). The membrane was positioned between two cylindrical compartments both containing aqueous phases (source phase was 5 mL of 0.1 M solution of salt, receiving phase consisted of 400 mL of water). The support consisted of thin porous poly(tetrafluoroethylene) membrane filters (PALL, 25 mm diameter, 0.2 μm pore size) immobilizing a carrier in the membrane solvent and *o*-nitrophenyl *n*-octyl ether to afford a 1×10^{-3} M solution. To dissolve the carrier, a small amount of dichloromethane was added, which was then evaporated under a reduced pressure. The measurements were performed at 25 °C at least in duplicate. Values of transport constants for various cations with triazine-modified calixarene are presented in Table 1. Transport of the nitrates of La^{3+} and Ga^{3+} in the absence of the carrier is low. The transport of $La(NO_3)_3$ is much higher than that of $Ga(NO_3)_3$ due to the increased ionic radius of the lanthanum cation compared to that of the gallium cation.

TABLE 1. Transport of $La(NO_3)_3$ and $Ga(NO_3)_3$ at 0.1 M of Carrier of 4a and 5a

	J (10^7 mol m^{-2} s^{-1})		
salt	**4a**	**5a**	without carrier
$La(NO_3)_3$	6.09 ± 0.18	20.9 ± 0.1	1.33 ± 0.02
$Ga(NO_3)_3$	0.693 ± 0.03	1.36 ± 0.03	0.626 ± 0.03

In conclusion, a convenient one-step procedure for the C−C coupling of 1,2,4-triazinones with calixarene based on a nucleophilic attack of the phenol moiety at the unsubstituted C-6 carbon atom of the triazine ring has been elaborated. Conditions for the formation of the cone or 1,3-alternate conformers have been found. It has been shown that modified calixarenes are effective compounds for transport of La^{3+} cations.

Experimental Section

3-Aryl-1,2,4-triazin-5(2*H*)-ones 3a−c were prepared according to references.[8]

25,26,27,28-Tetraacetoxycalix[4]arene (2a). A suspension of calix[4]arene (0.12 mmol) in a mixture of TFA (1 mL) and acetic anhydride (0.5 mL) was stirred at 20 °C for 40 min until calix[4]arene **1** was completely dissolved. The solvent was removed in vacuo. The residue was triturated with diethyl ether, and the solid obtained was filtered off. Yield 83%, mp 243−245 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 7.37−7.38 (1H, m, Ar), 7.09−7.12 (2H, m, Ar), 3.62 (2H, br s, CH_2), 2.33 (3H, br s, O−Ac). Anal. Calcd for $C_{36}H_{32}O_8$: C 72.96; H 5.44. Found: C, 72.77; H, 5.67.

25,26,27,28-Tetratrifluoroacetoxycalix[4]arene (2b). A suspension of calix[4]arene (0.12 mmol) in a mixture of TFA (1 mL) and trifluoroacetic anhydride (0.5 mL) was stirred at 20 °C for 40 min. The precipitate was filtered off. Yield 67%, mp > 230 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 7.18−7.23 (1H, m, Ar), 7.01−7.09 (2H, m, Ar), 3.75 (2H, br s, CH_2). ^{19}F NMR, δ, ppm (DMSO-d_6): 87.99 (br s). Anal. Calcd for $C_{36}H_{20}O_8F_{12}$: C, 53.48; H, 2.49. Found: C, 53.12; H, 2.58.

5,11,17,23-Tetra[1-trifluoroacetyl(acetyl)-3-(*R*)-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]-25,26,27,28-tetraoxy(acetoxy)calix[4]arene (4 and 5) (General Procedure). A suspension of 3-(*R*)-1,2,4-triazin-5(2*H*)-one (1.9 mmol) and calix[4]arene (0.5 mmol) in a mixture of TFA (2 mL) and trifluoroacetic (acetic) anhydride (1 mL) was stirred at 20 °C for 7 days until reagents were completely dissolved. The reaction mixture was evaporated to dryness. The residue was treated with diethyl ether. The precipitate was filtered off, recrystallized from methanol, and dried over P_2O_5.

5,11,17,23-Tetra[1-acetyl-3-phenyl-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]-25,26,27,28-tetraacetoxycalix[4]arene (4a). Yield 78%, mp > 230 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 11.68−11.75 (4H, set of singlets, NH), 7.87−7.96 (8H, m, Ph), 7.47−7.53 (12H, m, Ph), 6.88−7.03 (8H, set of singlets, Ar), 5.98−6.01 (4H, set of singlets, C(6)−H), 3.46−3.52 (8H, br s, CH_2), 2.32−2.43 (12H, set of singlets, O−Ac), 1.18−1.27 (12H, set of singlets, Ac). ^{13}C NMR, δ, ppm (DMSO-d_6): 20.13−2.16 ($OCOCH_3$), 21.82−21.84 ($NCOCH_3$), 37.76−37.78 (CH_2), 56.26−56.33 (C(6)−H_{triaz}), 127.29−127.47 (C(Ar)−H, *o*-Ph), 129.48−129.54 (*m*-Ph), 131.13−131.14 (C−C(3)), 131.19−131.20 (*p*-Ph), 133.27−133.136 (C−C(6)), 133.77−133.95 (C−CH_2), 141.16−141.19 (C(3)), 148.64−148.67 (C−OAc), 166.18−166.19 (C(5)), 168.03−168.24 ($OCOCH_3$), 171.53−171.57 ($NCOCH_3$). Anal. Calcd for $C_{80}H_{68}N_{12}O_{16}$: C,

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66.11; H, 4.72; N, 11.56. Found: C, 65.76; H, 4.84; N, 11.26. Mass spectrum, *m*/*z*: 1492.382 (1453.44 [M+] + 38.942 [K+]); 1476.438 (1453.44 [M+] + 22.998 [Na+]).

5,11,17,23-Tetra[1-acetyl-3-(2-pyridyl)-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]-25,26,27,28-tetraacetoxycalix[4]arene (4c). Yield 52%, mp > 230 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 10.96 (4H, br s, NH), 8.66−8.72 (4H, m, Py), 8.14−8.16 (4H, m, Py), 7.93−7.95 (4H, m, Py), 7.53−7.55 (4H, m, Py), 6.93−7.02 (8H, m, Ar), 5.94−6.01 (4H, set of singlets, C(6)−H), 3.57 (8H, br s, CH_2), 2.32−2.38 (12H, set of singlets, O−Ac), 1.17−1.39 (12H, set of singlets, Ac). Anal. Calcd for $C_{76}H_{64}N_{16}O_{16}$: C, 62.63; H, 4.42; N, 15.38. Found: C, 63.01; H, 4.78; N, 14.99.

5,11,17,23-Tetra[1-trifluoroacetyl-3-phenyl-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]calix[4]arene (5a). Yield 56%, mp > 225 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 11.74 (4H, br s, NH), 7.89−7.97 (8H, m, Ph), 7.47−7.52 (12H, m, Ph), 6.84−6.89 (8H, set of singlets, Ar), 5.64−5.69 (4H, set of singlets, C(6)−H), 3.74 (8H, br s, CH_2). ^{19}F NMR, δ, ppm (DMSO-d_6): 93.10 (br s). ^{13}C NMR, δ, ppm (DMSO-d_6): 32.1, 32.2 (CH_2), 56.7, 56.8, 56.87, 56.9 (C(6) triazine), 115.32 (CF_3, q, J = 287 Hz), 11 signals of aromatic carbons: 143.9, 144.0 (CPh−OH), 152.07, 152.09, 152.18 (N=CPh−N), 155.3 (q, CF_3CO, J = 32 Hz), 163.2, 163.29, 163.33, 163.38, 163.41 (C=O triazine). Anal. Calcd for $C_{72}H_{48}N_{12}O_{12}F_{12}$: C, 57.60; H, 3.22; N, 11.19. Found: C, 58.00; H, 3.21; N, 10.92. Mass spectrum, *m*/*z*: 1540.156 (1501.218 [M+] + 38.942 [K+]); 1524.118 (1501.218 [M+] + 22.99 [Na+]).

5,11,17,23-Tetra[1-trifluoroacetyl-3-(4-methylphenyl)-1,4,5,6-dihydro-5-oxo-1,2,4-triazin-6-yl]calix[4]arene (5b). Yield 72%, mp 226−230 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 11.64−11.74 (4H, set of singlets, NH), 7.76−7.82 (8H, set of doublets, Tol), 7.30−7.34 (8H, set of doublets, Tol), 6.80−6.84 (8H, set of singlets, Ar), 5.69−5.74 (4H, set of singlets, C(6)−H), 3.68 (8H, br s, CH_2), 2.36 (12H, s, CH_3). ^{19}F NMR, δ, ppm (DMSO-d_6) 93.81 (br s). ^{13}C NMR, δ, ppm (DMSO-d_6): 20.69 (CH_3), 32.78 (CH_2), 56.63 (C(6)), 114.61 (CF_3), 154.65 ($COCF_3$), 163.31 (C(5)), 117.49, 121.79, 122.03, 122.30, 124.48, 124.62, 124.90, 126.43, 127.32, 129.09, 130.03, 141.19, 143.82 (CAr). Anal. Calcd for $C_{76}H_{56}N_{12}O_{12}F_{12}$: C, 58.62; H, 3.63; N, 10.80. Found: C, 58.75; H, 4.02; N, 10.72.

5,11,17,23-Tetra(3-(2-pyridyl)-5-oxy-1,2,4-triazin-6-yl)calix[4]arene (6). A suspension of 3-(2-pyridyl)-1,2,4-triazin-5(2*H*)-one (164 mg, 0.96 mmol) and calix[4]arene (100 mg, 0.24 mmol) in a mixture of TFA (1.5 mL) and trifluoroacetic anhydride (1.5 mL) was stirred at 20 °C for 8 days until reagents were completely dissolved. The reaction mixture was evaporated to dryness. The residue was treated with diethyl ether. The precipitate was filtered off, and the product was separated by using flash chromatography with CH_2Cl_2−CH_3COOEt (20:1) as eluent. Yield 24%. ^{1}H NMR, δ, ppm (DMSO-d_6): 14.01 (4H, br s, N(2)−H), 7.34−8.76 (16H, m, Py), 7.00−7.07 (8H, set of singlets, Ar), 3.87−4.40 (8H, br s, CH_2), 3.44 (2H, q, J = 7.2 Hz, $CH_3COOCH_2CH_3$), 1.88 (3H, m, $CH_3COOCH_2CH_3$), 1.08 (3H, t, J = 7.2 Hz, $CH_3COOCH_2CH_3$). Anal. Calcd for $C_{60}H_{40}N_{16}O_8 \cdot C_4H_8O_2$: C, 63.99; H, 4.03; N, 18.66. Found: C, 63.57; H, 4.48; N, 18.26.

5,11,17,23-Tetra[3-phenyl-1,4,5,6-tetrahydro-5-oxo-1,2,4-triazin-6-yl]calix[4]arene (7). Pyridine (0.32 mmol) was added to a suspension of **5a** (0.067 mmol) in methanol (3 mL). The reaction mixture was refluxed for 4 h. The precipitate was filtered off. Yield 75%, mp 320−322 °C. ^{1}H NMR, δ, ppm (DMSO-d_6): 10.79 (1H, br s, NH), 10.80 (1H, br s, NH), 10.82 (1H, br s, NH), 10.86 (1H, br s, NH), 7.77−7.79 (8H, m, Ph), 7.37−7.42 (12H, m, Ph), 6.79−7.02 (8H, set of singlets, Ar), 6.82 (1H, br s, N(1)−H), 6.85 (1H, br s, N(1)−H), 6.86 (1H, br s, N(1)−H), 6.89 (1H, br s, N(1)−H), 4.09 (1H, br s, C(6)−H), 4.11 (1H, br s, C(6)−H), 4.12 (1H, br s, C(6)−H), 4.13 (1H, br s, C(6)−H), 3.57 (8H, br s, CH_2). Anal. Calcd for $C_{64}H_{52}N_{12}O_8$: C, 68.82; H, 4.67; N, 15.05. Found: C, 68.43; H, 5.01; N, 14.72.

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Supporting Information Available: Experimental procedures for compounds; ^{1}H, ^{13}C spectra and ^{1}H−^{13}C HMBC spectra of **4a**, ^{1}H−^{1}H NOESY spectrum of **4a**, ^{1}H−^{13}C HETCOR spectrum of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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