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Ipso-Nitration of Calix[6]azacryptands: Intriguing Effect of the Small Rim Capping Pattern on the Large Rim Substitution Selectivity

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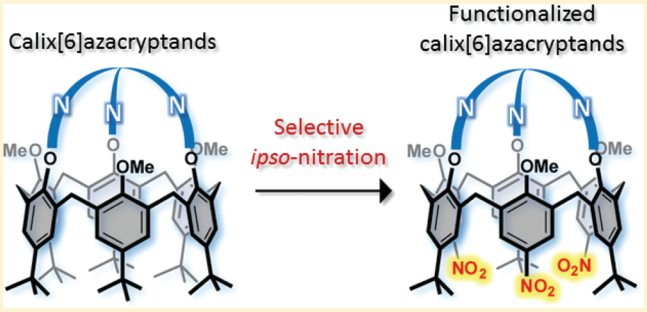
Supporting Information

ABSTRACT: The *ipso*-nitration of calix[6]arene-based molecular receptors is a important synthetic pathway for the elaboration of more sophisticated systems. This reaction has been studied for a variety of capped calixarenes, and a general trend for the regioselective nitration of three aromatic units out of six in moderate to high yield has been observed. This selectivity is, in part, attributed to the electronic connection between the protonated cap at the small rim and the reactive sites at the large rim. In addition, this work highlights the fact that subtle conformational properties can drastically influence the outcome of this reaction.



INTRODUCTION

Selective functionalization of macrocycles is a key issue. Indeed, it allows grafting functions to cavity-based receptors.[1] Compared to cucurbituryl[2] and cyclodextrins,[3] methodologies for calixarenes have been largely developed.[4] They are mainly based on the interactions between the neighboring phenol groups at the small rim. The hydrogen-bonding connections and/or alkaline cation-binding ability allow directing of the nucleophilic reactivity of the phenol units. Whereas this allowed the development of various methods for the selective small rim functionalization, strategies allowing the selective introduction of functions at the large rim are basically restricted to (i) removal of the *t*Bu groups allowing the *para*-condensation of acyl derivatives and (ii) *ipso*-substitution of the *t*Bu-aromatic unit with strong electrophilic reagents.[4] Selectivity at the large rim is an issue because of the poor communication between ArH or Ar*t*Bu units with each other.

In this paper, we describe a successful strategy based on the control of the large rim reactivity by the small rim substitution pattern. Taking advantage of the methodologies developed for the selective small rim functionalization, we highlighted the possible tuning of the large rim reactivity toward electrophiles. More precisely, we have shown that the substitution pattern at the small rim by specific groups allows the differentiation of the reactivity in the *para*-position of the aromatic phenolic groups. When bearing in the β-position groups basic enough to be protonated by a Bronsted acid, the phenol unit becomes deactivated toward electrophilic reagents such as NO_2^+ or $SOCl^+$ generated in solution. This strategy was revealed to be powerful enough to direct *ipso* as well as non-*ipso* electrophilic substitution at the large rim by nitro[5] and chlorosulfonyl[6] groups toward the units that are not deactivated. Such a finding has opened the route to the synthesis of a variety of calixarene selectively functionalized at the large rim as schematized in Figure 1 for calix[6]arene nitro derivatives (**1**).

This strategy allowed us to introduce a variety of functional groups[7] through, for example, a sequence of reduction, diazotation, and Cu-catalyzed Huisgen 1,3-dipolar cycloaddition reactions giving rise to receptors endowed with multipoint recognition properties,[8] ditopic ligands for metal ions,[9] or water-soluble receptors.[10] It is also interesting that the substitution pattern at the large rim allows the size to be tuned and the opening of the cone cavity to act as an endoreceptor.[11] Wanting to apply this methodology to calix[6]azacryptands (Figure 2),[12] we found surprising and interesting results that highlight the importance of conformational freedom/constrains of the calix macrocycle on the reactivity of its aromatic units at the large rim. The results reported here concern two uncapped calix[6]arenes (**1a**,**b**) and three kinds of capped macrocycles,

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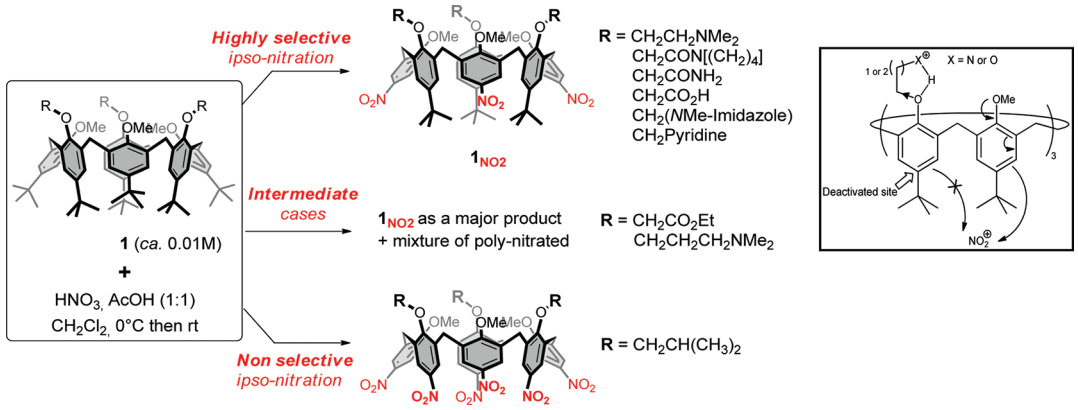


Figure 1. *Ipso*-nitration of 1,3,5-trisubstitued calix[6]arenes. Inset: rationalization of the selectivity.

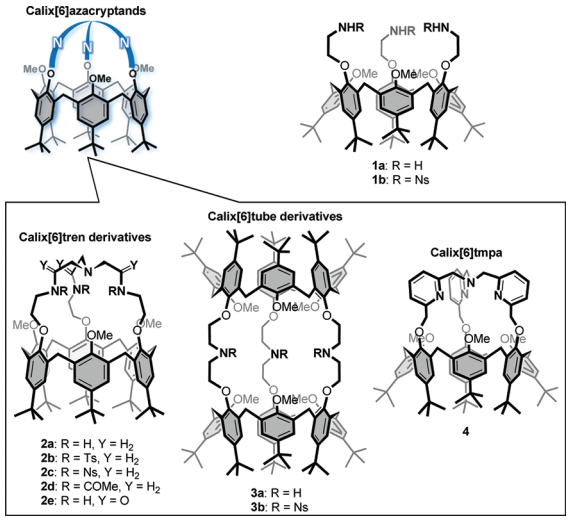


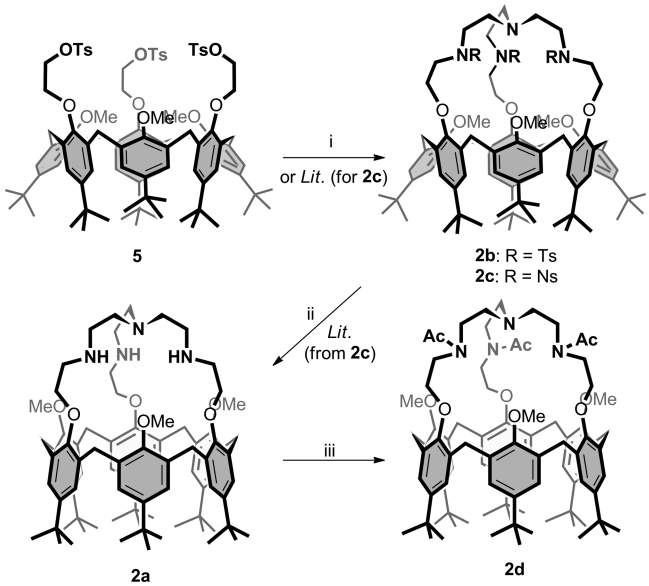
Figure 2. Calix[6]azacryptands and uncapped calix[6]arenes considered herein.

so-called tren (**2**),[13] tube (**3**), and tmpa (**4**),[14] that differ not only by their functions but also, importantly, by their flexibility (Figure 2).

RESULTS AND DISCUSSION

Syntheses of the Starting Calix[6]arenes. Similar to the known nosyl derivative **2c**,[15] the triply bridged calixarene **2b** was synthesized through a [1 + 1] macrocyclization reaction under basic conditions between a tren derivative bearing sulfonamido groups and the 1,3,5-tris-tosylcalix[6]arene **5** (Scheme 1). After flash chromatography on silica gel (FC), pure calix[6]azacryptand **2b** was obtained in 33% yield.[16] Calix[6]arene **2d** was obtained in 98% yield from the known calix[6]tren **2a**[15] by reaction with acetyl chloride in the presence of triethylamine (TEA). All of the other starting calix[6]arenes, i.e., **1a,b**, **2a,c,e**, **3a,b**, and **4**, were prepared according to previously reported procedures. In particular, **1a** was obtained through reduction of the corresponding tris-azido derivative,[17] **2a** and **3a** through deprotection of the corresponding nosyl derivatives **2c** and **3b**,[18] **2e** through a [1 + 1] macrocyclization between **1a** and nitrilotriacetic acid,[19] and **4** through a [1 + 1] macrocyclization between 1,3,5-tris-O-methylated calix[6]arene and a tmpa derivative.[20] It is noteworthy to mention that, while the ^{1}H NMR spectra of **2a**–**c** and **2e** in $CDCl_3$ display sharp signals characteristic of a

Scheme 1. Syntheses of the Calix[6]tren Derivatives 2[a]



[a]For compounds **b** and **d**: (i) $N(CH_2CH_2NHTs)_3$, Cs_2CO_3/K_2CO_3, DMF, rt then 90 °C, 33%; (ii) (from **2c**) PhSH, Na_2CO_3, DMF, 50 °C, 75%; (iii) AcCl, TEA, THF, −40 °C then rt, 98%.

C_{3v} symmetrical species, a broad and complicated NMR spectrum was observed for **2d**. However, this latter spectrum exhibited a classical C_{3v}-symmetrical NMR pattern at high temperature (373 K) in $C_2D_2Cl_4$.[21] This temperature-dependent behavior can be likely ascribed to the *cis*–*trans* isomerism of the N-Ac groups.[22] Note that, similar to **2c**, the methoxy groups of **2b** possess a significant high-field shifted resonance (δ_{OMe} = 2.28 ppm), indicating their self-inclusion into the cavity.[23]

***Ipso*-Nitration Reactions of the Calix[6]arenes 1a,b, 2a–e, 3a,b, and 4.** All of the *ipso*-nitration reactions were performed under the same experimental conditions, i.e., dissolution of the calix[6]arene derivative in CH_2Cl_2 and addition of a mixture of fuming nitric acid and glacial acetic acid (1:1, v/v) at 0 °C. The reaction mixtures were then stirred at rt and monitored by ESI mass spectrometry (ESI-MS) analysis (Table 1).

First, similarly to what was reported in the case of the tris-aminocalix[6]arenes **1a** and **3a**, selective *ipso*-nitration of the anisole units of **2a** afforded the 1,3,5-tris-nitrated calix[6]arene $\mathbf{2a}_{NO2}$ (Scheme 2 and Table 1, entries 1, 3, and 8). Thus, with

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Table 1. *Ipso*-Nitration Reactions of Calix[6]arenes 1a,b, 2a–e, 3a,b, and 4

entry	starting material	selective nitration of the anisole units	product	time (h)	isolated yield (%)
1 (lit.)	**1a**	yes	$\mathbf{1a}_{NO2}$	1	55
2	**1b**	no	$\mathbf{1b}_{NO2}$	4	44
3	**2a**	yes	$\mathbf{2a}_{NO2}$	4	63[a]
4	**2b**	yes	$\mathbf{2b}_{NO2}$	4	93
5	**2c**	yes	$\mathbf{2c}_{NO2}$	4	95
6	**2d**	yes	$\mathbf{2d}_{NO2}$	8	83
7	**2e**	no[b]	$\mathbf{2e}_{NO2}$	4	
8 (lit.)	**3a**	yes	$\mathbf{3a}_{NO2}$	4	35[a]
9	**3b**	no[c]	$\mathbf{3b}_{NO2}$	4	
10	**4**	yes	$\mathbf{4}_{NO2}$	ca. 20	ca. 90[d]

[a]Overall yield for the three-step sequence (see the text). [b]A mixture of penta- and hexanitrated products was observed by ESI-MS analysis of the crude material. [c]A mixture of polynitrated products was observed by ESI-MS analysis of the crude material. [d]The isolated solid contains ca. 5% of a mixture of di- and tetranitrated product; see the Supporting Information.

all these polyamino calix[6]arenes, the selectivity of the nitration reaction is in good agreement with the model displayed in Figure 1, i.e., a deactivation of the aromatic units bearing the amino arms through protonation of the primary or secondary amino groups. Note that a sequence involving the synthesis/purification/deprotection of a tris-carbamate derivative was necessary in order to isolate pure $\mathbf{2a}_{NO2}$. The relatively moderate yields observed for the nitration of calix[6]arenes **1a**, **2a**, and **3a** are not due to a lack of selectivity (no other nitrated products were observed by ESI-MS analysis and no other products could be isolated) and are attributable to the competitive degradation of the primary and secondary amino arms that are quite sensitive to oxidizing media.

Conversely, no selectivity was a priori expected with the derivatives **1b**, **2b–c**, and **3b** since, according to their pK_a values, their sulfonamido groups should not be protonated under the reaction conditions. As anticipated, nitration of **3b** led to a complicated mixture of poly-nitrated compounds and **1b** gave the hexa-nitrated calixarene $\mathbf{1b}_{NO2}$ as the sole isolable reaction product (Scheme 3 and Table 1, entries 2 and 9). However, *ipso*-nitration of the tosyl and nosyl derivatives of calix[6]tren **2b** and **2c** was revealed to be highly selective, and the resulting 1,3,5-tris-nitrated calix[6]arenes $\mathbf{2b}_{NO2}$ and $\mathbf{2c}_{NO2}$ were isolated in high yield (Scheme 3 and Table 1, entries 4 and 5).

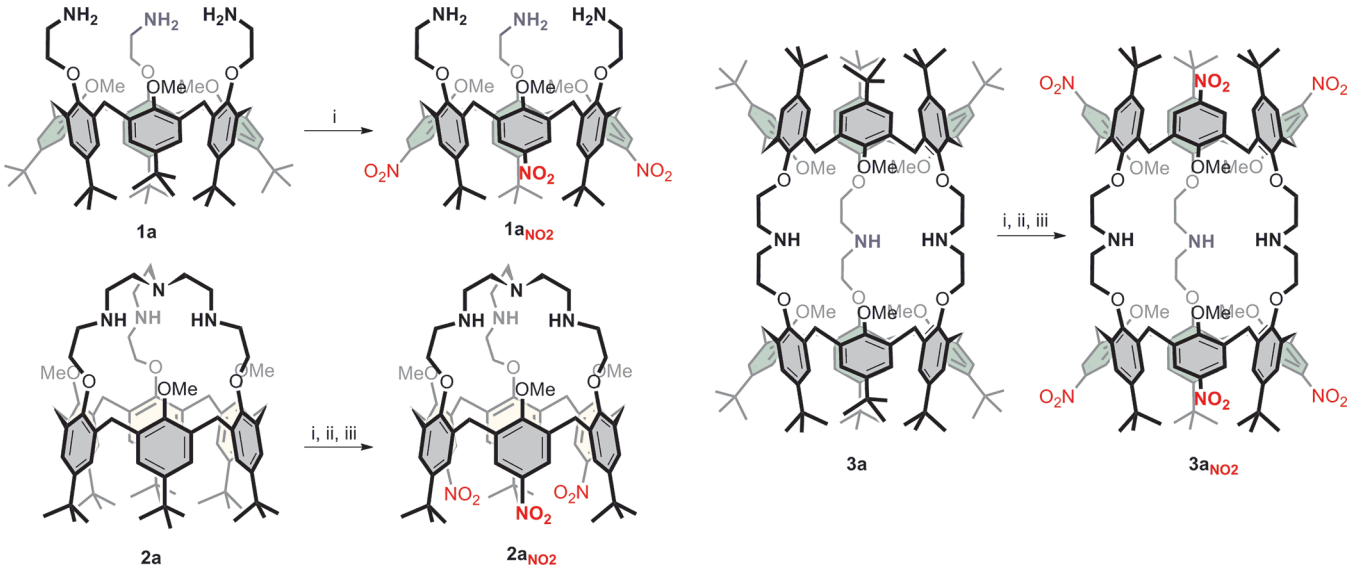
Similarly to **2b** and **2c**, the tren based tris-amido calix[6]-arene **2d** led selectively to the corresponding 1,3,5-tris-nitrated derivative $\mathbf{2d}_{NO2}$ (Scheme 4 and Table 1, entry 6). In strong contrast, the closely related tris-amido calix[6]arene **2e** afforded a mixture of penta- and hexa-nitrated compounds (Scheme 4 and Table 1, entry 7), which were clearly identified by ESI-MS analysis but revealed to be difficult to separate by FC.[24]

Finally, calix[6]tmpa **4** also underwent a selective transformation to provide compound $\mathbf{4}_{NO2}$ (Scheme 4 and Table 1, entry 10). However, the nitration process revealed to be much slower: after 4 h of reaction, a mixture of di- and trinitrated products was obtained under conditions where the other calix-substrates were fully tris-nitrated.[5] After 20 h, traces of tetra-nitrated product were detected in the crude reaction mixture (analyzed by ESI-MS), whereas $\mathbf{4}_{NO2}$ became the very major product (>90%). A detailed kinetic analysis of the nitration of calix[6]tmpa, monitored by ESI-MS, is shown in the Supporting Information. The data were fitted according to a three-step mechanism assuming that each step follows a pseudo first order rate law vs the substrate calixarene **4** derivative, according to

$$\mathbf{4} \xrightarrow{k_1} \text{mono-nitrated } \mathbf{4} \xrightarrow{k_2} \text{di-nitrated } \mathbf{4} \xrightarrow{k_3} \text{tris-nitrated } \mathbf{4} = \mathbf{4}_{NO2}$$

where k_i stands for the pseudo-rate constant of step (i). The fitted data clearly show that the nitration process becomes slower as the calix[6]tmpa is nitrated: $k_1 = 4.0k_2$ and $k_2 = 7.5k_3$. However, the decrease in the k_i values ($k_1 > k_2 > k_3$) is more important than that corresponding to a pure statistical correction ($k_1 = 3/2k_2$; $k_2 = 2k_3$) due to the variation of the number of available *t*Bu-anisole sites. This indicates that the nitration of the *i*th anisol induces a structural/electronic

Scheme 2. *Ipso*-Nitration Reactions of Calix[6]arenes 1a, 2a, and 3a[a]



[a]Key: (i) HNO_3/AcOH (1:1, v/v), CH_2Cl_2, 0 °C then rt; (ii) Boc_2O, TEA, THF, 0 °C then rt; (iii) TFA, CH_2Cl_2, rt.

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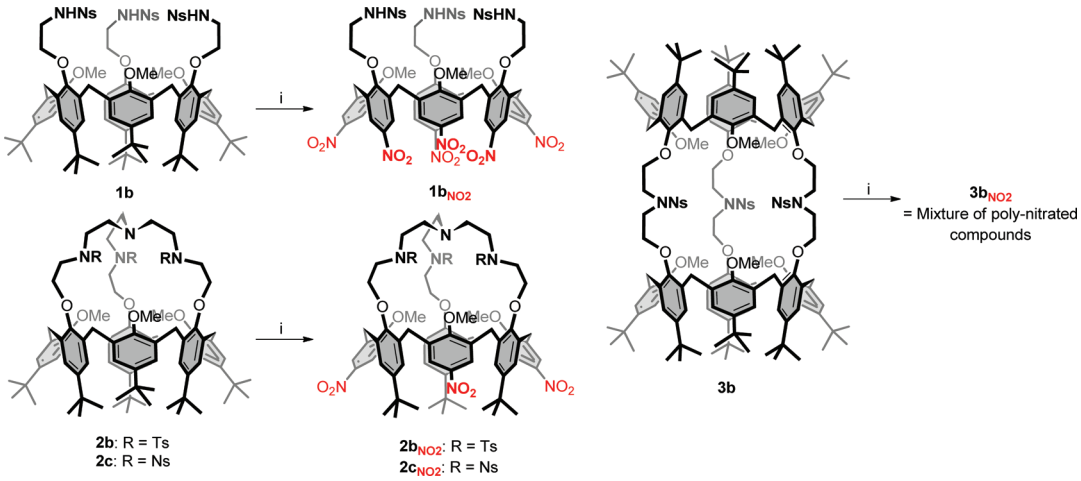
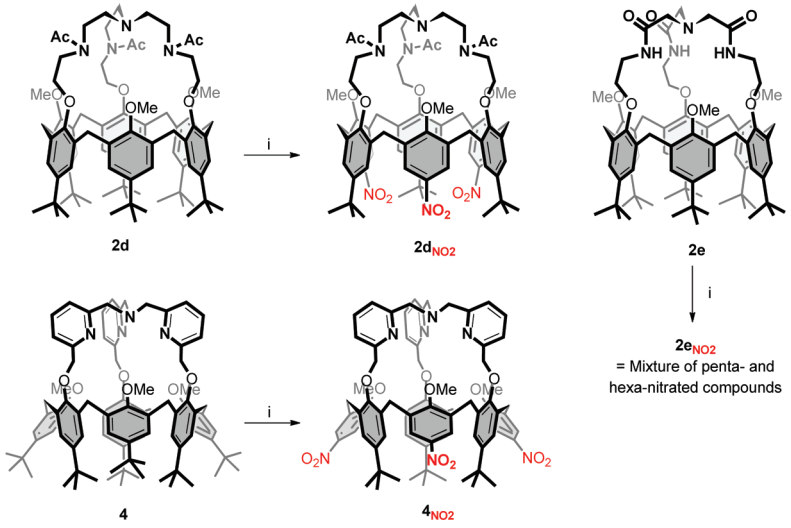
Scheme 3. *Ipso*-Nitration Reactions of Sulfonamido Calix[6]arenes b and c[a]



[a]Key: (i) HNO_3/AcOH (1:1, v/v), CH_2Cl_2, 0 °C then rt.

Scheme 4. *Ipso*-Nitration Reactions of Tris-amido Calix[6]arenes 2d and 2e and Calix[6]TMPA 4[a]



[a]Key: (i) HNO_3/AcOH (1:1, v/v), CH_2Cl_2, 0 °C then rt.

modification leading to an intrinsic decrease of the reactivity of the $(3 - i)$ remaining positions. These observations suggest that the tmpa cap imposes constrains that are different from both the tris-methylpyridyl (type **1**) and tren (type **2**) cases, which are both much more selective and much more reactive.

NMR Characterization of New 1,3,5-Tris-nitrated Calix[6]arenes 2a$_{NO2}$–d$_{NO2}$ and 4$_{NO2}$. The ^{1}H NMR spectra of **2a$_{NO2}$–d$_{NO2}$** and **4$_{NO2}$** in $CDCl_3$ are characteristic of C_{3v} symmetrical species and all signals were assigned by extensive 2D NMR analyses.[25] First, in all cases, the selective *ipso*-substitution of three alternating *t*Bu groups was confirmed by the presence of a single resonance that integrates for 27 protons. Moreover, it was possible to deduce from the following NMR data that the nitro groups are situated on the anisole units: (i) the *t*Bu and methoxy groups of compounds **2b$_{NO2}$**, **2c$_{NO2}$** and **4$_{NO2}$** display high-field chemical shifts (i.e., δ_{tBu} = 1.02, 1.09, and 0.96 ppm; δ_{OMe} = 2.65, 2.77, and 2.67 ppm, respectively), suggesting that all these groups are directed toward the inside of the cavity and, as a result, are not connected to the same phenolic units. A similar conclusion can be made for **2a$_{NO2}$** and **2d$_{NO2}$** with the difference that their OMe and *t*Bu groups are turned toward the outside of the cavity (δ_{tBu} = 1.36 and 1.19 ppm; δ_{OMe} = *ca.* 3.7 and 3.6 ppm, respectively). (ii) HMBC NMR experiments undertaken with compounds **2b$_{NO2}$** and **2c$_{NO2}$** show a series of cross-peaks indicating that the methoxy groups are located on the aromatic units bearing the nitro groups.

Thus, these extensive NMR studies clearly confirm the structure of the 1,3,5-tris-nitrated calix[6]arenes **2a$_{NO2}$-d$_{NO2}$** and **4$_{NO2}$**.

Selectivity of the Nitration Process. This study has highlighted surprising differences in the reactivity of the calix derivatives vs nitration when they are capped or uncapped.

(1) The *N*-sulfonamido and *N*-acetamido calix[6]tren derivatives (**2b**,**c** and **2d**, respectively) are nitrated with remarkable regioselectivity, which allows the efficient synthesis of their tris-nitro derivatives with high yields, no chromatography being required for their isolation as pure compounds. This represents an interesting alternative to the direct nitration of the unprotected tren derivative **2a** that gives rise to low and hardly reproducible yields.

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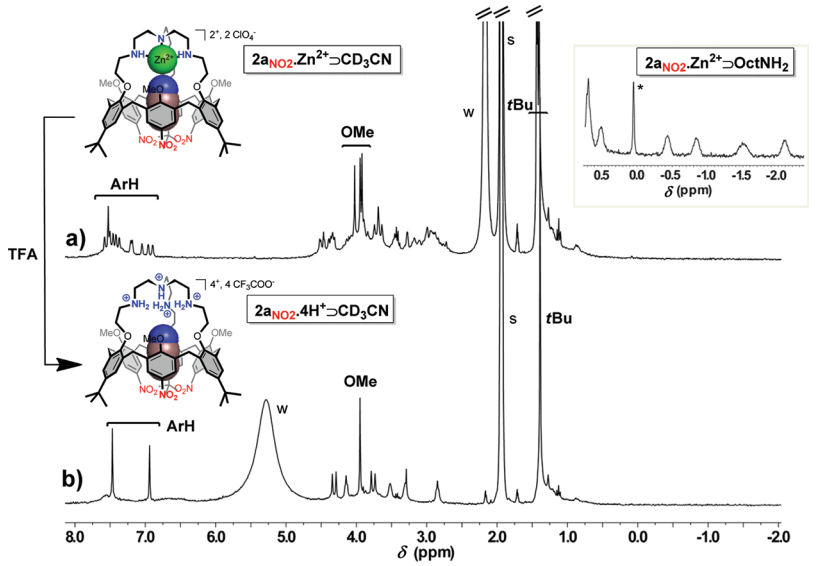

Figure 3. ^{1}H NMR spectra (300 MHz, 295 K) in CD_3CN of (a) **2a$_{NO2}$·Zn^{2+}⊃CD$_3$CN** obtained upon the addition of 1 equiv of $Zn(ClO_4)_2·6H_2O$ to **2a$_{NO2}$**; (b) **2a$_{NO2}$·4H$^+$⊃CD$_3$CN** obtained after the subsequent addition of TFA. Inset: High-field region of the ^{1}H NMR spectrum of **2a$_{NO2}$·Zn^{2+}⊃OctNH$_2$** obtained after addition of few equivalents of $OctNH_2$ to **2a$_{NO2}$·Zn^{2+}⊃CD$_3$CN**. Key: w, water; s, residual solvent; *, residual grease.

(2) In strong contrast, their uncapped and tube analogues (**1b** and **3b**) or the related trenamide derivative (**2e**) do not display any selectivity vs the nitration process. A plausible explanation for this surprising difference in selectivity possibly lies in the much higher conformational rigidity of the aromatic cavity of **2b** and **2c** induced by the covalent tren cap presenting tris-substituted nitrogen connections. An important steric crowding at the level of these nitrogen connections may disfavor the local planar conformation required for the conjugation between the nitrogen lone pairs and the sulfonamido/acetamido groups of **2b**,**c** and **2d**. As a result, the nitrogen atoms may be basic enough to be protonated under the strongly acidic conditions of the nitration reaction, leading to the efficient deactivation of the corresponding aromatic units linked to the tren cap.[26]

(3) The tmpa case also raises questions. First, the nitration process is not as regioselective as for its uncapped tris-methylpyridyl analogue (Figure 1, compound **1**) or more flexible tren-capped related compounds **2**. This may be attributed to the difficult polyprotonation of the rigid cap as reported previously.[21] Indeed, the calix macrocycle imposes a geometry where the nitrogen atoms of the pyridyl units face each other, which make difficult the polyprotonation of the tmpa cap, in spite of a strong propensity for a first protonation event. As a result, the deactivating effect of the connected aromatic units toward the electrophilic attack of NO_2^+ due to the withdrawing effect of the protonated pyridyl residues is not as efficient as for the related open analog (type **1**) compound or more flexible nonaromatic tren derivatives (type **2**). This may explain the lower selectivity in the nitration reaction for the tmpa capped **4** compound relative to substrates of type **1** and **2**.

(4) The second question raised by tmpa derivative **4** is related to the relatively slow reaction rate of the nitration compared to the other calix-substrates and its anticooperative behavior for the polynitration. The structural features that differentiate the tmpa-capped calixarenes from the other capped derivatives are not only a much more rigid calix core but also the alternation of the aromatic walls. Indeed, the more rigid tmpa cap (compared to a tren derivative), made out of cyclic and planar pyridine residues, forces the connected aromatic units to adopt an *in*-position relative to the anisole units, as shown by XRD analysis and ^{1}H NMR spectroscopy.[20] Once nitrated, the less bulky anisole walls tend to flip more toward an *in*-position at the large rim as shown by the outward movement of the methoxy groups (δ_{OMe} = 2.67 vs 2.53 ppm for **4$_{NO2}$** and **4**, respectively). Conversely, the remaining *t*Bu-aryl units flip toward an *out*-position (δ_{tBu} = 0.96 vs 0.86 ppm for **4$_{NO2}$** and **4**, respectively). The rocking movement of the aromatic walls in alternate position, initiated by the replacement of the bulky *t*Bu groups by nitro substituents at the sterical constrained large rim, may well lead, progressively, i.e., as the nitration proceeds, to the decrease of the spatial accessibility of the remaining *t*Bu-substituted anisol units. The consequent decrease of their reactivity would then explain the anticooperativity of the substitution process.

All these observations highlight the fact that selectivity is actually the result of privileged orientations adopted by the different aromatic units, which, in turn, depend on the conformational properties of the cap as a slight structural alteration at the level of the cap or the calix substitution pattern can strongly influence a reaction occurring at the level of the large rim, both in terms of reactivity (rate) and regioselectivity.

Evaluation of the Host–guest Properties of the Tris-nitro Calix[6]cryptands. In order to test whether or not the tris-nitrated calix[6]azacryptands still display interesting complexation properties, preliminary NMR binding studies were achieved with the open calix[6]azacryptand **2a$_{NO2}$**.[27] The host–guest properties of the other new calix[6]azacryptand that can bind metal ions, i.e., **4$_{NO2}$**, will be published elsewhere. First, upon addition of 1 equiv of $Zn(ClO_4)_2·6H_2O$ to a CD_3CN solution of **2a$_{NO2}$**, a completely distinct but complicated NMR pattern was obtained. This NMR spectrum is characteristic of a nonsymmetrical C_1-calixarene species: three singlets for the *t*Bu as well as for the OMe and twelve singlets for the ArH are indeed apparent (Figure 3a). By analogy with the results

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obtained with **2a**,[28] this NMR profile clearly corresponds to the dicationic complex $\mathbf{2a_{NO2}{\cdot}Zn^{2+}{\supset}CD_3CN}$ with an intracavity acetonitrile molecule coordinated to the metal center. Compared to the free ligand $\mathbf{2a_{NO2}}$, the OMe signals of the complex are downfield shifted (δ_{OMe} > ca. 3.9 ppm), indicating that these groups have been expelled from the cavity by the coordinated acetonitrile molecule. Similarly to the parent complex $\mathbf{2a{\cdot}Zn^{2+}{\supset}CD_3CN}$, the chirality of $\mathbf{2a_{NO2}{\cdot}Zn^{2+}{\supset}CD_3CN}$ arises from the heterochirality of the three NH stereocenters.[29] As expected, the coordinated solvent molecule was found to be exchangeable. For example, the addition of a few equivalents of primary amines (i.e., $PrNH_2$, $OctNH_2$) led to their intracavity binding as testified by the presence of high-field signals below 0 ppm assigned to their alkyl chain (inset Figure 3). Finally, upon the addition of an excess of trifluoroacetic acid (TFA) to $\mathbf{2a_{NO2}{\cdot}Zn^{2+}{\supset}CD_3CN}$ in CD_3CN, a well-resolved and simpler C_{3v}-symmetrical NMR pattern was obtained (Figure 3b). Again, by analogy with what was observed with **2a**, it is possible to deduce that this NMR spectrum corresponds to the tetracationic host–guest complex $\mathbf{2a_{NO2}{\cdot}4H^{+}{\supset}CD_3CN}$.[30] All these results show that the remarkably versatile host–guest properties of this class of receptors are preserved.

CONCLUSION

We have shown that the selective *ipso*-nitration reaction of calix[6]arenes can be extended to calix[6]azacryptands. Indeed, the introduction of three nitro groups in alternate positions has been achieved in high yields with several calix[6]tren derivatives and calix[6]tmpa, compounds that are widely used as molecular receptors for metal ions, neutral molecules, and ammonium ions. As previously reported, the results show the drastic influence that the nature of the substituents at the small rim has on the nitration reactions taking place at the large rim. However, this work also highlights that the electronic connection between the two rims is not the only factor influencing the selectivity and that the conformational properties of the small rim part can also orient the selectivity of the *ipso*-nitration and influence the reaction rate. Finally, preliminary binding studies have shown that the complexation properties of the tris-nitrated calix[6]tren are preserved despite a more widely open cavity. This work opens interesting perspectives for the design of a new generation of calix[6]-azacryptands decorated at the large rim with various functional groups. In this regard, the selective introduction of water-soluble or ion binding groups is currently being explored in our laboratories.

EXPERIMENTAL SECTION

All experiments were performed under argon. Solvents were dried by conventional methods and distilled immediately prior to use. Routine ^{1}H NMR spectra were recorded at 200, 300, or 600 MHz. ^{13}C NMR spectra were recorded at 100,75, or 62.5 MHz. NMR spectra were referenced to residual solvents. 2D NMR spectra (COSY, HSQC, HMBC) were recorded to complete signal assignments. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Electrospray ionization (ESI) mass spectra were recorded with an ESI-MS apparatus equipped with an ion-trap using the following settings: Flow rate: 10 μL·min^{-1}, spray voltage: 5 kV, capillary temperature: 160 °C, capillary voltage: −15 V, tube lens offset voltage: −30 V. Melting points (mp) are uncorrected. $N(CH_2CH_2NHTs)_3$,[31] 5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris(2-tosylethoxy)calix[6]arene **5**, calix[6]arenes **1a**,**b**, $\mathbf{1a_{NO2}}$, **2a**, **2c**, **2e**, **3a**,**b**, $\mathbf{3a_{NO2}}$, and **4**, were prepared according to literature procedures (see the text).

$X_6Me_3tren(Ts)_3$ (2b). Cs_2CO_3 (0.048 g, 0.149 mmol) and K_2CO_3 (0.120 g, 0.868 mmol) were added to a solution of 1,3,5-tris-tosylcalix[6]arene **5** (0.455 g, 0.282 mmol) in anhydrous DMF (10 mL) at room temperature. The resulting mixture was vigorously stirred, and a solution of $N(CH_2CH_2NHTs)_3$ (0.188 g, 0.308 mmol) was slowly added at room temperature. After being stirred for 2 h, the reaction mixture was heated at 90 °C for 24 h. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with distilled water (20 mL). The organic solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography [CH_2Cl_2 then CH_2Cl_2/EtOAc (95:5, v/v)], giving **2b** as a pale yellow solid. Yield: 33% (0.173 g, 0.101 mmol). Mp = 193–194 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.83 (d, 6H, ArH_{Ts}, J = 8.3 Hz), 7.24 (s, 6H, ArH), 7.11 (d, 6H, ArH_{Ts}, J = 8.1 Hz), 6.83 (s, 6H, ArH), 4.29 (d, 6H, ArCH_2^{ax}, J = 14.7 Hz), 4.06 (t, 6H, OCH_2CH$_2$N, J = 4.3 Hz), 3.86 (t, 6H, OCH$_2$CH_2N, J = 4.6 Hz), 3.76 (t, 6H, CH$_2$NCH_2CH$_2$N, J = 7.8 Hz), 3.08 (d, 6H, ArCH_2^{eq}, J = 14.7 Hz), 2.97 (t, 6H, CH$_2$NCH$_2$CH_2N, J = 8.2 Hz), 2.28 (s, 9H, OCH_3), 2.23 (s, 9H, CH_{3Ts}), 1.37 (s, 27H, *t*Bu), 0.84 (s, 27H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 154.6, 150.2, 146.3, 146.0, 143.2, 137.9, 133.7, 133.1, 130.0, 127.8, 127.3, 123.8, 72.6, 61.0, 54.9, 49.1, 48.9, 34.4, 34.2, 31.8, 31.1, 28.8, 21.6 ppm. HRMS (ESI+): calcd for $C_{102}H_{133}N_4O_{12}S_3$ $[M + H]^+$ 1701.9077, found 1701.9084.

$X_6Me_3tren(acetyl)_3$ (2d). Anhydrous TEA (0.32 mL, 2.26 mmol) was added to a solution of calix[6]tren **2a** (0.312 g, 0.251 mmol) in THF (25 mL) at −40 °C. After 5 min, freshly distilled acetyl chloride (0.16 mL, 2.26 mmol) was added. A white precipate appeared, and the reaction mixture was stirred at room temperature for 16 h. The mixture was then filtered off in order to remove the ammonium salt. The solvent was evaporated to dryness affording **2d** as a pale yellow solid. Yield: 98% (0.338 g, 0.25 mmol). Mp = 213–215 °C dec. IR (KBr): ν = 1652 (C═O) cm^{-1}. ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 373 K): δ = 7.23 (s, 6H, ArH), 6.99 (bs, 6H, ArH), 4.60 (d, 6H, ArCH_2^{ax}, J = 15.1 Hz), 4.25 (bs, 6H, OCH_2CH$_2$N), 3.91 (m, 15H, OCH$_2$CH_2N + OCH_3), 3.43 (d, 6H, ArCH_2^{eq}, J = 15.0 Hz), 2.94 (bs, 6H, CH$_2$NCH_2CH$_2$N), 2.63 (bs, 6H, CH$_2$NCH$_2$CH_2N), 2.22 (s, 9H, C(O)CH_3), 1.35 (s, 27H, *t*Bu), 0.99 (s, 27H, *t*Bu) ppm. HRMS (ESI+): calcd for $C_{87}H_{121}N_4O_9$ $[M + H]^+$ 1365.9128, found 1365.9122. Due to the *cis*–*trans* isomerism of the N-Ac groups (see the text), a complex and uninterpretable ^{13}C NMR (100 MHz, $CDCl_3$, 298K) spectrum was obtained for **2d** (see the Supporting Information).

$^{(NO2)3}X_6Me_3tren$ ($\mathbf{2a_{NO2}}$). According to the procedure described for $\mathbf{2c_{NO2}}$, **2a** (0.223 g, 0.179 mmol) was reacted with a HNO_3/AcOH solution (2.20 mL, 1:1, v/v) in CH_2Cl_2 (20 mL) (reaction time: 4 h). After workup, compound $\mathbf{2a_{NO2}}$ was isolated as an orange solid (0.238 g, 0.197 mmol). This residue was then solubilized in THF (19 mL), and TEA (0.22 mL, 1.57 mmol) was added. After the mixture was cooled at 0 °C, Boc_2O (0.257 g, 1.18 mmol) was added and the resulting mixture stirred under argon at room temperature for 16 h. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, and the organic layer was washed with water. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography [CH_2Cl_2/AcOEt (8:2)] to give $\mathbf{^{(NO2)3}X_6Me_3tren(N\text{-}Boc)_3}$ $\mathbf{2'a_{NO2}}$ as a white solid. Yield: 63% (0.170 mg, 0.112 mmol). To a solution of $\mathbf{2'a_{NO2}}$ (0.033 g, 0.022 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise 0.2 mL of TFA (2.3 mmol). The mixture was then stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (10 mL). The organic solution was washed with a NaOH solution (1 M). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and the solvent removed in vacuo to obtain $\mathbf{2a_{NO2}}$ in quantitative yield (0.027 g, 0.022 mmol). It is noteworthy that the compound $\mathbf{2a_{NO2}}$ revealed to be quite unstable and thus difficult to purify and to store. Hopefully, full characterization of the carbamate derivative $\mathbf{2'a_{NO2}}$ was successfully achieved.

$\mathbf{2'a_{NO2}}$. Mp = 240–242 °C dec. IR ($CHCl_3$): ν = 1681 (C═O), 1522 (NO_2) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 298 K): δ = 7.95–

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7.65 (m, 6H, ArH), 7.09 (bs, 6H, ArH), 4.53 (d, 6H, $ArCH_2^{ax}$, J = 14.6 Hz), 4.04 (bs, 6H, OCH_2CH_2N), 3.73−3.35 (m, 21H, $ArCH_2^{eq}$, OCH_3 + OCH_2CH_2N), 3.10−2.60 (m, 12H, $CH_2NCH_2CH_2N$), 1.45−1.38 (m, 27H, tBu_{Boc}), 1.14 (s, 27H, tBu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298K): δ = 28.5, 28.6, 29.3, 29.6, 31.4, 34.5, 47.7, 47.9, 49.9, 54.5, 61.1, 61.2, 77.4, 79.9, 124.8, 125.2, 125.4, 125.8, 131.9, 135.7, 143.4, 148.0(7), 148.1(3), 151.0, 151.3, 155.2, 155.5, 162.9 ppm. $C_{85}H_{121}N_7O_{21}\cdot 3H_2O$ (1575.86): C, 64.64; H, 7.56; N, 6.28. Found: C, 64.48; H, 7.56; N, 6.28.

$2a_{NO2}$. Mp = 215−216 °C dec. IR ($CHCl_3$): ν = 1522 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 298 K): δ = 7.36 (s, 6H, ArH), 7.23 (s, 6H, ArH), 4.29 (d, 6H, $ArCH_2^{ax}$, J = 16.4 Hz), 3.80−3.60 (m, 15H, OCH_3 + $ArCH_2^{eq}$), 3.43 (bs, 6H, OCH_2CH_2N), 2.51 (bs, 6H, OCH_2CH_2N), 2.40 (bs, 6H, $CH_2NCH_2CH_2N$), 2.24 (bs, 6H, $CH_2NCH_2CH_2N$), 1.36 (s, 27H, tBu) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 298 K): δ = 160.5, 154.0, 147.6, 144.1, 135.6, 131.3, 128.5, 122.6, 73.5, 60.7, 54.0, 48.2, 34.5, 31.6 ppm.

$^{(NO2)3}X_6Me_3tren(Ts)_3$ ($2b_{NO2}$). According to the procedure described for **$2c_{NO2}$**, **2b** (0.163 g, 0.096 mmol) was reacted with a mixture of HNO_3/AcOH (2 mL, 1:1, v/v) in CH_2Cl_2 (16 mL) (reaction time: 4 h), giving **$2b_{NO2}$** as an orange solid. Yield: 93% (0.157 mg, 0.089 mmol). Mp = 176−178 °C dec. IR (KBr): ν = 1525 (NO_2) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 298 K): δ = 7.96 (s, 6H, ArH), 7.80 (d, 6H, ArH_{Ts}, J = 7.8 Hz), 7.18 (d, 6H, ArH_{Ts}, J = 7.8 Hz), 6.93 (s, 6H, ArH), 4.38 (d, 6H, $ArCH_2^{ax}$, J = 14.9 Hz), 4.03 (t, 6H, OCH_2CH_2N, J = 4.2 Hz), 3.74 (t, 6H, OCH_2CH_2N, J = 4.5 Hz), 3.62 (t, 6H, $CH_2NCH_2CH_2N$, J = 8.0 Hz), 3.33 (d, 6H, $ArCH_2^{eq}$, J = 15.0 Hz), 2.86 (t, 6H, $CH_2NCH_2CH_2N$, J = 8.1 Hz), 2.65 (s, 9H, OCH_3), 2.34 (s, 9H, CH_{3Ts}), 1.02 (s, 27H, tBu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 162.8, 150.6, 148.0, 143.6, 143.4, 137.7, 135.7, 132.2, 130.0, 127.3, 125.7, 125.0, 73.8, 61.4, 53.5, 49.0, 48.5, 34.5, 31.3, 29.5, 21.6 ppm. HRMS (ESI+): calcd for $C_{90}H_{106}N_7O_{18}S_3$ $[M + H]^+$ 1668.6757, found 1668.6725.

$^{(NO2)3}X_6Me_3tren(Ns)_3$ ($2c_{NO2}$). To a solution of **2c** (0.326 g, 0.182 mmol) in CH_2Cl_2 (32 mL) was added dropwise a mixture of HNO_3/AcOH (4 mL, 1:1, v/v) at 0 °C under argon. After addition, the resulting solution was warmed up to room temperature and stirred for 4 h. The reaction mixture was then poured into an aqueous ammonia solution (2.5%, 60 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, washed with water (2 × 50 mL), and dried over Na_2SO_4. The yellow solution was filtered, and the solvent was then removed in vacuo to afford **$2c_{NO2}$** as an orange solid. Yield: 95% (0.305 g, 0.173 mmol). Mp = 188−190 °C dec. IR (KBr): ν = 1547 (NO_2), 1525 (NO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 298 K): δ = 8.18 (dd, 3H, ArH_{Ns}, J = 1.0 Hz, J = 8.1 Hz), 7.83 (s, 6H, ArH), 7.65−7.48 (m, 9H, ArH_{Ns}), 7.02 (s, 6H, ArH), 4.41 (d, 6H, $ArCH_2^{ax}$, J = 14.8 Hz), 4.08 (bs, 6H, OCH_2CH_2N), 3.91 (bs, 6H, OCH_2CH_2N), 3.79 (t, 6H, $CH_2NCH_2CH_2N$, J = 7.8 Hz), 3.33 (d, 6H, $ArCH_2^{eq}$, J = 15.0 Hz), 2.82 (t, 6H, $CH_2NCH_2CH_2N$, J = 7.8 Hz), 2.77 (s, 9H, OCH_3), 1.09 (s, 27H, tBu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 162.8, 150.7, 148.3, 148.0, 143.4, 135.6, 133.9, 133.7, 132.2, 131.9, 131.0, 125.5, 125.3, 124.1, 74.5, 61.4, 52.8, 48.6, 48.1, 34.5, 31.3, 29.6 ppm. HRMS (ESI+): calcd for $C_{87}H_{96}N_{10}O_{24}NaS_3$ $[M + Na]^+$ 1783.5659, found 1783.5690.

$^{(NO2)3}X_6Me_3tren(acetyl)_3$ ($2d_{NO2}$). According to the procedure described for **$2c_{NO2}$**, **2d** (0.321 g, 0.235 mmol) was reacted with a mixture of HNO_3/AcOH (3 mL, 1:1, v/v) in dry CH_2Cl_2 (20 mL) (reaction time: 8 h). After workup, the crude product was triturated with Et_2O to isolate **$2d_{NO2}$** as an orange solid. Yield: 83% (0.260 g, 0.195 mmol). Mp = 196−198 °C dec. IR (KBr): ν = 1648 (C═O), 1525 (NO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 373 K): δ = 7.63 (bs, 6H, ArH_{NO2}), 7.19 (s, 6H, ArH_{tBu}), 4.43 (d, 6H, $ArCH_2^{ax}$, J = 15.0 Hz), 3.93 (m, 6H, OCH_2CH_2N), 3.72−3.61 (m, 15H, $ArCH_2^{eq}$ + OCH_3), 3.49 (m, 6H, CH_2N), 3.19 (m, 6H, $CH_2NCH_2CH_2N$), 2.72 (m, 6H, CH_2N), 2.02 (s, 9H, $C(O)CH_3$),1.19 (s, 27 H, tBu) ppm. HRMS (ESI+): calcd for $C_{75}H_{94}N_7O_{15}$ $[M + H]^+$ 1332.6802, found 1332.6823.

$^{(NO2)6}X_6Me_3$tris(2-(2-nitrobenzenesulfonamide)ethoxy) ($1b_{NO2}$). Similarly to the procedure described for **$2c_{NO2}$**, **1b** (0.101 g, 0.059 mmol) was reacted with a mixture HNO_3/AcOH (1 mL, 1:1, v/v) in CH_2Cl_2 (8 mL) (reaction time: 4 h). The crude product was purified by flash chromatography [CH_2Cl_2, CH_2Cl_2/EtOAc (95:5, v/v), CH_2Cl_2/EtOAc (90:10, v/v), CH_2Cl_2/MeOH (95:5, v/v) then CH_2Cl_2/MeOH (70:30, v/v)], giving **$1b_{NO2}$** as an orange solid. Yield: 44% (43 mg, 0.026 mmol). Mp = 182−184 °C dec. IR (KBr): ν = 1540 (NO_2), 1522 (NO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 363 K): δ = 8.09−7.75 (m, 18H, ArH + ArH_{Ns}), 7.40 (bs, 6H, ArH), 4.22 (m, 12H, $ArCH_2^{ax}$ + $ArCH_2^{eq}$), 4.08 (t, 6H, OCH_2CH_2N, J = 6.0 Hz), 3.55 (s, 9H, OCH_3), 3.42 (m, 6H, OCH_2CH_2N) ppm. HRMS (ESI+): calcd for $C_{69}H_{60}N_{12}O_{30}NaS_3$ $[M + Na]^+$ 1655.2603, found 1655.2598. Note that the ^{13}C NMR (100 MHz, DMSO-d_6, 298 K) spectrum of **$1b_{NO2}$** was also recorded; however, most of the peaks were too broad to be apparent (see the Supporting Information).

$^{(NO2)3}X_6Me_3tmpa$ (4_{NO2}). According to the procedure described for **$2c_{NO2}$**, **4** (0.250 g, 0.187 mmol) was reacted with a HNO_3/AcOH solution (1.6 mL, 1:1, v/v) in CH_2Cl_2 (25 mL) (reaction time: ca. 20−23 h). Then, a solution of NaOH (3M) was added at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried with Na_2SO_4, filtered, and evaporated to dryness. A brown/yellow solid is obtained (0.230 g), containing **4_{NO2}** as a major compound (ca. 95%) together with variable amounts of dinitrated **4** product (0−8%) and tetra-nitrated **4** product (2−7%). Yield in **4_{NO2}** (as isolated): ca. 90% (0.17 mmol) mp =202−204 °C. IR (KBr): ν = 1522 (NO_2) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 300 K): δ = 8.10 (s, 6H, ArH_{NO2}), 7.62 (m, 3H, ArH_{py}), 7.52 (m, 3H, ArH_{py}), 7.12 (d, 3H, ArH_{py}, J = 7 Hz), 6.83 (s, 6H, ArH_{tBu}), 5.42 (s, 6H, $PyCH_2O$), 4.45 (d, 6H, $ArCH_2^{ax}$, J = 15 Hz), 3.69 (s, 6H, $PyCH_2N$), 3.60 (d, 6H, $ArCH_2^{eq}$, J = 15 Hz), 2.67 (s, 9H, OCH_3), 0.96 (s, 27H, tBu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$, 300 K): δ = 163.83, 158.25, 157.87, 152.08, 147.20, 143.36, 136.94, 136,05, 132.92, 126.47, 125.13, 122.32, 118.19, 75.05, 61.98, 60.23, 34.33, 31.54, 31.29 ppm. HRMS (ESI+): calcd for $C_{78}H_{82}N_7O_{12}$ $[M + H]^+$ 1308.6021, found 1308.6058.

■ ASSOCIATED CONTENT

Supporting Information

1D, 2D NMR spectra of all new compounds, variable-temperature ^1H NMR studies of **2d**, **$2d_{NO2}$**, and **4_{NO2}** (monoprotonated by TFA), kinetic studies of the nitration of **4**, and ESI-MS spectrum of **4_{NO2}**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) Prolonged time reaction did not change the ratio of penta-nitrated vs hexa-nitrated compounds. This may indicate that the hexa-nitrated derivative can be only obtained from one of the two possible penta-nitrated regioisomers.
(25) In the case of $\mathbf{2d}_{NO2}$, the NMR spectrum had to be recorded at high *T* (373 K) in DMSO-d_6 in order to show a C_{3v} symmetrical NMR pattern. Again, this temperature-dependent behavior can be likely due to the *cis*−*trans* isomerism of the *N*-Ac groups of $\mathbf{2d}_{NO2}$.
(26) It is noteworthy that a ^{1}H NMR study of the protonation of the sulfonamido derivative $\mathbf{2c}_{NO2}$ was undertaken; unfortunately, only broad and noninterpretable spectra were obtained.
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