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Efficient synthesis of amino-protected calix[4]arenes selectively functionalized with iron chelator ICL670 designed as platform for iron recognition

Pascal Rouge [a,d], Mathieu Becuwe [b,d], Alexandra Dassonville-Klimpt [a,d], Sophie Da Nascimento [a,d], Jean-François Raimbert [a,d], Dominique Cailleu [c,d], Emmanuel Baudrin [a,d], Pascal Sonnet [a,d,*]

[a] UMR-CNRS 6219, Laboratoire des Glucides, Faculté de Pharmacie, Université de Picardie Jules Verne, 1 rue des Louvels, 80039 Amiens Cedex, France
[b] Laboratoire de Réactivité et Chimie des Solides, UMR CNRS 6007, Université de Picardie Jules Verne, 33 Rue Saint Leu, 80039 Amiens Cedex, France
[c] Plate-forme analytique, Université de Picardie Jules Verne, 80039 Amiens Cedex, France
[d] Institut de Chimie de Picardie, FR3085 CNRS, Université de Picardie Jules Verne, 33 Rue Saint Leu, 80039 Amiens Cedex, France

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ABSTRACT

The development of selective electrochemical iron sensor is still a challenging task. One promising possibility is to use organically functionalized inorganic particles, for instance silica, as sensitive element. Herein, we report on the design and synthesis of calix[4]arene-based platforms modified with ICL670 iron chelator and alkylamino chain(s). These new molecular edifices could be easily grafted on silica particles. The strategy relies on selective calix[4]arenes functionalizations by alkylamino chains at the lower rim, in *partial-cone* or 1,3-*alternate* conformations. The different synthesis routes are presented and discussed.

1. Introduction

Understanding the iron metabolism has become important because of its vital biological role. It is not an easy task and necessitates the development of new tools enabling the selective detection of specific ions, ideally in situ. Besides these biological applications, such systems could also be profitably deciding for environmental control, allowing continuous on-line detection.[1] Fe^{3+} is a major transition metal for all organisms and present only as trace amounts in its ligand-free form. It is an essential element for the critical steps of the cellular metabolism, such as cell progression, growth, and division, including DNA synthesis.[2] For the specific medicinal applications, the developed ion sensors should be ideally integrated in miniaturized systems. For such a case, electrochemical detection is one of the simplest and cheapest type of measurements, and more specifically the potentiometric detection. Very few Fe^{3+} sensors have been reported so far[3] and thus sensing and quantification of Fe^{3+} is still a challenging task. We are now following a bottom-up approach for the specific development of sensitive materials, which can be used in electrochemical sensor. This comes from the knowledge that the sensing mechanism of most of the sensitive materials used so far lies in the establishment of ionic surface equilibriums.[4] The surface of inorganic sensitive materials in contact with the electrolyte to analyze can thus be seen as an assembly of complexing sites, initially present or formed during an aging step, and which can be more or less specific for the ions to detect. Thus, it was attempting to synthesize directly such a system. Formation of silica, selected as matrix, can be easily controlled (formation of films, mesostructures, nanoparticles,…) and functionalized for the development of different sensor types.[5] For the development of iron sensor, the key is to use macrocycles, which could efficiently and specifically bind iron and furthermore which can be easily grafted onto the matrix. The present work aims at preparing calix[4]arene-based platforms modified with iron chelators and which could be considered as good candidates for such purpose.

The prepared platforms should be selective for the Fe^{3+} complexation and thus minimizing chelation with other important biologically cations present in the serum, such as Zn^{2+} and Cu^{2+}. The thermodynamic stability of Fe^{3+} complexes (iron octahedral environment) can be maximized by incorporating the six coordinating atoms into a single macromolecular structure thereby creating a hexadentate ligand.[6] Among three molecules that are presently used in therapeutics, we have chosen to use the orally active tridentate ICL670 (4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl] benzoic acid, deferasirox Fig. 1).[7] To its advantage, this compound can be easily synthesized (two steps), and can to be grafted onto the

* Corresponding author. E-mail address: pascal.sonnet@u-picardie.fr (P. Sonnet).

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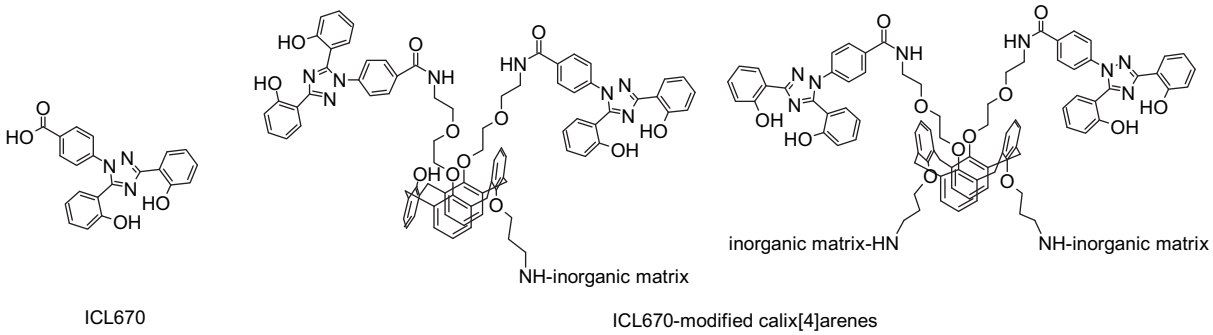


Fig. 1. ICL670 and ICL670-modified calix[4]arenes for the formation of hybrid material.

multivalent calix[4]arene platform through the carboxylic function, which is not involved in the Fe^{3+} chelation. Calix[4]arenes (C4R), which have been largely reported for the sensitive and selective recognition of various metal ions,[8] were chosen as an ideal platform for the preorganization of the ICL670 iron chelator. The possibility of selective functionalization at the lower rim (iron chelator and inorganic matrix grafting group) together with different possible C4R conformations (*partial-cone*, 1,2- or 1,3-*alternate* or *cone*) bring a useful versatility to these macromolecules.

In this work, we present below the routes to prepare new selectively amino-protected calix[4]arenes. These orthogonally amino protections allowed us to synthesize the key C4R intermediates substituted at the lower rim by ICL670 as the iron chelator and by an alkylamino spacer that could be used for the grafting with a halogenopropyl modified silica-matrix (Fig. 1).

2. Results and discussion

Recently, Böhmer et al.[9] reported on the synthesis of calix[4]arenes fixed in the 1,3-*alternate* conformation and substituted selectively by precursors of amino groups (ω-bromonitrile and ω-bromophthalimide). For the present investigation, we have chosen to synthesize such calixarene locked in the 1,3-*alternate* (or *partial cone*) conformation as it allows a selective functionalization of both sides of the molecule (namely iron chelators on one side and the inorganic matrix on the other one). The reactional sequence used to prepare the key calixarenes, before the grafting onto inorganic matrix, is depicted in Fig. 2. A first O-alkylation of the calix[4]arene **1** was accomplished using a iodoalkylphthalimide to obtain an intermediate *syn*-1,3-diether, which was converted into a mixed tetra-ether **2**–**5** fixed in the 1,3-*alternate* or *partial cone* conformation after a second alkylation in the presence of cesium carbonate. A first selective deprotection of the phthalimide groups allowed the incorporation of the iron chelator (ICL670), which was then followed by a second deprotection step or by a reduction leading to calixarenes **6** and **7**. The obtained amino-calixarenes **6**and **7** (from nitrile or carbamate) will give us the opportunity, by an S_N reaction, to graft the iron ligand-based platform onto the inorganic matrix.

The unsubstituted calixarene **1**, used as starting material, was prepared according to a two-steps synthesis developed by Gutsche from *p-tert*butylphenol.[10] For the reaction with this calixarene **1**, the iodo compound **8** can be synthesized by two routes from the same intermediate **10**, obtained by aminoprotection of hydroxyethyloxyethylamine **9** in quantitative yield (Scheme 1). The first (route A) is a one-step reaction, known as Garregg–Samuelsson's reaction,[11] which uses as halogenating reagent PPh_3I_2 in the presence of imidazole. The iodo compound **8** was obtained with a 68% yield but two disadvantages would limit the use of this method for large scale; (i) distillation of large quantities of pyridine and toluene and (ii) purification of substantial quantities of triphenylphosphine oxide. Another route (route B) was then preferred via the mesylate **11** to obtain the compound **8** in two steps with a global yield of 78%.

The first type of amino protecting groups was introduced by a selective alkylation of the calix[4]arene **1** with 4 equiv of iodo compound **8** in the presence of 2 equiv of K_2CO_3 as a base, in refluxing acetonitrile for 7 days (Scheme 2). This alkylation led selectively in 74% yield to the diametrically substituted calixarene **12** in the *cone* conformation, as indicated by the ^1H NMR spectrum. A typical AB pattern was observed for the methylene bridge Ar*CH*$_2$Ar protons (J=12.9 Hz) at 3.06 ppm for the equatorial protons and 3.97 ppm for the axial protons. In order to maintain the 1,3-*alternate* conformation for the final calix[4]arene, the second etherification was achieved with an excess of Cs_2CO_3 as a base.[12] Thus, calixarene **12** was engaged

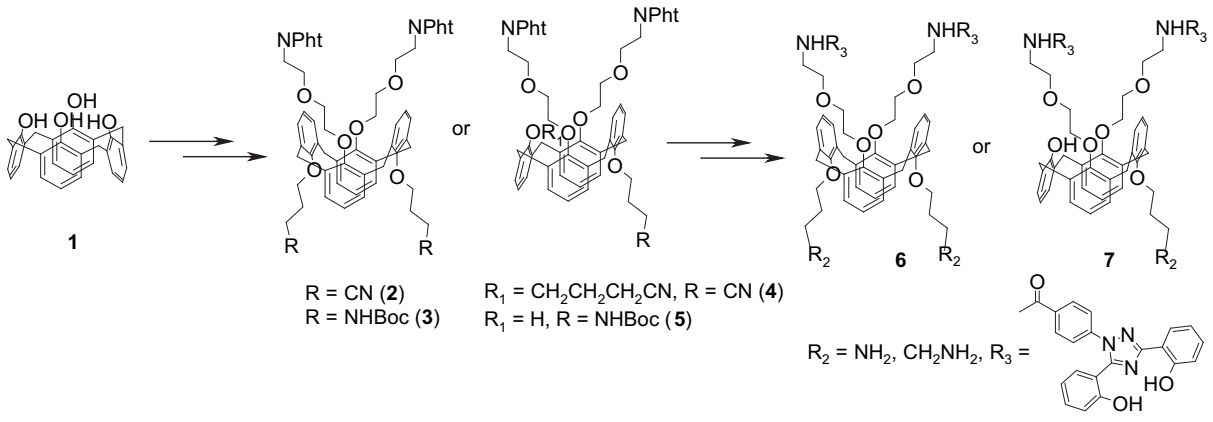
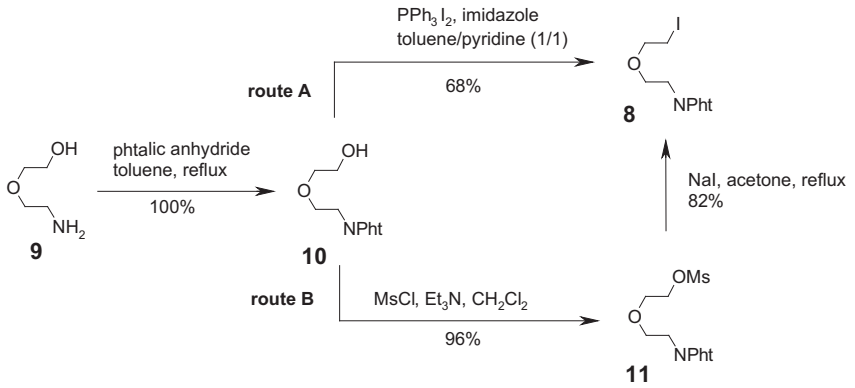
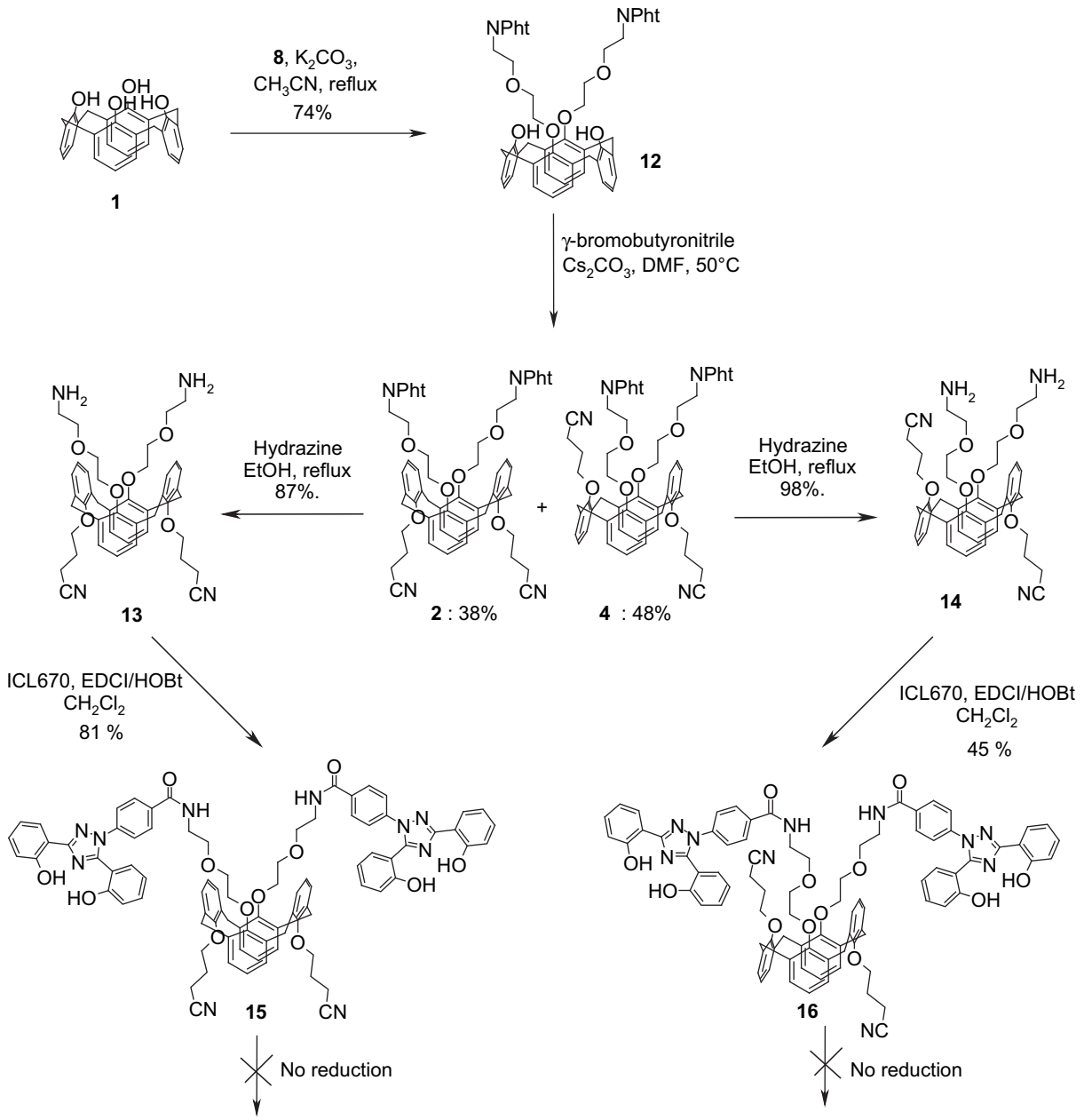


Fig. 2. Reactional sequence used to synthesize the key calixarenes as a preliminary step for the formation of the hybrid material.



Scheme 1. Synthesis of the iodo arm spacer.



Scheme 2. Synthesis of the mono or dinitrilealkyl dilCL calix[4]arenes in *partial cone* or in 1,3-*alternate* conformation.

in reaction with 10 equiv of γ-bromobutyronitrile and 10 equiv Cs_2CO_3 in DMF at 50 °C for 2 weeks. A mixture of calixarene in the 1,3-*alternate* **2** and in the *partial cone* **4** conformation was obtained in 76% yield. Both conformers were separated by chromatography and their structure was confirmed though analysis of their ^{1}H NMR spectrum. Due to the different ether group in **2**, the methylene protons are not identical and appear as a pair of doublet (AB system, J=16.1 Hz) at 3.70 ppm and 3.78 ppm (connected to C at 38.19 ppm). This small difference of chemical shift ($\Delta\delta$=0.08 ppm) confirms the 1,3-*alternate* conformation. The NMR analysis of the *partial cone* conformer **4** shows two different AB systems (^{1}H NMR); one pair of doublet (J=13.3 Hz) at 2.91 ppm and 3.90 ppm lied with the C at 30.3 ppm and another pair of doublet (J=13.4 Hz) at 3.49 ppm and 3.68 ppm connected to the C at 36.74 ppm. Moreover the ^{1}H NMR displays four different doublets (Ar*H* protons) at 6.35 ppm, 6.77 ppm, 6.99 ppm, and 7.21 ppm, which confirm the *partial cone* conformation. Each conformer was functionalized separately, in two steps, by two ICL670 in order to form the corresponding hexadentate iron chelators (Scheme 2). The phthalimido deprotections of **2** or **4**, was realized with hydrazine in boiling ethanol leading to the corresponding aliphatic diamines, **13** or **14** with good yields without reduction of the nitrile functions. These deprotected calixarenes were then functionalized, using a peptidic coupling reaction, with the well known tridentate iron(III) chelator ICL670, which was previously synthesized in two steps according to the procedure of Steinhauser et al.[13] The best peptidic coupling was obtained with the use of EDCI/HOBt in DCM leading to 1,3-*alternate* calixarene **15** (81% yield) or *partial cone* calixarene **16** (45% yield). At last, the reduction of the nitrile groups is necessary to form the corresponding amino iron chelator calix[4]arenes, which could then be coupled to the inorganic matrix by classical S_N reaction. For this, various reaction conditions have been tried; (i) by several hydrogenation conditions with Nickel[9] or Palladium catalysts and (ii) with different hydrides, such as sodium borohydride,[14] lithium aluminium hydride or $BH_3 \cdot Me_2S$.[15] The complete conversion of the starting material was observed only with lithium aluminium hydride in boiling THF or with $BH_3 \cdot Me_2S$ in refluxing THF. However, because of a lack of selectivity, these kinds of hydrides led to complex and inseparable mixtures.

Since the promising orthogonal protection of amines with phthalimide and nitrile had failed, we decided to try another alternative strategy using a carbamate (Boc) as amino protecting groups in place of nitrile. To the best of our knowledge, few examples of O-alkylation of calixarene with Boc-protected halogenoalkylamine are described in the literature.[16] The *N*-Boc bromopropylamine, which can easily be synthesized in quantitative yield from the bromopropylamine hydrobromide,[17] was chosen as precursor for arm spacer between the calixarene and the inorganic matrix. The synthesis of the Boc-protected calixarenes **3** and **5** were initially considered by using the same procedure described for **2** and **4** (calixarene **12** with 10 equiv of *N*-Boc bromopropylamine and 10 equiv Cs_2CO_3 in DMF at 50 °C for 2 weeks). Unfortunately, a complex mixture of products inseparable by chromatography was obtained. To solve this problem, the reaction temperature was decreased (0 °C for 2 h then rt for 4 days vs 50 °C). With these new conditions (Scheme 3), the two desired monoBoc or diBoc-protected calixarenes were isolated, after chromatography purification, in 22% yield for **3** (1,3-*alternate* conformation) and in 30% yield for **5** (*partial cone* conformation). Interestingly, the calixarene **5** can be obtained in 63% yield by reducing the base quantity by half.

The 1,3-*alternate* conformation of the compound **3** was confirmed by NMR analysis. As for the compound **2**, the methylene protons display one AB system with a small difference of chemical shifts (3.70 ppm and 3.78 ppm). The methylene carbons appear at 36.93 ppm. For the compound **3**, there are four kinds of aromatic protons for the calixarene part; two triplets and two doublets. The NMR analysis of the compound **5**, as for the compound **4**, indicates two pair of doublets at 3.09 ppm (d, J 13.2 Hz)/4.10 ppm and at 3.72 ppm/4.01 ppm, connected to, respectively, the carbon at 30.59 ppm and 37.56 ppm, confirming the *partial cone* conformation. For the compound **5**, there are seven kinds of aromatic protons for the calixarene part; three triplets and four doublets.

The phthalimide groups of the Boc-protected calixarenes **3** and **5** were removed using an excess of hydrazine in boiling ethanol to lead, respectively, to **17** (60% yield) and **18** (66% yield). The peptidic coupling reactions between the tridentate iron(III) chelator ICL670 and these diamino free calixarenes **17** and **18** gave the hexadentate calixarenes **19** and **20** in 14% and 56% yield, respectively. Finally, the deprotection of the carbamate groups was afforded with success in TFA to obtain the expected calix[4]arenes **6** (1,3-*alternate*) and **7** (*partial cone*) in 65% and 100% yield, respectively.

For the calixarene **6**, the NMR analysis indicate one AB system, include in the massif at 3.60 ppm, lied with one methylene carbon at 37.72 ppm. For the compound **7**, two pairs of doublet again are found, which are connected to the two different methylene carbons (30.62 ppm and 37.93 ppm). NMR spectra for compounds **19** and **6**, which are in 1,3-*alternate* conformation and for compounds **20** and **7**, which are in partial cone conformation show the same kind of signal that respectively compounds **3** and **17** (one AB system, 1,3-*alternate* conformation) and compounds **5** and **18** (two AB systems, partial cone conformation).

As a first step, to check if the formed platforms present indeed sensing properties toward iron (III) species, we undertook a first potentiometric test. To realize these measurements, the calixarene derivative **7** was grafted onto silica particles through a nucleophilic substitution between the free amino group included in the structure and a chloropropyl functionalized silica's nanoparticle. The coupling was performed in dry acetonitrile under reflux for 36 h. The corresponding solid-state NMR spectra of the recovered washed particles confirm the grafting process (Fig. 3).

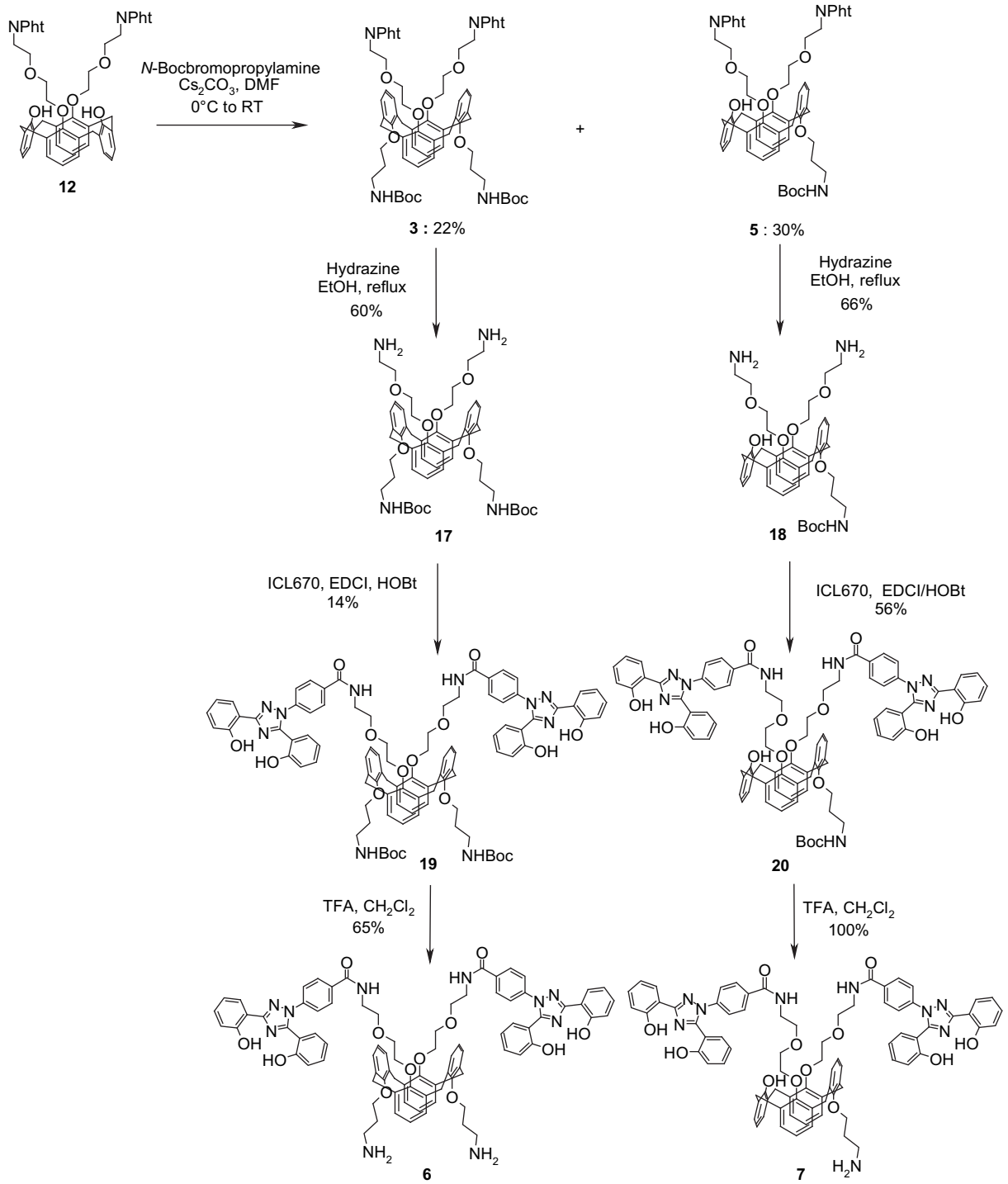
Indeed, the calixarene derivative is clearly observed on the spectrum of the hybrid material. On the basis of the liquid ^{13}C NMR spectrum of the platform, the different component of the ICL670 chelator, i.e., the carbonyl and phenolic quaternary carbon, triazole fragment resonance, and the different aromatic carbon, are observed at 170–152 ppm, 146–138 ppm, and 136–113 ppm, respectively. Furthermore, additional peaks corresponding to the alkyl chain (32 ppm) and also to the $-CH_2-O$ carbon (65–74 ppm) are present and confirm the well-introduction of the organo-chelator onto the silica nanoparticles. A thorough description of the synthesis and characterization of this hybrid material will be published in a forthcoming paper.

The new hybrid material was then incorporated in a PVDF-HFP matrix to form an electrode according to Belcore's technology as reported previously.[18] The potential of the porous plastic electrode obtained containing the hybrid material as a sensing element was measured against a classical saturated calomel electrodes (SCE) as a function of the dissolved iron (III) concentration ($FeCl_3$ from Acros) (Fig. 4).

The concentration was changed by decades and leads to well defined voltage plateau. In similar conditions, a chloropropyl-modified silica based electrode did not show any evolution of the equilibrium voltage when the concentration was modified. This is thus a clear proof of the specific interaction of iron(III) with the platform, which most likely occurs through the formation of a hexadentate complex.

3. Conclusion

The selective functionalization of calix[4]arenes by alkylamino chains at the lower rim, in *partial-cone* or 1,3-*alternate* conformations, was examined. The orthogonally amino protections allowed



Scheme 3. Synthesis of the mono or diaminoalkyl diICL calix[4]arenes in 1,3-*alternate* **6** or in *partial cone* **7** conformation.

us to synthesize in four steps, from the key diphtalimido calixarene **12**, the monoamino or diaminoalkyl calixarenes **6** (1,3-*alternate*) and **7** (*partial cone*). They are substituted, at the lower rim, by two iron(III) chelators ICL670 and by one or two alkylamino chain(s). We prove here that such calixarene-based platforms modified with iron chelators can be successfully used as building block for the formation iron sensors. For that purpose, the calixarenes **6** and **7** can be grafted by nucleophilic substitution reaction to a modified silica-matrix. We are actually pursuing this route and better characterizing the formed systems.

4. Experimental

4.1. General remarks

Column chromatography was performed on Kielselgel 60 (40–63 μm) ASTM (Merck). Reactions were analyzed on precoated silica gel 60 F_{254} plates (Merck) and the compounds were visualized with a UV lamp (254 nm) and phosphomolybdic acid in EtOH. Melting points were determined on a Stuart SMP3 apparatus and reported uncorrected. ^{1}H and ^{13}C NMR spectra were

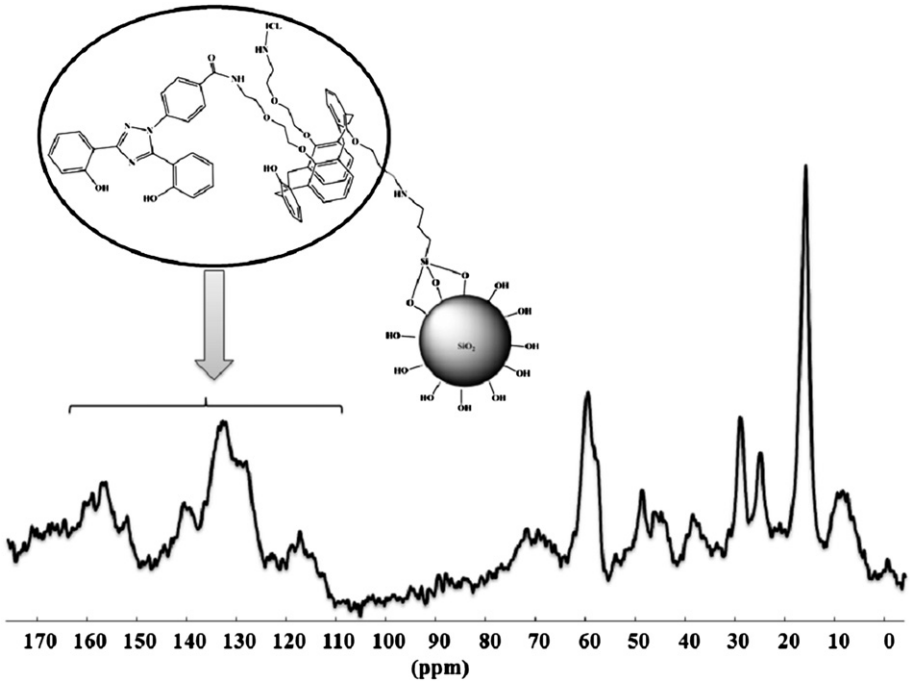


Fig. 3. Solid-state ^{13}C NMR spectra of the hybrid material including the new organochelator entities.

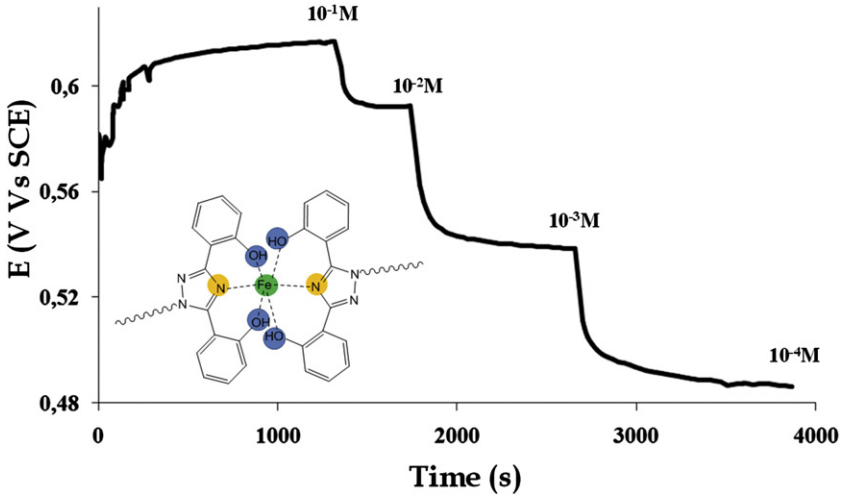


Fig. 4. Potentiometric response of the new electrode toward iron (III) aqueous solution over a range from 10^{-1} mol/L to 10^{-4} mol/L.

recorded on a Bruker 600, 500 or 300 spectrometers. The chemical shifts are reported in parts per million (d) and the signals are quoted as s (singlet), br s (broad singlet), d (doublet), br d (broad doublet), dd (doublet of doublet), dt (doublet of trilplet), t (triplet), br t (broad triplet), q (quartet), br q (broad quartet), m (multiplet). *J* values are given in Hertz. Signal assignment was made using HMBC, HSQC, COSY, and NOESY experiments when necessary. Mass spectra and high resolution mass spectra (electrospray in positive mode—ESI$^+$) were recorded on a Waters Q-TOF Ultima apparatus. The ^{13}C solid-state NMR spectra were obtained on a Bruker AVANCE 500 spectrometer with a 4 mm probe and executive frequencies of 100.62 MHz. The experiments were performed with a magic angle spinning frequency set to 5 kHz, a contact time of 3 ms and using a CPTOSS sequence to suppress rotating bands. All commercially available products were used without further purification unless otherwise specified.

4.2. Synthesis

4.2.1. 2-[2-(2-Hydroxyethoxy)ethyl]-1H-isoindole-1,3(2H)-dione ***10****.* A solution of phthalic anhydride (74 g, 500 mmol) and 2-(2-hydroxyethyl)ethanolamine (52.5 g, 500 mmol) in toluene (450 mL) was heated under reflux in a three-necked round bottom flask fitted with a Dean–Stark apparatus. After 24 h, toluene was removed under reduce pressure and the oily residue is left at rt overnight to crystallize. White solid (116.7 g) was obtained. Yield: 100%, mp=63–64 °C; IR (ATR, cm^{-1}): 3540, 1766, 1701; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.53 (t, *J*=4.6 Hz, 2H), 3.61 (t, *J*=4.6 Hz, 2H), 3.67 (t, *J*=5.6 Hz, 2H), 3.83 (t, *J*=5.6 Hz, 2H), 7.55 (dd, *J*=5.5, 3.1 Hz, 2H), 7.60 (dd, *J*=5.5, 3.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.92, 62.00, 68.63, 72.63, 123.64, 132.38, 134.38, 168.76. ESI$^+$-MS: 258 $[MNa]^+$.

4.2.2. 2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]ethyl methanesulfonate ***11****.* Methanesulfonyl chloride (34.6 mL) was

slowly added to a cold solution of alcohol **10** (70 g, 298 mmol) and Et_3N (84 mL, 596 mmol) in CH_2Cl_2 (250 mL). The reaction mixture was stirred at rt for 5 h. After that, the reaction mixture was diluted with CH_2Cl_2 (500 mL) and then filtrated. The organic phase was washed successively with 1 M HCl (2×75 mL), saturated solution of $NaHCO_3$ (75 mL), and brine. The organic phase was dried over Na_2SO_4, filtered, and the CH_2Cl_2 was evaporated under reduced pressure to yield compound **11** (91 g, 96%) as a light orange solid. Mp=96–98 °C; IR (ATR) ν_{max} cm^{-1}: 1769, 1702; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (s, 3H), 3.72–3.77 (m, 4H), 3.90 (t, J=5.4 Hz, 2H), 4.29–4.32 (m, 2H), 7.70–7.74 (m, 2H), 7.83–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.26, 37.52, 68.16, 68.63, 72.63, 123.64, 132.38, 134.38, 168.76. ESI^+-MS: 336 $[MNa]^+$, ESI^+-HRMS $[MNa]^+$: calculated for $[C_{13}H_{15}NSO_6Na]^+$: 336.0518. Found: 336.0526.

4.2.3. 2-[2-(2-Iodoethoxy)ethyl]-1H-isoindole-1,3(2H)-dione ***8***. NaI (62.7 g, 427 mmol) was added to a solution of mesylate **11** (89 g, 284 mmol) in acetone (150 mL). The reaction mixture was stirred to reflux for 20 h. The solvent was removed under vacuum. The oily residue was dissolved in CH_2Cl_2 (300 mL) and washed with 10% (m/m) aqueous Na_2SO_3 then with water. The organic phase was dried over Na_2SO_4 and the CH_2Cl_2 was evaporated under reduced pressure to yield compound **8** (81 g, 82%) as white crystals. Mp=79–81 °C; IR (ATR) ν_{max} cm^{-1}: 1769, 1697; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.18 (t, J=6.7 Hz, 2H), 3.69–3.76 (m, 4H), 3.90 (t, J=5.7 Hz, 2H), 7.69–7.72 (m, 2H), 7.83–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.78, 37.32, 67.50, 71.19, 123.31, 132.15, 133.99, 168.28. ESI^+-MS: 368 $[MNa]^+$(100), 713 $[M_2Na]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $[C_{12}H_{12}NO_3INa]^+$: 367.9760. Found: 367.9775.

4.2.4. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-dihydroxycalix[4]arene, cone 12. A slurry of calix[4]arene **1** (10 g, 23.6 mmol), anhydrous K_2CO_3 (6.5 g, 47.2 mmol), and iodide **8** (32.5 g, 94.4 mmol) in dry CH_3CN (150 mL) was heated to reflux for 1 week. After removal of CH_3CN, the residue was dissolved with CH_2Cl_2 (250 mL). The organic phase was washed successively with water (30 mL), 1 M HCl (2×20 mL), H_2O (20 mL), and brine. The mixture was dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by crystallization in CH_2Cl_2/MeOH (2:3; v/v) to yield compound **12** (14.9 g, 74%) as white crystals. Mp=199–200 °C; IR (ATR) ν_{max} cm^{-1}: 3320, 1773, 1709; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.06 (d, J=12.9 Hz, 4H), 3.97 (d, J=12.8 Hz, 4H), 4.02–4.07 (m, 16H), 6.47 (t, J=7.4 Hz, 2H), 6.65 (t, J=7.6 Hz, 2H), 6.79 (d, J=7.5 Hz, 4H), 6.82 (d, J=7.6 Hz, 4H), 7.40 (m, 4H), 7.48 (m, 4H), 7.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.43, 38.53, 68.98, 70.44, 75.66, 119.3, 123.12, 125.71, 128.54, 128.62, 129.14, 132.24, 133.89, 134.24, 151.88, 153.06, 168.89. ESI^+-MS: 881 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $[C_{52}H_{46}N_2O_{10}Na]^+$: 881.3050. Found: 881.3008.

4.2.5. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))-calix[4]arene. A slurry of calixarene **12** (5 g, 5.83 mmol) and dry Cs_2CO_3 (19 g, 58.3 mmol) in 80 mL of dry DMF was heated at 50 °C under argon atmosphere for 1 h 30 min. After this, a solution of γ-bromobutyronitrile (5.8 mL, 58.3 mmol) was introduced and the reaction mixture was stirred at 50 °C under argon atmosphere for 5 days. After cooling to rt, water was added (200 mL). Aqueous phase was extracted with AcOEt (2×100 mL). The combined organic layers were washed successively with 0.2 N HCl (2×10 mL), water (10 mL), and brine (25 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by chromatography (CH_2Cl_2/AcOEt 9:1) to yield the 1,3-*alternate* conformer **2** (2.2 g, 38%) as white gum and the *partial cone* conformer **4** (2.8 g, 48%) as a white gum.

4.2.6. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))-calix[4]arene, 1,3-alternate ***2***. IR (ATR) ν_{max} cm^{-1}: 2871, 2239, 1769, 1704; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.66 (t, J=6.9 Hz, 4H), 1.92 (t, J=7.4 Hz, 4H), 3.07 (t, J=6.3 Hz, 4H), 3.51 (t, J=6.3 Hz, 4H), 3.55 (t, J=5.8 Hz, 4H), 3.59 (t, J=6.4 Hz, 4H), 3.70 (d, J=16.1 Hz, 4H), 3.78 (d, J=16.1 Hz, 4H), 3.83 (t, J=5.8 Hz, 4H), 6.81 (t, J=7.3 Hz, 2H), 6.84 (t, J=7.1 Hz, 2H), 7.00 (d, J=7.5 Hz, 4H), 7.03 (d, J=7.5 Hz, 4H), 7.67 (dd, J=5.5, 3.1 Hz, 4H), 7.80 (dd, J=5.4, 3.1 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.83, 26.24, 37.87, 38.19, 67.84, 68.16, 68.88, 69.09, 120.32, 122.79, 123.26, 123.61, 129.65, 130.07, 132.54, 133.91, 134.34, 134.53, 156.50, 156.75, 168.58. ESI^+-MS: 1015 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $C_{60}H_{56}N_4O_{10}Na$: 1015.3894. Found: 1015.3875.

4.2.7. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))-calix[4]arene, partial cone ***4***. IR (ATR) ν_{max} cm^{-1}: 2920, 2873, 2242, 1709; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.61 (q, J=7.5 Hz, 2H), 1.99–2.06 (m, 2H), 2.23 (m, 4H), 2.91 (d, J=13.3 Hz, 2H), 3.21 (t, J=7.2 Hz, 2H), 3.45 (t, J=6.5 Hz, 2H), 3.49 (d, J=13.7 Hz, 2H), 3.68 (d, J=13.4 Hz, 2H), 3.69–3.76 (m, 8H), 3.78–3.82 (m, 2H), 3.88–3.96 (m, 8H), 6.35 (d, J=7.4 Hz, 2H), 6.45 (t, J=7.5 Hz, 2H), 6.77 (d, J=7.0 Hz, 2H), 6.86 (t, J=7.4 Hz, 1H), 6.99 (m, 3H), 7.21 (d, J=7.5 Hz, 2H), 7.59–7.62 (m, 4H), 7.71–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.01, 14.09, 25.37, 27.21, 30.30, 36.74, 37.95, 68.10, 69.63, 70.43, 72.08, 73.17, 120.03, 121.46, 122.30, 123.29, 123.47, 123.63, 129.20, 129.43, 129.48, 131.33, 132.37, 132.93, 134.12, 134.17, 134.33, 136.75, 155.16, 156.54, 157.23, 168.56. ESI^+-MS: 1015 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $C_{60}H_{56}N_4O_{10}Na$: 1015.3894. Found: 1015.3833.

4.2.8. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-bis-(1-(3-(tert-butyloxycarbonyl) aminopropyloxy))calix[4]arene. A solution of *N*-Boc bromopropylamine (555 mg, 2.33 mmol) in anhydrous DMF (4 mL) was added at 0 °C under Argon atmosphere to a slurry of calix[4]arene **12** (200 mg, 0.233 mmol), and anhydrous Cs_2CO_3 (762 mg, 2.33 mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred at 0 °C for 2 h then at rt for 4 days. After this time, 0.1 M HCl aqueous (50 mL) was added. This aqueous phase was extracted with ethyl acetate (2×40 mL). The combined organic layers were washed successively with 0.1 M HCl aqueous (10 mL), water (10 mL), and brine. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (CH_2Cl_2/AcOEt 8:2) to yield 1,3-*alternate* conformer **3** (60 mg, 22%) as a white solid and *partial cone* conformer **5** (70 mg, 30%) as a white foam.

4.2.9. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26,28-bis-(1-(3-(tert-butyloxycarbonyl) aminopropyloxy))calix[4]arene, 1,3-alternate ***3***. Mp=156–158 °C; IR (ATR) ν_{max} cm^{-1}: 3417, 2978, 2930, 2902, 2869, 1708; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 18H), 1.64 (br t, 4H), 2.99–3.01 (m, 4H), 3.35–3.37 (m, 4H), 3.47 (m, 4H), 3.59–3.73 (m, 16H), 3.92 (t, J=5.7 Hz, 4H), 4.82 (br s, 2H), 6.70 (t, J=7.4 Hz, 2H), 6.79 (t, J=7.4 Hz, 2H), 6.97 (d, J=7.5 Hz, 4H), 7.01 (d, J=7.5 Hz, 4H), 7.68–7.71 (m, 4H), 7.82–7.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.56, 30.58, 36.93, 37.54, 37.86, 67.84, 69.21, 69.57, 79.03, 122.11, 122.30, 123.22, 129.47, 129.85, 132.17, 133.38, 133.89, 134.04, 156.07, 156.16, 156.45, 168.23. ESI^+-MS: 1195 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $C_{68}H_{76}N_4O_{14}Na$: 1195.5256. Found: 1195.5255.

4.2.10. 25,27-Bis-(1-(2-(2-phthalimidoethoxy)ethoxy))-26-(1-(3-(tert-butyloxycarbonyl) aminopropyloxy))-28-hydroxycalix[4]arene, partial cone ***5***. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 1.49 (m, 2H), 2.65 (m, 2H), 2.88 (m, 2H), 3.09 (d, J=13.2 Hz, 2H), 3.72–4.01 (m,

22H), 6.54 (t, J=7.4 Hz, 1H), 6.72 (t, J=7.5 Hz, 2H), 6.84 (d, J=7.6 Hz, 2H), 6.86 (dd, J=7.5, 1.5 Hz, 2H), 6.93 (dd, J=7.5, 1.5 Hz, 2H), 7.01 (t, J=7.5 Hz, 1H), 7.28–7.31 (d, J=7.5 Hz, 2H), 7.61–7.67 (m, 4H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.84, 28.52, 30.59, 37.56, 37.70, 37.91, 68.28, 69.45, 70.17, 72.71, 78.51, 118.67, 122.32, 123.04, 123.23, 123.83, 128.06, 128.24, 129.02, 129.28, 130.85, 132.03, 133.72, 133.94, 134.00, 152.51, 154.30, 155.72, 156.47, 168.28. ESI$^+$-MS: 1039 $[MNa]^+$. ESI$^+$-HRMS $[MNa]^+$: calculated for $C_{60}H_{61}N_3O_{12}Na$: 1038.4153. Found: 1038.4170.

4.3. General procedure for deprotection of the phthalimido group of calix[4]arenes 13–14 and 17–18

A 35% aqueous solution of hydrazine (10 mmol) was added to slurry of phthalimidocalixarene (1 mmol) in absolute EtOH (50 mL). The reaction mixture was heated to reflux for 7 h. Solvents were removed under reduced pressure. The residue was manipulated in ethyl acetate (50 mL). The resulting precipitate was filtered and washed with small volumes of AcOEt. The combined organic phases were washed successively with a 2 M NaOH aqueous, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated by rotary evaporation.

4.3.1. 25,27-Bis-(1-(2-(2-aminoethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))calix[4]arene, 1,3-alternate ***13***. Manipulation in Et_2O. Yield 87%; white gum; IR (ATR) ν_{max} cm^{-1}: 3369, 2920, 2875, 2326, 2246; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.71 (br q, J=6.6 Hz, 4H), 1.97 (t, J=7.2 Hz, 4H), 2.86 (br s, 4H), 3.08 (br t, J=6.0 Hz, 4H), 3.40 (br t, 4H), 3.61 (br t, J=6.1 Hz, 4H), 3.65 (br t, J=6.1 Hz, 4H), 3.78 (d, J=16.0 Hz, 4H), 3.86 (d, J=16.0 Hz, 4H), 6.85 (t, J=7.5 Hz, 2H), 6.89 (t, J=7.3 Hz, 2H), 7.06 (d, J=7.4 Hz, 4H), 7.10 (d, J=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.88, 26.29, 38.17, 42.29, 68.00, 68.90, 69.35, 73.72, 120.25, 122.82, 123.16, 129.70, 130.03, 133.94, 134.45, 156.61, 156.80. ESI$^+$-MS: 733 $[MH]^+$. ESI$^+$-HRMS $[MH]^+$: calculated for $C_{44}H_{53}N_4O_6$: 733.3965. Found: 733.3938.

4.3.2. 25,27-Bis-(1-(2-(2-aminoethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))calix[4]arene, partial cone ***14***. Yield 98%; white gum; IR (ATR) ν_{max} cm^{-1}: 3371, 2919, 2868, 2244, 2159; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.79 (br q, J=7.2 Hz, 2H), 2.12 (br q, J=6.9 Hz, 2H), 2.32 (m, 4H), 2.93 (br s, 4H), 3.11 (d, J=13.2 Hz, 2H), 3.56–3.64 (m, 10H), 3.75 (br s, 4H), 3.81–3.87 (m, 4H), 3.98–4.02 (m, 2H), 4.12 (d, J=13.2 Hz, 2H), 6.47 (d, J=7.4 Hz, 2H), 6.55 (t, J=7.5 Hz, 2H), 6.88 (d, J=7.1 Hz, 2H), 6.96 (t, J=7.4 Hz, 1H), 7.06 (t, J=7.4 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 7.36 (d, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.10, 14.55, 25.66, 27.22, 30.56, 36.80, 42.32, 69.79, 70.62, 72.36, 73.60, 73.71, 119.97, 121.39, 122.41, 123.16, 123.71, 129.34, 129.58, 131.38, 132.99, 134.00, 134.42, 136.73, 155.42, 156.72, 157.41. ESI$^+$-MS: 733 $[MH]^+$. ESI$^+$-HRMS $[MH]^+$: calculated for $C_{44}H_{53}N_4O_6$: 733.3965. Found: 733.3985.

4.3.3. 25,27-Bis-(1-(2-(2-aminoethoxy)ethoxy))-26,28-bis-(1-(3-(tert-butyloxycarbonyl) aminopropyloxy))calix[4]arene, 1,3-alternate ***17***. Chromatography (CH_2Cl_2/MeOH/NH_4OH 37% 80:20:3). Yield 60%; white gum; IR (ATR) ν_{max} cm^{-1}: 3359, 2922, 2866, 1697; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51 (s, 18H), 1.65–1.72 (m, 4H), 2.87–2.95 (m, 4H), 2.98–3.08 (m, 4H), 3.38–3.48 (m, 4H), 3.49–3.60 (m, 8H), 3.68 (d, J=14.8 Hz, 2H), 3.70–3.80 (m, 10H), 6.79 (t, J=7.5 Hz, 2H), 6.83 (t, J=7.5 Hz, 2H), 7.02 (d, J=7.5 Hz, 4H), 7.10 (d, J=7.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.54, 30.55, 36.91, 37.85, 41.50, 69.42, 69.55, 70.16, 72.61, 79.08, 122.24, 122.46, 129.69, 129.99, 133.59, 133.91, 156.06, 156.17, 156.56. ESI$^+$-MS: 913 $[MH]^+$. ESI$^+$-HRMS $[MH]^+$: calculated for $C_{52}H_{73}N_4O_{10}$: 913.5327. Found: 913.5300.

4.3.4. 25,27-Bis-(1-(2-(2-aminoethoxy)ethoxy))-26-(1-(3-(tert-butyloxycarbonyl)amino propyloxy))-28-hydroxycalix[4]arene, partial cone ***18***. Chromatography over silica gel (CH_2Cl_2/MeOH/NH_4OH 37% 90:10:2). Yield 66%; white gum; IR (ATR) ν_{max} cm^{-1}: 3329, 2980, 2929, 2892, 2871, 1698; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9H), 1.65 (br t, 2H), 2.95 (m, 2H), 3.26 (d, J=13.2 Hz, 2H), 3.32 (br t, 2H), 3.61–3.93 (m, 17H), 4.16–4.26 (m, 5H), 6.67 (t, J=7.4 Hz, 1H), 6.76 (t, J=7.4 Hz, 2H), 6.85–6.86 (d, J=7.0 Hz, 2H), 7.00 (dd, J=7.2, 1.3 Hz, 2H), 7.05 (d, J=7.4 Hz, 2H), 7.10 (t, J=7.4 Hz, 1H), 7.37 (d, J=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.49, 30.30, 30.62, 37.68, 38.31, 69.15, 70.54, 72.57, 78.66, 119.49, 122.97, 124.23, 128.03, 128.59, 129.38, 129.66, 131.20, 133.47, 133.69, 133.81, 152.12, 153.68, 155.78, 156.53. ESI$^+$-MS: 756 $[MH]^+$. ESI$^+$-HRMS $[MH]^+$: calculated for $C_{44}H_{58}N_3O_8$: 756.4224. Found: 756.4214.

4.4. General coupling procedure for the peptidic coupling with ICL670: synthesis of calix[4]arenes 6 and 7

A solution of carboxylic acid (1.1 equiv/equiv NH_2 group), HOBt (1.1 equiv/equiv NH_2 group), and EDCI (1.1 equiv/equiv NH_2 group) in CH_2Cl_2 (10 mL) was stirred at rt for 15 min. Aminocalixarene (1 mmol) was added and the reaction medium was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and this organic phase was washed successively with 1 M HCl aqueous, saturated $NaHCO_3$ aqueous, water, and brine. The organic phase was dried over Na_2SO_4 then evaporated by rotary evaporation. The crude product was purified by chromatography.

4.4.1. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))calix[4]arene, 1,3-alternate ***15***. Chromatography (CH_2Cl_2/MeOH 98:2). Yield 81%; beige solid; mp=162–168 °C; IR (ATR) ν_{max} cm^{-1}: 3259, 2920, 2873, 1647, 1621, 1610, 1586; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.66 (br q, 4H), 1.97 (t, J=7.3 Hz, 4H), 3.23 (t, J=5.3 Hz, 4H), 3.35–3.45 (m, 6H), 3.50–3.70 (m, 10H), 3.77 (d, J=16.3 Hz, 4H), 3.85 (d, J=16.4 Hz, 4H), 6.62 (t, J=7.3 Hz, 2H), 6.79 (t, J=7.5 Hz, 2H), 6.87 (m, 18H), 7.23–7.37 (m, 6H), 7.52 (d, J=8.4 Hz, 4H), 7.97 (d, J=8.4 Hz, 4H), 8.06 (d, J=8.0 Hz, 2H), 9.66 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.45, 25.68, 37.95, 40.30, 67.58, 69.37, 69.48, 69.61, 110.33, 113.20, 117.13, 118.31, 119.11, 119.81, 119.94, 122.66, 122.82, 125.98, 127.61, 127.84, 128.82, 129.58, 129.72, 131.84, 133.01, 133.78, 134.02, 135.72, 140.53, 152.08, 156.34, 156.47, 157.84, 159.64, 166.41. ESI$^+$-MS: 1466 $[MNa]^+$. ESI$^+$-HRMS $[MNa]^+$: calculated for $C_{86}H_{78}N_{10}O_{12}Na$: 1465.5698. Found: 1465.5739.

4.4.2. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26,28-bis-(1-(3-cyanopropoxy))calix[4]arene, partial cone ***16***. Chromatography (CH_2Cl_2/MeOH 98:2). Yield 45%; beige solid; mp=148–149 °C; IR (ATR) ν_{max} cm^{-1}: 3295, 3052, 2923, 2864, 1740, 1649, 1621, 1611, 1587; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85–1.90 (m, 2H), 2.05–2.15 (m, 2H), 2.30–2.40 (m, 4H), 3.09 (d, J=13.2 Hz, 2H), 3.44 (br t, 2H), 3.60–3.67 (m, 4H), 3.75–3.95 (m, 16H), 4.02–4.15 (m, 4H), 6.45 (d, J=7.4 Hz, 2H), 6.55 (t, J=7.4 Hz, 2H), 6.66 (t, J=7.5 Hz, 2H), 6.90–6.98 (m, 8H), 7.04–7.09 (m, 6H), 7.15 (d, J=8.2 Hz, 4H), 7.32–7.40 (m, 6H), 7.46 (d, J=8.2 Hz, 4H), 7.91 (d, J=8.2 Hz, 4H), 8.15 (d, J=7.2 Hz, 2H), 9.65 (s, 2H), 11.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.14, 14.68, 25.58, 27.19, 30.48, 36.88, 40.68, 69.81, 70.09, 70.81, 72.10, 73.37, 110.42, 113.64, 117.53, 118.80, 119.51, 119.79, 120.38, 121.84, 122.57, 123.00, 123.91, 126.47, 128.07, 128.91, 129.20, 129.42, 129.69, 131.22, 132.27, 132.77, 133.43, 133.97, 134.45, 136.20, 136.66, 140.73, 152.56, 155.15, 156.59, 156.89, 157.47, 158.42, 159.95, 166.57. ESI$^+$-MS: 1466 $[MNa]^+$. ESI$^+$-HRMS $[MNa]^+$: calculated for $C_{86}H_{78}N_{10}O_{12}Na$: 1465.5698. Found: 1465.5717.

4.4.3. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26,28-bis-(1-(3-(tert-

butyloxycarbonyl)aminopropyloxy))calix[4]arene, 1,3-alternate ***19***. Chromatography (CH_2Cl_2/MeOH 95:5). Yield 14%; beige solid; mp=114–116 °C; IR (ATR) ν_{max} cm^{-1}: 3327, 3068, 2924, 2864, 1692, 1647, 1621, 1611, 1587; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 18H), 1.57–1.63 (m, 4H), 2.95–3.02 (m, 4H), 3.41–3.79 (m, 28H), 4.95 (br s, 2H), 6.63–6.73 (m, 4H), 6.83 (t, *J*=7.3 Hz, 2H), 6.97–7.07 (m, 14H), 7.29–7.37 (m, 6H), 7.49 (br d, *J*=8.1 Hz, 4H), 7.95 (br d, *J*=8.0 Hz, 4H), 8.08 (dd, *J*=8.7, 2.4 Hz, 2H), 9.75 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.53, 30.41, 37.21, 37.74, 40.29, 69.06, 69.65, 69.77, 70.19, 79.09, 110.68, 113.28, 117.13, 118.13, 119.20, 119.88, 122.18, 122.55, 125.68, 127.54, 128.08, 128.80, 129.77, 131.75, 132.93, 133.78, 133.84, 135.54, 140.43, 152.04, 156.13, 156.21, 156.51, 156.76, 157.61, 159.65, 166.38. ESI^+-MS: 1647 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $C_{94}H_{98}N_{10}O_{16}Na$: 1645.7060. Found: 1645.7091.

4.4.4. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26-(1-(3-(tert-butyloxycarbonyl)aminopropyloxy))-28-hydroxy calix[4]arene, partial cone ***20***. Chromatography (CH_2Cl_2/MeOH 95:5). Yield 56%; beige solid; mp=146–148 °C; IR (ATR) ν_{max} cm^{-1}: 3283, 3060, 2916, 2871, 1702, 1648, 1621, 1612, 1587; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 1.47–1.50 (m, 2H), 2.75–2.77 (m, 2H), 3.24–3.28 (m, 4H), 3.57–3.92 (m, 17H), 4.11–4.19 (m, 5H), 6.65 (t, *J*=7.4 Hz), 6.69–6.83 (m, 4H), 6.90–7.17 (m, 14H), 7.25–7.45 (m, 11H), 7.71–7.81 (m, 6H), 8.15 (dd, *J*=7.4, 1.6 Hz, 2H), 9.94 (s, 2H), 10.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.51, 30.19, 30.49, 37.80, 38.00, 40.14, 69.64, 69.98, 72.36, 78.76, 111.34, 113.47, 117.20, 118.02, 119.40, 119.85, 120.25, 122.35, 124.39, 125.02, 127.50, 128.42, 128.63, 128.78, 129.49, 129.72, 130.75, 131.69, 132.93, 133.35, 133.64, 134.04, 134.75, 140.56, 151.94, 152.07, 153.58, 155.81, 156.65, 156.76, 157.19, 159.86, 166.55. ESI^+-MS: 1488 $[MNa]^+$. ESI^+-HRMS $[MNa]^+$: calculated for $C_{86}H_{83}N_9O_{14}Na$: 1488.5957. Found: 1488.5928.

4.5. General procedure for the deprotection of carbamate groups: synthesis of calix[4]arenes 6 and 7

A solution of carbamate calix[4]arene (1 mmol) in CH_2Cl_2/TFA 10:1 (20 mL) was stirred at rt overnight. The solvent was removed by evaporation then the residue was dissolved in ethyl acetate or CH_2Cl_2 (100 mL). This organic phase was washed successively with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4 and concentrated by rotary evaporation.

4.5.1. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26,28-bis-(aminopropyloxy)calix[4]arene, 1,3-alternate ***6***. Chromatography (CH_2Cl_2/MeOH/NH_4OH 37% 80:20:3 to 70:30:3). Yield 65%; beige solid; mp=168–170 °C; IR (ATR) ν_{max} cm^{-1}: 3261, 3063, 2923, 2864, 1645, 1611, 1587; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.68–1.80 (m, 4H), 2.58–2.76 (m, 4H), 3.40–4.00 (m, 28H), 6.55–6.68 (m, 4H), 6.72 (t, *J*=7.8 Hz, 2H), 6.87–7.10 (m, 14H), 7.20–7.40 (m, 6H), 7.48 (br d, *J*=7.1 Hz, 4H), 7.87 (br d, *J*=7.1 Hz, 4H), 8.03 (br d, *J*=7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.71, 37.72, 40.18, 69.60, 69.68, 111.70, 113.42, 117.16, 118.08, 118.93, 119.85, 122.90, 125.12, 125.54, 127.46, 128.60, 128.72, 130.00, 131.71, 132.84, 133.73, 134.13, 135.26, 140.50, 152.28, 156.27, 156.51, 156.60, 157.85, 159.89, 166.51. ESI^+-HRMS $[MH]^+$: calculated for $C_{84}H_{83}N_{10}O_{12}$: 1423.6191. Found: 1422.6213.

4.5.2. 25,27-Bis-(1-(2-(2-[4-(3,5-bis-(2-hydroxyphenyl)-1,2,4-triazol-1-yl)phenyl]carbamoyl ethoxy)ethoxy))-26-aminopropyloxy-28-hydroxycalix[4]arene, partial cone ***7***. Yield 100%; white gum; IR (ATR) ν_{max} cm^{-1}: 3271, 3065, 2917, 2872, 1649, 1611, 1588; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.43 (br t, 2H), 3.16–3.18 (d, *J*=13.2 Hz, 2H), 3.28 (br t, 2H), 3.55–3.60 (m, 6H), 3.66–3.71 (m, 6H), 3.85–3.93 (m, 6H), 4.06–4.13 (m, 4H), 6.67 (t, *J*=7.5 Hz, 1H), 6.74–6.77 (m, 3H), 6.83 (br d, *J*=7.4 Hz, 2H), 6.96–7.09 (m, 11H), 7.12 (dd, *J*=7.9, 1.5 Hz, 2H), 7.29–7.34 (m, 9H), 7.37 (dt, *J*=7.7, 1.7 Hz, 2H), 7.56 (br t, 2H), 7.75 (d, *J*=8.5 Hz, 4H), 8.15 (dd, *J*=7.8, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 30.62, 31.95, 37.93, 39.08, 40.12, 69.83, 69.91, 69.94, 72.36, 111.63, 113.50, 117.18, 117.88, 119.23, 119.81, 120.42, 122.53, 124.28, 124.92, 127.46, 128.55, 128.58, 128.63, 128.67, 129.45, 129.58, 130.60, 131.65, 132.85, 133.33, 133.85, 134.00, 134.90, 140.51, 151.74, 152.12, 153.72, 156.68, 156.70, 157.26, 159.91, 166.64. ESI^+-MS: 1366 $[MH]^+$. ESI^+-HRMS $[MH]^+$: calculated for $C_{81}H_{76}N_9O_{12}$: 1366.5613. Found: 1366.5615.

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References and notes

1. (a) De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Radamacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515; (b) Czarnik, A. W.; Desvergne, J.-P. *Chemosensors for Ion and Molecule Recognition*; Kluwer: Dordrecht, The Netherlands, 1997; (c) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3.
2. Andrews, N. C. *N. Engl. J. Med.* **1999**, *341*, 1986.
3. (a) Xiang, Y.; Tong, A. *Org. Lett.* **2006**, *8*, 1549; (b) Ghosh, S.; Chakrabarty, R.; Mukherjee, P. S. *Inorg. Chem.* **2009**, *48*, 549; (c) Weerasinghe, A. J.; Schmiesing, C.; Varaganti, S.; Ramakrishna, G.; Sinn, E. *J. Phys. Chem. B* **2010**, *114*, 9413.
4. (a) Tani, Y.; Umezawa, Y. *Bunseki Kagaku* **2003**, *52*, 491; (b) Sauvage, F.; Tarascon, J.-M.; Baudrin, E. *Microchim. Acta* **2009**, *164*, 363.
5. Walcarius, A. *Chem. Mater.* **2001**, *13*, 3351.
6. Liu, Z. D.; Hider, R. C. *Med. Res. Rev.* **2002**, *22*, 26.
7. Steinhauser, S.; Heinz, U.; Bartholomä, M.; Weyhermüller, T.; Nick, H.; Hegetschweiler, K. *Eur. J. Inorg. Chem.* **2004**, *21*, 4151.
8. (a) Kim, J. S.; Quang, D. T. *Chem. Rev.* **2007**, *107*, 3780; (b) Park, S. Y.; Yoon, J. H.; Hong, C. S.; Souane, R.; Kim, J. S.; Matthews, S. E.; Vicens, J. *J. Org. Chem.* **2008**, *73*, 8212; (c) Joseph, R.; Ramanujam, B.; Acharya, A.; Rao, C. P. *J. Org. Chem.* **2009**, *74*, 8181; (d) Leray, I.; Valeur, B. *Eur. J. Inorg. Chem.* **2009**, *24*, 3525; (e) Senthilvelan, A.; Ho, I.-T.; Chang, K.-C.; Lee, G.-H.; Liu, Y.-H.; Chung, W.-S. *Chem.—Eur. J.* **2009**, *15*, 6152; (f) Pathak, R. K.; Dikundwar, A. G.; Guru Row, T. N.; Rao, C. P. *Chem. Commun.* **2010**, *46*, 4345.
9. Danila, C.; Bolte, M.; Böhmer, V. *Org. Biomol. Chem.* **2005**, *3*, 172.
10. (a) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; Hyun No, K.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409; (b) Gutsche, C. D.; Lee-Gin, L. *Tetrahedron* **1986**, *42*, 1633.
11. Garregg, P. J.; Samuelsson, B. *Synthesis* **1979**, *6*, 469.
12. (a) Veerboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 5394; (b) Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, *57*, 7066.
13. Steinhauser, S.; Heinz, U.; Bartholomä, M.; Weyhermüller, T.; Hanspeter, N.; Hegetschweiler, K. *Eur. J. Inorg. Chem.* **2004**, *21*, 4151.
14. (a) Cho, J. K.; Kim, D.-W.; Namgung, J.; Lee, Y.-S. *Tetrahedron Lett.* **2001**, *42*, 7443; (b) Caddick, S.; Haynes, A. K. de K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513; (c) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, 763; (d) Periasamy, M.; Thirumalaikumar, M. *J. Organomet. Chem.* **2000**, *609*, 137; (e) Chen, X.; Dings, R. P.; Nesmelova, I.; Debbert, S.; Haseman, J. R.; Maxwell, J.; Hoye, T. R.; Mayo, K. H. *J. Med. Chem.* **2006**, *26*, 7754.
15. (a) Halouani, H.; Dumazet-Bonnamour, I.; Perrin, M.; Lamartine, R. *J. Org. Chem.* **2004**, *69*, 6521; (b) Mikulášek, L.; Grüner, B.; Dordea, C.; Rudzevich, V.; Böhmer, V.; Haddaoui, J.; Hubscher-Bruder, V.; Arnaud-Neu, F.; Čáslavský, J.; Selucký, P. *Eur. J. Org. Chem.* **2007**, *13*, 4772.
16. (a) Gaetano, Y.; Clarot, I.; Regnouf-de-Vains, J.-B. *Tetrahedron Lett.* **2009**, *42*, 5793; (b) Sénèque, O.; Reinaud, O. *Tetrahedron* **2003**, *59*, 5563.
17. Sibille, P.; Lopez, S.; Brabet, I.; Valenti, O.; Oueslati, N.; Gaven, F.; Goudet, C.; Bertrand, H.-O.; Neyton, J.; Marino, M. J.; Amalric, M.; Pin, J.-P.; Acher, F. C. *J. Med. Chem.* **2007**, *50*, 3585.
18. Le Poul, N.; Baudrin, E.; Morcrette, M.; Gwizdala, S.; Masquelier, C.; Tarascon, J.-M. *Solid State Ionics* **2003**, *159*, 149.