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p-(3-Carboxy- and 3-carboxymethyl-1-adamantyl)calix[4]arenes: synthesis and arming with amino acid units

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Abstract—Adamantylcalix[4]arenes carboxylated at the upper rim have been synthesized by a convenient one-step procedure from *p*-H-calix[4]arene and carboxylated 1-adamantanols. Selective and exhaustive lower rim alkylation along with upper rim modification by amino acid fragments have been carried out. Preliminary evaluation of the novel N-linked peptidocalixarenes as ionophores for ion-selective electrodes is reported.

One of the topics of current calixarene chemistry is the design and synthesis of multifunctional molecular receptors. Generally parent calixarenes begin to act as synthetic receptors only after appropriate regio- and stereoselective functionalization of the phenolic oxygens at the lower rim, and/or the aromatic *para* positions of the phenyl rings at the upper rim.[1]

Upper rim carboxylated calixarenes have turned out to be highly attractive building blocks for the construction of molecular receptors for amines,[2] metal ions,[3] aromatic hydrocarbons,[4] etc. The ionizable and hydrogen-bonding carboxylic groups let the calixarene macrocycles form self-associated dimers[5] as well as molecular capsules with complementary calixarenes.[6] However, calixarenes carrying carboxyl groups either directly attached[7] or further removed from the *p*-position of the upper rim by $-CH_2-$,[8] $-(CH_2)_2-$,[9] CH=CH,[10] or $-C_6H_4$-linkers[2b] usually require several-step procedures starting from the *p*-H-calixarene.

In this letter, we report our results on the design and one-step synthesis of a new type of carboxylated calix[4]arene possessing an enlarged hydrophobic cavity *p*-(3-carboxy-1-adamantyl)- and *p*-(3-carboxymethyl-1-adamantyl)-calix[4]arenes together with preliminary studies of the receptor properties of their derivatives, peptidocalixarenes.

It has been demonstrated recently that exhaustively adamantylated calix[4]arenes can be easily prepared from *p*-H-calix[4]arene and 3-R-1-adamantanols (R = alkyl or aryl) in trifluoroacetic acid (TFA).[11,12] The introduction of functionally modified adamantanols (e.g., R is a COOH- or NH_2-containing group) in this reaction appeared attractive, since it could lead to upper rim functionalized calixarenes with a free lower rim for further modification. Herein we report the first direct procedure for the synthesis of adamantylcalix[4]arene tetrols carboxylated at the upper rim.

Initially it was revealed that the interaction of *p*-H-calix[4]arene **1** and 3-carboxy-1-adamantanol **2a** in TFA under the conditions proposed for *p*-(1-adamantyl)-calix[4]arene[11] gave a mixture of adamantylated products. This outcome is apparently connected with the difficulty of generation of the adamantyl cations carrying electron-acceptor COOH groups. Full adamantylation of the macrocycle **1** was carried out by intensive heating under reflux with 3-carboxy-1-adamantanol in $TFA/C_2H_4Cl_2$ in the presence of a catalytic amount of trifluoromethanesulfonic acid and gave *p*-(3-carboxy-1-adamantyl)calix[4]arene **3** in 96% yield. The reaction of 3-carboxymethyl-1-adamantanol **2b** with **1** proceeded much more readily and tetraacid **3b** was formed at 60–65 °C in quantitative yield in the absence of CF_3SO_3H (see Scheme 1).[13]

Keywords: Carboxylated calixarenes; Upper rim adamantylation; Peptidocalixarenes; ISE.
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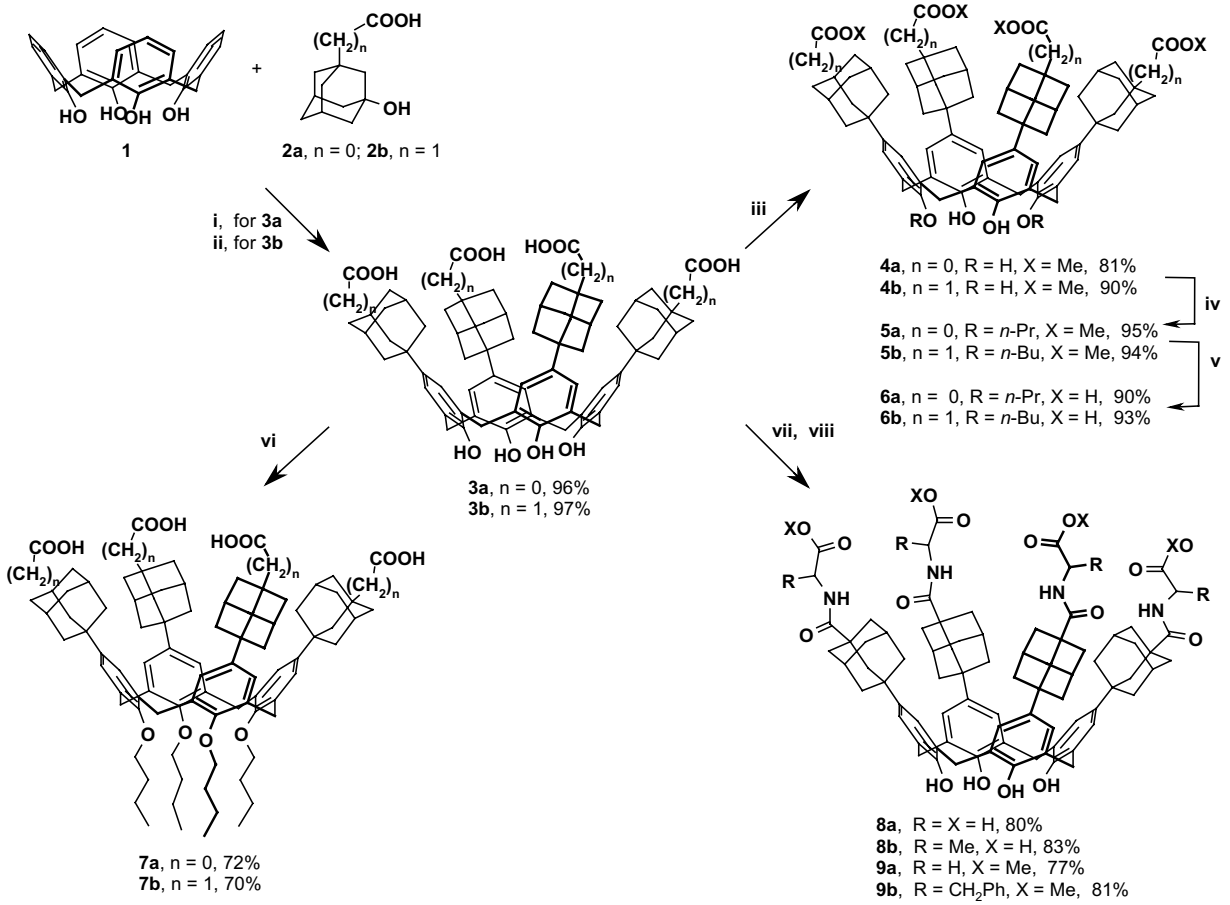

Scheme 1. (i) $CF_3COOH/C_2H_4Cl_2$ (1:1 v/v), CF_3SO_3H (cat), 85–90 °C, 12 h; (ii) $CF_3COOH/C_2H_4Cl_2$ (1:1 v/v), 60–65 °C, 9 h; (iii) MeOH–THF, H_2SO_4 (cat); (iv) *n*-PrI (or *n*-BuI), K_2CO_3, MeCN, 24 h, reflux; (v) KOH, EtOH, 12 h, reflux; (vi) *n*-BuI, NaH, DMF, 24 h, rt; (vii) $SOCl_2$, 1.5 h, reflux; (viii) $HCl{\cdot}NH_2$ CHRCOOX (R = H, Me, CH_2Ph; X = H, Me), NEt_3, THF, 12 h, rt.

As follows from the temperature dependent ^1H NMR spectra, tetracids **3a**,**b** possess unusually high coalescence temperatures (T_c) for the *cone–cone* interconversion. Tetracarboxy derivative **3a** has $T_c = 37$ °C in DMSO, whereas it is known,[14] that *p-tert*-butylcalix[4]arene has $T_c = 18$ °C in this solvent. The acid **3b** with tetracarboxymethyl substituents in the adamantyl nuclei showed evident solubility in chlorohydrocarbons (~15 mg/mL in $CHCl_3$), with an exceptionally high T_c in these solvents. Thus, for a $C_2D_2Cl_4$ solution of the named acid, the T_c was 95 °C, while *p*-(1-adamantyl)-calix[4]arene had $T_c = 53$ °C in $CDCl_3$. The fact that the T_c values are high may be due to the fact that in the *cone* conformation the carboxyl groups of **3a**,**b** are convergent and able to form intramolecular hydrogen bonds. The T_c and ^1H NMR chemical shifts of **3b** in $CDCl_3$ remained constant within the concentration range of 10^{-4}–10^{-3} M.

In previous reports, it was shown that the substitution pattern on the lower rim of a calix[4]arene strongly affects its binding properties at the upper rim.[15] Taking into account the possibility of using the macrocycles obtained for constructing molecular receptors, we developed procedures for full and 1,3-selective lower rim alkylation of the acids **3** (Scheme 1). Established procedures are essential for rigidifying the conformation of calixarenes or their fixation in the *cone* conformation.

Selective alkylation of the distal phenolic hydroxyls of **3** was carried out in three steps. Heating of **3** under reflux in $MeOH/H_2SO_4$ (cat.) gave ester derivatives **4**, subsequent 1,3-bis-etherification of which with *n*-alkyl iodide/K_2CO_3/MeCN proceeded smoothly to give **5**. Mild hydrolysis of the ester functions of **5** then resulted in the carboxylated calix[4]arenes **6**,[16] partially alkylated at the lower rim. Exhaustive alkylation of tetraacids **3** with *n*-alkyl iodides (RI, R = *n*-Pr, *n*-Bu) and NaH in DMF gave compounds **7**.[17] In both cases the alkylation reaction proceeded with complete stereoselectivity for the *cone* conformation. This was confirmed by the presence of only an AX system for the $ArCH_2Ar$ protons ($\delta \approx 3.4$ and 4.2 ppm) in the ^1H NMR spectra in $CDCl_3$ of compounds **5**–**7**, and only a triplet for the corresponding carbon at about δ 32.0 ppm in the ^{13}C NMR spectra.[18]

The attachment of biogenic fragments to the molecular skeleton of a calixarene leads to hybrid molecules of interest in supramolecular chemistry. In particular, peptidocalixarenes[1,19] display recognition properties towards substrates of peptide origin,[20] electroneutral

organic guests,[21] and organic and metal ions.[22] To construct novel ionophores for biologically relevant ammonium guests, for example, amino acid ester salts, we used the *p*-(3-carboxy-1-adamantyl)calix[4]arenes **3a** for the synthesis of N-linked peptidocalixarenes.

It was demonstrated that adamantylcalix[4] arenes having amino acid (Gly, **8a**, and D,L-Ala, **8b**) or amino acid ester (Gly, **9a**, and L-Phe, **9b**) units at the upper rim could be obtained via the acyl chloride of **3a** as an intermediate by condensation with the corresponding amino acid hydrochlorides in the presence of Et_3N in THF (Scheme 1). The conformational properties of compounds **8** and **9** were studied in solution by ^1H and ^{13}C NMR spectroscopy. The tetramino acids **8** are conformationally mobile compounds in d_6-DMSO solution. The conjugates with amino acid esters **9** adopt the cone conformation in $CDCl_3$ solution, which was indicated by the presence of two doublets for the methylene bridge signals in the ranges 3.4–3.6 and 4.2–4.3 ppm ($J = 12$–14 Hz) and from the equivalence of the aromatic protons of the calixarene cavity in their ^1H NMR spectra.[23]

The macrocycles **8** and **9** having polar binding groups arranged at the periphery of the enlarged apolar cavity (which mimics the hydrophobic pocket of natural receptors) may be considered as hybrid molecular receptors and may be useful in complex formation with organic substrates such as amino acids and their esters. Thus, the tetraglycine methyl ester **9a** was examined as a neutral carrier in a poly(vinyl chloride)-derived ion-selective electrode (ISE)[24] for methyl esters of amino acid hydrochlorides (MeAA)·H^+Cl^-.

Preliminary measurements showed that the glycine derivative **9a** is an effective carrier according to the EMF potential responses of a PVC-membrane electrode in solutions of the methyl ester hydrochlorides of phenylalanine (MePhe), tyrosine (MeTyr), isoleucine (MeIle). It was found that electrodes in the presence of ionophore **9a** gave a good Nernstian response of 56–58 mV/decade^{-1} to the activity of (MeAA)·H^+ ions within the concentration ranges 1×10^4 1×10^1, 5×10^4 1×10^1, 5×10^5 1×10^{-1} M. The membrane without the ionophore gave less than a Nernstian slope (ca. 40–44 mV/decade^{-1}).

The potentiometric selectivity coefficients were measured by the separate solution method with respect to the protonated phenylalanine ester (Fig. 1), which was chosen as a target ion due to its high electrode response in 0.01 M solution. The polymeric membrane displayed modest selectivity for (MePhe)·H^+ over different amino acid esters. This observed lack of selectivity may be attributed to insufficient preorganization of the macrocycle with an unsubstituted lower rim and/or shielding of the adamantane fragments.

In summary, we have developed a direct and effective synthesis of carboxylated adamantylcalixarenes with an enlarged hydrophobic cavity together with procedures for full and 1,3-selective lower rim alkylation of these acids. The compounds obtained promise to serve as molecular platforms for the design of calixarene receptors. The synthesis of conjugates of 3-carboxy-1-adamantylcalix[4]arene with α-amino acids has also been carried out. It has been shown that an ISE PVC membrane in the presence of glycine functionalized calix[4]arene **9a** displayed selectivity towards protonated amino acid esters in comparison with inorganic ions of groups I and II. However, the selectivity of the membrane was found to be low for amino acid esters. Future structural refinement of the calixarene hosts will be carried out in order to tune the selectivity with regards to amino acid derivatives.

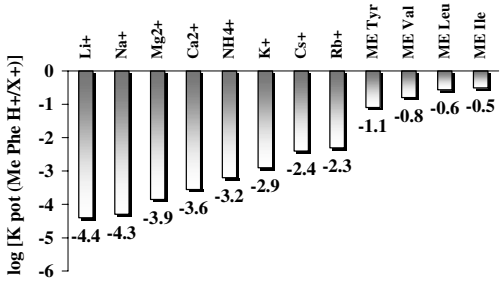

Figure 1. Potentiometric selectivity coefficients ($\log K$ (MePhe·H^+/X^+)) for a PVC membrane containing **9a**.

Acknowledgements

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13. General procedure for the synthesis of **3**: A mixture of *p*-H-calix[4]arene **1** (106 mg, 0.25 mmol), 3-*R*-1-adamantanol **2** (1.5 mmol) in equal volumes of TFA and $C_2H_4Cl_2$ (1.5/1.5 mL) and in the presence of a catalytic amount of CF_3SO_3H (0.02 mL for **3a**) was kept at 85–90 °C for 12 h in the case of **3a** or at 60–65 °C for 9 h in the case of **3b**. On completion of the reaction, the solvents were removed under reduced pressure. The resulting dark oil was treated with hot water and the precipitate formed was filtered. The crude product was washed with methanol (3×5 mL) followed by hot methanol (3×5 mL) and hexane (3×5 mL), and recrystallized from $CHCl_3$/methanol. *p*-(3-Carboxy-1-adamantyl)calix[4]arene **3a**. Yield 96%; mp > 360 °C. ^{1}H (300 MHz, d_6-DMSO), δ (ppm): 7.13 (s, 8H, Ar), 4.07 (brs, 4H, ArCH_2Ar), 3.67 (brs, 4H, ArCH_2Ar), 2.10 (s, 8H, CH^{Ad}), 1.60–1.90 (m, 48H, CH_2^{Ad}); ^{13}C NMR (75 MHz, d_6-DMSO), δ (ppm): δ C^{AdR}: 178.27 (COOH), 44.07 (C^{Ad}), 41.35 (C^{Ad}), 40.77 (C^{Ad}), 37.85 (C^{Ad}), 35.42 (C^{Ad}), 35.22 (C^{Ad}), 28.22 (C^{Ad}); δ C$^{calixarene\ skeleton}$: 147.00, 143.02, 128.09 (ArC), 125.15 (ArCH); 31.34 (ArCH_2Ar). Anal. Calcd for $C_{72}H_{80}O_{12}$ (1137.43): C, 76.03; H, 7.09. Found: C, 75.92; H, 7.11.
p-(3-Carboxymethyl-1-adamantyl)calix[4]arene **3b**. Yield 97%; mp 240–245 °C. ^{1}H (300 MHz, d_6-DMSO), δ (ppm): 7.10 (s, 8H, Ar), 4.14 (brs, 4H, ArCH_2Ar), 3.55 (brs, 4H, ArCH_2Ar), 2.08 (s, 8H, CH^{Ad}), 1.96 (s, 8H, CH_2COOH), 1.50–1.80 (m, 48H, CH_2^{Ad}); ^{13}C NMR (75 MHz, d_6-DMSO), δ (ppm): δ C^{AdR}: 172.51 (COOH), 48.28 (C^{Ad}), 48.18 (*C*H$_2$COOH), 41.42 (C^{Ad}), 40.72 (C^{Ad}), 35.94 (C^{Ad}), 35.48 (C^{Ad}), 32.93 (C^{Ad}), 28.75 (C^{Ad}); δ C$^{calixarene\ skeleton}$: 146.84, 143.44, 128.12 (ArC), 125.11 (ArCH); 31.22 (ArCH_2Ar). Anal. Calcd for $C_{76}H_{88}O_{12}$ (1193.54): C, 76.48; H, 7.43. Found: C, 76.29; H, 7.25.
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16. 25, 27-Dipropoxy-*p*-(3-carboxy-1-adamantyl)calix[4]arene **6a**. Yield 90%; mp 265–269 °C. ^{1}H (300 MHz, d_6-DMSO), δ (ppm): 8.04 (s, 2H, OH), 7.04 (s, 4H, Ar), 7.01 (s, 4H, Ar), 4.15 (d, J = 12.3 Hz, 4H, ArCH_2Ar), 3.98 (t, 4H, OCH_2CH$_2$CH$_3$), 3.45 (d, J = 12.3 Hz, 4H, ArCH_2Ar), 2.15–1.55 (m, 8H, CH^{Ad} + m, 48H, CH_2^{Ad} + 4H, OCH$_2$CH_2CH$_3$), 1.30 (t, 6H, OCH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, d_6-DMSO), δ (ppm): δ C^{AdR}: 178.48, 178.32 (*C*OOH), 44.25, 43.72 (C^{Ad}), 42.02, 40.88 (C^{Ad}), 41.78 (C^{Ad}), 37.98, 37.87 (C^{Ad}), 35.71 (C^{Ad}), 35.40 (C^{Ad}), 35.33 (C^{Ad}), 35.17 (C^{Ad}), 28.35 (C^{Ad}), 28.26 (C^{Ad});δ C$^{calixarene\ skeleton}$: 150.62, 149.89, 146.37, 140.83, 133.19, 127.53 (ArC), 125.24, 124.90 (ArCH); 31.31 (ArCH_2Ar); δ C$^{lower\ rim\ substituents}$: 77.95 (O*C*H$_2CH_2CH_3$), 23.15 (OCH$_2$*C*H$_2CH_3$), 11.00 (OCH$_2CH_2$*C*H$_3$). Anal. Calcd for $C_{78}H_{92}O_{12}$ (1221.60): C, 76.69; H, 7.59. Found: C, 76.28; H, 7.35.
25,27-Dibutoxy-*p*-(3-carboxymethyl-1-adamantyl)calix[4]-arene **6b**. Yield 81%; mp 202–205 °C. ^{1}H (300 MHz, $CDCl_3$), δ (ppm): 8.10 (s, 2H, OH), 6.99 (s, 4H, Ar), 6.83 (s, 4H, Ar), 4.30 (d, J = 14.2, 4H, ArCH_2Ar), 3.98 (t, 4H, OCH_2CH$_2$CH$_2$CH$_3$), 3.32 (d, J = 14.2, 4H, ArCH_2Ar), 2.25–1.95 (m, 8H, CH_2CO + 8H, CH^{Ad}), 1.50–1.90 (m, 48H, CH_2^{Ad} + 8H, OCH$_2$CH_2CH_2CH$_3$), 1.04 (t, 6H, OCH$_2$CH$_2$CH$_2$CH_3). Anal. Calcd for $C_{84}H_{104}O_{12}$ (1305.76): C, 77.27; H, 8.03. Found: C, 76.85; H, 7.79.
17. 25,26,27,28-Tetrabutoxy-*p*-(3-carboxy-1-adamantyl)calix[4]-arene **7a**. Yield 72%; mp 239–242 °C. ^{1}H (300 MHz, $CDCl_3$), δ (ppm): 6.76 (s, 8H, Ar), 4.42 (d, J = 13.9 Hz, 4H, ArCH_2Ar), 3.85 (t, 8H, OCH_2CH$_2$CH$_2$CH$_3$), 3.12 (d, J = 13.9 Hz, 4H, ArCH_2Ar), 1.44–2.11 (m, 8H, CH^{Ad} + 48H, CH_2^{Ad} + 16H, OCH$_2$CH_2CH_2CH$_3$), 1.01 (t, 12H, OCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, d_6-DMSO), δ (ppm): δ C^{AdR}: 178.30 (*C*OOH), 43.94 (C^{Ad}), 42.15 (C^{Ad}), 40.75 (C^{Ad}), 38.00 (C^{Ad}), 35.37 (C^{Ad}), 35.27 (C^{Ad}), 28.29 (C^{Ad}); δ C$^{calixarene\ skeleton}$: 153.24, 143.08, 133.44 (ArC), 124.23 (ArCH); 30.07 (ArCH_2Ar); δ C$^{lower\ rim\ substituents}$: 74.79 (O*C*H$_2CH_2CH_2CH_3$), 32.08 (OCH$_2$*C*H$_2CH_2CH_3$), 19.03 (OCH$_2CH_2$*C*H$_2CH_3$), 14.03 (OCH$_2CH_2CH_2$*C*H$_3$). Anal. Calcd for $C_{88}H_{112}O_{12}$ (1361.87): C, 77.61; H, 8.29. Found: C, 77.15; H, 7.90.
25,26,27,28-Tetrabutoxy-*p*-(3-carboxymethyl-1-adamantyl)-calix[4]arene **7b**. Yield 73%; mp 188–193 °C. ^{1}H (300 MHz, $CDCl_3$), δ (ppm): 6.76 (s, 8H, Ar), 4.42 (d, J = 13.7 Hz, 4H, ArCH_2Ar), 3.85 (t, 8H, OCH_2CH$_2$CH$_2$CH$_3$), 3.14 (d, J = 13.7 Hz, 4H, ArCH_2Ar), 2.15 (s, 8H, CH^{Ad}), 1.96 (s, 8H, *C*H$_2$COOH), 1.43–1.80 (m, 48H, CH_2^{Ad} + 16H, OCH$_2$CH_2CH_2CH$_3$), 1.01 (t, 12H, OCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): δ C^{AdR}: 178.27 (*C*OOH), 48.61* (C^{Ad}), 46.38* (*C*H$_2$CO), 43.13 (C^{Ad}), 41.96 (C^{Ad}), 36.12 (C^{Ad}), 35.86 (C^{Ad}), 33.70 (C^{Ad}), 29.26 (C^{Ad}); δ C$^{calixarene\ skeleton}$: 153.81, 143.40, 133.90(ArC), 124.31 (ArCH); 30.95 (ArCH_2Ar); δ C$^{lower\ rim\ substituents}$: 75.15 (O*C*H$_2CH_2CH_2CH_3$), 32.32 (OCH$_2$*C*H$_2CH_2CH_3$), 19.33 (OCH$_2CH_2$*C*H$_2CH_3$), 14.12 (OCH$_2CH_2CH_2$*C*H$_3$). *—assignments may be interchanged. Anal. Calcd for C_{92} H_{120} O_{12} (1417.98): C, 77.93; H, 8.53. Found: C, 77.45; H, 8.06.
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23. *p*-[3-(*N*-Methoxycarbonylmethyl)carbamoyl-1-adamantyl]-calix[4]arene **9a**. Yield 77%; mp 220–230 °C (decomp.). ^{1}H (300 MHz, $CDCl_3$), δ (ppm): 10.32 (s, 4H, OH), 7.01 (s, 8H, Ar), 6.31 (t, J = 6.0 Hz, 4H, NH), 4.24 (d, J = 13.4 Hz, 4H, ArCH_2Ar), 3.98 (d, J = 5.2 Hz, 8H, NHCH_2), 3.71 (s, 12H, COCH_3), 3.48 (d, J = 13.4 Hz, 4H, ArCH_2Ar), 2.28 (brs, 8H, CH^{Ad}), 1.60–1.95 (m, 48H, CH_2^{Ad}); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): δ C^{AdR}: 177.66 (*C*OOCH$_3$), 170.56 (CONH), 52.11 (COO*C*H$_3$), 44.87 (C^{Ad}), 41.90 (C^{Ad}), 41.60 (NH*C*H$_2$ CO), 41.02 (C^{Ad}), 38.11 (C^{Ad}),

35.94 (C^{Ad}), 35.43 (C^{Ad}), 28.66 (C^{Ad}); δ $C^{calixarene\ skeleton}$: 146.85, 143.22, 127.73 (ArC), 125.40 (ArCH); 32.44 (Ar*C*H_2Ar). Anal. Calcd for $C_{84}H_{100}N_4O_{16}$ (1421.75): C, 70.96; H, 7.09; N, 3.94. Found: C, 70.49; H, 6.90; N, 3.83.

p-[3-(*N*-Methoxycarbonyl(phenylmethyl)methyl)carbamoyl-1-adamantyl]calix[4]arene **9b**. Yield 81%; mp 186–190 °C (decomp.). ^{1}H (300 MHz, $CDCl_3$), δ (ppm): 7.25–7.05 (m, 20H, Ph), 7.02 (s, 8H, Ar), 6.12 (d, J = 9.1 Hz, 4H, NH), 4.86 (m, CH, 4H), 4.28 (d, J = 12.7 Hz, 4H, ArC*H*$_2$Ar), 3.73 (s, 12H, $COCH_3$), 3.52 (d, J = 12.7 Hz, 4H, ArC*H*$_2$Ar), 3.12 (m, 8H, C*H*$_2$Ph), 2.20 (brs, 8H, CH^{Ad}), 1.60–1.95 (m, 48H, CH_2^{Ad}); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): δ C^{AdR}: 176.68 (*C*$OOCH_3$), 172.04 (CONH), 135.82 (C^{Ph}), 129.11 (CH^{Ph}), 128.30 (CH^{Ph}), 126.93 (CH^{Ph}), 52.59 (COO*C*H_3), 52.12 (NHCH), 44.78 (C^{Ad}), 41.94 (C^{Ad}), 41.62* (Ph*C*H_2), 41.41* (C^{Ad}), 38.13 (C^{Ad}), 36.01 (C^{Ad}), 35.32 (C^{Ad}), 28.54 (C^{Ad}); δ $C^{calixarene\ skeleton}$: 146.78, 143.17, 127.62 (ArC), 125.39 (ArCH); 32.45 (Ar*C*H_2Ar). *—assignments may be interchanged. Anal. Calcd for $C_{112}H_{124}N_4O_{16}$ (1782.25): C, 75.48; H, 7.01; N, 3.14. Found: C, 75.11; H, 6.83; N, 3.05.

24. The procedure for the preparation of the polymeric membrane was as follows: PVC (62 mg, an average polymerization degree of 70), plasticizer *o*-NPOE (124 mg), the calixarene neutral carrier **9a** (10 mg) and $NaBPh_4$ (4 mg) were mixed and dissolved in THF (1.5 mL). A semi-transparent flexible membrane of thickness 0.3–0.4 mm was obtained after the solvent was allowed to evaporate at rt over a period of 24 h. The PVC membrane electrodes were pre-conditioned by immersion in a 0.01 M (ME Phe)·HCl solution at least 10 h prior to use. The membrane electrochemical activity was investigated by measuring the EMF of the following electrochemical cell at ambient temperature: Ag, AgCl|int. soln. (1×10^{-1}M (ME Phe). HCl)|modified PVC membrane|sample|KCl (satd)|AgCl, Ag.