Amphiphilic and cation-complexing compounds based on peptidoamines

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The synthesis of different types of amphiphilic compounds containing peptidoamine groups leads to surfactants with original properties such as the ability to coordinate metal ions. Water soluble acylcarcinine and alkylamidocarnosine surfactants are compared and the preparation of a silyloxyalkylamidocarnosine is described. The latter can be copolymerised with tetraalkoxysilanes to yield amphipathic organo-mineral solids that are also good ligands for metal cations.

We have been interested for some time in peptidoamines, a generic term describing pseudo-oligopeptides. Amongst these, compounds comprising an imidazole group stemming from histidine or histamine,[1,2] such as carcinine[3] and carnosine,[4] are of special interest. When they are connected to a hydrophobic moiety the resulting compounds generally show surfactant properties. We have indeed found that lipo-oligopeptide-like structures are surface active;[5] in the same manner, a peptidoamine group may represent the hydrophilic part in this type of molecule. Moreover, amphiphilic molecules of this type containing a pseudopeptide are likely to complex metal cations[6] and to have anti-oxidative properties.[7] These features are due to the presence of a pseudopeptide moiety containing an imidazole ring.[8] We have therefore synthesised surfactants incorporating peptidoamines as polar headgroups as well as a hydrophobic part.[9]

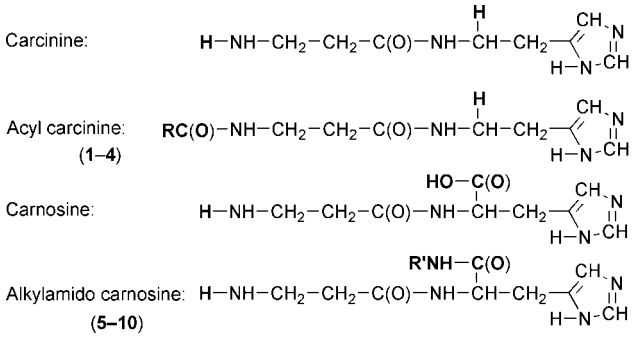
Depending on the properties of the products initially produced, we have modified the structures in order to improve their complexing and surfactant characteristics. Following this procedure, two series of molecular surfactants, containing either a perhydrogenated or a perfluorinated alkyl chain as the hydrophobic portion, have been prepared with the aim of finding the most appropriate structures for grafting onto a solid support. The grafted silica, bearing a peptidoamine as the hydrophilic group, constitutes a second type of amphiphilic material.

For the preparation of the molecular surfactants, the alkyl chains are introduced in the form of fatty acids or amines, linked to the rest of the molecule by an amide bond. The silica compounds have been prepared starting from 3-(triethoxysilyl) propylamine (TESPA) to which carnosine is linked by amidification *via* the carboxyl group of its histidine moiety.

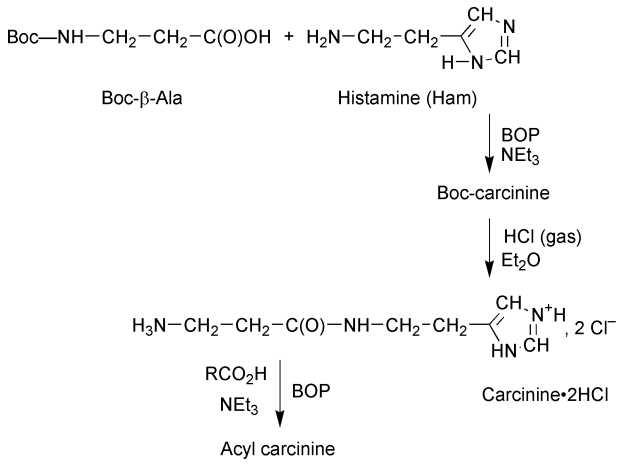
Results and discussion

Synthesis of acyl and perfluoroacyl carcinines

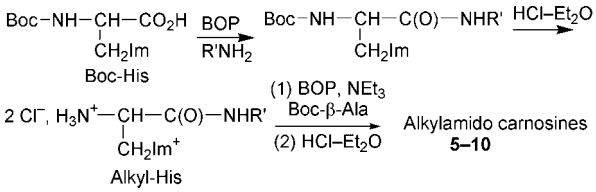
Carcinine and its analogues **1**–**4** (Scheme 1) have been prepared following classical methods that were modified in order to optimise the yields of the desired pseudopeptide derivatives. The first synthesis of carcinine was described by Arnould and Frentz.[10] By using a methodology from the procedure indicated in this article, we have been able to improve considerably the yields of the preparation. Starting from Boc-*β*-alanine and histamine, the coupling reaction is achieved by activation with BOP [benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate] in chloroform solution. The Boc protecting group is then hydrolysed *in situ* by treatment with hydrochloric acid in ether, leading to the solid product with an overall yield of 85%. The same procedure has been used to synthesise other pseudopeptide derivatives; in all these cases yields are excellent.[11] The coupling reaction with the hydrophobic moiety is carried out directly with the pseudopeptide



Scheme 1



Scheme 2

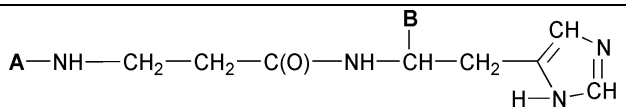


Scheme 3

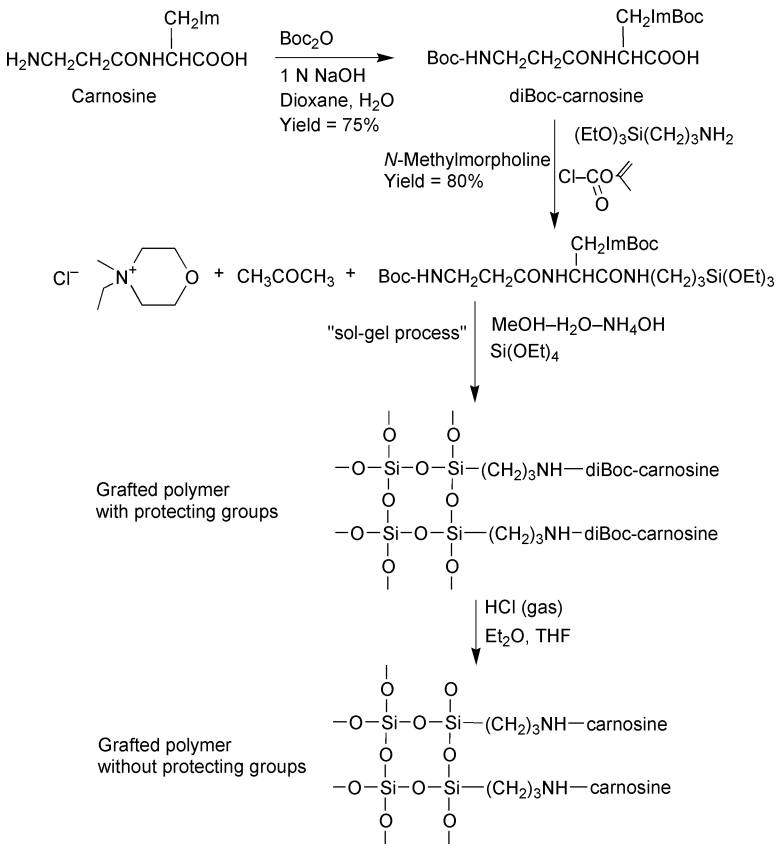
obtained. The fatty acids, both perhydrogenated and perfluorinated, are activated with BOP as the coupling agent (Scheme 2).

The results of complexation studies on compounds **1**, **2**, and **3** (Table 1) with the Cu^{2+} cation reveal a very low capacity of these molecules to complex the divalent copper ion. It seems as if these structures are less appropriate for the complexation of metal cations as compared with free carcinine and its derivatives, which have been proven to be good ligands for ions

Table 1 Amphipathic compounds: acyl carcinines, alkylamido carnosines and silyloxyalkylamido carnosines



	A	B	Yield (%)	CMC/10^4 mol L^{-1}
1	$C_5F_{11}CF{=}CH{-}C(O)$	H	61	56
2	$C_7F_{15}CF{=}CH{-}C(O)$	H	74	7.5
3	$H(CH_2)_9{-}C(O)$	H	65	77
4	$H(CH_2)_{11}{-}C(O)$	H	73	6.8
5	H	$C(O){-}NH{-}(CH_2)_8H$	84	—
6	H	$C(O){-}NH{-}(CH_2)_{10}H$	80	95
7	H	$C(O){-}NH{-}(CH_2)_{14}H$	81	—
8	H	$C(O){-}NH{-}C_2H_4C_6F_{13}$	67	72
9	H	$C(O){-}NH{-}C_2H_4C_8F_{17}$	68	9.2
10	H	$C(O){-}NH{-}(CH_2)_3SiOEt_3$	79	—



Scheme 4

such as Zn^{2+} or Cu^{2+} in the studies of Henry *et al.*[8] It has been shown by these authors that the terminal amino group is strongly implicated in the formation of the metal complexes.

Our first synthetic approach using the amino group to create a link with the hydrophobic part *via* a peptide bond thus leads to surfactants in which the electron-donor capacity of the corresponding nitrogen atom is largely diminished due to the carboxyl moiety in the vicinity. In order to preserve their complexing ability it seems necessary therefore to keep a free terminal amino group in the structure of the surface-active molecules.

Synthesis of alkyl and perfluoroalkylamido carnosines

These considerations have led us to substitute carcinine for carnosine in the molecular structure, thereby allowing us to link the hydrophobic side-chain in the form of an alkyl amine to a carboxyl group, thus leaving the terminal amino group free for the complexation of cations. Hence the peptide part of the molecule should have similar coordinating properties to a pseudocarcinine (Scheme 1) and show comparable surfactant characteristics.

The synthetic pathway to these derivatives starts from carnosine protected by a Boc moiety on the terminal amino group; the coupling with the hydrophobic alkylamine is achieved by activation with BOP (Scheme 3).

The linkage of the hydrophobic chain *via* an amide bond in the alkylamido carnosines should enhance the hydrophilic character of these surfactants as compared to acyl carcinines and increase their solubility in water without affecting their coordinating ability. The experimental results confirm this hypothesis. Indeed, the critical micellar concentrations (CMC) of acyl carcinine with a comparable hydrophobic part (*e.g.* compounds **1** or **2**) are lower than those of the corresponding alkylamido carnosines **8** or **9**, respectively (Table 1).

As for the coordinating properties, measurements with the copper(II) ion give evidence for the excellent ligand characteristics of these molecules, which are comparable to those of unsubstituted carcinine.

Synthesis of silyloxyalkylamido carnosine

These observations have led us to prepare an amphiphilic and coordinating material based on the alkylamido carnosine structure. By introducing a silyloxy group into the structure, we were able to synthesise in a further step a supported amphipathic coordinating material by sol–gel copolymerisation (Scheme 4).

The synthesis of the silyloxyalkylamido carnosines starts with the preparation of a monomer containing a trialkoxysilane group. The monomer is obtained by amide coupling between the amino group of 3-aminopropyltriethoxysilane (TESPA) and the carboxyl group of carnosine. The amino groups of the latter (terminal and imidazole NH_2) have to be protected by Boc substituents. In order to avoid solvolysis of the triethoxysilane moiety during the synthesis, which would lead to uncontrolled polymerisation, it is necessary to preclude the introduction of water or alcohols, even in trace amounts. We have therefore chosen isopropenyl chloroformiate as the coupling agent, yielding easily removable by-products such as carbon dioxide and acetone during the reaction. An excess of the agent itself can easily be evaporated under reduced pressure. Hydrochloric acid generated during the synthesis is trapped with *N*-methylmorpholine; the hydrochloride formed is removed by treatment with diethyl ether (Scheme 4).

The monomers are obtained in good yields. They are subsequently polymerised following the so-called sol–gel procedure,[12] which consists of a copolymerisation under controlled conditions at ambient temperature in the presence of a tetraalkoxysilane, in this case tetraethoxysilane (TEOS), using ethanol as co-solvent and ammonia in a catalytic amount.[13] The ethanol, water, and ammonia are added simultaneously to the TEOS–monomer mixture to avoid any premature reaction.

The copolymer precipitates several hours after mixing. The solvents are slowly evaporated; after 5 days, a dry white solid is obtained, which is washed thoroughly with dichloromethane and methanol. The product was analysed by ^{13}C and ^{29}Si solid state NMR.

The Boc protecting groups are removed from the polymeric material by treatment with gaseous HCl. Removal from the monomer implies the risk of premature uncontrolled polymerisation. The removal of the Boc groups is verified by the disappearance of its characteristic absorption ($\nu_{CO} = 1680$ cm^{-1}) in the IR spectrum of the product.

Coordination to copper(II) ions

In order to verify the ability of the amphiphilic compounds described above to complex divalent metal cations, we have added dilute (10^{-4} M) copper nitrate in 0.01 molar KNO_3 to solutions or, in the case of substituted silica, to suspensions of the amphiphiles and monitored the concentration of free copper by means of an ion-selective electrode (ISE) at constant pH. As shown in Fig. 1(a), in the presence of silica-grafted carnosine, the electrode potential remains stable at a

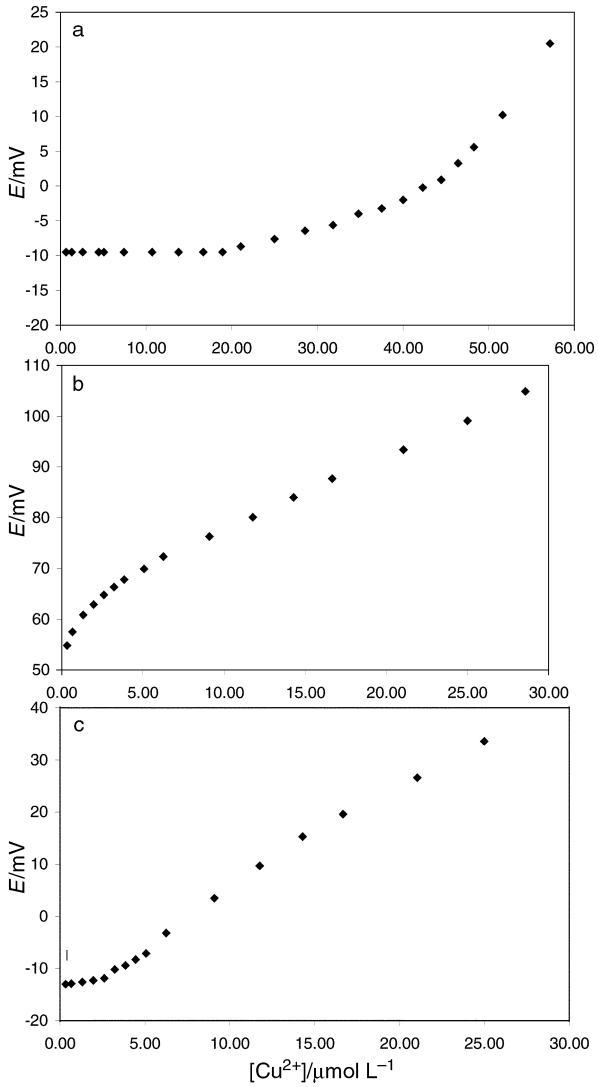


Fig. 1 Ion-selective electrode measurements of copper(II) ion activity in the presence of silica-bound carnosine (a), decanoylcarcinine **3** (b) and decylamidocarnosine **6** (c) as a function of total copper concentration. $T = 25\,°C$, pH = 6.

low value up to a total copper concentration of 20 μM. This means that all added copper in this region is strongly bound to the ligand until all coordination sites at the surface of the silica are saturated with metal ions. Above this value, the activity of free Cu^{2+} ions increases with the total copper concentration.

The situation is quite different in the presence of decylcarcinine [Fig. 1(b)]. The concentration of free Cu^{2+} rises immediately as the copper concentration is increased, giving evidence for the very low coordinating capacity of this compound in which the terminal amino group is engaged in an amide bond. When this group is present, however, as in decyl carnosine [Fig. 1(c)] the copper ions are bound in a similar way as above.

Conclusion

A simple and efficient method for the synthesis of perhydrogenated or perfluorinated lipo-peptidoamines, like carcinine or carnosine, is reported. It gives access to two kinds of original products: amphiphilic molecular compounds and an amphiphilic material constituted of grafted silica, obtained by copolymerisation of new carnosine silane derivatives. We are presently examining whether this approach can be applied to other oligopeptides.

It has been shown that the capacity of amphiphilic compounds based on peptidoamines to complex divalent transition metal ions and in particular copper(II) depends to a large extent on the presence of free amino groups in their structure. By choosing the appropriate peptidoamine (*e.g.* carnosine instead of carcinine) as the starting material for the syntheses the coordinating capacity of the products could be significantly enhanced. The immobilisation, in a second step, of the ligands in a silica-like structure by controlled polymerisation of appropriate amphiphilic monomers has yielded original organo-mineral compounds in which the affinity of the peptidoamine groups for divalent cations is preserved. Further studies on the coordination of these products to copper and other cations are under way and will be published later.

Experimental

Experimental protocols

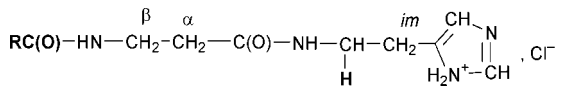
All solvents were reagent grade and used without further purification. The progress of reactions and the purity of products were evaluated on thin layer silica gel chromatographic (TLC) plates (Merck, Kieselgel 60 F_{254}) with ethyl acetate–hexane or chloroform–methanol mixtures as eluents.

Purification was carried out by flash silica gel column chromatography with the same eluents. Melting points were determined with an electronic apparatus (Electrothermal) and have not been corrected. The proton (^1H) and fluorine (^{19}F) NMR spectra were recorded on Bruker AM 400 or AC 250 spectrometers. The chemical shifts, δ, are reported downfield from internal tetramethylsilane (TMS) and $CFCl_3$, respectively. The IR spectra were recorded on Perkin–Elmer 580D or 1600 FTIR spectrometers. The elemental analyses were carried out at the Centre de Microanalyses du CNRS (Vernaison, France). They agree with the proposed structures and illustrative results are reported for some compounds.

Syntheses

Preparation of carcinine (*β*-alanyl-histamine). Boc-*β*-alanine (10 mmol) is dissolved in chloroform (50 mL) and 3 equiv. of diisopropylethylamine or triethylamine, 1 equiv. of histamine (Ham) and 1 equiv. of BOP are added to the solution. The mixture is stirred at room temperature for 12 h. The solvent is evaporated under reduced pressure. The crude residue is recovered in the form of a white paste. The removal of the Boc protecting group on the terminal amino group is achieved by slowly adding 20 mL of a 1 N HCl solution in diethyl ether to the crude product. The mixture is stirred at room temperature for 2 h. The product obtained is washed with four 50 mL portions of diethyl ether. The crude compound is extracted with boiling ethyl acetate to yield a white powder after filtration. It is recrystallised from methanol–ethyl acetate. Yield: 71% (white crystals). IR: ν_{NH} 3400–3250, ν_{CO} 1717, $\nu_{imidazole}$ 1620 cm^{-1}. NMR ^1H (D_2O): δ 2.67 ($CH_2\alpha$, t, $J = 7$), 2.97 (CH_{2im}, t, $J = 6.65$), 3.25 ($CH_2\beta$, t, $J = 7$) 3.53 (NCH_2, t, $J = 6.65$ Hz), 7.3 and 8.61 ($2CH_{im}$).

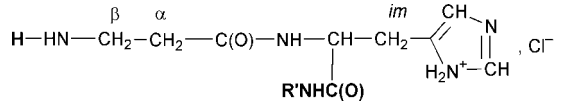
Preparation of acyl carcinines 1–4. The appropriate alkyl fatty acid (2.4 mmol) and 1 equiv. of BOP are added to a solution of carcinine · 2HCl (0.6 g) in acetonitrile (25 mL) and 1 g of diisopropylethylamine or triethylamine. The mixture is stirred at room temperature for 12 h. The precipitate is filtered off and washed with 10 mL of hot chloroform (3 times) and with 5 mL of cold distilled water. The product is a white powder, obtained in 61 to 74% yield (see Table 1). IR: ν_{NH} 3400–3200, ν_{CO} 1720 $\nu_{imidazole}$ 1620 cm^{-1}.



Perfluorinated surfactants.[14] **1**: (*Z*)-Perfluoro-2H-oct-2-enecarboxycarcinine · HCl, yield 0.8 g (61%) and **2**: (*Z*)-perfluoro-2H-dec-2-enecarboxycarcinine · HCl, yield 1.17 g (74%). IR: $\nu_{C=C}$ 1660 cm^{-1}; ^1H NMR (CD_3OD): δ 2.65 ($CH_2\alpha$, t, $J = 7$, 2.95 (CH_{2im}, t, $J = 7$, 3.30 ($CH_{2\beta}$, t, $J = 7$), 3.59 (NCH_2, t, $J = 7$, 6.00 (CF=CH, d, $J_{H\text{-}F} = 31$ Hz), 7.31 and 8.60 (2 CH_{im}), ^{19}F NMR (CD_3OD): δ −82 (CF_3, d, $J_{F\text{-}F} = 10$ Hz), −119 (CF_2C, m), −108 (CF, m), −127 to −123 [$(CF)_n$, m]. Elemental analysis for **2** ($C_{18}H_{15}F_{16}N_4O_2Cl$, MW = 658) calc. (found): C 32.82 (32.34); H 2.30 (2.19); N 8.50 (8.34); F 46.14 (45.98%).

Hydrogenated surfactants. **3**: Decylcarboxycarcinine · HCl, yield 0.6 g (65%) and **4**: dodecylcarboxycarcinine · HCl, yield 0.7 g (73%). ^1H NMR (CD_3OD): δ 0.95 (CH_3, t, $J = 6.5$), 1.17 [$(CH_2)_n$, m)], 1.47 (CH_2, m), 2.17 [$CH_2C(O)$, t, $J = 7.5$], 2.67 ($CH_2\alpha$, t, $J = 7$), 2.97 (CH_{2im}, t, $J = 7$), 3.30 ($CH_{2\beta}$, t, $J = 7$), 3.59 (NCH_2, t, $J = 7$ Hz), 7.31 and 8.60 (2 CH_{im}). Elemental analysis for **3** ($C_{18}H_{33}N_4O_2Cl$, MW = 372) calc. (found): C 57.97 (57.84); H 8.92 (8.59); N 15.02 (14.84%).

Preparation of alkylamido carnosines 5–9. *Preparation of aminoalkyl histidines.* One equivalent of the fatty amine RNH_2, 1 equiv. of BOP, and 2 equiv. of triethylamine are added to a solution of 3 mmol of Boc-His in acetonitrile (200 mL). The mixture is stirred at room temperature for 15 h. The precipitate is filtered off and washed three times with 10 mL of acetonitrile. The crude product is dissolved in ethyl acetate (120 mL), washed twice with 20 mL of a solution of 2 N HCl, 20 mL of brine and twice with 30 mL of a saturated solution of sodium bicarbonate. The organic phase is dried over magnesium sulfate and the solvent evaporated under reduced pressure. The products are white powders with melting points: Boc-His-NHC_8H_{17}: 146 °C; Boc-His-$NHC_{10}H_{21}$; 151 °C; Boc-His-$NHC_{14}H_{29}$: 158 °C; Boc-His-$NHC_2H_4C_6F_{13}$: 166 °C; Boc-His-$NHC_2H_4C_8F_{17}$: 171 °C.



Boc removal. The mixture of Boc-His-NHR (2.5 mmol) in THF (30 mL) is stirred at room temperature for 12 h with a saturated solution of HCl in anhydrous ether (40 mL). The solvents are evaporated under reduced pressure. The product

obtained is the dihydrochloride of His-NHR; it is used as such for the coupling step with Boc-β-Ala.

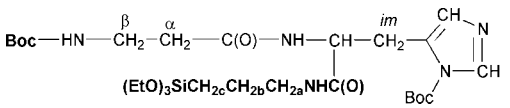
Preparation of BOC-β-Ala-His-NHR. One equivalent of the corresponding His-NH-R prepared above, 1 equiv. of BOP, and 4 equiv. of triethylamine are added to a solution of 2 mmol of Boc-β-Ala in acetonitrile (150 mL). The mixture is stirred at room temperature for 24 h. The precipitate is filtered off and washed three times with 10 mL of acetonitrile. The crude product is dissolved in ethyl acetate (120 mL), washed twice with 20 mL of a solution of 2 N HCl, 20 mL of brine and twice with 30 mL of a saturated solution of sodium bicarbonate. The organic phase is dried over magnesium sulfate and the solvent is evaporated under reduced pressure. The products are white powders; they are used directly for the synthesis of the corresponding aminoalkylamidocarnosine · 2HCl. The protecting groups are removed with a saturated solution of HCl in a similar way as described above for Boc-His-NHR. The aminoalkylamido carnosine dihydrochlorides are obtained as white powders. General spectroscopic characteristics: IR: ν_{NH} 3420–3270, ν_{CO} 1644, $\nu_{imidazole}$ 1543 cm^{-1}.

Hydrogenated surfactants. **5**: octylaminocarnosine · 2HCl, yield 0.76 g (84%); **6**: decylaminocarnosine · 2HCl, yield 0.7 g (80%); **7**: tetradecylaminocarnosine · 2HCl, yield 0.8 g (81%). ^{1}H NMR (CD_3OD): δ 0.90 (CH_3, t, $J = 7$), 1.30 [$(CH_2)_n$, m]), 1.50 (CH_2, m), 2.72 ($CH_2\alpha$, m), 3.15 (CH_{2im}, 1H, dd, $J = 6$ and 12), 3.20 ($CH_2\beta$ and NCH_2, t, $J = 4.5$), 3.25 (CH_{2im}, 1H, dd, $J = 4.5$ and 12 Hz), 4.75 (CH, m), 7.40 and 8.80 (2 CH_{im}, s). Elemental analysis for **5** ($C_{17}H_{33}N_5O_2Cl$, MW = 409) calc. (found): C 49.75 (49.64); H 8.11 (7.95); N 17.07 (17.64%).

Perfluorinated surfactants. **8**: 2*H*,2*H*,3*H*,3*H*-perfluorooctylaminocarnosine · 2HCl, yield 0.87 g (67%); **9**: 2*H*,2*H*,3*H*,3*H*-perfluorodecylaminocarnosine · 2HCl, yield 1.01 g (68%). ^{1}H NMR (CD_3OD): δ 2.65 ($CH_2\alpha$, t, $J = 7$), 2.95 (CH_{2im}, t, $J = 7$), 3.30 ($CH_{2\beta}$, t, $J = 7$), 3.59 (NCH_2, t, $J = 7$), 6.00 (CF=CH, d, $J_{H\text{-}F} = 31$ Hz), 7.31 and 8.60 (2 CH_{im}); ^{19}F NMR (CD_3OD): $\delta = -82$ (CF_3, d, $J_{F\text{-}F} = 10$ Hz), -119 (CF_2C, m), -108 (CF, m), -127 to -123 [$(CF_2)_n$, m]. Elemental analysis for **9** ($C_{19}H_{20}F_{17}N_5O_2Cl_2$, MW = 743) calc. (found): C 30.66 (30.45); H 2.71 (2.89); N 9.41(9.23); F 43.39 (42.59%).

Preparation of grafted silica. *Preparation of diBoc-carnosine*. Di-*tert*-butyl dicarbonate (0.04 mol, 2.2 equiv.) is added at 0 °C to a solution of 0.017 mol of carnosine in a mixture of 10 mL of water, 20 ml of dioxane and 10 ml of 1 N aqueous NaOH. After stirring for 30 min at room temperature, the solution is concentrated under reduced pressure to 50% of its initial volume and then 30 mL of ethyl acetate is added. The mixture is acidified with 1 N HCl at 5 °C to pH 2. The aqueous phase is extracted with ethyl acetate. The organic phase is dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue is thoroughly washed with Et_2O. IR: ν_{NH} 3200–3400, ν_{CO} 1655, ν_{CO} 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 and 1.60 [CH_3(Boc), s], 2.40 ($CH_2\alpha$, d, $J = 7$), 3.10 (CH_{2im}, 1H, dd, $J = 8$ and 16), 3.25 (CH_{2im}, 1H, dd, $J = 4.5$ and 16), 3.45 ($CH_2\beta$, m), 4.65 (CH, m), 5.25 (NH, m), 6.75 (NH, d, $J = 7$), 7.25 (CH_{im}, s), 8.15 (CH_{im}, s, 1H).

Preparation of the (triethoxysilyl)alkylamidocarnosine monomer. **10**: *N*-Methylmorpholine (0.01 mol) is added under argon to a solution of 0.01 mol of di-Boc-carnosine in 50 mL of tetrahydrofuran. After cooling the solution to -15 °C a mixture of 0.01 mol of isopropenyl chloroformiate and 0.01 mol of 3-aminopropyltriethoxysilane in 10 ml of THF is introduced into the reaction vessel. The solution is allowed to warm up to room temperature; after filtration of the precipitate the solution is evaporated under reduced pressure and the residue is washed with Et_2O to yield a white solid. IR: ν_{NH} 3200–3400, ν_{CO} 1655, ν_{CO} 1680 cm^{-1}. ^{1}H NMR (CD_3OD): δ 0.60 (CH_{2a}, t, $J = 6$), 1.35 (CH_3, t, $J = 9$), 1.50 [CH_3(BOC), s], 1.60 (CH_{2b}, m), 1.65 [CH_3(BOC), s], 2.50 ($CH_2\alpha$, m), 2.95 (CH_{2im}, dd, $J = 8$ and 16), 3.15 (CH_{2im}, dd, $J = 4.5$ and 16), 3.25 ($CH_2\beta$, m), 3.45 (CH_{2c}, m), 3.85 (CH_2, q, $J = 9$ Hz), 4.65 (CH, m), 5.60 (NH, m), 7.10 (NH, m), 7.30 (CH_{im}, s), 8.05 (CH_{im}, s).



Polymerisation. A mixture of 4.29 g of water, 22.47 g of ethanol and 0.22 g of NH_3 is introduced into a solution of 4.23 g of monomer diBoc-**10** in 6.82 g of tetraethoxysilane. The mixture is left at room temperature for 5 days, allowing the evaporation of the solvents. The solid is then washed with methanol and dichloromethane. IR: ν_{NH} 3200–3400 ν_{CO} 1655 ν_{CO} 1680 cm^{-1}. ^{13}C (solid) NMR: δ 10; 20; 30; 40; 120–140; 160; 175. ^{29}Si (solid) NMR: δ -110.

Removal of the Boc protecting group. HCl gas is introduced in a suspension of the polymer in Et_2O. The mixture is stirred for 12 h at room temperature. The solid is filtered and washed with Et_2O. ^{13}C (solid) NMR: δ 10; 20; 40; 120–140; 175. ^{29}Si (solid) NMR: δ -110.

Surface activity

The surface tension measurements were made either with a Dognon–Abribat or a Krüss K10T tensiometer using the Wilhelmy plate method in order to assess the critical micellar concentrations of the compounds from surface tension *vs.* concentration plots.

Aqueous solutions of the surfactants were prepared starting from stock solutions of known concentration by successive dilutions with distilled water. Their surface tension γ was measured at 25 °C after complete equilibration of the system. Each value is a mean of three successive measurements. The estimated error of the surface tension measurements is ± 1 mN m^{-1}.

Potentiometry

The coordination equilibria were investigated by potentiometric titrations in aqueous solution at a constant ionic strength of 0.01 mol L^{-1} (KNO_3) and $T = 298 \pm 1$ K by using a titration apparatus including a Radiometer PHM 240 precision digital ion-meter and a copper(II) ion-selective electrode. The pH was monitored permanently during the titration and adjusted if necessary by addition of base.

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