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Amphiphilic analogues of peptidoamines with perfluorinated side chains Synthesis and preliminary investigations of their surfactant and complexing abilities

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Abstract

A new synthetic pathway for preparing perfluorinated β-alanines is described. 2-Perfluoroalkyl-ethanols are oxidized, dehydrofluorinated, substituted with an azide group and finally hydrogenated with excellent yields. The C-perfluoroalkylated β-alanines obtained in this way are subsequently used as hydrophobic moieties for the synthesis of amphiphilic lipo-peptides and lipo-peptidoamines. The choice of the peptidoamine structure is justified by the anti-oxidative and complexing properties of natural analogues such as carcinine and carnosine. Measurements of the surface tension of aqueous solutions of the compounds synthesized reveal their surfactant properties. Potentiometric and spectroscopic investigations give evidence for their good ability to complex copper(II) ions in solution.

Keywords: Perfluoroalkyl-β-alanine; Perfluoroalkyl-peptidoamine; Surfactants; Critical concentration; Complexation

1. Introduction

Many biological applications use fluorinated organic compounds and chemical research in this field gives rise to numerous publications [1,2]. The surfactants pertaining to this family are of particular interest for the preparation of fluids capable to transport respiratory gases [3–5]. However, the high concentrations of oxygen supplied by these solutions may lead to the formation of toxic derivatives (peroxides, free radicals) [6] in amounts such that the natural defense mechanisms of the organism can no longer cope with them [7].

We have, therefore, attempted to solve this difficulty by synthesizing molecules bearing a perfluorinated hydrophobic chain which exhibit simultaneously surfactant and potentially anti-oxidative properties. Among the bio-protecting substances certain metal complexes of pseudopeptides of the peptidoamine type are known for their anti-oxidative action [8,9]. We have shown previously [10] that lipo-oligopeptide structures are surface active. The peptidoamines containing an imidazol moiety stemming from histidine or histamine structures [11–13], in particular carcinine [14] and carnosine [15,16] seemed to us the most promising. The structures of these two dipeptides are shown in Scheme 1.

Both contain the β-alanine moiety linked via a peptide bond either to histidine (in carnosine) or to histamine (in carcinine). We have described efficient syntheses of β-perfluoroalkyl-β-alanines previously [17]. These compounds may be used as hydrophobic junction modules in modular synthetic pathways [18,19]. In this paper we describe the preparation of carnosine and carcinine analogues starting from β-perfluoroalkyl-β-alanines, and the investigation of some of their physico-chemical properties. The new compounds are surfactants and good ligands for divalent cations such as copper(II).

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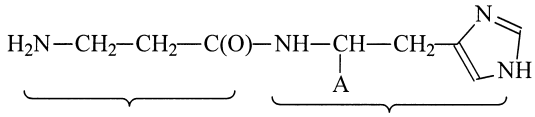


A = CO_2H : carnosine [β-alanyl-histidine (β-Ala-His)]

A = H : carcinine [β-alanyl-histamine (β-Ala-Ham)]

Scheme 1. Structures of carnosine and carcinine.

2. Results and discussion

2.1. Syntheses

We have prepared three series of compounds (Schemes 2 and 3). They are amphiphilic pseudopeptide analogues of the lipo-oligopeptide (series **3AA*n***) or the lipo-peptidoamine type (series **1B*n*** and **2A*n***). The latter derive either from carnosine (series **1B*n***) or from carcinine (series **2A*n***). They contain a hydrophobic perfluoroalkyl chain of ***n*** carbon atoms, which is attached to the peptidoamine via a C–C bond (Scheme 2).

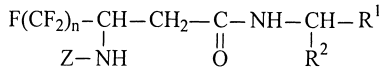
The synthesis of these compounds has been achieved the following reaction pathways indicated in Scheme 3, starting from commercially available 2-perfluoroalkyl-ethanols **4**. In previous publications, we had described the first steps leading to compounds **8** [17] and the subsequent preparation of the β-perfluoroalkyl-β-alanines derived from intermediates similar to **9** [20]. In this paper, we complete the description of the syntheses with the preparation of the *N*-protected-β-perfluoroalkyl-β-alanines **10**. The latter have been used to prepare the desired surfactants in a further step.

For all compounds of structure **10**, derivatives protected by the benzyloxycarbonyl group **Z** on the nitrogen atoms have been synthesized in order to prepare the series of single-chain surfactants following classical methods [21,22]. In order to optimize the experimental conditions for the coupling reaction, we have started with the condensation of alanine methyl ester, a non-functional aminoacid derivative, on the surfactant precursors. We have used different activators for these couplings which are classically employed in peptide syntheses: dicyclohexylcarbodiimide (DCC) [21,22]; mixed anhydrides in combination with isopropenyl chloroformate [22,23], and benzo-triazolyl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) [24,25]. After the usual deprotection steps,

Table 1
Yields of coupling reactions with three different activation agents[a]

Compound	*n*	R^1	R^2	Yield (%)		
				BOP	DCC	Mixed anhydrides
Z-3AA5-Me	5	CH_3	CO_2Me	80	75	45
Z-3AA7-Me	7	CH_3	CO_2Me	80	65	40
Z-3AA9-Me	9	CH_3	CO_2Me	60	55	25
Z-2A5	5	CH_2-Im	H	75	55	40
Z-2A7	7	CH_2-Im	H	70	45	30
Z-2A9	9	CH_2-Im	H	75	50	–
Z-1B5-Me	5	CH_2-Im	CO_2Me	65	40	–
Z-1B7Me	7	CH_2-Im	CO_2Me	60	40	–

[a] Structure of the products:



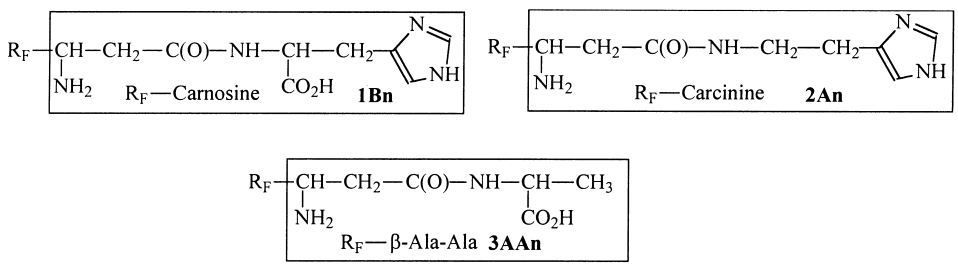
.

these reactions yield the series of lipo-pseudopeptides **3AA*n***. The activation via mixed anhydrides proves to be less efficient than the other methods. For the reaction with histidine (series **1B*n***) or with histamine (series **2A*n***), we have, therefore, chosen BOP or DCC as coupling agents. For all these syntheses, the purification of the products is rather difficult so that the yields of pure products do not exceed 50–75% (Table 1).

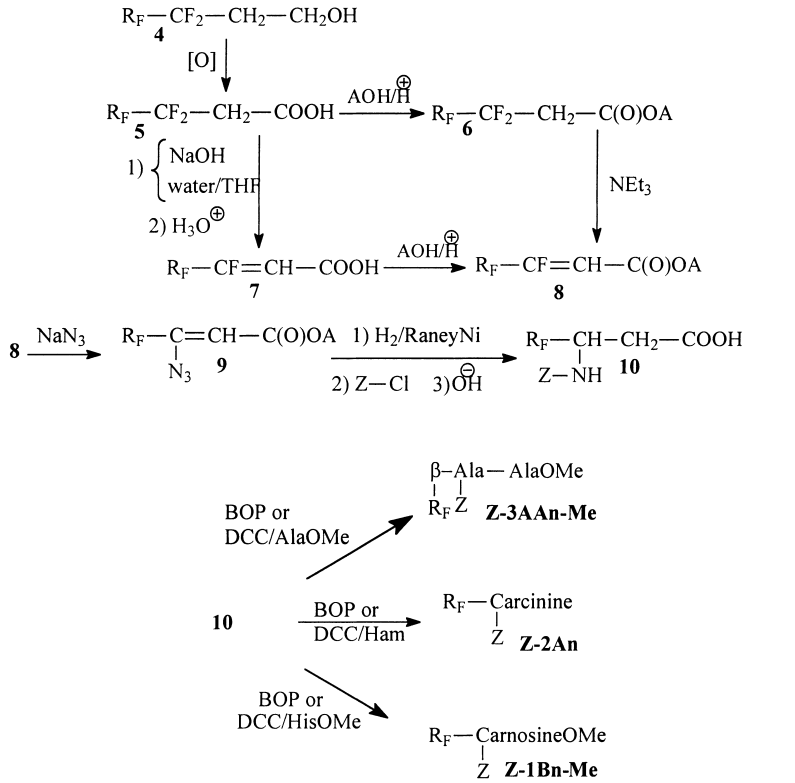
The hydrogenolysis of the above intermediates with a Pd/C catalyst leads to the unprotected compounds **3AA*n*, 1B*n*** et **2A*n*** (Table 2) via the removal of the benzyloxy-carbonyl group **Z** from the terminal amino group (Scheme 4). In this way, we readily obtain the amphiphilic analogues of carcinine (series **2A*n***).

While the hydrogenolysis yields the carcinine analogues immediately by removing the only protecting group on the amine function, the other series of products (**3AA*n*** and **1B*n***) still bear an ester group on the carboxyl function. It may be hydrolyzed under usual basic conditions (Scheme 5) to yield the series of lipopeptide surfactants (**3AA*n***) and that of the R_F*n*-carnosine type (**1B*n***). The results are summarized in Table 3.

The syntheses described above have satisfactory yields and the methods used should allow an easy scaling up of the preparations. We have prepared a derivative of carnosine (**1B5**) as well as two lipo-oligopeptides **3AA5** and **3AA7** in sufficient quantity (several grams) to investigate the surface



Scheme 2. Structures of amphiphilic lipo-oligopeptides, analogues of carnosine and carcinine. Single-chain surfactants.



Ham = Histamine; A = CH_3, C_2H_5; R_F = C_5F_{11}, C_7F_{15}, C_9F_{19}; Z = $C_6H_5OC(O)$

Scheme 3. Synthesis of amphiphilic perfluoroalkyl-pseudopeptides.

Table 2
Hydrogenolytic removal of the *N*-carbobenzyloxy group **Z**[a]

Compound	*n*	R^1	R^2	Yield (%)
3AA5-Me	5	CH_3	CO_2CH_3	78
3AA7-Me	7	CH_3	CO_2CH_3	75
3AA9-Me	9	CH_3	CO_2CH_3	58
2A5[b]	5	CH_2-Im[c]	H	80
2A7[b]	7	CH_2-Im[c]	H	85
2A9[b]	9	CH_2-Im[c]	H	50
1B5-Me	5	CH_2-Im[c]	CO_2CH_3	65
1B7-Me	7	CH_2-Im[c]	CO_2CH_3	75

[a] Structures of products **2AA*n*—Me**, **1A*n***, **1B*n*-Me**:

$$F(CF_2)_n-\underset{\underset{NH_2}{|}}{CH}-CH_2-\underset{\underset{O}{||}}{C}-NH-\underset{\underset{R^2}{|}}{CH}-R^1$$

[b] R_F*n*-carcinine.
[c] Im = imidazole.

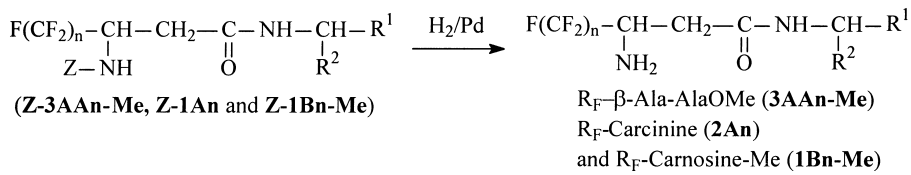
activity of these compounds and the ability of surfactant **1B5** to complex the divalent copper ion.

3. Preliminary studies of physico-chemical properties

3.1. Surface activity

We have measured the surface tension γ of aqueous solutions of the compounds mentioned above at different concentrations *C*. The curves $\gamma = f$ (log C) are shown in Fig. 1.

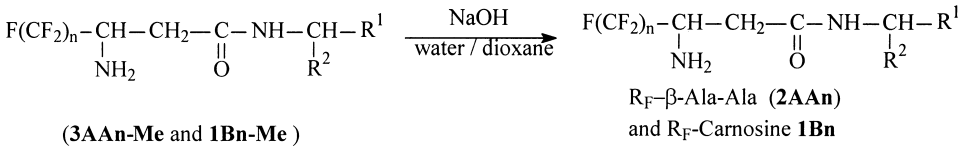
The intersection of the linearly decreasing and the horizontal branch of each curve yields immediately the value of the CMC and the minimal surface tension γ_{CMC}. The intersecting solid lines shown in Fig. 1 are the result of a linear



(**Z-3AAn-Me, Z-1An** and **Z-1Bn-Me**)

R_F–β-Ala-AlaOMe (**3AAn-Me**)
R_F-Carcinine (**2An**)
and R_F-Carnosine-Me (**1Bn-Me**)

Scheme 4. Hydrogenolysis of protecting groups.

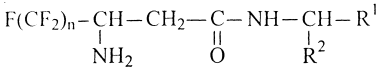


Scheme 5. Hydrolysis of protecting groups.

Table 3
Results of the hydrolysis of the methyl ester group[a]

Compound	*n*	R′	R^1	R^2	Analogue	Yield (%)
3AA5H	5	H	CH_3	CO_2H	–	80
3AA7H	7	H	CH_3	CO_2H	–	85
3AA9H	9	H	CH_3	CO_2H	–	55
1B5H[b]	5	H	CH_2-Im	CO_2H	R_F5-carnosine	75
1B7H[b]	7	H	CH_2-Im	CO_2H	R_F7-carnosine	80

[a] Structure of the products:



[b] R_F*n*-carnosine.

regression calculation based on the corresponding experimental values.

Table 4 summarizes the results of these measurements. For comparison, we have included the values obtained by other authors [10,19,26,27] for compounds with structures similar to the above surfactants. It may be noticed that the γ_{CMC}-values of the perfluorinated amphiphilic products synthesized in this work are very close to those usually found for this type of compounds.

The surfactants prepared by Hamdoune and coworkers [10,27] represent a series of non-ionic lipo-oligopeptide amphiphiles bearing a perfluorinated alkyl chain. These products are rather water soluble and their γ_{CMC}-values range from 16 to 19 mN/m [27,28]. For these non-ionic perfluoro-lipo-peptides the addition of two CF_2 groups leads to a decrease of the CMC by a factor of about 10. In a similar way, the increase in chain length by one CF_2 group in the non-ionic surfactants synthesized by Achilefu and coworkers [26,29] lowers the CMC by a factor of 3. The properties of the new compounds compare favorably with these observations. The decrease of the CMC between the perfluoro-lipo-peptides **3AA5** and **3AA7** is also of the order of 10. The derivative **1B5** bears the same hydrophobic chain as **3AA5** (Scheme 6) and the two compounds could, therefore, be

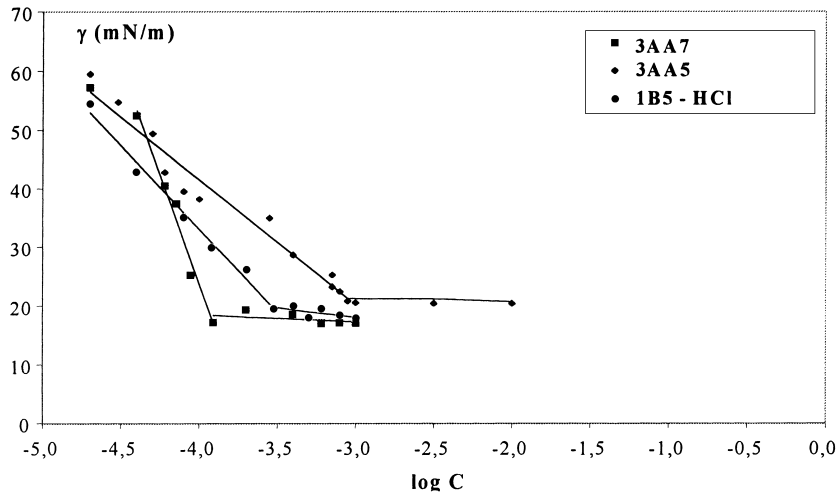
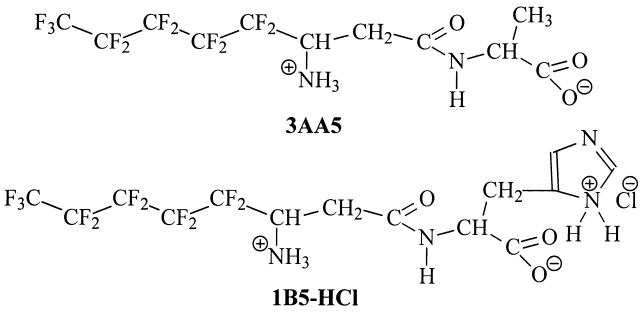


Fig. 1. Surface tension measurements for surfactants **1B5-HCl** (•), **3AA5** (◆), and **3AA7** (■).

Table 4
Minimal surface tension (γ_{CMC}) and critical micelle concentration (CMC) for aqueous solutions of derivatives **3AA5**, **3AA7,** and **1B5-HCl** as well as of analogous compounds reported in the literature

Compound	$\gamma_{CMC} \pm 1$ mN/m	CMC $\times 10^4$ m/l	Factor[a]	Reference
1B5-HCl: R_F5-carnosine, HCl	19	29.5	~3	This work
3AAC5 C5Ala-Ala	19	10		This work
3AAC7 C7Ala-Ala	16	1.2	~10	This work
$F(CF_2)_6$-CH_2-$(OC_2H_4)_4$-OH	18	1.17	~3	[26]
$F(CF_2)_7$-CH_2-$(OC_2H_4)_4$-OH	17	0.41		[26]
$F(CF_2)_6$-CH_2-$(OC_2H_4)_4$-OCH_3	18	1.15	~3	[26]
$F(CF_2)_7$-CH_2-$(OC_2H_4)_4$-OCH_3	17	0.39		[25]
$F(CF_2)_6$-CH_2-C(O)-Gly-Sar-$GlyNH_2$	17	15	~10	[10,27]
$F(CF_2)_8$-CH_2-C(O)-Gly-Sar-$GlyNH_2$	16	1.3		[10,27]
FC_6N_3PC (Scheme 7)	23	7.6	~5	[19]
FC_6NH_3PC (Scheme 7)	25	38		[19]

[a] For explanations see the text.



Scheme 6. Chemical structure of surfactants **3AA5** and **1B5**.

expected to behave similarly. In fact, while the γ_{CMC}-values are indeed very close to each other, the CMC-values are in favor of **1B5** by a factor of 3.

Although the hydrophobic tails of the two compounds are identical, the hydrophilic parts differ significantly. The alanine moiety in **3AA5** is replaced by a histidine substituent in **1B5**. It is well known that the hydrophilic character of histidine is more pronounced than that of alanine [30,31]. The higher CMC-value observed for **1B5** is, therefore, not surprising. Moreover, the imidazole ring is protonated by an equivalent of HCl. Compared to the zwitterion **3AA5**, an additional charge is situated on the hydrophilic part which, due to repulsion effects, is unfavorable to aggregation and delays the formation of micelles.

Another analogy may be established between the surfactants of this work and the zwitterionic perfluoro-lysolecithin FC_6N_3PC on one hand and the cationic surfactant FC_6NH_3PC on the other (Scheme 7), prepared and studied by Papadopoulos and coworkers [19,32]. The two surfactants bear identical hydrophobic tails but, due to the additional charge on the latter, their CMC-values differ by a factor of ca. 5 (7.6×10^{-4} and 38×10^{-4} mol l^{-1}, respectively).

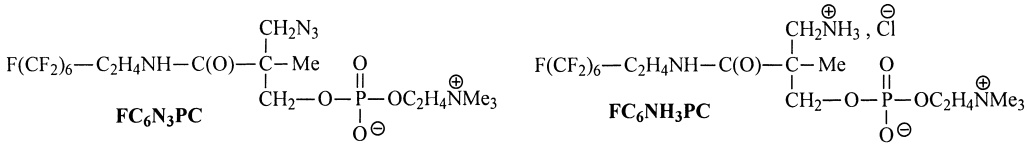
The above results show clearly that the new products synthesized are indeed, as expected, typical surfactants. The comparison with analogous molecules reveal a classical behavior both for their surface activity and for their critical micelle concentrations.

We had also suggested that the presence of a peptidoamine moiety in these compounds might be favorable for the complexation of metal ions such as Cu^{2+} [33] unless their coordinating ability of the carnosine subunit be reduced by the strong electron-withdrawing effect of the perfluoro-alkyl side chain. A preliminary investigation described below reveals that the complexing capacity for copper ions of the peptidoamine group in our surfactants is largely preserved.

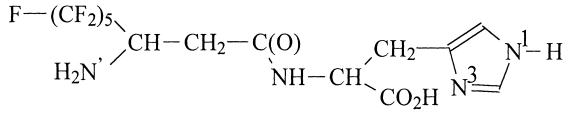
3.2. Complexation of Cu(II)

The p*K*-values and complexing properties of compound **1B5** the structure of which is shown in Scheme 8, have been investigated by acid–base titrations and UV–VIS spectroscopy.

The titration curves obtained for different metal-to-ligand ratios in the system Cu(II)- "C_5F_{11} — carnosine" (**1B5**) are



Scheme 7. Structure of lyso-lecithin analogues [19].



Scheme 8. Structure of "C_5F_{11}-carnosine" **1B5**, showing the numbering of imidazole nitrogen atoms.

Table 5
p*K*-values for free **1B5** and literature values for carnosine

	This work	Gajda [35]	Sovago [36]	Brookes [37]
pK_{COOH}	1.24	2.66	2.53	2.60
pK_{N3}	6.11	6.77	6.84	6.83
$pK_{N'}$	9.81	9.38	9.30	9.46

shown in Fig. 2. They give evidence for the complexing ability of the surfactant molecule. Curve a corresponds to the titration of **1B5** without copper; it displays two inflection points related to the neutralization of the two weak acid functions of the compound (deprotonation of the imidazolium nitrogen followed by deprotonation of the terminal nitrogen atom, the carboxyl proton being neutralized at the beginning of the titration). Curve b corresponds to a solution containing copper and the ligand in a 1:2 ratio, and curve c to a similar solution but with a copper-to-ligand ratio of 1.

The shift of curves b and c is in agreement with a strong co-ordination of compound **1B5** to the Cu^{2+} ion.

The p*K*-values of the different protonated sites of the free ligand have been extracted from the titration curves by using the PSEQUAD software developed by Zekany [34]. They are listed in Table 5 (second column). For comparison those reported in previous literature for unsubstituted carnosine are also included in the table.

In spite of the electron-withdrawing character of the perfluoroalkyl chain, supposed to increase the acidity of the amino group in the α-position ($N'H_2$), a decrease in acidity is actually observed, whereas the other protonated sites become more acid as expected. This observation may be explained by local variations of the p*K*-values of the titrated functions when the molecules are engaged in micellar structures.

The results from the titration experiments combined with those of complementary UV–VIS investigations are in agreement with a structure of the copper complex schematically shown below. At pH values above 7.5, the titration data show that three nitrogen binding sites are available for co-ordination to copper and the maximum in the electronic spectra of the copper ion, situated at ~620 nm suggests, according to Billo [38], that three nitrogen atoms are engaged in the first co-ordination sphere of the metal ion Scheme 9.

Since the ligand **1B5** binds efficiently to copper(II), similar types of complexes can be predicted for other divalent transition ions such as Ni^{2+} and Co^{2+}. A more detailed investigation of the structure and the stability of the complex compounds containing the new surfactants described above is under way.

4. Experimental section

4.1. Syntheses

4.1.1. 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

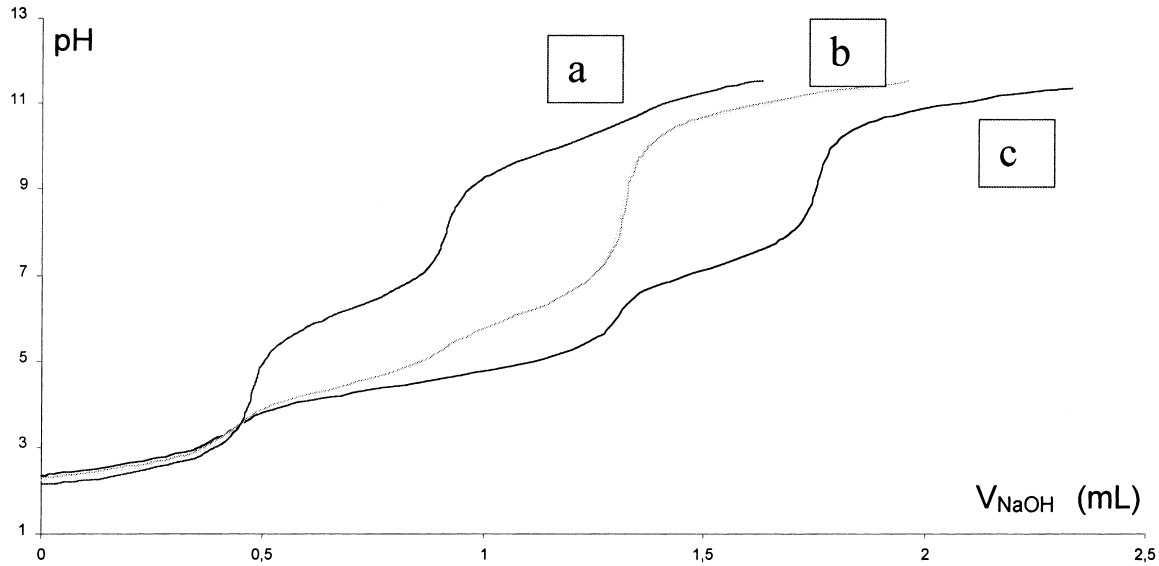
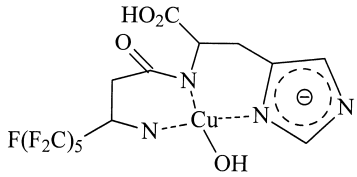


Fig. 2. Titration curves of the system Cu^{2+}-**1B5** with 0.1 M NaOH starting from 5 ml of 8.9×10^{-3} M **1B5** and (a) 0; (b) 2, and (c) 4.25 ml of 9.9×10^{-3} M $Cu(ClO_4)_2$ solutions.



Scheme 9. Schematic structure of the copper(II) — "R_F5-carnosine" (**1B5**) complex.

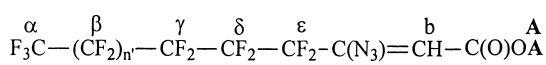
chromatographic (TLC) plates (Merck, Kieselgel 60 F_{254}) with eluents ethyl-acetate/hexane or chloroform/methanol. Purification is carried out by flash silica gel column chromatography with the same eluents. Melting points were determined with an electronic apparatus (Electrothermal) and have not been corrected. The proton ^{1}H and fluorine ^{19}F NMR spectra were recorded on a Bruker AM 400 or AC 250 spectrometer. The chemical shifts δ are reported in parts per million (δ in ppm) downfield from internal tetramethylsilane (TMS) or $CFCL_3$, respectively. The IR spectra were recorded on a Perkin-Elmer 580D or 1600 FTIR spectrometer. The elemental analyses were carried out at the "Centre de microanalyses du CNRS, Vernaison, France". They agree with the proposed structures, their values are shown below for several compounds. Mass spectra were enregistred on Fisons TRIO 1000 apparatus.

4.2. Syntheses of surfactants **2A*n***, **1B*n***, and **3AA*n***

4.2.1. Preparation of "azides" of type 9

General procedure for methyl-3-perfluoroalkyl-3-azido-prop-2-enoate **9*n*-Me** and ethyl-3-perfluoroalkyl-3-azido-prop-2-enoate **9-*n*-Et**. To a solution of the appropriate ester **8** (15 mmol) [17] in 80 ml of formamide, are added 10 equivalents of sodium azide. The mixture is stirred at room temperature for 16 h. Water (50 ml) is added and the mixture is extracted with ether (3 × 75 ml). The ether phases are washed with water (2 × 30 ml) and dried over magnesium sulfate; the solvent is evaporated under reduced pressure and the crude residue purified by flash chromatography (eluent: AcOEt/hexane 1:1) Table 6.

Products **9-*n*-A** (**A** = Me or Et)



Spectroscopic characteristics: IR ν[N_3]: 2158 cm^{-1}; ν[C(O)]: 1724 cm^{-1}; ν[C=C]: 1654 cm^{-1}.

NMR ($CDCl_3$) [^{1}**H**] for **A** = Me, δ = 3.75 ppm (OCH_3, s, 3H) and for **A** = Et, δ = 1.10 ppm (CH_3, t, 3H, ^3J_H = 8.0 Hz); δ = 4.20 ppm (OCH_2, q, 2H, ^3J_H = 8.0 Hz); **b**: δ = 6.00 ppm (s, 1H). [^{19}**F**] α: δ = −81.40 ppm (t, 3F, ^3J = 14.5 Hz); β: δ = −126.75 ppm (m, 2F); γ: δ = −123.10 ppm (m); δ: δ = −122.40 ppm (m, 2F); ε: δ = −115.00 ppm (t, 2F, ^3J_F = 14.5 Hz).

Microanalyses for **9-7-Me**: Calcd. for $C_{11}H_4F_{15}N_3O_2$ (M = 495.15): C% 26.68, H% 0.81, N% 8.49, F% 57.55; Found C% 26.97, H% 0.91, N% 8.34, F% 58.10. For 9-7-Et: Calcd. for $C_{12}H_6F_{15}N_3O_2$ (M = 509.17): C% 28.31, H% 1.19, N% 8.25, F% 55.97; Found C% 28.81, H% 1.27, N% 8.42, F% 56.12.

4.2.2. Preparation of **Z**-β-perfluoroalkyl-β-alanines of type 10

General procedure for 3-perfluoroalkyl-3-(*N*-benzyloxy-carbonyl)-amino-propanoic acids **10-*n*** (**R_F-Z-β-Ala-OH**).

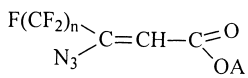
Hydrogenation of compounds of type **9**: to a solution of the appropriate "azide" **9** (20 mmol) in 50 ml of methanol and 10 ml of ethyl acetate, in a stainless steel hydrogenation bomb of approximately 250 ml capacity, are added 10 ml of an aqueous suspension of Raney nickel. The mixture is stirred under 80 bars of hydrogen at 80°C for 12 h. After a renewal of hydrogen gas, the reaction is continued under the same conditions for 18 h. After filtration the solvent is evaporated under reduced pressure. The crude residue is purified by flash chromatography (eluent: AcOEt/hexane 1:1) Table 7.

Spectroscopic characteristics: IR: ν[NH_2], 3400–3250 cm^{-1}.

NMR ($CDCl_3$) [^{1}**H**] for **A** = Me, δ = 3.64 ppm (OCH_3, s, 3H) and for **A** = Et, δ = 1.24 ppm (CH_3, t, 3H,^3J_H = 8.0 Hz); δ = 4.24 ppm (OCH_2, q, 2H, ^3J_H = 8.0 Hz); **c**: δ = 2.85 ppm (dd, 2H, ^2J = 16.0 Hz and ^3J = 8.0 Hz); **d**: δ = 5.15 ppm (m, 1H); **e**: δ = 6.30 ppm (m, 2H). [^{19}**F**] α: δ = −79 ppm (t, 3F, ^3J = 10 Hz); β: δ = −126 to −121 ppm; γ: δ = −118 ppm (m, 2 or 4F); δ: δ = 112 ppm.

4.2.2.1. Amine protection. To a stirred dispersion of the above perfluoroalkyl-β-alanine ester (10 mmol) in 35 ml of an aqueous solution of sodium hydrogen carbonate (1N),

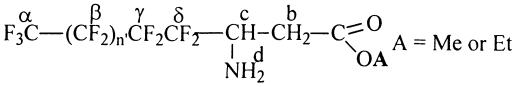
Table 6
Properties of compounds **9**



A = Me or Et

Compound	Aspect	MM (g/mol)	mp (°C)	n_{20}^D	Rf (AcOEt/hexane)	Yield (%)
9-5-Me	Oil	395.13	–	1.321	0.87	78
9-7-Me	Oil	495.15	–	1.354	0.85	75
9-9-Me	Solid	595.16	46	–	0.72	75
9-5-Et	Oil	409.15	–	1.369	0.83	80
9-7-Et	Oil	509.17	–	1.376	0.80	80
9-9-Et	Solid	609.19	52	–	0.52	73

Table 7
Properties of hydrogenated compounds



Compound	MM (g/mol)	Rf (AcOEt)	Yield (%)
$C_5F_{11}CH(NH_2)CH_2CO_2Me$	371.16	0.30	70
$C_7F_{15}CH(NH_2)CH_2CO_2Me$	471.17	0.34	75
$C_9F_{19}CH(NH_2)CH_2CO_2Me$	571.19	0.41	55
$C_5F_{11}CH(NH_2)CH_2CO_2Et$	385.17	0.33	82
$C_7F_{15}CH(NH_2)CH_2CO_2Et$	485.19	0.35	80
$C_9F_{19}CH(NH_2)CH_2CO_2Et$	585.20	0.44	60

benzyl-chloroformate (1.1 equivalent) is added dropwise at 5°C. The mixture is stirred for 16 h at room temperature. The solid is filtered off and washed with hexane (2 × 10 ml) Table 8.

Spectroscopic characteristics: IR ν[NH], 3321 cm^{-1}; ν[C=O carbamate], 1711 cm^{-1}; ν[C=O ester], 1733 cm^{-1}; ν[C–F]: 1300–1100 cm^{-1}.

NMR CD_3COCD_3 [^{1}**H**] for **A** = Me, $\delta = 3.25$ ppm (OCH_3, s, 3H) and for **A** = Et, $\delta = 1.25$ ppm (CH_3, t, 3H, $^3J_H = 8.0$ Hz); $\delta = 4.15$ ppm (q, 2H, $^3J = 8.0$ Hz); **b**: $\delta = 2.65$ ppm (dd, 1H, $^2J = 16.0$ Hz, $^3J = 8.0$ Hz); **c**: $\delta = 4.90$ at 5.10 ppm (m, 1H); **d**: $\delta = 5.45$ ppm (d, 1H, $^2J = 8.0$ Hz); **e**: $\delta = 5.15$ ppm (s, 2H); **f**: $\delta = 7.10$ at 7.40 ppm (m, 5H). [^{19}**F**] α: $\delta = -82.40$ ppm (t, 3F, $^3J = 10.0$ Hz); β: $\delta = -127.70$ to -122.90 ppm (m); γ: $\delta = -119.50$ ppm (m, 2F); δ: $\delta = -112.00$ ppm (m, 2F).

4.2.2.2. Ester hydrolysis. To a solution of 8 mmol of the above protected ester in 10 ml of methanol are added 5 equivalents of a 2N sodium hydroxide solution in methanol/water (90/10). The mixture is stirred at room temperature for 3 h. The solvent is evaporated under reduced pressure. The crude product is dissolved in ethyl acetate (100 ml) and then added to 100 ml of 2N HCl. The aqueous phase is extracted with ethyl acetate (2 × 100 ml). The organic phase is dried over magnesium sulfate and the solvent is evaporated under reduced pressure. The crude residue is purified by flash chromatography (AcOEt/hexane 1:1) Table 9.

Spectroscopic characteristics: IR ν[OH]: 3100 at 3400 cm^{-1}; ν[NH]: 3321 cm^{-1}; ν[C=O carbamate]: 1681 cm^{-1}; ν[C=O acid]: 1712 cm^{-1}.

NMR (CD_3COCD_3) [^{1}**H**]; **b**: $\delta = 2.65$ ppm (dd, 1H, $^2J = 16.0$ Hz, $^3J = 12.0$ Hz) and $\delta = 2.85$ ppm (dd, 1H; $^2J = 16.0$ Hz, $^3J = 4.0$ Hz); **c**: $\delta = 4.10$ ppm (m, 1H); **e**: $\delta = 5.14$ ppm (s, 2H); **f**: $\delta = 7.28$ ppm (m, 5H); **d**: $\delta = 9.30$ ppm (m, 1H) **a**: $\delta = 10.45$ ppm (s, 1H). [^{19}**F**] α: $\delta = -81.40$ ppm (t, 3F, $^3J = 9.5$ Hz); β: $\delta = -126.40$ ppm at $\delta = -122.40$ ppm (m, 4F); γ: $\delta = -117.15$ ppm (m, 2F); δ: $\delta = -111.00$ ppm (m, 2F).

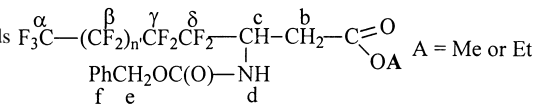
Microanalyses for **10-5**: Calcd. for $C_{16}H_{12}F_{11}NO_4$ ($M = 491.26$): C% 39.12, H% 2.46, N% 2.85, F% 42.54; Found C% 39.63, H% 2.70, N% 3.28, F% 43.10.

4.2.3. "Peptide-coupling" methods for the synthesis of **1B*n***, **2A*n*** *and* **3AA*n***

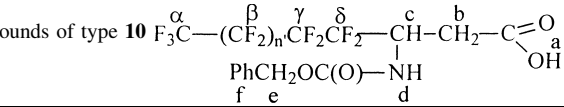
4.2.3.1. BOP activation method. The appropriate perfluoroalkyl-**Z**-β-alanine (10 mmol) is dissolved in acetonitrile (50 ml) and 3 equivalents of triethylamine, 1 equivalent of BOP and 1 equivalent of appropriate amino-acid ester are added. The mixture is stirred at room temperature for 4 h. The precipitate is filtered off and washed with hexane (2 × 30 ml), dissolved in ethyl acetate (50 ml), washed with 20 ml of 2N aqueous HCl, 20 ml of a saturated aqueous solution of $NaHCO_3$ and 20 ml of brine. The organic phase is dried over magnesium sulfate, the solvent is evaporated under reduced pressure and the crude residue purified by flash chromatography (MeOH/AcOEt 20/80) (see Table 1).

4.2.3.2. DCC activation method. The appropriate perfluoroalkyl-**Z**-β-alanine (10 mmol) is dissolved in dichloromethane (50 ml) and 2 equivalents of triethylamine, 1 equivalent of dicyclohexylcarbodiimide and 1 equivalent of the appropriate amino-acid ester are added. The mixture is stirred at room temperature for 18 h. The precipitate is filtered off, washed with hexane (2 × 30 ml), dissolved in ethyl acetate (50 ml), washed with 20 ml of 2N HCl, 20 ml of a saturated aqueous solution of $NaHCO_3$ and 20 ml of brine. The organic phase is dried over magnesium

Table 8
Properties of **Z**-protected compounds



Compound	MM (g/mol)	Rf (AcOEt)	mp (°C)	Yield (%)
$C_5F_{11}CH(NH\text{-}\mathbf{Z})CH_2CO_2Me$	505.28	0.58	74	85
$C_7F_{15}CH(NH\text{-}\mathbf{Z})CH_2CO_2Me$	605.30	0.55	78	82
$C_9F_{19}CH(NH\text{-}\mathbf{Z})CH_2CO_2Me$	705.32	0.49	87	65
$C_5F_{11}CH(NH\text{-}\mathbf{Z})CH_2CO_2Et$	519.31	0.58	79	84
$C_7F_{15}CH(NH\text{-}\mathbf{Z})CH_2CO_2Et$	619.34	0.53	81	80
$C_9F_{19}CH(NH\text{-}\mathbf{Z})CH_2CO_2Et$	719.35	0.47	93	62

Table 9
Characteristics of compounds of type **10** 

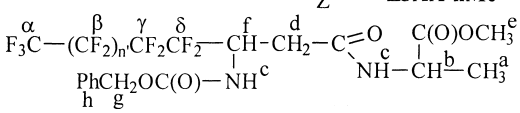
Compound	MM (g/mol)	Rf (AcOEt)	mp (°C)	Yield (%)
10-5: $C_5F_{11}CH(NH\text{-}\mathbf{Z})CH_2CO_2H$	491.26	0.68	131	85
10-7: $C_7F_{15}CH(NH\text{-}\mathbf{Z})CH_2CO_2H$	591.27	0.66	138	82
10-9: $C_9F_{19}CH(NH\text{-}\mathbf{Z})CH_2CO_2H$	691.29	0.61	151	65

sulfate; the solvent is evaporated under reduced pressure and the crude residue purified by flash chromatography (MeOH/AcOEt 20/80) see Table 1).

4.2.3.3. Mixed anhydride method. The appropriate perfluoroalkyl-Z-β-alanine (10 mmol) is dissolved in tetrahydrofuran (20 ml) and 1.1 equivalents of isopropenyl or isobutyl chloroformate are added rapidly at 2°C. The mixture is stirred for 5 min 1 equivalent of appropriate amino-acid ester, 3 equivalents of triethylamine are added and the mixture is stirred at 2°C for another 3 h. The solvent is evaporated under reduced pressure. The residue is dissolved in ethyl acetate (50 ml), washed with 20 ml of 2N HCl, 20 ml of a saturated aqueous solution of $NaHCO_3$ and 20 ml of brine. The organic phase is dried over magnesium sulfate, the solvent is evaporated under reduced pressure and the crude residue purified by flash chromatography (MeOH/AcOEt 20/80) (see Table 1).

For products **Z-3AA-*n*-Me** (with $n = 5$, 7, 9) (see Table 1).

Characteristics of RF—βAlaAlaOMe (Z) **Z3AA-nMe**



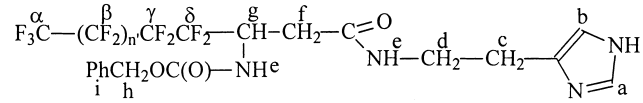
Spectroscopic characteristics: IR ν[NH]: 3390 cm^{-1}; ν[C=O amides]: 1653 cm^{-1}; ν[C=O carbamate]: 1711 cm^{-1}; ν[C=O ester]: 1734 cm^{-1}; ν[C–F]: 1100–1300 cm^{-1}.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 1.12$ ppm (M, 3H); **b**: $\delta = 3.85$ ppm (s, 1H); **d**: $\delta = 2.45$ ppm (dd, 2H); **e**: $\delta = 3.6$ ppm (s, 3H); **f**: $\delta = 5.05$ ppm (m, 1H); **g**: $\delta = 5.25$ ppm (m, 2H); **h**: $\delta = 7.20$ ppm (m, 5H). [^{19}**F**] α: $\delta = -81.50$ ppm (t, 3F, $^3J = 10.0$ Hz); β: $\delta = -126.80$ at -122.90 ppm (m); γ: $\delta = -118.50$ ppm (m, 2F); δ: $\delta = -110.00$ ppm (m, 2F).

Microanalyses for **Z-3AA-5-Me**: Calcd. for $C_{20}H_{19}F_{11}N_2O_3$ ($M = 576.36$): C% 41.68, H% 3.32, N% 4.86, F% 36.26; Found: C% 41.86, H% 3.37, N% 4.88, F% 37.04; for **Z-3AA-7-Me** Calcd. for $C_{22}H_{19}F_{15}N_2O_3$ ($M = 676.37$): C% 39.07, H% 2.83, N% 4.14, F% 42.13; Found C% 39.55, H% 2.92, N% 4.18, F% 42.21.

For products: **Z-2A-*n*** (R_F-**Z**-carcinine with $n = 5$, 7, 9) (see Table 1).

Characteristics of RF—Carcinine (Z) **Z2A-n**



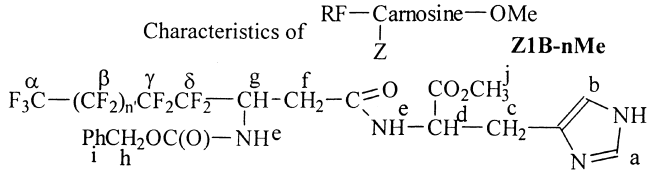
Spectral characteristics: IR ν[NH]: 3370 cm^{-1}: ν[C=O amides]: 1643 cm^{-1}; ν[C=O carbamate]: 1715 cm^{-1}; ν[C-F]: 1100–1300 cm^{-1}.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 7.60$ ppm (s, 1H); **b**: $\delta = 7.85$ ppm (s, 1H); **c**: $\delta = 2.80$ ppm (m, 2H); **d**: $\delta = 2.90$ ppm (m, 2H); **f**:$\delta = 2.50$ ppm (m, 2H); **h**: $\delta = 5.28$ ppm (m, 2H); **g**: $\delta = 4.60$ ppm (m, 1H); **i**: $\delta = 7.23$ ppm (m, 5H). [^{19}**F**] α: $\delta = -82.39$ ppm (t, 3F, $^3J = 10.0$ Hz); β: $\delta = -127.70$ to -122.90 ppm (m,); γ: $\delta = -119.50$ ppm (m, 2F); δ: $\delta = -112.00$ ppm (m, 2F).

Microanalyses for **Z-2A-5**: Calcd. for $C_{21}H_{19}F_{11}N_4O_3$ ($M = 584.38$): C% 43.16, H% 3.28, N% 9.59, F% 35.76; Found C% 43.47, H% 3.47, N% 9.78, F% 36.10; for **Z-2A-7** Calcd. for $C_{23}H_{19}F_{15}N_4O_3$ ($M = 684.40$): C% 40.36, H% 2.80, N% 8.19, F% 41.64; Found C% 40.65, H% 3.12, N% 8.55, F% 42.12.

For products **Z-1B-*n*-Me** (R_F-Z-β-Ala-HisOMe; R_F-**Z**-carnosine-OMe) (with $n = 5$, 7, 9) (see Table 1).

Characteristics of RF—Carnosine—OMe (Z) **Z1B-nMe**



Spectral characteristics: IR ν[NH]: 2928–3390 cm^{-1}: ν[C=O amides]: 1653 cm^{-1}; ν[C=O carbamate]: 1712 cm^{-1}; ν[C–F]: 1100–1300 cm^{-1}.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 7.40$ ppm (s, 1H); **b**: $\delta = 8.25$ ppm (s, 1H); **c**: $\delta = 2.70$ ppm (m, 2H); **d**: $\delta = 3.35$ ppm (s, 1H); **e**: δ=3.30 ppm (m, 3H); **f**: $\delta = 2.65$ ppm (m, 2H); **g**: $\delta = 5.10$ ppm (m, 1H); **h**: $\delta = 5.10$ ppm (s, 2H); **i**: $\delta = 7.40$ ppm (m, 5H). [^{19}**F**] α: $\delta = -77.80$ ppm (t, 3F, $^3J = 10$ Hz); β: $\delta = -124.0$ to -122.2 ppm (m); γ: $\delta = -118.5$ ppm (m, 2F); α: $\delta = -114.10$ ppm (m, 2F).

Microanalyses for **Z-1B-5-Me**: Calcd. for $C_{23}H_{21}F_{11}N_4O_5$ ($M = 642.42$): C% 43.00, H% 3.29, N% 8.72, F% 32.53; Found C% 43.24, H% 3.46, N% 8.94, F% 32.81; for **Z-1B-7-Me** Calcd. for $C_{25}H_{21}F_{15}N_4O_5$ ($M = 742.44$):

C% 40.44, H% 2.85, N% 7.55, F% 38.38; Found C% 40.85, H% 2.98, N% 7.52, F% 41.02.

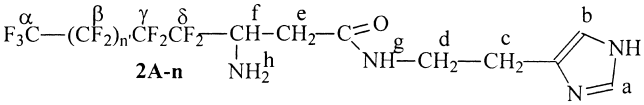
4.2.4. Hydrogenolysis and hydrolysis of protecting groups

4.2.4.1. Hydrogenolysis. Preparation of the products: **2A*n***: R_F-Carcinine; 1BnMe: R_F-carnosine-OMe and **3AA-*n*Me** (with $n = 5$, 7, 9) (see Table 2). Hydrogenation of compounds **Z3AA-*n*Me**; **Z2A-*n*** and **Z1B-*n*Me**: to a solution of the appropriate **Z**-compound (5 mmol) in 50 ml of methanol, placed in a stainless steel hydrogenation bomb of approximately 150 ml capacity, is added 0.1 g of Pd/C. The mixture is stirred at room temperature for 2 h under 30 bars of hydrogen. After the renewal of hydrogen gas, the reaction is continued under the same conditions for 4 h. After filtration, the solvent is evaporated under reduced pressure. The crude residue is purified by flash chromatography (AcOEt/hexane 80/20)). All products are white solids Table 10.

Microanalyses for **3AA-5Me** [methyl-3-perfluoropentyl-β-alanyl alaninate] Calcd. for $C_{12}H_{13}F_{11}N_2O_3$ ($M = 442.23$): C% 32.59, H% 2.96, N% 6.33, F% 47.26; Found C% 32.67, H% 3.17, N% 6.50, F% 48.08; for **3AA-7Me** [methyl-3-perfluoroheptyl-β-alanyl alaninate] Calcd. for $C_{14}H_{13}F_{15}N_2O_3$($M = 542.24$): C% 31.01, H% 2.42, N% 5.17, F% 52.55; Found C% 31.97, H% 2.68, N% 4.95, F% 53.14.

The products 2**A-*n*** [R_F-β alanyl-histidine = R_F-carcinine]

Characteristics of RF−Carcinine



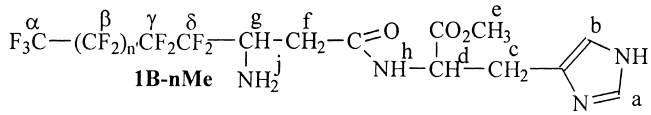
Spectroscopic characteristics: IR *ν*[NH]: 2928–3389 cm^{-1}; *ν*[CO amide]: 1653 cm^{-1}.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 7.60$ ppm, (s, 1H); **b**: $\delta = 7.85$ ppm, (s, 1H); **c**: $\delta = 2.80$ ppm, (m, 2H); **d**: $\delta = 3.05$ ppm, (m, 2H); **e**: $\delta = 2.85$ ppm, (m, 2H); **f** = **g**: $\delta = 5.10$ ppm, (m); **h**: $\delta = 3.25$ ppm, (m, 2H). [^{19}**F**] α: $\delta = -78.90$ ppm, (t, 3F), $^3J = 9.5$ Hz; β: $\delta = -123.90$ ppm, (m, 2F); γ: $\delta = -119.45$ ppm, (m, 4F); δ: $\delta = -114.65$ ppm, (m, 2F).

Microanalyses for **2A5** [3-perfluoropentyl-β-alanyl-histamine] Calcd. for $C_{13}H_{13}F_{11}N_4O$ ($M = 450.25$): C% 34.68, H% 2.91, N% 12.44, F% 46.41; Found C% 34.87, H% 3.17, N% 12.64, F% 46.10; for **2A7** [3-perfluoroheptyl-β-alanyl-histamine] Calcd. for $C_{15}H_{13}F_{15}N_4O$($M = 550.27$): C% 32.74, H% 2.38, N% 10.18, F% 51.79; Found C% 32.16, H% 2.42, N% 10.69, F% 51.14.

The products **1B-*n*Me** [R_F-β alanyl-histidine-OMe = R_F-carnosine-OMe] **1B-5Me** [methyl-3-perfluoropentyl-β-alanine histidinate] and **1B-7Me** [methyl-3-perfluoroheptyl-β-alanine histidinate].

Characteristics of RF—Carnosine—OMe



Spectroscopic characteristics: IR *ν*[NH]: 2928–3389 cm^{-1}: *ν*[C=O amide]: 1653–1712 cm^{-1}.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 7.60$ ppm, (s, 1H); **b**: $\delta = 7.85$ ppm, (s, 1H); **c**: $\delta = 2.80$ ppm, (m, 2H); **d**: $\delta = 3.05$ ppm, (m); **e**: $\delta = 3.65$ ppm, (s, 3H); **f**: $\delta = 2.80$ ppm, (m, 2H); **g**: $\delta = 4.60$ ppm, (m, 1H); **j**: $\delta = 6.25$ ppm, (m, 2H). [^{19}**F**] α: $\delta = -78.90$ ppm, (t, 3F, $^1J = 10.0$ Hz); β: $\delta = -124$ ppm, (m, 2F); γ: $\delta = -119.45$ ppm, (m, 4F); δ: $\delta = -114.65$ ppm, (m, 2F).

Microanalyses for **1B7Me** [methyl-3-perfluoroheptyl-β-alanyl-histidinate] Calcd. for $C_{17}H_{15}F_{15}N_4O_3$ ($M = 608.31$): C% 33.57, H% 2.49, N% 9.21, F% 46.85; Found C% 33.74, H% 2.67, N% 9.34, F% 47.24.

4.2.4.2. Hydrolysis. Preparation of the products: **1B-*n***: R_F-carnosine (with $n = 5$, 7, 9) (see Table 3).

4.2.4.2.1. Hydrolysis of esters. To a solution of 5 mmol of the appropriate ester **1B-*n*Me** in 20 ml of dioxane, are added 2.5 equivalents of a 1N aqueous solution of sodium hydroxide. The mixture is stirred at room temperature for 3 h. The solvent is evaporated under reduced pressure. The crude product is dissolved in ethyl acetate (100 ml), and

Table 10
Compounds obtained by saponification

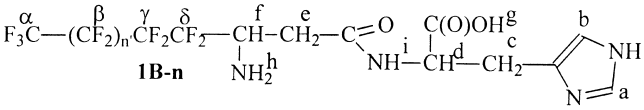
Code	Compound[a]	MM	Rf[a]	mp (°C)	Yield (%)
3AA-5Me	$C_5F_{11}CH(NH_2)CH_2C(O)NHCH(CH_3)CO_2CH_3$	442.23	0.57	147	85
3AA-7Me	$C_7F_{15}CH(NH_2)CH_2C(O)NHCH(CH_3)CO_2CH_3$	542.24	0.55	152	80
3AA-9Me	$C_9F_{19}CH(NH_2)CH_2C(O)NHCH(CH_3)CO_2CH_3$	642.26	0.52	163	57
2A-5	$C_5F_{11}CH(NH_2)CH_2C(O)NHCH_2CH_2$-Im	450.25	0.45	167	78
2A-7	$C_7F_{15}CH(NH_2)CH_2C(O)NHCH_2CH_2$-Im	550.27	0.45	172	75
2A-9	$C_9F_{19}CH(NH_2)CH_2C(O)NHCH_2CH_2$-Im	650.29	0.47	177	45
1B-5Me	$C_5F_{11}CH(NH_2)CH_2C(O)NHCH(CO_2CH_3)CH_2$-Im	508.29	0.48	182	75
1B-7Me	$C_7F_{15}CH(NH_2)CH_2C(O)NHCH(CO_2CH_3)CH_2$-Im	608.31	0.45	197	73

[a] Eluent: AcOEt/hexane 70/30; Im = imidazole.

acidified with 1N aqueous HCl to pH 1. The aqueous phase is extracted with ethyl acetate (2 × 100 ml). The organic phase is dried over magnesium sulfate and the solvent is evaporated under reduced pressure; the crude residue is purified by flash chromatography (AcOEt/hexane 1:1) and recristallized from hexane/ether or from chloroform.

The products **1B-*n*** [R_F-β alanyl-histidine = R_F-carnosine]: 1B-5 [3-perfluoropentyl-β-alanyl-histidine] and **1B-7** [3-perfluoroheptyl-β-alanyl-histidine] are white solids.

Characteristics of RF−Carnosine



1B-5 = R_F5-carnosine [$C_5F_{11}CH(NH_2)CH_2C(O)NHCHCO_2HCH_2$-Im; MM = 494.26]; Rf (AcOEt/hexane 70/30) 0.48; mp(°C) = 182; Yield: 75%. **1B-7** = R_F7-carnosine [$C_7F_{15}CH(NH_2)CH_2C(O)NHCHCO_2HCH_2$-Im; MM = 594.28]; Rf (AcOEt/hexane 70/30) 0.45; mp(°C) = 197; Yield: 73%.

Spectroscopic characteristics: IR *ν*[COOH]: 3450–3120 cm^{-1}; *ν*[N–H]: 3290–3215 cm^{-1}; *ν*[CO acide]: 1711 cm^{-1}; *ν*[CO amide]: 1690.

NMR (CD_3OD) [^{1}**H**] **a**: $\delta = 7.80$ ppm, (s, 1H); **b**: $\delta = 8.10$ ppm, (s, 1H); **c**: $\delta = 2.80$ ppm, (m, 2H); **d**: $\delta = 3.45$ ppm, (m, 1H); **e**: $\delta = 2.50$ ppm, (m, 2H); **f** and **i**: $\delta = 5.10$ ppm, (m, 2H); **g**: $\delta = 10.25$ ppm, (m, 1H); **h**: $\delta = 6.3$ ppm, (m, 2H). [^{19}**F**] α: $\delta = -82.39$ ppm (t, 3F), $^3J = 10.0$ Hz); β: $\delta = -127.70$ ppm at 122.90 ppm (m); γ: $\delta = -119.50$ ppm (m, 2F à 4F); δ: $\delta = -112.00$ ppm (m, 2F). Mass (scan EI) for **1B5** molecular peak 494 and for **1B7** molecular peak 594.

Microanalyses for **1B5** [3-perfluoropentyl-β-alanyl-histidine] Calcd. for $C_{14}H_{13}F_{11}N_4O_3$ ($M = 494.26$): C% 34.02, H% 2.65, N% 11.34, F% 42.28; Found C% 33.89, H% 2.75, N% 10.94, F% 42.05; for **1B7** [3-perfluoroheptyl-β-alanyl-histidine] Calcd. for $C_{16}H_{13}F_{15}N_4O_3$($M = 594.28$): C% 32.34, H% 2.20, N% 9.43, F% 47.95; Found C% 32.97, H% 2.58, N% 10.05, F% 48.14.

4.2.5. Physico-chemical properties

4.2.5.1. Surface activities. The surface tension measurements were made either with a Dognon–Abribat or a Krüss K10T tensiometer using the Wilhelmy-plate method.

Aqueous solutions of the perfluoroalkyl-oligopeptide **3AA*n*** and of the derivative R_F5-carnosine — HCl (1B5-HCl) have been prepared starting from stock solutions of known concentrations by successive dilutions with distilled water. Their surface tension γ has been 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 of ±1 mN/m.

4.2.5.2. Potentiometry. The protonation and coordination equilibria have been investigated by potentiometric titrations in aqueous solution at a constant ionic strength of 0.1 mol/l ($NaClO_4$) and $T = 298 \pm 1$ K under argon atmosphere by using an automatic titration apparatus including a Dosimat 665 autoburette (Metrohm), an Orion 710A precision digital pH-meter and an Orion 9103SC combined glass electrode. p*K*-values have been calculated from 4 independent titrations (ca. 100 data points each) by means of the PSEQUAD software [34].

4.2.5.3. UV–VIS spectrophotometry. The UV–VIS absorption spectra have been recorded on a Varian Cary 3E UV–VIS spectrophotometer. The ligand-to-metal ratio varied from 0 to 2.

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