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# Derivatives of glutamic acid as new surfactants

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**Summary.** Starting from glutamic acid, different types of surfactants have been synthesised by using original trimodular strategies. Monosubstituted zwitterionic amides of glutamic acid obtained with excellent yields show good surface activity.

The grafting of a second hydrophobic side-chain leads to bicatenar cationic surfactants or to disubstituted nonionic cyclic compounds. In order to reduce the hydrophobic character of the bicatenar surfactants, a second synthetic method has been developed, allowing the introduction of a polar sugar group into these molecules.

The surfactant properties of several of the products have been determined by physico-chemical methods such as surface tension measurements and compression isotherm studies by means of a Langmuir balance.

**Keywords:** Amino acids – Glutamic acid – Surfactant – Amide – Imide – Critical concentration

## Introduction

The synthesis of molecules with properties suitable for specific applications is one of the important objectives of modern organic chemistry. In this context we have been concerned for several years with the preparation and characterisation of new surfactants (Larpent, 1995).

These compounds are amphipathic molecules, generally characterized by the presence of two distinctly different regions in the same molecule: a lipophilic part (restrictively called hydrophobic) and a lipophobic or hydrophilic portion. The existence in the same molecule of two moieties, one with an affinity for the solvent and the other antipathetic to it, is termed amphiphily or amphipathy. Surface active agents constitute a versatile class of natural or synthetic compounds. They may contain a large variety of polar ionic or nonionic parts (called *head*) and apolar moieties (named *tail*), the latter consisting generally of long hydrocarbon chains (Attwood et al., 1983).

This dual nature is responsible for the phenomenon of surface activity, and of micellisation, formation of Molecular Organised Systems (Mittal, 1984) (lamellar phases, liquid crystals, vesicles, etc.), and their capacity of solubilisation by forming emulsions and microemulsions (Schick, 1987).

Our approach respects as much as possible the constraints of environmental compatibility as well as those imposed by the applications concerned. Therefore we have developed synthetic methods for surfactant molecules based on amino acids (Seguer et al., 1994, 1996; Allouch et al., 1996) or peptides (Selve et al., 1989, 1992).

In this paper we present a novel family of compounds derived from glutamic acid. For certain compounds, a sugar plays the role of the polar headgroup, and the apolar parts consist either of long-chain alcohols or fatty amines.

## Results and discussion

### *I. Syntheses*

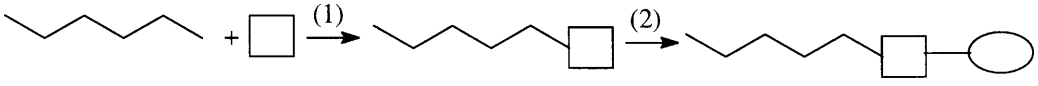
We have prepared the surfactant molecules following the trimodular pathway (Emmanouil et al., 1998; Rico-Lattes et al. 1997) shown in Scheme 1.

#### a) Strategy I

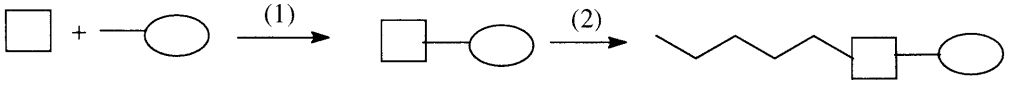
We have tried to prepare the surfactants by methods avoiding all the reactions necessitating protective groups. In analogy to the synthesis of ε-alkyl-lysine (Takizawa et al., 1975) we have synthesized the monoammonium salts of glutamic acid in a first step.

Since the pK values of the two carboxyl groups of glutamic acid differ by more than two units ($pK_\alpha$ = 2.19, $pK_\delta$ = 4.25) a good selectivity for the α-position during salt-formation is observed and the dehydration of the salt leads to a majority of the α-monoamide (>95%) with good yields (Table 1). The structure obtained (Scheme 2) is confirmed by comparison with authentic

**Strategy I** : (1) junction of Glu and hydrophobic chain and (2) addition of a polar headgroup



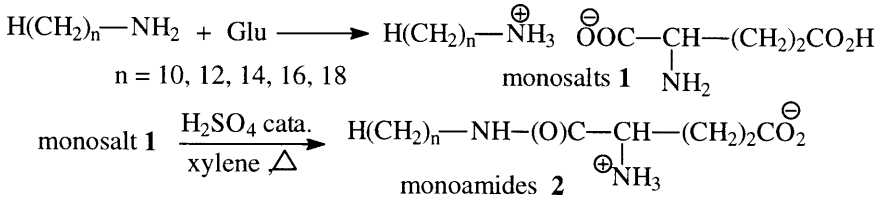

**Strategy II** : (1) junction of Glu and polar head and (2) addition of hydrophobic chain



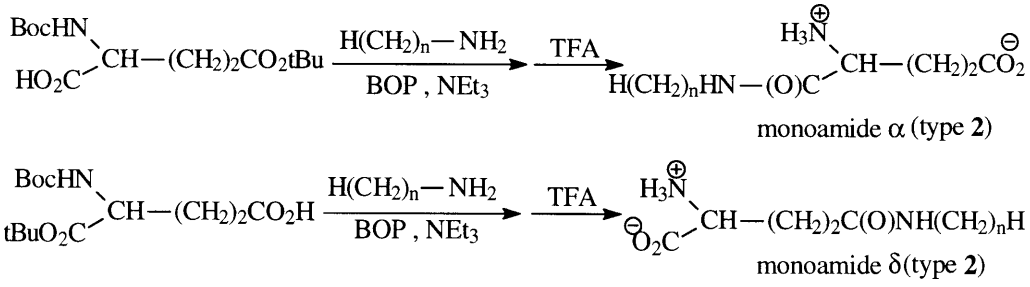

**Scheme 1.** Synthetic strategies for the preparation of surfactants

**Table 1.** Yields and melting points of α-monoamides **2** by dehydration of monosalts **1**

| n | 10 | 12 | 14 | 16 | 18 |
|---|---|---|---|---|---|
| Yield % | 70 | 74 | 76 | 75 | 79 |
| Mp °C | 102 | 105 | 106 | 108 | 109 |




**Scheme 2.** Monoamides obtained by dehydration of salts




**Scheme 3.** Monoamides (α and δ) obtained by classical methods

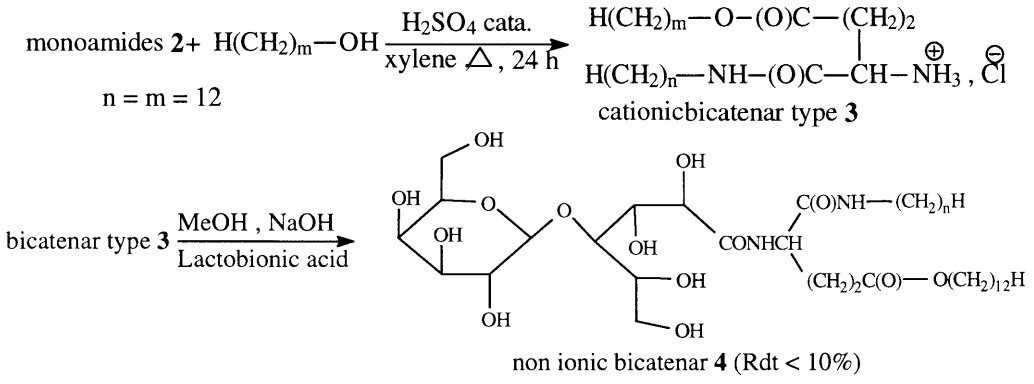
samples (α- and δ-monoamides) prepared by classical methods (Bodanszky, 1984) according to Scheme 3.

These molecules represent a family of monocatenar zwitterionic compounds.

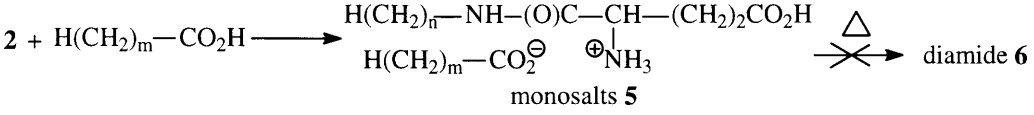
The esterification of the second carboxyl group with a long-chain alcohol leads to another family of bicatenar cationic surfactants **3** with good yields. Finally the reaction of the free aminogroup with lactobionic acid opens the way to a third family of bicatenar non-ionic derivatives **4** with yields below 10% (Scheme 4).

The amidation of monoamides **2** by a fatty acid reacting with the aminogroup has also been considered. The corresponding ammonium salt **5** is readily formed, but all attempts to obtain in a second step the diamides **6** by dehydration (Scheme 5) were unsuccessful.

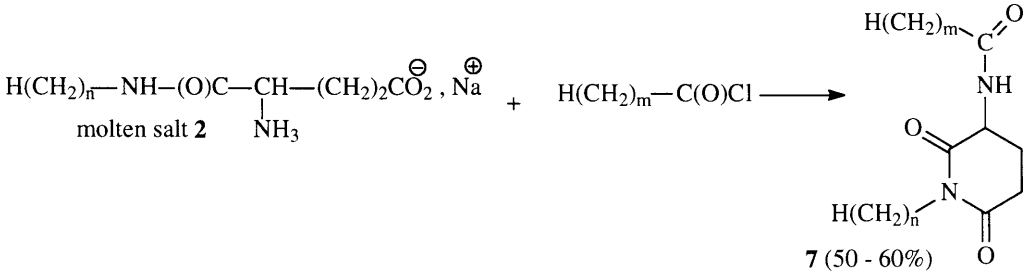
We have therefore carried out the amidation directly without any solvent by reacting the molten salts **2** with fatty acid chlorides. The reaction occurs readily, but the initially formed diamide is transformed intramolecularly into the cyclic imide **7** (Scheme 6) which is obtained with good yields (Table 2).




**Scheme 4.** Synthesis of bicatenar surfactants **3** and **4**




**Scheme 5.** Temptative preparation of diamides **6** by pyrolysis




**Scheme 6.** Direct reaction of acid chloride with the molten salt **2**

**Table 2.** Yields and melting points of cyclic-imides **7** obtained by reaction of acid chloride and molten salt **2** as function of chain-length (n, m)

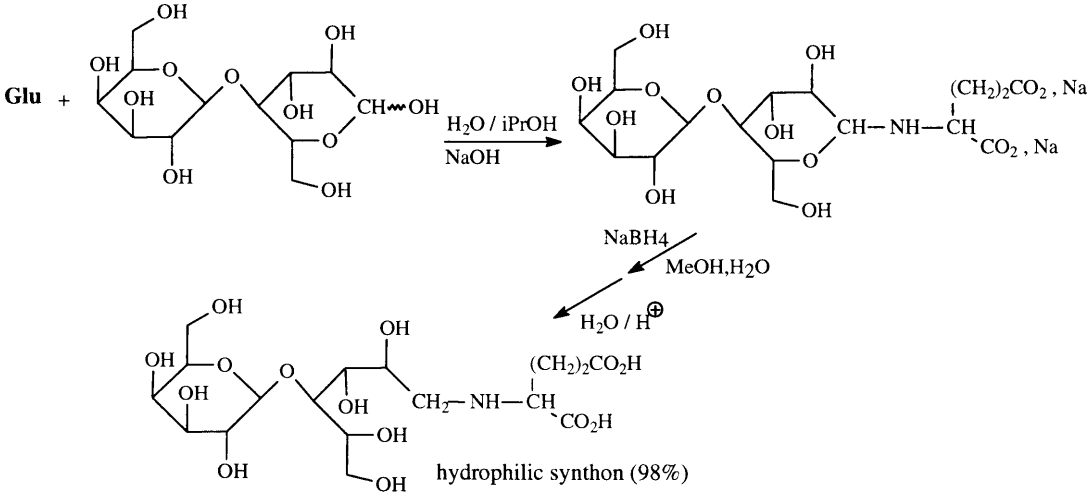
| n | 10 | 12 | 10 | 12 | 14 | 16 | 18 | 16 | 18 |
|---|---|---|---|---|---|---|---|---|---|
| m | 9 | 9 | 10 | 10 | 10 | 10 | 10 | 12 | 12 |
| Yield % | 55 | 50 | 50 | 62 | 52 | 56 | 30 | 55 | 56 |
| Mp °C | 137 | 137 | 136 | 128 | 128 | 131 | 132 | 132 | 132 |

To resume the results of this strategy we may say that the syntheses of the different families of compounds described show excellent results for monocatenar derivatives of the zwitterionic type **2** and the cationic products **3**. Derivatives of type **4** however are obtained with only rather poor yields. No efficient way has been found either for compounds of type **6**. For the imidic surfactants **7**, on the other hand, the reaction yields are quite satisfactory.

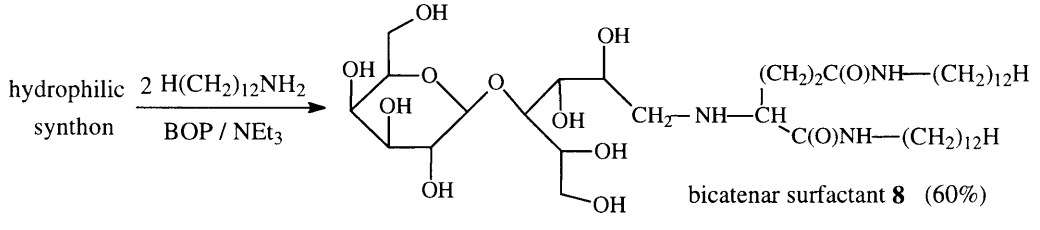
b) Strategy II

Since the bicatenar non-ionic derivatives **4**, the polar headgroup of which is formed by a sugar moiety, seemed interesting to us because of their potential applications, we have tried to find a different pathway to synthesise these products. The strategy consisted in preparing first the hydrophilic synthon and then to graft the hydrophobic modulus on it. This approach has the additional advantage that a greater variety of hydrophobic chains of different types may be introduced. We have condensed glutamic acid with lactose following a protocol inspired by the work of Caparros (1996). The condensation is carried out in a mixture of water and isopropanol at pH > 8. The imine formed has not been isolated but has been reduced in situ with sodium borohydride (Scheme 7).

The yields of these reactions are excellent. The hydrophilic synthon is obtained with 98% yield. It has been used to prepare the diamide **8** starting from dodecyl amine by activation with BOP (Castro et al., 1975; Selve et al., 1992) following the usual protocols for couplings with this agent (Scheme 8). The overall yield for surfactant **8** is of the order of 60% but can certainly be improved.




**Scheme 7.** Preparation of the hydrophilic synthon glutamic acid lactosamine




**Scheme 8.** Synthesis of diamide surfactant **8**

The method of synthesis of the different families of compounds derived from glutamic acid according to strategy II seems promising. It shows good results for the preparation of bicatenar derivatives of type **8**. On one hand the possibilities of the hydrophilic compound already prepared should be explored on a larger scale. On the other, synthons containing other sugar moieties (e.g. glucose) or sugar derivatives such as gluconic or lactobionic acid could represent extensions of interest.

## *II. Physico-chemical evaluation*

The solubility in water of compounds **2** is good but diminishes as expected when the length of the hydrophobic chain increases. It is sufficient however for C.M.C. measurements, even with the $C_{16}$ derivative. On the other hand the bicatenar cationic products **3** are poorly soluble in water ($<10^{-8}$ mol.cm$^{-3}$) much the same as the cyclic imides **7** which could however be studied as monomolecular films by the Langmuir balance technique. The bicatenar compounds **4** and the salts **1** and **5** are moderately soluble in aqueous media and show surfactant and bioactive properties which are still under study.

### a) Critical concentrations

The amides **2** studied differ only by n, the number of carbon atoms in the hydrophobic chain. Table 3 shows the critical concentrations CC and the surface tension $\gamma$ at the CC for the different compounds.

For all the products the break in the curve $\gamma = f(\log C)$ is well pronounced confirming the purity of the compounds. The critical concentrations decrease as expected with increasing chain length n. $\gamma_{cc}$-values are of the order typical for hydrogenated monocatenar surfactants. The slight increase with chain-length however might indicate that the kinetics of adsorption at the air/water interface are very slow for this type of compounds so that complete equilibrium has not been reached even after 30 min waiting time.

### b) Compression isotherm for cyclic imides

For the characterisation of the bicatenar cyclic imides **7** by means of a Langmuir balance, the compounds have been spread after dissolution in chloroform on an air/water interface in the form of a monomolecular film. The

**Table 3.** Surface tension $\gamma_{cc}$ and critical concentration CC for monoamides **2** as function of chain-length n

| n | 10 | 12 | 14 |
|---|---|---|---|
| $\gamma_{cc}$ (mN.m$^{-1}$) | 38 | 44 | 53 |
| CC (mol.cm$^{-3}$) $\cdot 10^5$ | 316 | 7.9 | 3.2 |

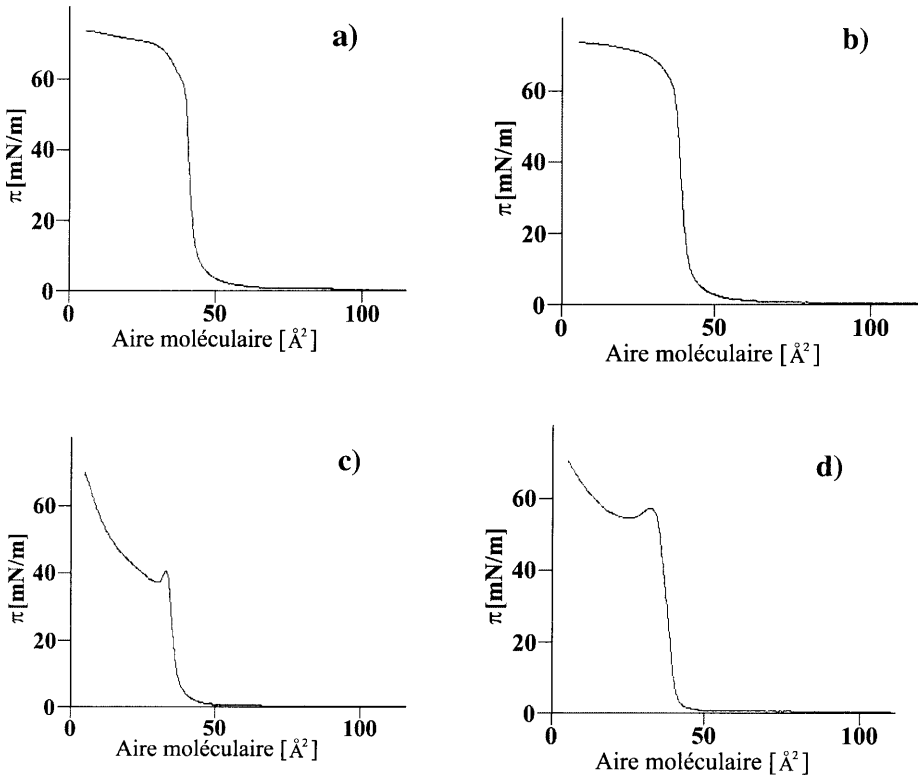



**Fig. 1.** Compression isotherms at 25°C as measured on a Langmuir balance, of monomolecular films of surfactants **7** with different chain-lengths. **a** n = 16, m = 14; **b** n = 16, m = 12; **c** n = 18, m = 14; **d** n = 18, m = 12 (for the signification of n and m, see Scheme 6)

compression isotherms for the different products (Fig. 1) show a steep increase of surface pressure near a value of 40 Å², corresponding to the formation of a quasi-solid phase in which the molecules are tightly packed at the interface.

The areas per polar headgroup calculated from these curves are 42, 38, 42, and 41 Å² for the products with n = 16, m = 14; n = 16, m = 12; n = 18, m = 14; and n = 18, m = 12, respectively.

## Material and methods

### *Apparatus*

IR spectra have been recorded on a Perkin-Elmer 1,600 FT spectrometer by using liquid films or KBr pellets.

NMR spectrometry has been performed either on a Bruker AM 250 or on a Bruker AM 400 apparatus. Chemical shifts are given in ppm with respect to TMS as internal standard and coupling constants are given in Hz.

For the determination of melting points an electronic Electrothermal equipment or a Kofler bank have been used. No corrections have been applied.

Measurements of critical concentrations have been performed on a Krüss K10ST instrument.

The Langmuir balance used for the measurement of compression isotherms is a LB 5000 model from KSV, Finland.

## *C.M.C. measurements*

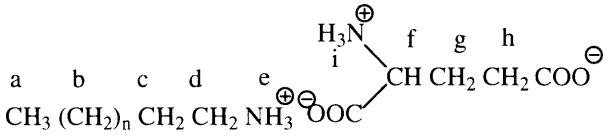
The direct dispersion of **2** in water being difficult for the compounds bearing long hydrophobic chains, we have dissolved these products in ethanol before preparing the final samples. It had been shown before that ethanol concentrations up to 2% in water do not influence the surface tension of the solution. For all the samples prepared the ethanol content is therefore inferior to 2%. Measurements have been carried out at 21°C after equilibration of the solutions during 30 min.

## *Syntheses*

### a) 1rst strategy

*Salts of glutamic acid* **1**: 0.2 mol of alkylamine dissolved in 40 ml of methanol are added dropwise to 0.2 mol of glutamic acid in 60 ml of water. After stirring for 20 min the salt precipitates. It is collected on a filter, washed with methanol and dried *in vacuo*. The product is a white solid. Analysis:

**Formula**

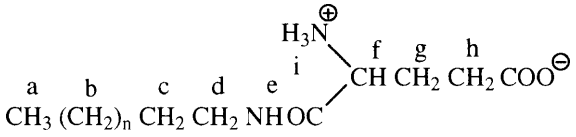



| | | | | |
|---|---|---|---|---|
| **Chain length n** | 11 | 13 | 15 | 17 |
| **Yield %** | 98 | 75 | 77 | 80 |
| **Mp °C** | 143 | 138 | 134 | 138 |
| **IR ν(COO⁻) cm⁻¹** | 1,637.8 | 1,635.7 | 1,637.8 | 1,635.7 |

**$^1$H-NMR** for n = 11 (solvent $CDCl_3$ + TFA*): a (0.99; t; 3H; J = 40); b (1.39; s; 18H); c (1.75; t; 2H; J = 80); d (3.08; t; 2H; J = 80); e (6.55; t; 3H; J = 80); f (4.25; s; 2H); g (2.23; m; 2H); h (2.75; t; 2H; J = 80); i (7.38; s; 3H). *TFA = Trifluoroacetic acid.

*Monoamides* **2**. 1 mol of the salt **1** is dispersed in 750 ml of xylene in a reactor equipped with a magnetic stirrer and a Dean-Stark separator. After addition of 10 drops of $H_2SO_4$ the mixture is refluxed until the expected volume of water is obtained (~48 h). The raw product is diluted with ether and the precipitate filtered off and dried *in vacuo*. The compound obtained is a white powder. Analysis:

**Formula**



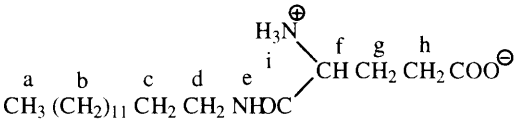

| | | | | |
|---|---|---|---|---|
| **Chain length n** | 11 | 13 | 15 | 17 |
| **Yield %** | 74 | 72 | 63 | 49 |
| **Mp °C** | 109 | 109 | 109.5 | 104 |
| **IR ν(COO⁻) cm⁻¹** | 1,703.2 | 1,708.8 | 1,709.0 | 1,710.9 |

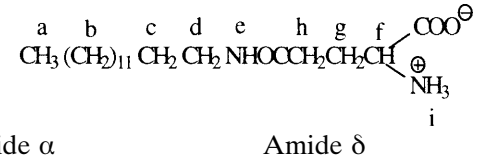
**$^1$H-NMR** for n = 11 (solvent $CDCl_3$ + TFA): a (1.2; t; 3H; J = 40); b (1.41; s; 18H); c (1.64; t; 2H; J = 40); d (3.36; t of d; 2H; J = 40); e (6.57; s; 3H); f (4.48; t; 2H; J = 40); g (2.2; q; 2H; J = 40); h (2.64; t; 2H; J = 40).

*Monoamides α and δ.* In a reactor equipped with a magnetic stirrer 1 g of glutamic acid blocked in the α-position (BOC Glu O$^t$Bu) or in the δ-position (BOC Glu(O$^t$Bu) OH) is

dissolved in 15 ml of acetonitrile, together with 1 equivalent of triethylamine and 1 equivalent of BOP. Another equivalent of triethylamine and 1 equivalent of long-chain alkylamine are added simultaneously and the mixture is stirred at room temperature for 4 h. The solvent is distilled off and the yellow residue is dissolved in 50 ml of ethylacetate. After several extractions with acid and basic aqueous solutions, the organic phase is dried over magnesium sulphate, and the solvent removed *in vacuo*. The product obtained is dissolved in a mixture of 15 ml of trifluroacetic acid (TFA) and 15 ml of dichloromethane. The mixture is stirred for 2 h at room temperature and then evaporated under reduced pressure. Analysis:

**Formula**



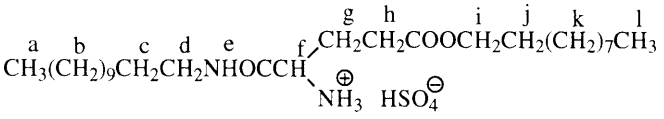


| | Amide α | Amide δ |
|---|---|---|
| **Yield %** | 94 | 92 |
| **Mp °C** | 60 | 208 |
| **IR ν(COO⁻) cm⁻¹** | 1,663.8 | 1,639 |

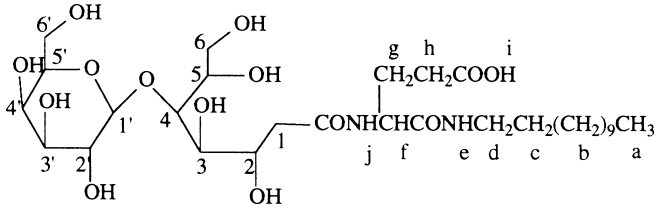
**$^1$H-NMR** (solvent $CDCl_3$ + TFA):

Amide α: a (0.9; t; 3H); b (1.31; s; 18H); c (1.60; t; 2H); d (3.4; t of d; 2H); e (7.25; s; 3H); f (4.47; t; 2H); g (2.35; q; 2H); h (2.91; t; 2H); i (7.70; s; 3H)
Amide δ: a (1.0; t; 3H); b (1.4; s; 18H); c (1.64; t; 2H); d (3.34; t of d; 2H); e (7.35; s; 3H); f (4.53; t; 2H); g (2.58; q; 2H); h (2.92; t; 2H); i (7.75; s; 3H)

*Amidoester of glutamic acid* **3**. 40 mmol of monoamide **2** are dispersed in 250 ml of toluene in a reactor equipped with a Dean-Stark separator. After addition of 0.6 equivalent of $H_2SO_4$ the mixture is refluxed for 48 h. The residue is washed with ether and the product is recovered in the form of a viscous brown oil after evaporation of the solvent. Yield: 81%. Formula:

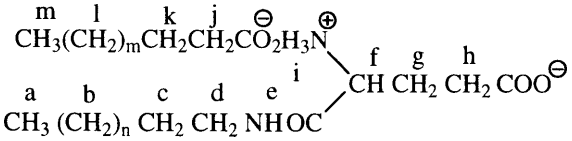


Analysis: **IR** (ν(COOR): 1,735 cm$^{-1}$; (ν(CONH): 1,684 cm$^{-1}$; **$^1$H NMR** for n = 11 ($CDCl_3$): a, l (0.9; t; 3H); b (1.30; s; 18H); c (1.65; t; 2H); d (3.5; t of d; 2H); e (6.25; s; 3H); f (4.6; t; 2H); g (2.21; q; 2H); h (2.72; t; 2H); i (3.54; t; 2H; J = 40); j (1.72; t; J = 40); k (1.31; s; 14H)
*Surfactant* **4**. 3.8 mmol of lactobionic acid are dispersed in a solution of $^1/_2$ equivalent of sodium hydroxyde in 25 ml of methanol. At 45°C 1 equivalent of monoamide **2** dissolved in the same medium is added and the mixture stirred at this temperature for 5 days. After filtration the solvent of the liquid phase is evaporated under vacuum and the solid obtained is extracted with ether.
Yield 30.7%; Analysis: Mp 110.5°C; **IR** (ν(COOR): 1,654.1 cm$^{-1}$; (ν(CONH): 1,710.5 cm$^{-1}$)
Formula:



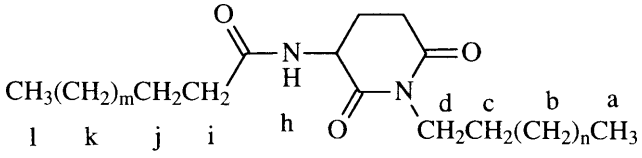
**$^1$H NMR** ($D_2O$ + TFA). Aminoacid substructure: a (0.86; t; 3H); b (1.29; s; 18H); c (1.55; t; 2H); d (3.29; m; 2H); e (6.80; s; 3H); f (4.42; t; 2H); g (2.35; q; 2H); h (2.61; t; 2H).
Sugar substructure: CHOH; $CH_2OH$; OH (1 to 6 and 1′ to 6′): 3.3 to 5.1 ppm; 22H.

*Alkylcarboxylate of glutamic acid monoamide* **5**. 0.02 mol of glutamic acid monoamide **2** is dissolved in a hot mixture of 30 ml of methanol and 10 ml of water. 0.02 mol of alkylcarboxylic acid, solubilized in 30 ml of methanol, is added to the mixture under vigorous stirring. After cooling to ambient temperature the salt precipitates. Filtration, rinsing with methanol, and drying *in vacuo* yields a white solid. Analysis:

| **Formula** |  | | | |
|---|---|---|---|---|
| **Chain length n** | 9 | 11 | 11 | 11 |
| **Chain length m** | 8 | 8 | 10 | 12 |
| **Yield %** | 90 | 95 | 97 | 96 |
| **Mp °C** | 75 | 71 | 68 | 70 |
| **IR ν(COO⁻) cm⁻¹** | 1,733 | 1,731 | 1,734 | 1,731 |

**$^1$H-NMR** for n = 9, m = 8 (solvent $CDCl_3$ + TFA): a, m (0.87; t; 6H; J = 7.05); b, l (1.26; s; 26H); c (1.51; t; 2H); d (3.26; t of d; 2H; J = 6.7); e (6.40; t; 1H); f (4.18; t; 1H); g (2.20; m; 2H); h (2.54; m; 2H); i (7.80; s; 3H); J (2.33; t; 2H; J = 7.5); k (1.62; t; 2H; J = 7.45).

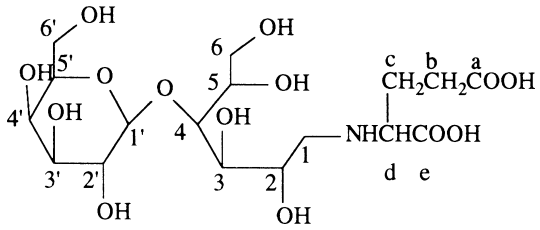
*Cyclic imide* **7**. 5 mmol of alkylcarboxylic acid chloride is added dropwise to 5 mmol of glutamic acid monoamide **2** molten at 130°C in a reactor under inert nitrogen atmosphere. The temperature is maintained as long as an evolution of gaseous HCl is observed. The brown solid obtained after cooling is dissolved in hot ethanol. The product precipitates after cooling the solution to −5°C. Filtered and dried under vacuum it appears as a white solid. Analysis:

| **Formula** |  | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Chain length n** | 9 | 11 | 9 | 11 | 13 | 15 | 17 | 15 | 17 |
| **Chain length m** | 8 | | | | 10 | | | | 12 |
| **Yield %** | 55 | 50 | 50 | 62 | 52 | 56 | 30 | 55 | 56 |
| **Mp °C** | 137 | 137 | 136 | 128 | 128 | 131 | 132 | 132 | 132 |

**IR** $\nu C_n(N\underline{CO}CH_2)$: 1,695 cm$^{-1}$; $\nu C_m(\underline{CO}NH)$: 1,655 cm$^{-1}$; $\nu(\underline{CO}_{cycle})$: 1,740 cm$^{-1}$;
**$^1$H-NMR** for n = 9, m = 8 (solvent $CDCl_3$ + TFA): a, l (0.87; t; 6H; J = 7.05); b, k (1.27; s; 26H); c (1.48; t; 2H; J = 6.55); d (3.27; t of d; 2H); e (2.64; m; 2H); f (2.27; m; 2H); g (4.70; t; 2H); h (6.57; t; 1H); i (2.98; t; 2H); j (1.62; t; 2H; J = 7.05).

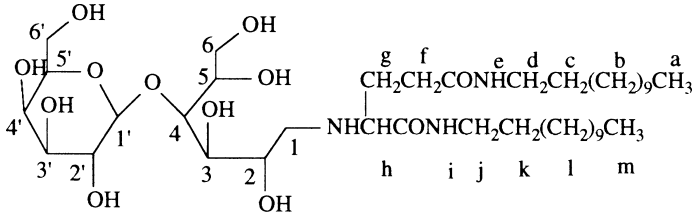
b) 2$^{nd}$ strategy

*Glutamic acid lactosamine.* 0.05 mol of lactose and 0.03 mol of glutamic acid are dissolved in a mixture of 100 ml of isopropanol and 60 ml of water. After stirring for 24 h at room temperature, a two-phase system is formed. It is refluxed for 1 h at 60°C and then cooled in an ice bath. A solution of 0.04 mol of $NaBH_4$ in 30 ml of water is added dropwise to the mixture. After warming up to room temperature 2 g of Amberlite (R) IR 120 (acid form) suspended in 10 ml of water are added portionwise and the solution is stirred for another 30 min. The two phases are separated, the lower phase evaporated to dryness, redissolved in toluene and filtered. After removing the solvent, the solid product is dried under vacuum. Yield: 82.4%. Formula:



Analysis: Mp > 250°C; **IR**: ν(CONH): 1,552 $cm^{-1;}$
**$^{13}$C NMR** ($D_2O$) Aminoacid substructure: a (178); b (34); c (28.5); d (55); e (182).
Sugar substructure: 1 (71.5); 2 (49.5); 3 (55.3); 4 (71.5); 5 (63.5); 6 (75.5); 1′ (105); 2′ (69); 3′ (73.2); 4′ (73); 5′ (63.5); 6′ (61).

*Glutamic acid lactosamine diamide* **8**. 2 equivalents of monalkyl amine and 2 equivalents of triethylamine are added slowly to a mixture of 4.3 mmol of glutamic acid lactosamine dissolved in 20 ml of dimethylformamide, 2 equivalents of BOP (benzotriazolyl-oxy-tris(dimethylamino) phosphonium hexafluorophosphate) and 2 other equivalents of triethylamine under vigorous stirring. The reaction mixture is stirred for 1 week at room temperature. The solvent is removed under reduced pressure and the solid product redissolved in 50 ml of ethylacetate. The organic solution is washed several times with acid and basic aqueous phases. The organic phase is dried over magnesium sulphate, and the solvent evaporated under vacuum. Yield: 55%. Formula:



Analysis: Mp 110.5°C; **IR** ν(CONH): 1,754 $cm^{-1}$.
**$^{1}$H NMR** ($D_2O$ + TFA):
Aminoacid substructure: a, m (0.89; t; 6H); b, l (1.40; s; 36H); c (1.55; t; 2H); d, j (3.20; t; 4H); e (6.90; s; 1H); f (2.64; t; 2H); g (2.20; q; 2H); h (2.50; t; 2H); i (7.30; s; 1H); k (2.65; t; 2H).
Sugar substructure: CHOH; $CH_2OH$; OH (1 to 6 and 1′ to 6′); 3.2 to 4.9 ppm; 22H.

## Conclusion

Different methods for the synthesis of surface active derivatives of glutamic acid have been developed. They give access to a family of zwitterionic monosubstituted monoamides of glutamic acid with excellent yields. The compounds obtained show good surface properties. Whereas the first strategy of synthesis did not give an easy access to bicatenar surfactants with polar headgroups of the sugar type, the second method provided these compounds with satisfactory yields. These surfactants are particularly attractive since they form a variety of molecularly organised systems such as lamellar phases, bilayers, vesicles, etc. The second strategy described here is easily upgradable for the preparation of larger amounts of substances. The surfactant properties of the different families of products obtained have still to

be evaluated in detail, and their bacteriostatic and hemolytic activity to be examined.

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