Synthesis, characterization and surface-active properties of surfactants having dipeptidyl linkage as hydrophilic group

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A homologous series of surfactants, N-(phe-gly) glycerol ether, has been synthesized from phe-gly dipeptide and product of the reaction of epichlorohydrin and aliphatic alcohols with alkyl chains of 10-15 carbon atoms. Specifically, the critical micelle concentration, effectiveness of surface tension reduction, maximum surface excess, minimum surface area and standard free energies of micellization and of adsorption have been determined from aqueous surface tension measurements using the Wilhelmy plate technique. All the surfactants have good surface properties and wetting capability. They are slightly soluble in water and highly soluble in alkaline methanol and alkaline water. As compared to the tryptophan-based surfactants, the studied surfactants have low CMC.

Experimental
Pure epichlorohydrin, aliphatic alcohols with 10-15 carbon atoms, pure toluene, sulfuric acid, absolute methanol, chloroform and hexane were supplied by Merck (Darmstadt, Germany) and dipeptide phenylalanyl-glycine (phe-gly) by Nova Biochem (Lauffelfingen, Switzerland).

Progress of the reaction as well as the purity of intermediates were monitored by thin layer chromatographic analysis, which was performed on aluminum sheets coated with silica gel (Mark) with chloroform as developing solvent. All the surfactants have good surface properties and wetting capability. They are slightly soluble in water and highly soluble in alkaline methanol and alkaline water. As compared to the tryptophan-based surfactants, the studied surfactants have low CMC.

Preparation of N-[3-alkyloxy-2-hydroxy propyl]-phenylalanyl glycine 4(a-f)
A solution of absolute methanol containing 0.01 mmol of 1(a-f) with 0.015 mmol of phe-gly (2) with approx. 0.5 g of sodium hydroxide...
(until pH 12) was stirred under reflux for 6-7 hr. The reaction was monitored by TLC (ninhydrin solution)\(^{11}\) (Scheme 1).

The solution containing compounds 3(a-f) was adjusted to pH 3 with a 10% aqueous solution of hydrochloric acid. Under these conditions 4(a-f) precipitated as white solids. The solids were filtered, washed three or four times with distilled water and finally with methanol and dried under vacuum. The solids were purified by solubilization in alkaline methanol and then clarified with charcoal. The precipitation was carried out with 10% HCl at pH 3. This process was repeated several times to obtain white solids corresponding to products 4(a-f). The surfactants 4(a-f) were characterized by elemental analysis as summarized in Table 1.

### Surface tension measurements

Surface tension measurements at equilibrium were carried out with a KSV sigma 70 tensiometer (Hamburg, Germany) fitted with a Wilhelmy plate and thermosted with temperature control of 25 ± 0.2°C. All solutions containing compounds 4(a-f) at different concentrations were prepared at pH 12 with deionized water and 0.1 \(N\) NaOH and stored in closed glass bottles for 24 hrs before measurement. For the very dilute solutions \((1 \times 10^{-6}-1 \times 10^{-3} M)\) an aging time of 50 min for equilibrium was allowed, whereas for the highly concentrated solutions \((1 \times 10^{-3} M)\), the time was 20 min.

#### Results and discussion

The synthetic pathways for the preparation of proposed compounds are outlined in Scheme 1. There are three steps: (i) preparation of mono substituted chlorohydrins 1(a-f); (ii) alkylation of \(\alpha\)-amino group of phenylalanine of dipeptide phe-gly 3(a-f); and, (iii) preparation of pure \(N[3-(alkyloxy)-2-hydroxy propyl] phenylalanyl-glycine\) 4(a-f).

In the second step, the peptide nitrogen of dipeptide phe-gly does not interfere with alkylation of the \(\alpha\)-amino group of phenylalanyl part of dipeptide because its lone pair is delocalized and has secondary hydrogen which is not readily available for alkylation in the presence of primary hydrogen at this group. Surfactants 4(a-f) were obtained in good yields and their melting points were higher than those of tryptophan\(^{11}\). They were obtained as white crystalline solids that were slightly soluble in water and soluble in alkaline methanol and alkaline water solutions with an isoelectric range of pH 4-10 (i.e. the pH at which the mobility of ionic micelles is zero). Their purity was more than 99\% as observed through elemental analysis. Their physical and analytical data are summarized in Table 1.

For all compounds 4(a-f), the IR spectra showed adsorption bands in the region 3400-3240 cm\(^{-1}\), which were due to OH and NH stretching vibrations. Adsorption peaks at 1580 and 1610 cm\(^{-1}\) suggest the existence of carboxylate in (COO\(^-\)) and alkylamine (–NH) as a zwitter ion.
The $^1$H NMR spectra were in accordance with the proposed structures and contained all expected chemical shifts for both the alkoxypropanol and phenylalkyl-glycine moieties. Since the compounds are soluble only in alkaline methanol, the labile protons (OH, NH, and COOH) could not be detected.

Also, the protons attached to the hetero atoms and the protons of the phe-gly moiety gave a series of complex multiplets in the 2.50-3.75 ppm region. The $^{13}$C NMR spectra were more informative. All the carbons gave characteristic chemical shifts close to calculated values. It is worth mentioning that some of the carbonyl carbons gave two peaks corresponding to two diastereoisomeric structures. Since compounds 4 have two asymmetric centres, they are mixtures of two diastereoisomers (DL and LL).

The mass spectrum of compound 4a, having a hydrophobic alkyl chain of 10 carbon atoms, showed a molecular ion peak corresponding to $[M+H]^+$ at $m/z$ 437 as well as fragments corresponding to ions $[M+H]^+–[N\text{H}=\text{CH}_2]$ at $m/z$ 406, $[M+H]^+–[\text{CO+H}_2\text{O}]$ at $m/z$ 391, and $[M+H]^+–[\text{C}_6\text{H}_5]$ at $m/z$ 359, $[M+H]^+–[\text{C}_8\text{H}_{16}]$ at $m/z$ 325 and $[M+H]^+–[\text{OH-R}]$ at $m/z$ 279. In general, compounds 4(a-f) showed the same fragmentation pattern. These data, along with elemental measurements, are also in agreement with the assigned structure 4 (Scheme 1).

**Surface active properties of surfactants 4(a-f)**

The compounds 4(a-f) are insoluble in aqueous solution in the pH range 4-10. Consequently, the surface-active study of compound 4 was undertaken in alkaline solution at pH 12. It is assumed that at this pH, surfactants 4(a-f) behave as carboxylate containing anionic surfactant with aromatic residues. Figure 1 shows plots of surface tension ($\gamma$) versus log $C$ (logarithmic values of surfactant concentration) for all surfactant homologs 4(a-f) in alkaline solution. The surface active parameters, such as critical micelle concentration, effectiveness of surface tension reduction ($\pi_{\text{cmc}}$), efficiency of adsorption ($pC_{20}$), minimum surface area ($A_{\text{min}}$) and maximum surface excess ($\Gamma_{\text{max}}$) were determined from the curves at 25°C (Table 2). The CMCs were determined from intersection points in the $\gamma$ versus log $C$ plots. The absence of a minimum in the curves reflects the high purity of the new compounds. The CMC values were found to decrease as the number of methylene groups (-$\text{CH}_2$-) in the alkyl side chains gradually increased from decyl chain up to pentadecyl chain$^{13,14}$. This was seen from log CMC versus number of C-atoms in alkyl side chains in surfactants. This usually happens in a homologous series of anionic, cationic and nonionic surfactants$^{15-17}$. The decrease in CMC values can be attributed to a decrease in the solubility of the surfactant molecules, i.e., the hydrophobicity of the surfactant molecule increases with the increase in the number of methylene groups. The molecules having longer alkyl chain tend to form micelles at lower concentrations overcoming the repulsion resulting from their head groups in the aqueous medium.

The surface tension ($\gamma$) is not affected by the change in concentration above CMC, and hence $\gamma$ values at the CMC were used to calculate surface pressure (effectiveness) values: $\pi_{\text{cmc}}=\gamma^0–\gamma$, where $\gamma^0$ is the surface tension measured for pure water at the appropriate temperature and $\gamma$ is the surface tension at the CMC. There is a regular decrease in $\gamma_{\text{cmc}}$ with increasing alkyl chain length of the 4(a-f) as expected$^{11,13,16}$. The most efficient surfactant is the one which lowers the surface tension most at the CMC.

The values of ($\Gamma_{\text{max}}$) have been calculated using the Gibbs adsorption equation, $\Gamma_{\text{max}}=1/nRT\ [d\gamma/d\ln C]$, where $\Gamma_{\text{max}}$ is the surface excess, $d\gamma$ is the surface pressure, $C$ is the concentration and $n$ is the number of particles furnished by each molecule of the surfactant in solution which is 2 (uni-univalent electrolyte).

![Fig.1—Surface tension versus log C plots for surfactants 4(a-f) in aqueous solution at pH 12.](image-url)
The average area occupied by the surfactant molecule at the air/water interface of the surfactant solution, i.e., the minimum surface area \(A_{\text{min}}\) and has been calculated using the equation, \(A_{\text{min}} = 10^{4/N} \times \Gamma_{\text{max}}\), where \(N\) is the Avogadro's number. The surface excess, \(\Gamma_{\text{max}}\), and the area per molecule \(A_{\text{min}}\) vary with the molecular structure, showing a larger area per molecule with increasing alkyl chain length which indicates that the molecules are less tightly packed at the air/water interface for the flexible, longer alkyl chain surfactants.\(^{12}\)

Further, the values of efficiency of adsorption, \(pC_{20}\), are useful in comparing the efficiency of adsorption of surfactant on air/water interface\(^{17}\). The larger the \(pC_{20}\) value, the more efficiently the surfactant is adsorbed at the interface and the more efficiently it reduces surface tension. This increases quite linearly with the increase of number of carbon atoms in alkyl chain of surfactants \(4(a-f)\) (Table 2). The numerical values of \(pC_{20}\) of the phe-gly based surfactants are certainly some units higher than those of the tryptophan surfactants.\(^{11}\)

The synthesized surfactants are always negative, indicating that micellization is a spontaneous process. At a constant temperature, \(-\Delta G^0_{\text{mic}}\) increases with an increase in the number of carbon atoms throughout the surfactant molecules (Table 2). Further, \(\Delta G^0_{\text{ads}}\) values have been calculated using the relation, \(\Delta G^0_{\text{ads}} = \Delta G^0_{\text{mic}} - 6.023 \times 10^{-4} \pi_{\text{mic}} A_{\text{min}}\).

An increase in \(-\Delta G^0_{\text{ads}}\) values supports the idea of micellization over adsorption on the solution surface to overcome the repulsion forces occurring at the water/hydrophobe interface (Table 2). The values of \(\Delta G^0_{\text{ads}}\) and \(\Delta G^0_{\text{mic}}\) are always negative due to the spontaneity of these two processes.

The present investigation has proved that the incorporation of dipeptide, such as phe-gly into alkyl monoglyceride ether derivatives yields novel glycerol-type surfactants with better surface properties. Such surfactants may be used as ecofriendly surfactants so as to reduce the problem of chemical pollution caused by commonly used conventional synthetic surfactants. These anionic surfactants are recommended as detergents, emulsifiers, wetting agents and antistatic agents. They may also be used as lubricants and corrosion inhibitors.

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References