New Non-ionic Surfactants: Alkyl Polyoxyethylene Diethers of Isomeric Dimethylxanthines

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ABSTRACT

Novel isomeric nonionic surfactants of the polyoxyethylene (POE) ether type possessing terminal dimethylxanthine functions related to caffeine have been prepared using a polyoxyethylene cetyl monoether as the starting material. The surface tension properties indicate that, compared to the parent compound and its chloride derivative, these derivatives show pronounced changes in the critical micelle concentration (CMC) and pre-CMC slope but relatively minor changes in the minimum surface tension value. The findings are discussed also in terms of efficiency and effectiveness of surfactants. The evidence indicates that the structure of the terminal hydrophilic portion can have a significant effect on interfacial packing. The cloud points of the chloride derivative and the xanthine derivatives were considerably lower than that of the parent ether. Cloud point curves for the ether, the chloride, and the xanthines over the dilute concentration range show similar features.

INTRODUCTION

In the literature there have been few reports of the preparation and properties of terminal derivatives of polyoxyethylene nonionic surfactants, as exemplified by the cetyl ether, cetomacrogol (I), involving substitution of the hydroxyl group.

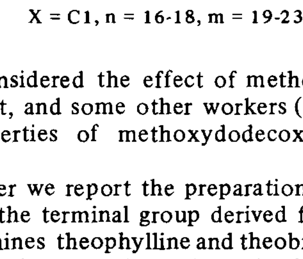
$$C_2H_{2n+1}\cdot[O.CH_2.CH_2]_m.X$$

$$X = OH, n = 16\text{-}18, m = 19\text{-}23 \qquad (I)$$

$$X = Cl, n = 16\text{-}18, m = 19\text{-}23 \qquad (II)$$

Schott (1) considered the effect of methoxyl substitution on cloud point, and some other workers (2,3) reported the micellar properties of methoxydodecoxyethylene decyl ether.

In this paper we report the preparation of nonionic surfactants with the terminal group derived from the isomeric dimethylxanthines theophylline and theobromine (III, IV), which may be classed as derivatives of caffeine. These compounds were prepared by reacting the chloride derivative (II) of cetomacrogol with excess of the sodium salt of the appropriate dimethylxanthine (theophylline and theobromine).



$R^1 = C_nH_{2n+1}\cdot[O.CH_2.CH_2]_m$, R^2 = Me (III)
(Theophylline R^1=H,R^2=Me)

R^1 = Me, $R^2 = C_nH_{2n+1}\cdot[O.CH_2.CH_2]_m$ (IV)
(Theobromine R^1=Me,R^2=H)

The dimethyl xanthines possess strongly polar moieties in the molecule and are sparingly soluble in water. We considered that the ability of alkylxanthines to self-associate in aqueous solutions (4) might alter the interfacial and micellar properties of these nonionic surfactants. Accordingly, we have examined the effect on the surface tension and cloud point of hydroxyl replacement by dimethylxanthines and chloride.

EXPERIMENTAL PROCEDURES

Materials

Cetomacrogol 1000 B.P.C. (Glovers Chemicals Ltd., Leeds, England), thionyl chloride (Riedel, Seelze 1, West Germany), pyridine A.R. (Mallinckrodt, St. Louis, MO), and theobromine (Merck, Darmstadt, West Germany) were used *without further purification*. The same batch of cetomacrogol was used throughout this work. Theophylline (Boehringer-Ingelheim, West Germany) was recrystallized from water, mp 272-275 C. Doubly distilled deionized water was used for the preparation of all surfactant solutions.

Preparation of the Caffeine Derivatives of the Cetyl Polyether

The chloride derivative of the parent ether was prepared in the standard manner using thionyl chloride in the presence of pyridine. The white wax obtained from the reaction was purified by repeated benzene extraction from its hot aqueous solution (5) and then recrystallized from isopropyl ether. It was characterized as *the chloride* by IR spectroscopy and microanalysis (Cl found 3.11, calculated 3.15% on the basis of MW 1130).

The dimethylxanthines were converted to their sodium salts by reaction with an equivalent quantity of sodium hydroxide in aqueous solution and subsequent evaporation of solvent. The sodium salts were then reacted in at least 100% excess with the chloride derivative of cetomacrogol in 2-ethoxyethanol under reflux. A crude wax was obtained by benzene extraction of the concentrated reaction mixture. The material was purified first by toluene extraction of the oil which precipitated from the heated aqueous solution (5), and then by precipitation as its hydrochloride using hydrogen chloride in anhydrous alcoholic-ether or ether, followed by reformation of the base.

The structures of the theobromine and theophylline derivatives (III, IV) were confirmed by their IR spectra (sharp double peak at 1650 and 1700 cm^{-1}, characteristic of methylxanthines, and a broad band between 1075 and 1150 cm^{-1}, typical of $(C_2H_4O)_n$), UV absorption (λ_{max} 272-274 nm, characteristic of caffeine), and NMR spectra in D_2O, δ 1.30 (ca. 30H, s, CH_2) δ 3.65-3.75 (ca. 90H, s, C_2H_4O,N-CH_3). Nitrogen analysis was as follows: theophylline derivative (III) 4.45%, theobromine derivative (IV) 4.24% (calculated 4.41% on basis of MW 1270). The refractive indices (n_D^{60}) of the materials were: parent ether (I) 1.4518, chloride (II) 1.4513, theophylline derivative (III) 1.4653, *theobromine* derivative (IV) 1.4618.

Surface Tension

The du Nouy ring method was employed at 25 C using

TABLE I

Surface Tensions, CMC Values, and Molecular Areas of Cetomacrogol and Derivatives

	CMC (10^3 g/l)	Surface tension at CMC γ (dynes/cm)	Pre-CMC slope ($d\gamma$/dlog C)	Area per molecule ($Å^2$)
Cemtomacrogol (I)	12	40.0	11.8	80
Chloride (II)	8.3	39.2	12.2	76
Theophylline derivative (III)	3.9	37.0	18.6	51
III-HCl	3.9	38.7	18.2	52
Theobromine derivative (IV)	5.5	38.9	16.7	57
IV-HCl	3.3	39.6	19.5	49

the usual precautions (6) and corrections (7). The critical micelle concentration (CMC) values for cetomacrogol (I) agree with those of Hugo and Newton (8) measured by surface tension and light absorption. The molecular areas were calculated from the slope of the linear portion of the γ-log C plot near the CMC using the simplified Gibbs equation (9,10) in the region of saturation absorption (11,12).

Cloud Point Measurements

A sample of 10 ml in a small Erlenmeyer flask fitted with a thermometer (0.1 C accuracy) was stirred magnetically and heated in a water bath. The temperature at which the solution became visibly turbid was taken as the cloud point. The readings were reproducible to within 0.5 C.

Apparatus

IR spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer, UV spectra were recorded on a Unicam SP 1800 Spectrophotometer, and NMR spectra were recorded on a JEOL C-60H Spectrometer. Surface tensions were measured on a Fisher semi-automatic Surface Tensiometer with a 6 cm circumference platinum ring. An Abbe 60 Refractometer was used for the measurement of refractive index.

RESULTS AND DISCUSSION

Surface Activity

Surface tension-log concentration plots were made for cetomacrogol (I), its chloride derivative (II), the xanthine derivatives (III, IV), and their corresponding hydrochloride salts in aqueous solutions. Curves typical of surface-active agents showing sharp breaks at the CMC were obtained, the straight line portion below the CMC extending over a 20- to 30-fold concentration range. Their slopes, representing the regions of saturation adsorption, were used to calculate average areas per molecule. Calculated areas per molecule, CMC values, and surface tension values above the CMC are given in Table I.

From the results it is evident that xanthine substitution in the terminal hydroxyl position of the 19-23 POE chain significantly enhances the efficiency of these molecules as surface-active agents, as measured by the concentration required to produce a given reduction in surface tension, using Rosen's definition (13). The minimum value to which a surfactant can lower the surface tension, termed the effectiveness, frequently runs counter to the efficiency of a surfactant (13). However, with these derivatives the effectiveness is also enhanced. The CMC values are reduced progressively by substitution of the hydroxyl group by chlorine and the xanthine groups, respectively, consistent with reduced hydrophilicity of the surfactant molecule.

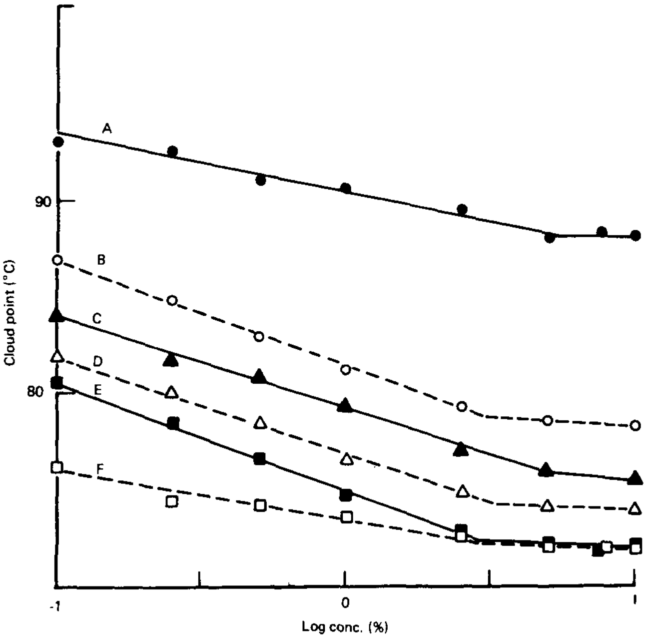


FIG. 1. Cloud point curves of cetomacrogol and derivatives: A = I, B = IV-HCl, C = IV, D = III, E = III-HCl, F = II. The numbering corresponds to that in Table I. Cloud points measured in water except for A in 1N NaCl.

The slope values show that cetomacrogol (I) and its chloride derivative (II) behave similarly, whereas in the isomeric xanthine derivatives (III, IV) the slope is considerably increased. There is no appreciable difference between the xanthines. The increase in slope means that the areas per molecule have been significantly lowered (Table I), while the average number of EO and alkyl CH_2 groups have been kept constant. The effect of the insertion of the xanthines is thus equivalent to a reduction in the number of EO groups. The pre-CMC slopes and the areas per molecule of the xanthine derivatives are equivalent to an effective reduction in EO group number from 24 to under 14 in this series (14). That this is not just due to removal of the hydroxyl group is shown by the small change observed in the chloride surfactant. It could be that the large planar structure of the xanthines prevents or diminishes the coiling of the hydrated POE chain, the area of the latter determining the area of the molecule (11,14), whereas the hydroxyl and chloride functions do not.

Reduction in surface free energy or in the area per molecule due to a specific orientation of the xanthine at the air-liquid interface seems unlikely, as does xanthine interaction with the hydrocarbon chain, in view of its limited solubility in hydrocarbon solvents. Consequently, it seems that the explanation lies in configurational effects involving the POE chain and/or xanthine ring interactions in water (4,15-17).

It is interesting that the final surface tension values have not been reduced to a significant extent in spite of the large increase in slope. Thus, from Donbrow's calculations (14) we can see that for polydisperse polyoxyethylene n-hexadecanols, an increase in slope from only 11.6 to 15.9 was followed by a more significant drop in surface tension values (38.5 to 34.3) than in the present derivatives (Table I).

The xanthine hydrochlorides (III-HCl, IV-HCl) gave plots and values similar to those given by the bases (Table I), possibly a manifestation of the almost total hydrolysis of the salt in water, the pK_b of the closely related parent compound, caffeine, being 14.2 (Merck Index).

Cloud Point

The variation in cloud point with structure at any one concentration is interesting; thus values at 1% w/v were: cetomacrogol (I) ca. 110 C, (90.7 C in 1N NaCl), theobromine derivative hydrochloride (IV-HCl) 81.1 C, theobromine derivative (IV) 79.3 C, theophylline derivative (III) 78.6 C, theophylline derivative hydrochloride (III-HCl) 74.8 C, and the halide (II) 73.6 C. Schott (1) noted that replacement of the terminal hydroxyl by a methoxyl group depressed cloud point considerably; for example, the cloud point of $C_{12}H_{25}(OCH_2CH_2)_{12}OCH_3$ (78 C) was 22 C below that interpolated for $C_{12}H_{25}(OCH_2CH_2)_{11.5}OH$, both materials having similar calculated HLB values. In reviewing the factors affecting cloud point, Schott (1) considered a variety of structural features in both the hydrophilic and hydrophobic portions, none of which, however, was shown to have such a pronounced effect as obtained here with substitution by chloride and xanthine groups.

The low cloud point of the organic chloride as compared with the more polar parent cetyl ether is expected. However, it is difficult to interpret the variations in cloud point between the xanthine bases and their hydrochlorides, since the acid formed by hydrolysis, which is virtually complete, would be expected to reduce cloud point in both cases due to the salting-out effect.

Earlier workers (1,19) stated that the cloud point is rather insensitive to the concentration of the surfactant. Our results on the cetyl ether in 1N NaCl and the halide in water indicate that the cloud point is influenced by concentration, a 0.1 to 7.5% w/v increase of which causes a fall of ca. 5 C and 4 C, respectively, whereas in the case of both the xanthine derivatives in water, the decrease was as much as 8 C over the same range. In Figure 1 there appears to be a negative linear relationship between the cloud point and the log concentration for all the surfactant solutions up to about 2.5% w/v after which the cloud point tends to become constant. Variations in the cloud points reported for a number of compounds (1) may well be explained by differences in concentrations used for their measurement.

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