

CATIONIC SURFACE-ACTIVE AGENTS

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SURFACE-ACTIVE agents, however these may be defined, fall into two classes :

Ionic surface-active agents, which are substances capable of ionisation in aqueous solution, and

Nonionic surface-active agents, which do not so ionise.

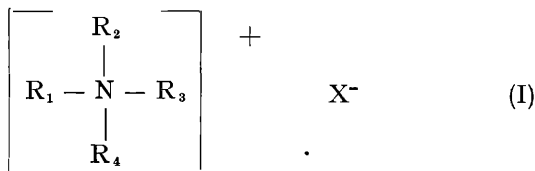
Where the surface-active properties of ionic compounds are associated with the anion the substances are termed *anionic surface-active agents* or simply anionics ; where these properties reside in the cation, *cationic surface-active agents* or cationics. Some compounds can behave both as cationic and anionic agents according to the *pH* of the medium, and this zwitterionic class is referred to generally as *ampholytic*.

The majority of surface-active ions are characterised by a chemical structure which is essentially linear, one end of these linear surface-active ions being composed of radicals which are hydrophilic and the other of hydrophobic radicals.

The ionic surface-active agents may be subdivided according to the nature of the hydrophilic or solubilising group contained by the active ion. Whereas the principal anionics utilise the carboxy ($-\text{COOH}$), sulphonic acid ($-\text{SO}_3\text{H}$) or sulphuric ester ($-\text{OSO}_3\text{H}$) solubilising groups, all cationic agents of major importance contain the basic nitrogen atom and are salts of primary, secondary or tertiary amines, or of quaternary ammonium bases.

Structure

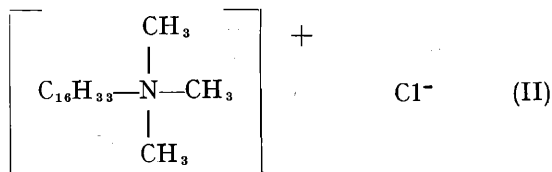
Cationics may therefore be represented by the type structure



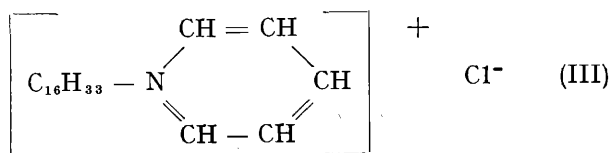
where R_1 , R_2 , R_3 , R_4 are natural or synthetic radicals or hydrogen, at least one of these substituents containing 8 to 22 carbon atoms. Only rarely is more than one substituent hydrophobic, and the remaining groups are commonly H, CH_3 , C_2H_5 or benzyl groups except where the compound is derived from a heterocyclic base, as, for example, with pyridinium and

* Milton Antiseptic Ltd., London, W.1.

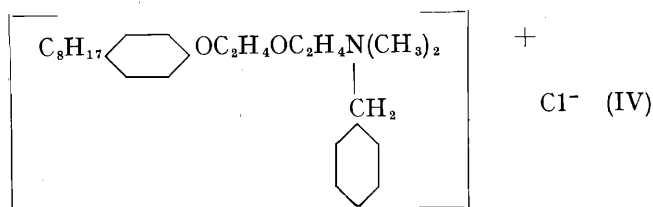
morpholinium salts. Three typical structures of fully substituted cationics are illustrated by cetyltrimethylammonium chloride, cetylpyridinium chloride, and *p-tert*-octylphenoxyethoxyethyl dimethylbenzylammonium chloride.



Cetyltrimethylammonium chloride



Cetylpyridinium chloride

*p-tert*-Octylphenoxyethoxyethyl dimethylbenzylammonium chloride

Cationics which contain one or more hydrogen groups, *i.e.*, non-quaternary compounds, are characterised in that the free base is formed and normally precipitated in alkaline media and so can only be employed effectively in acid solutions. Quaternary ammonium bases are sufficiently strong, however, for their salts to be stable in both acid and alkaline solution, and are only unstable in the presence of alkalis in those instances (*e.g.*, quaternary pyridinium salts) where the free base undergoes decomposition. For this reason, together with the fact that many free amines are primary skin irritants, the surface-active quaternary ammonium compounds are the sole class of cationic agent employed in cosmetic, toilet and pharmaceutical preparations, and discussion will be limited to this type of compound.

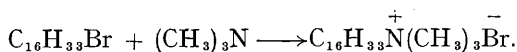
Manufacture

Most quaternary ammonium compounds are manufactured by reacting a tertiary amine with an ester. In some cases the amine or the ester is formed *in situ*. Examples :

Alkyltrimethylammonium Salts

A well-known member of this group of cationics is cetyltrimethylammonium bromide. It may be prepared by one of the following methods :

(a) By reacting cetyl bromide with trimethylamine :

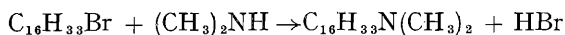


Excess amine is employed, which must be totally removed when isolating the product, traces which cannot be detected by normal analytical methods being sufficient to produce the characteristic fishy odour of trimethylamine.

The cetyl bromide is prepared by the action of anhydrous hydrogen bromide on cetyl alcohol.

The crude cetyltrimethylammonium bromide before purification may contain impurities arising from impure reagents and from side-reactions resulting from inadequate control of the reaction conditions. These impurities can be cetyl alcohol, hexadecene, hexadecyldimethylamine, tri- and tetra-methylamine bromides, among others.

(b) By reacting cetyl bromide (or chloride) with dimethylamine to yield cetyldimethylamine :



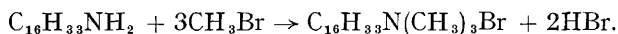
which is isolated and quaternised in the further step :



by reacting with methyl bromide.

This reaction is vigorously exothermic and produces a crude cetyltrimethylammonium bromide which is more readily purified than that from the preceding synthesis.

(c) Cetylamine is reacted with excess methyl bromide in the presence of caustic soda :



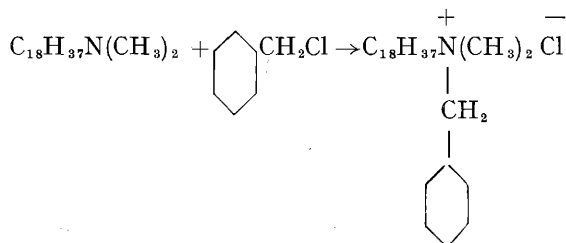
The sodium bromide which is produced in this reaction is difficult to remove completely from the product.

Alternatively, the primary amine may be methylated by reaction with formaldehyde and formic acid, followed by isolating the cetyldimethylamine and proceeding as in (b).

Alkyldimethylbenzylammonium salts

This type of cationic is typified by stearyldimethylbenzylammonium chloride. For this compound, one synthesis only is employed in industry.

Stearyldimethylbenzylammonium chloride.—Stearyldimethylamine is reacted with benzyl chloride :



This reaction is exothermic but the following difficulties are encountered : unless an excess of benzyl chloride is used, the crude product contains free tertiary amine which is difficult to remove ; if an excess of benzyl chloride is employed, this is more difficult still to remove from the product.

Differences between commercial samples of this type of material generally relate to the quantity of free amine, amine hydrochloride, benzyl alcohol and benzyl chloride which are present as impurities.

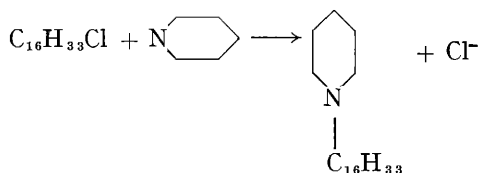
Some attempts have been made to synthesise by reacting the long-chain alkyl halide with benzyldimethylamine :



but the reaction velocity is low and poor yields are obtained. Purification of the crude is more difficult than with the alternative reaction above, and the general economics of the process are unsatisfactory.

Alkyl pyridinium halides

Cetylpyridinium chloride represents this type of compound. One synthesis only is commercially employed, the reaction between cetyl chloride and pyridine, itself a tertiary amine.



The cetyl chloride is prepared by hydrohalogenation of the alcohol under such conditions that no secondary halide is produced.¹

The reaction requires an excess of pyridine and some secondary reactions invariably occur such that isolation of a pure product can only be achieved by crystallising from a suitable solvent.

The alkylpyridinium bromides, in common with other quaternary bromides, are prepared more easily than the corresponding chlorides.

In each of the examples given the hydrophobic radical is united directly to the basic nitrogen atom. Some compounds are used in which the hydrophobic group is united to the ionic group by means of ester, amide or ether linkages, as with many anionic surface-active agents. One such compound is *p-tert*.octylphenoxyethoxyethyl dimethylbenzylammonium chloride² (IV.)

GENERAL PROPERTIES

With the infinite number of compounds which may be produced by varying the nature of the radicals R_1-R_4 attached to the quaternary nitrogen atom it is to be expected that markedly different properties will reside in the various compounds produced. Thus generalisation as to properties of the group as a whole is difficult, and failure to recognise this basic truth has led to many patently inaccurate statements in the literature. It is generally true to say that most cationics will react with anionics and other anions of high molecular weight to form poorly ionised, insoluble compounds, yet marked differences are shown in terms of such "incompatibilities," and one cannot argue from the specific to the general case as has been done by several authors (*e.g.*, Lawrence³).

The influence of modest variation of the groups R_1-R_4 on the properties of a quaternary ammonium compound is illustrated in the series :

cetyltrimethylammonium bromide
stearyltrimethylammonium bromide
cetyldimethylbenzylammonium bromide
stearyldimethylbenzylammonium bromide
stearyldimethylethylammonium bromide

wherein the visual appearance alone of aqueous solutions of the materials shows obvious differences to exist in the physical properties of these compounds.

With anionic detergents the nature of the non-surface-active ion affects the properties of the molecule as a whole, as, for example, the well-known cosmetic differences between the calcium, magnesium, potassium and amine soaps. So also with cationics the nature of the associated anion contributes to the properties of the compound as a whole. Where a quaternary ammonium compound is used in the presence of a particular anion, the properties are dictated by the ionic equilibrium which results. This has been used as the basis of a technique whereby it is possible to prepare

the quaternary salts of any acid, including those of weak or unstable acids, *e.g.*, nitrites, bicarbonates, sulphites, *etc.*⁴

Patents have been granted to workers who have "discovered" that the anion affects the properties of a particular cation, as in the case of the claim that the alkyltrimethylbenzylammonium bromides and iodides are more powerful bactericides than the corresponding chlorides.⁵ Apart from the fact that such differences have been reported previously,^{6,7} these disappear in practice when other substances are present which can displace and control the ionic equilibrium established by solution of the original quaternary salt in water alone. The test technique influences the results obtained also, and it is not uncommon to find that *in vitro* results bear no relation to those obtained *in vivo*.

Cationic surface-active agents possess similar properties to the anionics in respect of their ability to act as detergents, emulsifying agents, to foam, to reduce interfacial tension, *etc.*, but they are rarely used for these properties alone. The development of the cationics has been conditioned by those properties of many compounds of this class which are not possessed by anionics to any marked extent, principally their :

- (a) Bactericidal activity.
- (b) Adsorptive properties.
- (c) Fixation of direct dyestuffs.

Bactericidal Activity

Not all surface-active quaternary ammonium compounds are strongly bactericidal; the activity varies considerably with the structure of the compound in a manner which cannot be directly related to physical properties such as surface tension reduction. Table 1 illustrates the variation of activity observed using one test technique for some closely related compounds. For any one compound the bactericidal activity may be made to appear good or poor simply by varying the bacteriological test technique employed. This frequently makes comparison of results from different authors difficult.

TABLE 1

Method : United States Department of Agriculture, Circular 198. Results expressed as concentration of substance which will kill organisms of standard phenolic resistance in 10 minutes but not in 5.

Substances : Lauryldimethylbenzylammonium bromide (L.D.B.A.B.)
 Cetyldimethylbenzylammonium bromide (C.D.B.A.B.)
 Lauryldimethylbenzylammonium chloride (L.D.B.A.C.)
 Myristyldimethylbenzylammonium chloride (M.D.B.A.C.)
 Cetyldimethylbenzylammonium chloride (C.D.B.A.C.)
 Stearyldimethylbenzylammonium chloride (S.D.B.A.C.)
 Lauryltrimethylammonium bromide (L.T.A.B.)
 Myristyltrimethylammonium bromide (M.T.A.B.)
 Cetyltrimethylammonium bromide (C.T.A.B.)
 Stearyltrimethylammonium bromide (S.T.A.B.)

Author	Temperature	Substance	Organism	
			<i>Staph. aureus</i>	<i>E. typhosa</i>
Shelton, <i>et al.</i> ⁷	37° C.	L.D.B.A.B.	1 : 32,000	1 : 30,000
		C.D.B.A.B.	1 : 76,000	1 : 32,000
Valko and Dubois ⁶	37° C.	L.D.B.A.C.	1 : 40,000	—
		C.D.B.A.C.	1 : 15,000	—
		Mixture of L.D.B.A.C. + C.D.B.A.C.	1 : 27,000*	—
Valko and Dubois ⁶	20° C.	L.D.B.A.C.	1 : 20,000	1 : 16,000
		M.D.B.A.C.	1 : 21,000	1 : 17,000
		C.D.B.A.C.	1 : 14,000	1 : 11,000
		S.D.B.A.C.	1 : 5,000	1 : 7,000
Shelton, <i>et al.</i> ⁷	37° C.	L.T.A.B.	1 : 4,000	1 : 9,000
		M.T.A.B.	1 : 38,000	1 : 36,000
		C.T.A.B.	1 : 80,000	1 : 40,000
		S.T.A.B.	1 : 64,000	1 : 8,000
Valko and Dubois ⁶	20° C.	L.T.A.B.	1 : 6,500	1 : 5,000
		M.T.A.B.	1 : 12,000	1 : 11,000
		C.T.A.B.	1 : 14,000	1 : 10,000
		S.T.A.B.	1 : 9,000	1 : 5,000

* —“the killing dilution is that of L.D.B.A.C. alone.”

The precise mechanism by which micro-organisms are destroyed is not fully understood, although this problem has attracted considerable research (see, *e.g.*, ^{9,10}).

The best known and most widely used bactericidal quaternary ammonium compounds are those employed in medical and pharmaceutical practice, *i.e.*, Cetrimide B.P. and Benzalkonium Chloride B.P.C. and U.S.P. Cetrimide is a mixed alkyltrimethylammonium bromide containing the C₁₂-C₁₆ homologues, while benzalkonium chloride is a mixed alkyldimethylbenzylammonium chloride principally C₁₂-C₁₄. Regrettably, neither compound is subject to exact chemical specification, leading to considerable variations among materials which separately conform to the pharmaceutical requirements.¹¹

In most practical applications, the bactericidal quaternary ammonium compounds are employed in concentrations of the order of 50 to 500 p.p.m. In special cases, for example, when used as detergents with disinfectant properties and also when employed as emulsifying agents in cream preparation, the concentration is increased to 0.5 to 1.0 per cent.

Several reviews of the bactericidal properties and applications of quaternary ammonium compounds have appeared, *e.g.*, those of Lawrence.^{12,13}

Adsorptive Properties

Many quaternary ammonium compounds are strongly adsorbed on solid surfaces. This property has been utilised in many fields ranging from the flotation of minerals to antistatic treatments of plastic goods. They are adsorbed particularly by proteins, notably keratin. This property is one of the most valuable in relation to cosmetic uses of quaternary ammonium compounds, particularly in hair preparations of all types.

The most spectacular effect of the adsorption of quaternary ammonium compounds on the hair is to eliminate scroop from hair which has been washed with anionics, bleached, or permed ; the adsorbed film gives body to fine hair and yet softens coarse hair, is lubricant, and considerably reduces static. A recent paper on this subject is due to Mills, Ester and Henkin,¹⁴ while earlier reviews of this application of quaternary ammonium compounds have been published by Hilfer.^{15,16} The adsorption on skin is of value also in the formulation of barrier creams.

The extent to which any given quaternary is adsorbed is a function of the surface involved, the concentration of the solution, pH and temperature. With any one surface and constant conditions different quaternary ammonium compounds are adsorbed in differing degree. In general the maximum adsorption for cosmetic purposes is found with compounds containing a hydrophobic group comprising 16 to 22 carbon atoms.

Dyestuff Fixation

Direct dyes suffer from the disadvantage that they bleed in water ; the quaternary ammonium compounds prevent or reduce this effect. With these and other dyes, quaternary ammonium compounds may also act as levellers and restrainers, and as a result have come to be fairly widely used in colour rinses, particularly those of the shampoo type. Since actual chemical combination between the dye and the quaternary ammonium compound may occur, it is frequently found that the quaternary ammonium causes a change of shade which must be anticipated when formulating.

The alkyl pyridinium salts appear to be the most popular for this application, but several other quaternary ammonium compounds are also used.

L'Oreal¹⁷ have claimed the preparation of creams with dye content which contain both cationic and anionic surface-active agents.

ANALYSIS

It is clear from the foregoing discussion that comparatively small variations in either structure or purity of a quaternary ammonium compound can result in large variations in properties. Unfortunately many commercially available quaternary ammonium compounds are supplied under misleading names and frequently without specification. Thus "lauryl

pyridinium chloride" may be either a pure C_{12} derivative or, as with commercial grades of sodium lauryl sulphate, a mixture of homologues only part of which is C_{12} . Likewise it is widely believed that cetrimide is synonymous with cetyltrimethylammonium bromide (see, *e.g.*, ¹⁸); cetrimide is not and has never been cetyltrimethylammonium bromide, but simply contained cetyltrimethylammonium bromide as one component, as in the case of a number of products described as "cetyltrimethylammonium bromide."

Traditional methods of analysis cannot readily establish the composition or concentration of a quaternary ammonium compound, and new methods of analysis have had to be devised to resolve these difficulties.^{19,20,21,22}

QUATERNARY AMMONIUM COMPOUND FORMULATIONS

Typical formulations based on quaternary ammonium compounds have been reviewed previously.²³ The present discussion will therefore be limited to uses of major importance and in particular to current trends.

Bactericidal Use

A number of products covering widely different consumer applications are now available which utilise the bactericidal properties of quaternary ammonium compounds. These include antiperspirants and deodorants, barrier creams, antiseptic creams, dandruff remedies, baby creams, lotions and powders, after-shave lotions, together with various pharmaceuticals such as cough syrups and lozenges, oral preparations of antibiotics, and, of course, antiseptic fluids. Of interest in view of the introduction of by-laws governing the conduct of hairdressing establishments is the appearance of a quaternary ammonium compound based disinfectant which has been designed especially for use in hairdressing saloons and beauty parlours.^{24,25}

The vast majority of the above type of products contain as active bactericide either cetrimide, benzalkonium chloride or cetylpyridinium chloride.

Permanent Waving and other Hair Treatments

It has become widespread practice to use a quaternary ammonium compound preparation at one or another stage of permanent waving. The quaternary ammonium compound may be included with thioglycollate in waving lotions or creams, with the neutraliser, or used after the waving process as a conditioner or as a setting lotion. The last two types of product are more frequently used after normal shampooing.

The addition of quaternary ammonium compounds to peroxide bleaches in salon practice is popular, and Hudnut²⁶ have recently claimed the preparation of acid peroxide bleaches containing quaternary ammonium compounds.

Shampoos based on, or containing minor proportions of quaternary

ammonium compounds continue to attract interest. For example, L'Oreal²⁷ have claimed shampoo compositions containing cationic (c. 10 per cent), nonionic detergent (c. 2 per cent), carboxymethyl cellulose (1 per cent) and lactic acid (5 per cent). It would appear, however, that the preferred technique is to use a cationic as a separate treatment, perhaps largely because the cationics cannot compete economically with anionics as ordinary detergents.

In closing, a few remarks may be made concerning formulation of a new quaternary ammonium compound based product. This is simple so long as the quaternary ammonium compounds are not expected to behave like anionics. Except where common sense and experience guide, one should not be put off by the numerous statements in the literature about incompatibilities; the latter are sometimes most advantageous²³ and several compositions containing these incompatibilities have been mentioned in the literature. For example one patent²² claims the employment of the reaction product of equimolecular quantities of anionics and cationics in the preparation of ointments and skin creams. A further example has already been quoted.¹⁷

Viscosity can be increased in quaternary ammonium compound solutions or creams by the addition of gums, cellulose ethers, non-ionics, fatty alcohols, lipids, or by simple inorganic salts. Clear, watery solutions of some quaternary ammonium compounds may be gelled by the addition of a suitable salt. This effect is due to the normal salting-out caused by the electrolyte together with the conversion of part or whole of the quaternary ammonium compound to a new salt.

All other formulation problems are of the type applicable to all cosmetic products.

Acknowledgement

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