Inhibition of cholinesterase activity by two methylacridinium compounds

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9–Azido–10–methylacridinium methosulphate and 9-chloro-10-methylacridinium methosulphate are both monoquaternary ammonium compounds which are hydrolysed in aqueous or alcohol solvents. (Mair & Stevens, 1972). Both compounds have been shown to produce toxic effects in mice which suggest that death may occur as a result of inhibition of cholinesterase enzymes. The present experiments were therefore performed to determine whether these compounds inhibited cholinesterase *in vitro* and also to observe the effect of hydrolysis of the compounds on any inhibition of cholinestrase activity. I_{50} values were determined for both the azido and the chloro compound against purified acetylcholinesterase (AChE) from bovine erythrocytes, purified cholinesterase (ChE) from horse serum and against cholinesterase enzymes from rat brain homogenate. Acetylcholine (ACh) acetyl-β-methylcholine (Ac-β-MeCh) and butyrylcholine (BuCh) were used as substrates and the results are shown in Table 1.

Table 1. I_{50} *values as a molar concentration for the inhibition of cholinesterase activity by azido and chloro methylacridiniums.*

Enzyme	Methylacridinium Azido	Chloro	Substrate
AChE, Bovine erythocytes	$2{\cdot}9 \times 10^{-5}$	$5{\cdot}5 \times 10^{-3}$	ACh
ChE, Horse serum	$1{\cdot}9 \times 10^{-6}$	$3{\cdot}3 \times 10^{-4}$	ACh
	$4{\cdot}2 \times 10^{-6}$	$1{\cdot}2 \times 10^{-3}$	ACh
Rat brain homogenate	$3{\cdot}6 \times 10^{-6}$	$1{\cdot}0 \times 10^{-3}$	Ac-β-MeCh
	$1{\cdot}5 \times 10^{-6}$	$4{\cdot}4 \times 10^{-4}$	BuCh

The method used for determination of cholinesterase activity is a modification of the radiochemical method of Siakotos, Filbert & Hester (1969). The azido compound was shown to be a much more effective anticholinesterase than the chloro methylacridinium and this correlated well with the *in vivo* toxicity of the compounds.

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The effect of hydrotropic salts on the stability of liquid crystalline systems

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A study has been undertaken of the interaction between some short chain quaternary ammonium salts (hydrotropes) and liquid crystalline systems composed of surfactant + water + amphiphile. Photomicrography revealed progressive fragmentation of the liquid crystalline structure (peptization) which in almost all cases resulted in the formation of isotropic liquid (inverted micellar structure) and finally two isotropic liquids in equilibrium. Using the phase nomenclature of Lawrence (1961):

$$100\%\ \mathrm{LC} \rightarrow \mathrm{LC} + \mathrm{L_2} \rightarrow 100\%\ \mathrm{L_2} \rightarrow \mathrm{L_1} + \mathrm{L_2}$$

Some results are presented in Table 1 for an initial 100% LC system (focal conic structure) composed of 15% w/w n-hexadecyl trimethylammonium bromide + 70% w/w water + 15% w/w n-hexanol at 27·5°. Peptization concentrations, expressed as moles of hydrotrope per 100 g liquid crystal, represent the minimum quantity necessary to achieve the 100% L_2 state (mean of three determinations).

Table 1. *Peptization of liquid crystal by hydrotropes.*

Hydrotropic Salt	Concentration (mol/100g) × 10^3	Hydrotropic Salt	Concentration (mol/100g) × 10^3
$C_6H_{11}N^+H_3Br^-$	8·5	$Pr_4N^+Br^-$	9·4
$Me_4N^+I^-$	3·5	$Bu_4N^+Br^-$	24·2
$Me_4N^+Br^-$	4·9	$Pe_4N^+Br^-$	51·0
$Me_4N^+Cl^-$	6·2	$I^-Me_3N^+C_6H_{12}N^+Me_3I^-$	2·0
$Et_4N^+I^-$	3·5	$Br^-Me_3N^+C_6H_{12}N^+Me_3Br^-$	2·8
$Et_4N^+Br^-$	5·0	$Cl^-Me_3N^+C_6H_{12}N^+Me_3Cl^-$	3·3
$Et_4N^+Cl^-$	6·4	$Br^-Me_3N^+C_{10}H_{20}N^+Me_3Br^-$	3·1

The peptizing action of cyclohexylammonium bromide, a salt used in previous studies (Lawrence & Pearson, 1967), is exceeded by the Me_4N^+ and Et_4N^+ salts and by the highly active bis-quaternary ammonium salts; the effect decreases in the counter-ion sequence $I^- > Br^- > Cl^-$ in each case. The activity of the tetra-alkylammonium bromides shows a marked decrease after Et_4N^+ and proton magnetic resonance studies confirm the greater penetration of the higher members into the hydrocarbon regions of the smectic liquid crystals layers. Near infrared spectroscopy indicated that the wider rôle of water structure was involved in the peptization mechanism rather than a simple hydration effect. In addition to possible relevance to biological systems, the studies may provide a basis for a novel approach to the formulation of pharmaceutical preparations containing high concentrations of surfactants.

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Micellar interactions of bile salts with alkyltrimethylammonium bromides

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Numerous biologically-active quaternary ammonium compounds are surface-active. In the intestine these may interact with anionic bile salts to form ion-pairs, mixed micelles or insoluble complexes, which may influence bioavailability and reactivity of either species.

In this study the interaction of unconjugated bile salts, sodium cholate (NaC) and sodium deoxycholate (NaDC), with a model quaternary ammonium compound, tetradecyltrimethylammonium bromide (TTAB), was investigated at 25°. Solubility limits were determined by titrimetry. Homogenous solutions were investigated by surface tension, light scattering and viscosity. Results are summarized in the table.

System NaC mole ratio NaC : TTAB	cmc g ml^{-1} × 10^4 51·7[a]	M.M.W. × 10^{-3} ∿ 1[a]	[η] dl g^{-1} ·039	System NaDC mole ratio NaDc:TTAB	cmc g ml^{-1} × 10^4 20·7[a]	M.M.W. × 10^{-3} ∿ 2[a]	[η] dl g^{-1} ·061
4:1	1·39	8·6	·037	4:1	0·69	14·8	·051
2:1	1·18	12·3	·032	3:1	0·60	17·6	·050
1:1	1·00	14·6	·032	12:5	0·53	65·5	—
1:2	0·91	16·1	·040	2:1	0·52	110·0	·047
1:4	1·13	13·9	·050	1:2	0·54	50·0	·050
1:7	1·38	16·8	—	5:12	0·56	37·0	—
1:10	1·60	16·4	·066	1:3	0·57	16·3	·048
TTAB	11·1[b]	27·3[c]	·077	1:4	0·67	17·7	·052
				1:10	0·73	19·6	—

a Small, 1971; b Barry, Morrison & Russell, 1970; c Barry & Russell, 1972.