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Short communication

3-Alkylthiomethyl-1-ethylimidazolium chlorides. Correlation between critical micelle concentrations and minimum inhibitory concentrations

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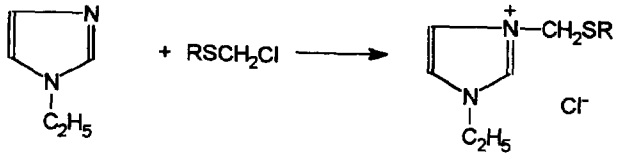
Summary — 3-Alkylthiomethyl-1-ethylimidazolium chlorides were prepared in high yield via an S_N1 reaction. The critical micelle concentration (CMC) values of studied chlorides were determined by surface tensiometry and the hydrophobicity index (HI) was calculated. The minimum inhibitory concentration (MIC) against various microorganisms such as cocci, rods, fungi and bacilli was studied. The quantitative relationship between the MIC, the CMC and the HI was calculated.

3-alkylthiomethyl-1-ethylimidazolium chloride / synthesis / S_N1 mechanism / cationic surfactant / minimum inhibitory concentration / critical micelle concentration / hydrophobicity index

Quaternary ammonium salts may be found in a multitude of products, including cosmetics, pharmaceuticals, common antiseptics, sanitizers, mildew preventives and algicides. A new group of quaternary ammonium salts is 3-alkylthiomethyl-1-ethylimidazolium chlorides **1a–f**, which we found in the reaction of 1-ethylimidazole with chloromethylalkyl sulfide.



1a: R=C_4H_9 **1d**: R=$C_{10}H_{21}$

1b: R=C_6H_{13} **1e**: R=$C_{12}H_{25}$

1c: R=C_8H_{17} **1f**: R=$C_{14}H_{29}$

We found that the reaction of chloromethylalkyl sulfide with 1-ethylimidazole ran according to an S_N1 mechanism. The first slow step of studied reaction is the formation of mesomeric cation which reacts rapidly with 1-ethylimidazole.

$$[\overset{+}{R}S{=}CH_2 \longleftrightarrow RS\text{-}\overset{+}{C}H_2]$$

We have noted that the dependence of rate constants on temperatures expressed with the Arrhenius equation for the reaction of 1-ethylimidazole with chloromethyloctyl sulfide in DMF is:

$$k = 2.37 \times 10^7 \exp(-69\,344)/RT[s^{-1}];\ r_k = 0.967$$

(r_k = coefficient of linear correlation). Activation energy is quoted in J/mol.

The minimum inhibitory concentration (MIC) of the chlorides **1a–f** against various microorganisms such as cocci, rods, fungi and bacilli was studied after 24 h of incubation (table I). The antibiotic activities are greatly correlated with the length of alkylthiomethyl chain. The decylthiomethyl and dodecylthiomethyl substituents are the most excellent.

One significant physicochemical property of 3-alkylthiomethyl-1-ethylimidazolium chlorides is their ability to form micelles in aqueous solution. The critical micelle concentration (CMC) values of studied chlorides **1a–f** were determined by the surface tension method and are shown in table I. In the micellar region the surface tensions are decreased to 29.0–25.0 mN/m.

We found that the quantitative correlation between CMC and MIC of 3-alkylthiomethyl-1-ethylimidazolium chlorides is defined as:

$$\log(1/MIC) = A\ \log CMC + B\ (\log CMC)^2 + C\ \log HI + D\ (\log HI)^2 + E$$

where HI is the hydrophobicity index, and A, B, C, D, and E are regression parameters. The hydrophobicity

Table I. Minimum inhibitory concentration log(1/MIC)[a] and critical micelle concentration logCMC[a] for chlorides **1a–f**.

Strain[b]	*log(1/MIC)*					
	1a	***1b***	***1c***	***1d***	***1e***	***1f***
Staphylococcus aureus NCTC 4163	4.05	4.35	4.69	5.12	5.08	4.83
Gaffkya tetragena PZH 2/49	3.50	4.35	5.05	5.45	5.70	5.27
Sarcina lutea ATCC 9341	3.52	3.75	4.69	5.12	5.39	5.13
Klebsiella pneumoniae 138	2.82	3.75	4.39	4.99	5.08	4.75
Serratia marcescens 6/46	2.20	2.84	3.79	5.12	3.87	3.95
Rhodothorula glutinis 29	3.85	4.05	5.00	5.12	5.08	4.93
Bacillus subtilis 32	3.35	4.05	4.39	4.43	4.47	4.49
–logCMC	0.42[c]	0.96	1.50	2.04	2.58	3.12[c]
HI	1.179	1.114	1.075	1.050	1.031	1.018

1a: 3-butylthiomethyl-1-ethylimidazolium; **1b**: 1-ethyl-3-hexylthiomethylimidazolium; **1c**: 1-ethyl-3-octylthiomethylimidazolium; **1d**: 3-decylthiomethyl-1-ethylimidazolium; **1e**: 3-dodecylthiomethyl-1-ethylimidazolium; **1f**: 1-ethyl-3-tetradecylthiomethylimidazolium. [a]Expressed as mol/L. [b]The number of microorganisms in 1 mL ranged from 3.4×10^4 to 4.8×10^5. [c]Extrapolated value.

index is defined as a ratio of the effective length n_{eff} to the actual number of carbon atoms n of the chain [1]:

$$HI = n_{eff}/n$$

The following relationship may be used for the calculation of the n_{eff} values of studied chlorides:

$$\log CMC = a - b\, n_{eff}$$

For 3-alkylthiomethyl-1-ethylimidazolium chlorides the a and b values were equal to 1.582 and 0.292 respectively.

The value n is the number of carbon atoms + 0.88 (sulfur atom) in the alkylthiomethyl chain. The value 0.88 represents the sulfur atom in the length as equivalent to one methylene group and was estimated from thermochemical study of aqueous micellar solution of 3-alkylthiomethyl-1-ethylimidazolium chlorides at 20 °C. The obtained HI values are shown in table I.

Mathematical data processing in the investigation of log(1/MIC) = f(CMC) was carried out using the program constructed for this purpose. The estimates of the parameters of this model were obtained using the least squares method. Table II shows the values obtained for A, B, C, D, E, r (correlation coefficient) and α (confidence interval).

The results presented demonstrate that there exists a relationship between the MIC, the CMC and the hydrophobicity index of 3-alkylthiomethyl-1-ethylimidazolium chlorides.

Experimental section

Chloromethylalkyl sulfide was prepared by passing HCl gas through a mixture of appropriate thiols and paraformaldehyde by using general procedure and have been reported elsewhere [2].

*General procedure for imidazolium chlorides **1a–f***

Chloromethylalkyl sulfide was dropped into 1-ethylimidazole with efficient mechanical stirring in anhydrous benzene. The mixture was heated under reflux for 4 h. The solvent was removed under reduced pressure. The product was extracted with hot hexane. The imidazolium chlorides were obtained as a hydroscopic oil with 90% yield and were vacuum dried at 60 °C. All prepared chlorides were stored over phosphoric anhydride. 3-Butylthiomethyl-1-ethylimidazolium chloride **1a** (oil) ^{1}H NMR ($CDCl_3$) δ ppm: 10.60 (s, 1H), 7.92 (s, 1H), 7.84 (s, 1H), 5.61 (s, 2H), 4.50 (q, J = 7 Hz, 2H), 2.71 (t, J = 7 Hz, 2H), 1.65 (t, J = 7 Hz, 2H), 1.54 (t, J = 7 Hz, 3H), 1.40 (m, 2H), 0.90 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ ppm: 135.9, 121.9, 121.2, 50.9, 44.8, 31.0, 30.4, 21.1, 15.0, 13.0.

Table II. Values for the parameters A, B, C, D and E.

Strain	*A*	*B*	*C*	*D*	*E*	*r*	α
Staphylococcus aureus NCTC 4163	–0.5131	–0.792	106.4	–250.7	–4.2709	0.9979	0.0000
Gaffkya tetragena PZH 2/49	–0.0297	–0.6598	–26.64	331.1	2.624	0.9702	0.0008
Sarcina lutea ATCC 9341	–1.974	–0.5681	–111	1027	5.480	0.9978	0.0000
Klebsiella pneumoniae 138	–5.307	–0.8859	77.66	–191.5	–3.794	0.9973	0.0000
Serratia marcescens 6/46	0.8746	–7.884	–121.2	518	8.451	0.9959	0.0000
Rhodothorula glutinis 29	1.669	–0.1046	–195.4	–1150	12.59	0.9728	0.0006
Bacillus subtilis 32	1.002	0.1147	–33.26	–127.1	6.772	0.9991	0.0000

Bactericidal properties

MICs for the test chlorides were determined by serial dilution. All studied microorganisms were obtained from the State Laboratory of Hygiene (Warsaw, Poland). Series of dilutions of aqueous solutions of the chlorides were prepared on the Muller-Hinton substrate or, in the case of fungi, on the Sabourand substrate. The samples were incubated at 37 °C for 24 h.

Surface active properties

The CMC was determined by means of surface tension isotherms at 20 °C. The surface tension values of aqueous solutions of imidazolium chlorides were measured by the ring method. We used a platinum ring of 10.4 mm ring radius and 0.2 mm wire radius, and a Teflon vessel of 10 cm diameter. For eliminating the error due to the formation of a finite contact angle at the ring, it is therefore sufficient to take off the ring after measurements of the solution and to rinse it with pure water [3]. The producibility of surface tension was within 2%.

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