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Study of local anesthetics. Part* 168

Critical micelle concentration of alkyloxy homologs of local anesthetic heptacainium chloride determined by ion sensitive electrode

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Abstract

The critical micelle concentrations (c.m.c.) of alkyloxy homologs of local anesthetic *N*-[2-(2-alkyloxyphenylcarbamolyoxy)-ethyl]-piperidinium chloride (C_nA) with n=3, 5, 7, 8, 10 and 12 carbons in alkyloxy substituent determined by surfactant ion sensitive electrode (ISE) depend exponentially on n: lnc.m.c.=0.70+0.49n and lnc.m.c.=0.57+0.62n at t=25 °C and pH≈4.5 in water and 0.1 mol.l^{-1} NaCl solution, respectively, where the free energy of transfer of the alkyloxymethylene group from the aqueous phase into the micelle hydrophobic interior is $\Delta G^0=(-0.49\pm0.008)RT$ in water and $\Delta G^0=(-0.62\pm0.06)RT$ in the 0.1 mol.l^{-1} NaCl solution. The enthalpic and entropic contributions to the standard Gibbs energy of micellization of heptacainium chloride (heptyloxy homologs of C_nA) in 0.1 mol.l^{-1} NaCl solution were calculated according to the phase separation model in the temperature range of 25–45 °C.

Keywords: Heptacainium chloride, ion sensitive electrode, micellization

Introduction

Local anesthetics reversibly block nerve impulses by disrupting permeability to sodium during an action potential. Onset of action is largely dependent on an agent's pharmacokinetics and the dosage given [1]. Potency and duration of action differ among the various agents. The more hydrophobic an agent, the greater the potency and the longer the duration of action. Molecular size influences the rate of dissociation of local anesthetics from their receptor sites; in this case, the smaller the molecule, the faster the dissociation [2].

Many local anesthetics in clinical use are hydrochloride salts of tertiary amine with an aromatic ring. Hence, they are amphiphilic molecules having moderate hydrophobity and hydrophilic group (quaternary ammonium) and show surface activities. Heptacainium chloride (C_7A) is one of the most potent local anesthetics – its relative surface anesthesia potency is approximately 100 times higher in comparison to the standard cocaine, while the relative surface anesthesia potenty of clinically used dibucaine is only 10 times higher [3]. Comparing to procaine, its relative efficiency to block the action potential on axons and nerves is 94 and 98 times higher, respectively, while the widely studied and clinically used lidocaine is only 7.1 and 3.4 times more efficient than procaine [3]. Besides local anesthetic potencies, C_7A and its homologs are efficient antimicrobials [4] and antiphotosynthetic agents [5].

In this work, we investigated the aggregate formation of alkyloxy homologs of local anesthetics C_nA with n=3, 5, 7, 8, 10 and 12 carbons in alkyloxy substituent from the potentiometric measurements. Amphiphilic-cation-specific electrodes most often use, as captor of potential, a specific membrane composed of a mixture of a polymer such as PVC, a plasticizer, and a carrier of the amphiphilic ion. For a given polymer, various plasticizers can be used to make „plastisols" that can be suitable for the preparation of specific membranes. We prepared membranes using polymer PVC as plasticizer and a carrier of the tetracaine ion. These membranes were mounted on an electrode support and used as ion sensitive electrode.

Results and Discussion

For illustration, the Fig. 1 shows the dependence of the electromotive force E (mV) upon the heptacainium chloride c ($mol.l^{-1}$) in saline solution. The expression of the electromotive force is given by the following equation:

$$E = E_o + (kRT/F) \log c^A \qquad (1)$$

Where E is the electromotive force, R the gas constant, F the Faraday constant, T the absolute temperature, k is a factor of correction and c^A the total C_7A concentration in the studied sample. We can divide the dependence of E upon log c to three parts: a linear loss of E (mV) from the concentration corresponding log $c=3.27 \times 10^{-5}$ $mol.l^{-1}$, then a more significant loss of E follows to $C = 7 \times 10^{-3}$ $mol.l^{-1}$ corresponding c.m.c.

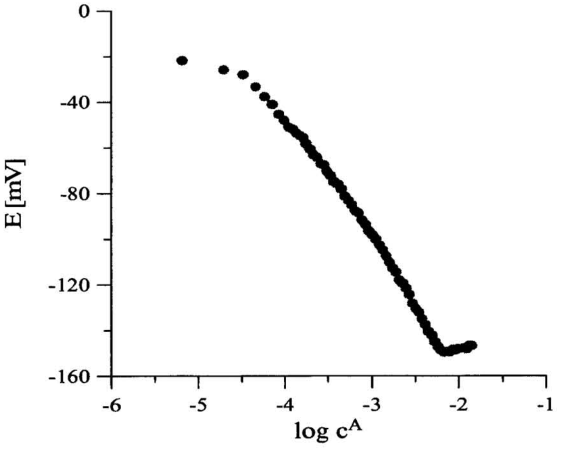

Fig. 1. Dependence of the electromotive force E (mV) upon the C_7A ($mol.l^{-1}$) in 0.1 $mol.l^{-1}$ NaCl solution at 25 °C.

The linear part of the curve on Fig.1, determined by a linear regression is RT/F=59.2±0.3 mV for the temperature T=298.15 K and the constant k=1, and is equal to the theoretical value of 59.17 mV. The sensitivity of measurements is ±0.3 mV. We observed dependences similar for the other anesthetic ones studied to various temperatures.

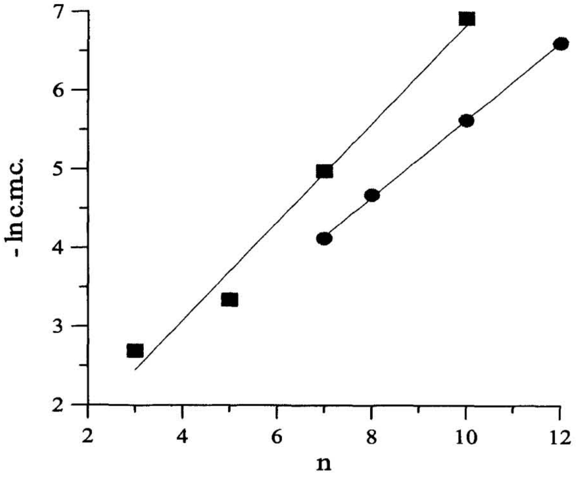

Fig. 2. Dependence of the ln(c.m.c.) of C_nA upon to the number of carbons n in the alkyloxy substituent (the full round points are c.m.c. measured in water, the full squares are c.m.c. measured in 0.1 NaCl mol.l^{-1}).

The results of measurement of the c.m.c. determined by the ISE upon to the number of carbons n in the alkyloxy substituent for the homologs of the C_7A of local anesthetic were presented in Fig. 2. We determined the c.m.c of C_nA in the water and 0.1 NaCl mol.l^{-1}.

All the experiments were carried out at room temperature T=25±0.3 °C. The representation of logarithmic curve of Fig. 2 shows that the variation of ln(c.m.c.) *vs.* n is form:

$$\ln(\text{c.m.c.}) = a + bn \qquad (2)$$

It is interesting to note that the slope of the straight lines obtained (the constant b), is related to the free energy ΔG^0, which is the free energy necessary for the transfer of a group of $-CH_2-$ in the chains alkyloxy of the local anesthetic of the aqueous medium to micelle. The relation between the constant b and the increase in the free energy $\delta\Delta G^0$ is given by the formula:

$$\delta\Delta G^0 = -2.303\ bRT \qquad (3)$$

We found that the value of $\delta\Delta G^0$ in water is equal to (-0.49 ± 0.08 RT) and in 0.1 mol.l^{-1} NaCl (-0.62 ± 0.06 RT). From the results of [6] we calculated the value of $\delta\Delta G^0$ in the case of the cinchocaine: it is equal (-0.78 ± 0.02 RT) in water and to (-1.60 ± 0.10 RT) in 0.9% of NaCl. We suppose that the differences found between our results and the results of [6] due the difference in size between the polar groups of the two anesthetics.

To carry out the thermodynamic interpretation, we examined the dependence of c.m.c. of local anesthetic C_7A upon temperature in the interval 25-45 °C. The results are shown in Fig. 3.

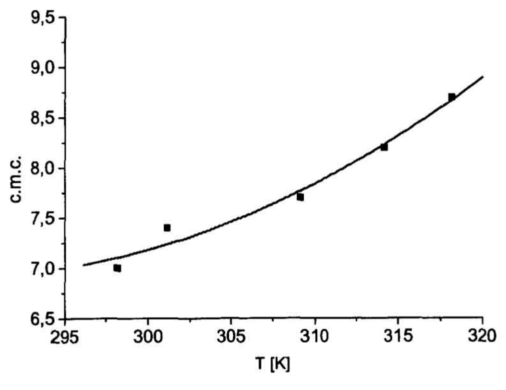

Fig. 2. Dependence of the c.m.c. of C_7A upon temperature in 0.1 mol.l^{-1} NaCl solution

The variation of the c.m.c. *vs.* temperature can be described by a polynomial of second order c.m.c. = $A+BT+CT^2$. Values of the coefficients A, B were calculated and are equal to A=10.136, B=–0.107 and C=0.00019, with the coefficient of correlation r^2=0.974. The temperature dependence of the c.m.c. of local anesthetic C_7A can be applied to calculate the enthalpy and entropy of micelle formation. According to the phase separation (PS_1 a PS_2) model [7], the standard Gibbs free energy of micelle formation, ΔG^o, is given by

$$\Delta G^o = \gamma\, RT\, \ln(\text{c.m.c.}) \qquad (4)$$

Where R = gas constant and γ = degree of counterion binding (if γ = 1 the anti-ions are completely ionized, if γ = 2 all the anti-ions are bound to micelles).

The enthalpy of micelle formation can be obtained by applying the Gibbs-Helmholtz equation 4

$$\Delta H^o = -\gamma\, T^2\, [\partial(\Delta G^o/T) / \partial T] = -\gamma\, RT^2\, \partial \ln(\text{c.m.c.}) / \partial T \qquad (5)$$

To evaluate the enthalpy of micelle formation, the cmc's are first correlated by a polynomial equation

$$\ln(\text{c.m.c.})\,(T) = a + bT + cT^2 \qquad (6)$$

where constants a, b and c are determined by least-squared regression analyses. The enthalpy of micelle formation is then calculated numerically by substituting eq 6 into eq 5

$$\Delta H^o = -\gamma\, RT^2\, (b + 2cT) \qquad (7)$$

Once the Gibbs free energy and the enthalpy of micelle formation are obtained, obviously, the entropy of micelle formation can be determined by

$$\Delta S^o = (\Delta H^o - \Delta G^o) / T \qquad (8)$$

Temperature (^oC)	ΔG^o ($kJ.mol^{-1}$)		ΔH^o ($kJ.mol^{-1}$)		ΔS^o ($kJ.mol^{-1}$)	
	PS_1	PS_2	PS_1	PS_2	PS_1	PS_2
25	−12.26	−24.52	−4.56	−9.12	0.0258	0.0516
28	−12.33	−24.66	−5.51	−11.02	0.0264	0.0528
36	−12.48	−24.96	−8.23	−16.46	0.0137	0.0274
41	−12.53	−25.06	−10.06	−20.12	0.0079	0.0158
45	−12.55	−25.10	−11.60	−23.20	0.0030	0.0060

Tab. 1. Determined thermodynamic parameters for micellization

Tab. 1 shows the temperature dependence of ΔG^o, ΔH^o and ΔS^o for local anesthetic C_7A in aqueous electrolyte solution. ΔG^o values are negative and decline slightly with temperature. In all temperature range, the micellization process is exothermic ($\Delta H^o < 0$). ΔS^o values are positive and decline with increasing temperature.

Experimental

Alkyloxy homologs of local anesthetic *N*-[2-(2-alkyloxyphenylcarbamolyoxy)-ethyl]-piperidinium chloride (C_nA) with n=3, 5, 7, 8, 10 and 12 carbons in alkyloxy substituent were prepared by a method as previously described [8]. NaCl (Lachema s.p., Brno) was used to prepare the stock solution with a concentration of 0.1 $mol.l^{-1}$. NaCl solution was used to prepare the local anesthetics solution with pH≈4.5-5 at 25-45 °C.

KNO_3 and KCl were analytically pure (Lachema, s.p., Brno) as filling-out solutions for electrodes. KNO_3 solution was used with 0.1 $mol.l^{-1}$ and formed the external solution of the electrode. Further, we prepared 100 ml saturated KCl solution formed the internal solution of the electrode.

A membrane with the tetracaine-SDS (sodium dodecyl sulphate) complex was prepared [9,10]. A little wheel of 5 mm diameter was cut out from the formed membrane about 0,1 mm thickness in a Petri dish and glued via a hole to the bottom of a plastic PVC tube using tetrahydrofurane.

The electrodes were constructed as follows: Ag/AgCl/saturated KCl/0.1 $mol.l^{-1}$ KNO_3/standard heptacainium chloride solution/PVC membrane/solution with a sample/0.1 $mol.l^{-1}$ KNO_3/saturated KCl/AgCl, Ag. The electromotoric force was measured with OP 208/1 pH meter (Radelkis, Hungary).

The concentration change of C_nA was measured using the automatic burette (Radelkis, Hungary) and controlled by a computer.

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