

Extraction of quaternary ammonium salts of heptacaine

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The paper deals with the transition of some local anaesthetically active quaternary ammonium salts of heptacaine from aqueous phase into octanol in the form of ion pairs. The dependence of the extraction constants on the size of an alkyl substituent is followed and the electronic spectra of the studied compounds are presented.

Изучается переход некоторых четвертичных аммониевых солей гептакаина, используемых при местной анестезии, из водной фазы в октанол в виде ионных пар. Исследовано изменение экстракционных констант при изменении величины алкильного заместителя. Приведены электронные спектры изучаемых соединений.

Transition of some biologically active compounds through the lipo-hydrophilic phase boundary may occur in the form of ion pairs. After the Swedish authors [1] the corresponding equilibrium is characterized by the extraction constant

$$K_{\text{ex}} = \frac{[\text{QX}]_0}{[\text{Q}^+]_w [\text{X}^-]_w} \quad (1)$$

where $[\text{QX}]_0$ is the ion pair concentration in the lipoidal phase after partition, $[\text{Q}^+]_w$ and $[\text{X}^-]_w$ are equilibrium concentrations of both ions in the aqueous phase. When the ionic strength of the aqueous phase changes, activities of ions are more appropriate than their equilibrium concentrations, as we pointed out previously [2]. A mean activity coefficient f_{\pm} is therefore brought in eqn (2)

$$K_{\text{ex},x} = \frac{[\text{QX}]_0}{[\text{Q}^+]_w [\text{X}^-]_w f_{\pm}^2} \quad (2)$$

The magnitude of extraction constants increases with the hydrophobicity of both ions [1]. The studied compounds are quaternary ammonium salts, namely bromides, so that another transition from the aqueous into lipoidal phase than in the form of ion pairs cannot be expected. The extraction of the studied bromides was experimentally followed in the systems octanol—water and octanol—aqueous phosphate buffer solution. The latter system was also used for measurements of partition constants of other local anaesthetics in our previous works [3, 4]. Several types of ion pairs can be formed in this system. In the case that the sum of concentrations of all ion pairs in octanol is either determined spectrophotometrically or calculated from the known total mass m of the quaternary salt in the system and the equilibrium concentration $[Q^+]_w$, it is possible to calculate the experimental extraction constant K'_{ex}

$$K'_{ex} = \frac{[QBr]_0 + [QH_2PO_4]_0 + 2[Q_2HPO_4]_0}{[Q^+]_w([Br^-]_w + [H_2PO_4^-]_w + 2[HPO_4^{2-}]_w[Q^+]_w f \pm) f \pm^2} \quad (3)$$

The numerator in eqn (3) is given by eqn (4)

$$[QBr]_0 + [QH_2PO_4]_0 + 2[Q_2HPO_4]_0 = \frac{m - [Q^+]_w V_w M}{V_o M} \quad (4)$$

where V_w and V_o (dm^3) are volumes of the aqueous and lipoidal phases, respectively, m (kg) is the mass and M (kg mol^{-1}) the molar mass of the studied compound. The last term in the parentheses of the denominator in eqn (3) follows from eqn (5)

$$K_{ex, Q_2HPO_4} = \frac{[Q_2HPO_4]_0}{[Q^+]_w^2 [HPO_4^{2-}]_w f \pm^3} \quad (5)$$

The expression in the parentheses of the denominator in eqn (3) can be evaluated if the composition of the aqueous phase before the extraction and $[Q^+]_w$ are known.

The calculation of the extraction constant in the system with two competitive anions was described previously [2]. If phosphate anions are taken as a whole, a similar calculation of the experimental constant $K'_{ex,P}$ with the phosphate anions can be carried out

$$K'_{ex,P} = \frac{[QH_2PO_4]_0 + 2[Q_2HPO_4]_0}{[Q^+]_w([H_2PO_4^-]_w + 2[HPO_4^{2-}]_w[Q^+]_w f \pm) f \pm^2} \quad (6)$$

The main subject of this study is the effect of the size of an alkyl chain on the K_{ex} values in a group of the studied new compounds which have not been physicochemically described yet.

Experimental

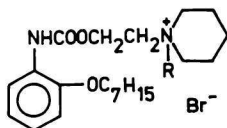
Studied compounds and chemicals

The studied compounds prepared by quaternization of heptacaine (piperidinoethylester of 2-heptyloxyphenylcarbamic acid) with corresponding alkyl bromide [5] are listed in Table 1. Logarithms of their relative surface local activity (standard cocaine) determined in

Table 1

Characteristics of the studied compounds

Logarithms of the surface local anaesthetic activity ($\log U_p$), the location (λ_{\max}) and the molar absorption coefficients (ϵ_{\max}) of the u.v. spectral maxima in aqueous solutions



Compound	R	$\log U_p$	$\lambda_{\max I}$ nm	$\epsilon_{\max I}$ $\text{m}^2 \text{mol}^{-1}$	$\lambda_{\max II}$ nm	$\epsilon_{\max II}$ $\text{m}^2 \text{mol}^{-1}$
H21	CH ₃	0.732	227	753	278	253
H22	C ₂ H ₅	1.164	227	779	278	279
H23	C ₃ H ₇	1.076	228	786	278	273
H24	C ₄ H ₉	0.623	228	786	279	276
H25	C ₅ H ₁₁	0.568	228	786	280	280
H26	C ₆ H ₁₃	0.301	229	786	280	282
H27	C ₇ H ₁₅	0.447	233	795	280	295
H28	C ₈ H ₁₇	Irritation	234	803	280	293
H29	C ₉ H ₁₉	Irritation	235	812	280	282
H30	C ₁₀ H ₂₁	Irritation	235	820	280	301

their recent pharmacological evaluation [5] are also given there. Other chemicals used were anal. grade.

Determination of extraction constants

The method was described elsewhere [2, 6], the used systems were octanol—water and octanol—aqueous phosphate buffer solution (0.013 mol KH₂PO₄ and 0.053 mol K₂HPO₄ in 1 dm³). Both phases were in advance mutually saturated. The systems with weighed amount of the studied compound and various volume ratios of the phases were shaken for 1 h at 25.0

$\pm 0.1^\circ\text{C}$, then the phases separated and the concentrations of the studied compound determined photometrically. Eqns (2—6) were used for calculations, the mean activity coefficient estimated as in [2]. The increase ΔV of the volume V_0 on the extraction (higher amount of the extracted compound) was calculated from eqn (7), neglecting eventual nonadditivity of the volumes

$$\Delta V = 1000 \frac{m - V_w M [Q^+]_w}{\rho} \quad (\text{dm}^3) \quad (7)$$

where ρ (kg m^{-3}) is the density, m (kg) the mass and M (kg mol^{-1}) the molar mass of the studied (extracted) compound. All the experiments were repeated 5—8 times.

Electronic spectra

Spectra of the studied compounds were measured on the instrument Spectromom 202 (MOM, Budapest) in water, phosphate buffer, and octanol. Quartz cells of the various thickness l were used and molar absorption coefficients ϵ calculated from the measured absorbance A and the concentration c by a common relationship $\epsilon = A/(cl)$.

Density of the compounds

A crystal of the studied compound was put in the glycerol—water mixtures and the density of the right mixture in which the crystal was just floating was determined with a pycnometer. Since the studied compounds dissolved slowly in the mixtures, a quick observation of the crystal was necessary.

Results and discussion

The survey of the basic spectral data of the studied compounds is given in Table 1. A comparison of the electronic spectra measured in water and in aqueous phosphate buffer showed no differences, in octanol most of the studied compounds exhibit a shift of the second band maximum by 1 nm. The band shape suggests that it is composed of several submerged bands.

Experimental extraction constants were measured with various volume ratios of the octanol and aqueous phase. The amount of the studied compounds was so adjusted that after extraction $[Q^+]_w$ was in the range of 5×10^{-5} — 2×10^{-4} mol dm^{-3} . For the compounds H27—H30 the calculation of ΔV from eqn (7) was necessary, their mean density was 1064 kg m^{-3} . The preliminary qualitative tests revealed easier transition of the studied cations into octanol in the form of ion pair with bromide than with phosphates. Calculated $K'_{\text{ex,P}}$ given in Table 2 confirm this finding. The mean values of the measured extraction constants $K_{\text{ex,Br}}$ with

Table 2

Extraction constants of the studied compounds ($\text{dm}^3 \text{mol}^{-1}$)

Compound	$K_{\text{ex,Br}}$	K'_{ex}	$K'_{\text{ex,P}}$
H21	$(2.20 \pm 0.20) \times 10^3$	$(1.27 \pm 0.02) \times 10^2$	1.06×10^2
H22	$(3.61 \pm 0.05) \times 10^3$	$(1.60 \pm 0.08) \times 10^2$	1.33×10^2
H23	$(7.45 \pm 0.60) \times 10^3$	$(2.74 \pm 0.08) \times 10^2$	2.27×10^2
H24	$(1.83 \pm 0.07) \times 10^4$	$(6.40 \pm 0.28) \times 10^2$	4.90×10^2
H25	$(6.75 \pm 0.09) \times 10^4$	$(4.88 \pm 0.30) \times 10^3$	4.43×10^3
H26	$(2.41 \pm 0.07) \times 10^5$	$(1.69 \pm 0.04) \times 10^4$	1.50×10^4
H27	$(8.13 \pm 0.10) \times 10^5$	$(9.70 \pm 0.16) \times 10^4$	6.02×10^4
H28	$(3.23 \pm 0.90) \times 10^6$	$(2.84 \pm 0.16) \times 10^5$	1.19×10^5
H29	$(1.59 \pm 0.07) \times 10^7$	$(1.15 \pm 0.03) \times 10^6$	1.89×10^5
H30	$(3.59 \pm 0.90) \times 10^7$	$(1.82 \pm 0.40) \times 10^6$	1.40×10^5

bromides and K'_{ex} with the whole multianion system are also in Table 2, in these cases, their standard errors are given. The preferred extraction of the quaternary ammonium cations with bromides is in accordance with our previous findings [2].

The dependence of the logarithm of extraction constants on the number of methylene groups in the quaternizing alkyl can be seen in Fig. 1. The slightly S-shaped dependences are probably of the logarithmico-exponential type. However, with regard to the size of the standard errors of the extraction constants and with the omission of the compound H21 (without methylene group in R), the dependence may be roughly approximated by straight lines indicating the following increments per one methylene group: $\Delta \log K'_{\text{ex}} = 0.56$, $\Delta \log K_{\text{ex,Br}} = 0.52$, and

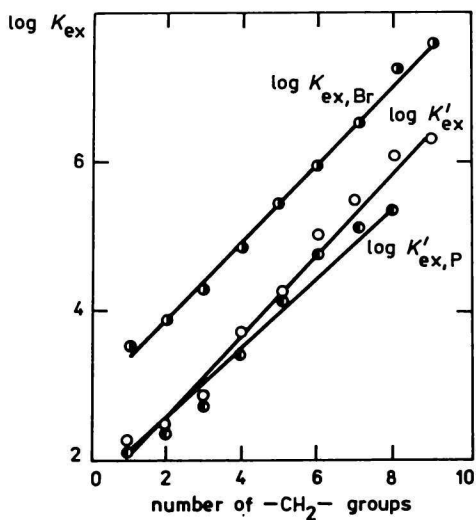


Fig. 1. Dependences of the logarithms of extraction constants on the number of methylene groups in alkyl substituent.

$\Delta \log K'_{cx,P} = 0.51$. For the calculation of the last increment the compound H30 was disregarded as well, since the observed decrease of its $K'_{cx,P}$ may be in connection with the limits of experiments. The found increments thus appear to be practically equal to the increment of the Hansch hydrophobicity parameter π for electroneutral molecules which is 0.54 per one methylene group [7]. At the same time, our increments of $\log K_{cx}$ in the octanol—water system are practically the same as the increment 0.5—0.6 found by *Schill et al.* [1] in the chloroform—water system.

An important factor is the local anaesthetic activity of the studied compounds but the comparison of $\log K_{cx}$ values with $\log U_p$ does not lead to unequivocal conclusions. Other biological effects of the compounds may play a role in this connection, e.g. the irritation suppressing the local anaesthesia. *Dettbarn et al.* [8] proved that local anaesthetics are bound to the active centrum from the inner side of the membrane. They must be therefore transported also through the lipoidal part of the membrane, common local anaesthetics in the form of electroneutral molecules. However, in the case of the studied compounds such a transport is possible only in the form of ion pairs.

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