

Extraction of heptacaine

"M. PEŠÁK, "F. KOPECKÝ, and "J. ČIŽMÁRIK

"Department of Physical Chemistry, Faculty of Pharmacy,
Komenský University, CS-832 32 Bratislava

"Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Komenský University, CS-832 32 Bratislava

Received 22 February 1982

*Paper published on the occasion of the 30th anniversary of the foundation
of the Faculty of Pharmacy, Komenský University, Bratislava*

The extraction of the protonized form of heptacaine was studied and its extraction constants with the anions Cl^- , Br^- , and H_2PO_4^- were determined in the octanol—water system.

Изучена экстракция протонированной формы гептакаина и определены ее экстракционные константы с тремя анионами Cl^- , Br^- и H_2PO_4^- в системе октанол—вода.

In the previous paper [1], a possibility of the transition of local anaesthetics through the lipo-hydrophilic phase boundary both in the basic form and in the form of ion pairs was pointed out. Two modes of transport may account for the changes of their biological activity observed at different experimental conditions. The extraction of ion pairs has been used for analytical purposes, e.g. heptacaine was determined after extraction with convenient indicators in chloroform [2]. The foundation of the ion pair extraction methods was worked out by Swedish authors [3].

Extraction constants of the local anaesthetic heptacaine with various X^- counter ions are followed in the presented paper. The extraction constant K_{ex} is given by eqn (1) where $[\text{BH}^+]_{\text{w}}$ is the equilibrium concentration of the protonized form of heptacaine (heptacainium) in the aqueous phase after extraction and $[\text{BHX}]_{\text{o}}$ is the equilibrium concentration of the ion pair in the organic phase. When the ionic strength of the used aqueous solutions is not constant, the mean activity coefficient f_{\pm} is conveniently included into the calculations

$$K_{\text{ex}} = \frac{[\text{BHX}]_{\text{o}}}{[\text{BH}^+]_{\text{w}} [\text{X}^-]_{\text{w}} f_{\pm}^2} \quad (1)$$

If two anions denoted as X^- and Z^- are present in the aqueous phase and the extraction constant $K_{\text{ex},X}$ with the former is known, the constant $K_{\text{ex},Z}$ can be calculated. The following equations indicate the procedure

$$[X^-]_{\text{w}} = \frac{c_X V_{\text{w}}}{V_{\text{w}} + K_{\text{ex},X} [\text{BH}^+]_{\text{w}} V_0 f \pm^2} \quad (2)$$

$$[\text{BHX}]_0 = K_{\text{ex},X} [\text{BH}^+]_{\text{w}} [X^-]_{\text{w}} f \pm^2 \quad (3)$$

$$[\text{BHZ}]_0 = \frac{m}{M V_0} - [\text{BH}^+]_{\text{w}} \frac{V_{\text{w}}}{V_0} - [\text{BHX}]_0 \quad (4)$$

$$[Z^-]_{\text{w}} = c_Z - \frac{[\text{BHZ}]_0 V_0}{V_{\text{w}}} \quad (5)$$

$K_{\text{ex},Z}$ is then calculated from eqn (1) after inserting $[Z^-]_{\text{w}}$ instead of $[X^-]_{\text{w}}$. In eqns (2–5), symbols V_{w} and V_0 (dm^3) are volumes of the respective phases, c_X and c_Z (mol dm^{-3}) analytical concentrations of the anions, m (kg) is the mass of heptacaine in the system, M (kg mol^{-1}) the molar mass of heptacaine.

Experimental

Material and methods

Heptacainium chloride (*N*-[2-(heptyloxyphenylcarbamoyloxy)ethyl]piperidinium chloride) was prepared as a potential local anaesthetic, its preparation and purity was described earlier [4]. Other chemicals used were anal. grade.

The extraction constants were measured by the recently described method [1] in the system octanol—acidified aqueous solution, at temperature $20 \pm 0.1^\circ\text{C}$. Aqueous solutions of heptacaine were acidified with HCl, HBr or H_3PO_4 . Concentration of H_2PO_4^- before the extraction was calculated from the dissociation constant [5] and measured pH (Radiometer PHM4, glass and calomel electrodes). The used aqueous phase was saturated in advance with octanol and the octanol with water. The volume of the aqueous phase was always 20 cm^3 , volumes of the octanol solutions were about 0.5 cm^3 . The transition of heptacaine into the octanol phase on the extraction brought about a slight increase of its volume. The concentration of heptacaine was measured photometrically in aqueous solutions with the MOM 202 (Budapest) spectrophotometer in u.v. region. Eqns (1–5) were used in the calculations and the approximate mean activity coefficients $f \pm$ were estimated after [6] from eqn (6), where I is the ionic strength

$$-\log f \pm = \frac{0.507 \sqrt{\{I\}}}{1 + \sqrt{\{I\}}} \quad (6)$$

Results and discussion

In the performed experiments, only ion pairs of heptacainium with a respective inorganic anion were extracted with octanol. Preliminary tests showed that inorganic acids themselves were not extracted with octanol. Since heptacaine has pK 8.9 [1], its protonized form prevails over the negligible concentration of the basic form in the acidic solution. The basic form takes part in the partition equilibria first of all in neutral and alkaline solutions [7].

The initial data, equilibrium concentrations, and the calculated extraction constants of heptacainium with Cl^- as counter ion are listed in Table 1. The initial data are the mean values from three measurements. The extraction constants K_{ex} defined by eqn (1) are given in Tables 1 and 2, in the former are also listed the experimental constants K'_{ex} , calculated without the activity coefficients. According to *Schill et al.* [3], the changes in K'_{ex} can be explained by a side reaction in any of the phases. As the calculated K'_{ex} varies with the concentration of the acid, such a side reaction might be the second acid—base equilibrium. However, the second pK of heptacaine was not found in the range of the pH scale, either with the spectrophotometry or with the potentiometry. The K'_{ex} value varies significantly

Table 1

Initial concentrations, mass of heptacainium chloride, equilibrium concentrations, extraction constants K'_{ex} and K_{ex} of heptacainium with Cl^- as counter ion

$\frac{c_{Cl}}{\text{mol dm}^{-3}}$	$\frac{m}{\text{mg}}$	$\frac{[BH^+]_w \cdot 10^5}{\text{mol dm}^{-3}}$	$\frac{[BHCl]_o \cdot 10^3}{\text{mol dm}^{-3}}$	$\frac{[Cl^-]_w}{\text{mol dm}^{-3}}$	$\frac{K'_{ex}}{\text{dm}^3 \text{ mol}^{-1}}$	$\frac{K_{ex}}{\text{dm}^3 \text{ mol}^{-1}}$
0.0166	0.813	5.78	1.75	0.0165	1840	2400
0.0168	3.284	23.1	7.21	0.0168	1860	2420
0.0171	5.748	40.3	12.7	0.0168	1870	2440
0.0410	3.284	15.4	10.3	0.0407	1640	2430
0.0413	5.748	26.6	18.0	0.0408	1660	2460
0.0414	8.211	38.6	25.7	0.0408	1630	2410
0.0819	3.284	10.6	12.2	0.0814	1410	2370
0.0821	4.921	15.5	18.3	0.0816	1450	2440
0.0824	7.344	23.3	27.2	0.0817	1430	2400
0.1634	3.284	6.97	13.6	0.1633	1190	2330
0.1637	5.748	11.8	23.8	0.1630	1240	2430
0.1640	8.211	17.1	33.8	0.1631	1210	2370

Table 2

Experimental concentrations and extraction constants K_{ex} of heptacainium with Br^- or $H_2PO_4^-$ as counter ion

Z^-	$\frac{m}{mg}$	$\frac{[BH^+]_w \cdot 10^5}{mol\ dm^{-3}}$	$\frac{[Cl^-]_w \cdot 10^4}{mol\ dm^{-3}}$	$\frac{[Z^-]_w \cdot 10^2}{mol\ dm^{-3}}$	$\frac{[BHCl]_0 \cdot 10^4}{mol\ dm^{-3}}$	$\frac{[BHZ]_0 \cdot 10^3}{mol\ dm^{-3}}$	$\frac{K_{ex}}{dm^3\ mol^{-1}}$
Br^-	8.016	12.7	10.0	10.03	1.74	34.4	4750
	5.010	7.77	6.26	10.06	0.666	21.7	4890
	3.006	4.91	3.76	10.09	0.253	13.0	4620
	2.000	3.20	2.51	10.10	0.110	8.72	4750
$H_2PO_4^-$	5.010	59.7	6.12	3.32	6.24	0.610	44.2
	3.006	35.6	3.71	3.32	2.21	0.607	73.8
	2.004	24.0	2.49	3.33	1.00	0.346	62.2

also with the ionic strength of the aqueous solution but it does not depend on the amount of heptacaine. On the other hand, the K_{ex} values calculated with the use of the approximate activity coefficients f_{\pm} given by eqn (6) are remarkably constant, within the range of experimental errors. The mean K_{ex} values of heptacainium chloride for four initial concentrations of HCl (four groups of data in Table 1) are 2420 ± 20 , 2430 ± 30 , 2400 ± 40 , and 2380 ± 50 , the respective activity coefficients f_{\pm} are 0.876, 0.822, 0.772, and 0.715.

Table 2 presents the experimental data and the results of the extraction of heptacainium with two couples of anions, namely Br^-/Cl^- and $H_2PO_4^-/Cl^-$. Values of f_{\pm} are 0.754 and 0.813 for the solutions with HBr and H_3PO_4 , respectively, the mean value of K_{ex} of heptacainium chloride is 2410. Further calculations with eqns (1–5) yield the values of K_{ex} 4750 ± 110 and 60 ± 15 for heptacainium with counter ions Br^- and $H_2PO_4^-$, respectively. Higher K_{ex} value of bromide in comparison with chloride is in accord with the published data [3] for other organic cations. Bromide ions exhibit even in aqueous solutions significantly greater binding, e.g. to the micelles of organic ammonium cations [8, 9]. The low value of K_{ex} with $H_2PO_4^-$ is an important factor for further study of the transport equilibria of local anaesthetics in an organism.

References

1. Pešák, M., Štolc, S., and Beneš, L., *Česk. Farm.* 29, 272 (1980).
2. Šubert, J., Blešová, M., Čižmárik, J., and Borovanský, A., *Pharmazie* 33, 589 (1978).
3. Schill, G., Borg, K. O., Modin, R., and Persson, B. A., in *Progress in Drug Metabolism*, Vol. 2. (Bridges, J. W. and Chasseaud, L. F., Editors.) P. 219. J. Wiley, London, 1977.

4. Čižmárik, J., Borovanský, A., and Švec, P., *Pharmazie* 33, 297 (1978).
5. Robinson, R. A. and Stokes, R. H., *Electrolyte Solutions*. (Russian translation.) P. 604. Izdatel'stvo inostrannoi literatury, Moscow, 1964.
6. Robinson, R. A. and Stokes, R. H., *Electrolyte Solutions*. (Russian translation.) P. 273 and 541. Izdatel'stvo inostrannoi literatury, Moscow, 1964.
7. Pešák, M., Kopecký, F., Čižmárik, J., and Borovanský, A., *Pharmazie* 35, 150 (1980).
8. Bartet, D., Gamboa, C., and Sepulveda, L., *J. Phys. Chem.* 84, 272 (1980).
9. Ozeki, S. and Ikeda, S., *Bull. Chem. Soc. Jap.* 54, 552 (1981).

Translated by F. Kopecký