

Ionization conditions for iontophoretic drug delivery. Electrical conductance and aggregation of lidocaine hydrochloride in 1-octanol at 25°C

Kiomars Karami, Hans Sjöberg, Per Beronius *

Physical Pharmaceutical Chemistry, Uppsala University, Uppsala Biomedical Center, P.O. Box 574, S-751 23 Uppsala, Sweden

Received 27 January 1997; accepted 26 April 1997

Abstract

The behaviour of lidocaine hydrochloride (LidH^+Cl^-) in 1-octanol at 25.00°C has been studied with respect to transport properties and aggregation by precision conductometry over the concentration interval 0.2–6 mM. The analysis of the conductance data, based on the conductance equation of Fuoss, Hsia, and Fernandez-Prini (FHFP equation), indicates that for concentrations up to 0.6 mM free LidH^+ and Cl^- ions are present in equilibrium with LidH^+Cl^- ion pairs. At higher concentrations there is strong evidence of formation of $(\text{LidH})_2\text{Cl}^+$ and LidHCl_2^- triple ions. Any dissociation of LidH^+ into Lid and H^+ is shown to be negligible within the concentration interval studied. The values $K_a = (127.6 \pm 2.7) \cdot 10^3$ and $K_T = 65$ of the ion pair and triple ion association constants, respectively, were obtained. The limiting molar conductivity, $\Lambda_0(\text{LidHCl}) = 1.969 \pm 0.031 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$, is less by a factor of about 50 as compared with the corresponding value for water as solvent medium. This effect can be only partly ascribed to the difference in viscosity between 1-octanol and water. The mobility of the triple ions is found to be 1/3 of that of the free ions. © 1997 Elsevier Science B.V.

Keywords: Iontophoresis conditions (prerequisites); Lidocaine hydrochloride; 1-Octanol; Molar conductivity; Ionic conductivity; Ion pairs; Triple ions

1. Introduction

Iontophoresis may be described as the permeation of ionized bioactive molecules of drugs across a biological membrane (normally skin) un-

der the influence of a weak direct electric current. It is an efficient and painless method of transdermal drug administration, e.g. of local anaesthetics; compare injection by syringe and needle. The efficiency of the iontophoretic process depends on the state of the drug (ionic and/or non-ionic form). The fraction of the drug present as ions

* Corresponding author.

depends mainly on the structure of the drug molecule, the character of the medium through which the drug molecules migrate, and the concentration of the drug. Hence, to optimize the conditions of the iontophoretic process access to basic physicochemical data for characterizing the drug-solvent system is required.

In this study aggregation and transport properties of lidocaine hydrochloride in 1-octanol as solvent at 25°C has been investigated by electrical precision conductance measurements; compare our previous conductometric study of this drug in aqueous solution (Sjöberg et al., 1996). 1-Octanol was considered to be an interesting solvent medium because of its frequent use in studies of factors affecting transport mechanisms. Walter and Kurz (1988) investigated the binding of drugs to human skin, where the partition of the drug between octanol and a phosphate buffer was used as a measure of the lipophilicity of the drug. Cornford et al. (1982) correlate brain uptake indices of acetamide, antipyrine, benzyl alcohol, and several other compounds with octanol/saline partition coefficients of these compounds. Loberg et al. (1979) studied membrane transport properties of several Tc-99 m complexes by determining the uptake index of the complex, the extent of protein binding, and the octanol/saline partition coefficient. Several other investigations, in which various effects have been correlated with octanol/water partition coefficients, may be found in the literature, see Ahmed et al. (1995), Hasinoff and Davey (1989).

2. Experimental

Crystalline lidocaine hydrochloride monohydrate (LidHCl·H₂O) and 1-octanol, were obtained from Sigma Chemical Co. USA. The density of the solid salt, 1.1961 g cm⁻³ at room temperature, was determined by means of an Acc Pyc 1330 density meter. Potassium chloride (Merck) for calibration of the conductivity cell was of suprapur grade.

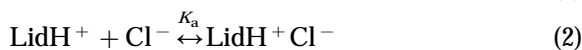
The conductivity of the 1-octanol used (HPLC grade; min. 99%; water content < 0.01%) was determined to $\kappa = 1.32 \cdot 10^{-9} \Omega^{-1} \text{ cm}^{-1}$. In cal-

culations the values $\epsilon = 9.85$ and $\eta = 0.073 \text{ cP}$ ($7.3 \cdot 10^{-3} \text{ N s m}^{-2}$) for the dielectric constant and viscosity, respectively, were used (Shkodin et al., 1969).

The equipment and the technique used to determine the molar conductivity of solutions of lidocaine hydrochloride in 1-octanol at $25.00 \pm 0.02^\circ\text{C}$ were similar to those previously described for this salt in aqueous solution (Sjöberg et al., 1996). The results of the measurements are given in Table 1, where the molar conductivity, Λ , is given at different LidHCl concentrations within the range 0.16–5.8 mM.

3. Analysis of conductance data

For solutions dilute enough to exclude the presence of higher electrolyte aggregates than ion pairs it appears reasonable to assume the following equilibria:



where K_d is the dissociation constant of LidH^+ and K_a and K are the ion pair association constants for formation of $\text{LidH}^+ \text{Cl}^-$ and $\text{H}^+ \text{Cl}^-$ respectively.

Table 1

Molar conductivity of lidocaine hydrochloride in 1-octanol at 25.00°C

$10^4 \cdot c \text{ (M)}$	$\Lambda \text{ (cm}^2 \Omega^{-1} \text{ mol}^{-1}\text{)}$	$10^4 \cdot c \text{ (M)}$	$\Lambda \text{ (cm}^2 \Omega^{-1} \text{ mol}^{-1}\text{)}$
1.5608	0.40897	10.297	0.17864
2.3293	0.34335	10.980	0.17364
3.0901	0.30388	11.657	0.16923
3.8433	0.27604	12.327	0.16585
4.5890	0.25490	12.991	0.16077
5.3273	0.23827	13.648	0.15882
6.0583	0.22442	14.300	0.15524
6.7822	0.21386	15.067	0.14936
7.4990	0.20533	29.831	0.11242
8.2088	0.19732	44.300	0.095485
8.9117	0.19080	58.484	0.085641
9.6079	0.18418		

To obtain an idea of the relative importance of these equilibria, access to reasonable values of K_d , K_a and K are required.

Equilibrium (1). Because of the much lower dielectric constant of 1-octanol, $\epsilon = 9.85$, as compared with water, $\epsilon = 78.3$ (Robinson and Stokes, 1965), the dissociation of LidH^+ into Lid and H^+ would be considerably less in 1-octanol as compared with water as solvent. The dissociation constant, $K_d = 6.93 \cdot 10^{-8}$, of LidH^+ in aqueous solution has been previously established (Sjöberg et al., 1996). Hence, for 1-octanol as solvent we conclude that $K_d < 6.93 \cdot 10^{-8}$.

Equilibrium (2). Ion pair association constants, K_a , of several 1:1-electrolytes in 1-octanol at 25°C have been previously reported (Beronius, 1978; Beronius and Pataki, 1980; Lindbäck, 1984). These association constants are of the order $K_a = 50 \cdot 10^3$.

Equilibrium (3). For hydrochloric acid in 1-octanol De Lisi et al. (1979) report the association constant $K = 57.8 \cdot 10^3$.

Estimates based on the values of the equilibrium constants K_d , K_a , and K quoted above, which are all given on the molar scale, indicate that the concentration of free protons is completely negligible for the range of LidHCl concentrations here investigated. Hence, in the following we will not include the Equilibria (1) and (3) in the analysis of our conductance data.

3.1. Lower concentration range: ion-pair formation

For pair-wise associated electrolytes the dependence of the molar conductivity, Λ , on concentration may according to the FHFP equation (Fuoss and Hsia, 1967, 1968; Fernandez-Prini, 1969) be expressed,

$$\Lambda = \Lambda_0 - S(c\alpha)^{1/2} + Ec\alpha \log(c\alpha) + J_1c\alpha - J_2(c\alpha)^{3/2} - K_a c\alpha \gamma^2 \Lambda \quad (4)$$

where Λ_0 , α , and γ are the limiting molar conductivity, the degree of dissociation, and the mean molar activity coefficient, respectively, of the electrolyte, S and E are coefficients, which depend on Λ_0 , solvent properties (ϵ and η), and the tempera-

ture, while the coefficients J_1 and J_2 depend, in addition, on the maximum distance between the centers of charge of the ions in the ion pair. This maximum distance was set equal to the Bjerrum radius, q , (Justice, 1971; Beronius, 1975, 1976) which for the present system is equal to 28.45 Å. The mean molar activity coefficient was calculated using the Debye-Hückel equation in the form,

$$\log \gamma = - \frac{1.8246 \cdot 10^6 (\epsilon T)^{-3/2} \sqrt{I}}{1 + 50.29 \cdot 10^8 (\epsilon T)^{-1/2} q \sqrt{I}} \quad (5)$$

where the ionic strength, $I = c\alpha$.

3.1.1. Evaluation of the ion pair association constant

Eq. (4) was rewritten in the form of a straight line,

$$y = \Lambda_0 - K_a c\alpha \gamma^2 \Lambda \quad (6a)$$

where,

$$y = \Lambda + S(c\alpha)^{1/2} - Ec\alpha \log(c\alpha) - J_1c\alpha + J_2(c\alpha)^{3/2} \quad (6b)$$

Starting with a preliminary value of K_a values of α were iteratively calculated for all concentrations investigated using Eq. (5) and the law of mass action,

$$K_a = (1 - \alpha)/(c\gamma^2 \alpha^2) \quad (7)$$

for Equilibrium (2) between free ions, LidH^+ and Cl^- , and ion-pairs, $\text{LidH}^+ \text{Cl}^-$.

Using a preliminary value of Λ_0 a straight line was then fitted according to Eq. (6a) to the points of y vs. $c\alpha \gamma^2 \Lambda$ using the method of least squares. Using the better estimates of K_a and Λ_0 thus obtained Eq. (6a) was applied again to the experimental points. This procedure was repeated until the desired convergence in K_a and Λ_0 was attained (difference between successive values of K_a and Λ_0 , respectively, less than $1 \cdot 10^{-6}$).

A graph according to Eq. (6a) based on the seven lowest concentration points is shown in Fig. 1. Calculations accounted for below indicate that the points in this diagram are all within the ion/ion pair concentration range. The equation of the least squares fitted straight line yield $K_a = (127.6 \pm 2.7) \cdot 10^3$ (molar scale) and $\Lambda_0 = 1.969 \pm 0.031 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$, where errors quoted are standard deviations.

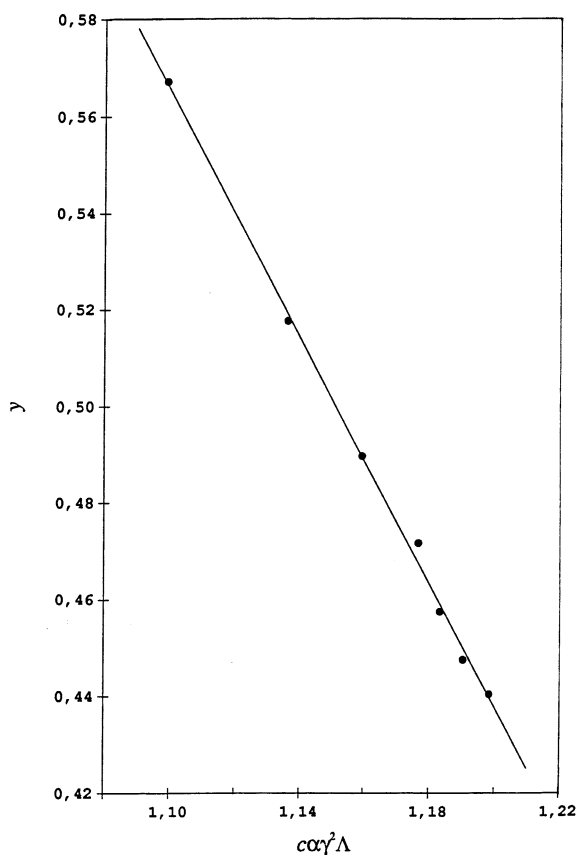


Fig. 1. Graph according to Eq. (6a) for LidHCl in 1-octanol at 25.0°C.

3.1.2. Upper limit of the ion/ion pair concentration range

Fuoss and Accascina (1959) have shown that for 1:1-electrolytes at 25°C higher association than pair-wise may be neglected up to a concentration limit, c_0 , given by the expression,

$$c_0 = 3.2 \cdot 10^{-7} \varepsilon^3 \quad (8)$$

which for 1-octanol as solvent ($\varepsilon = 9.85$) corresponds to $c_0 = 3.1 \cdot 10^{-4}$ M.

To establish c_0 experimentally, we investigated any dependence of K_a and $\sigma(\Lambda)$ (the standard deviation between experimental and calculated Λ -values) on the concentration range by increasing successively the upper concentration limit. The results are shown graphically in Figs. 2 and 3,

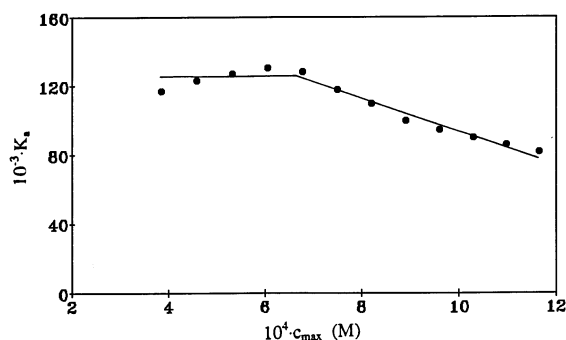


Fig. 2. Dependence of K_a , (same system as in Fig. 1) on the maximum concentration of LidHCl.

which show how K_a and $\sigma(\Lambda)$, respectively, depend on the maximum LidHCl concentration. These graphs indicate that there is a systematic decrease in K_a and a systematic increase in $\sigma(\Lambda)$ for concentrations exceeding approximately $6 \cdot 10^{-4}$ M. These observations indicate that higher association than pair-wise would be negligible up to this concentration. Hence, in the subsequent analysis of our data with respect to triple ion formation we adopted the values of K_a and Λ_0 calculated above on basis of the seven lowest concentration points ($c_{\max} < 6.1 \cdot 10^{-4}$ M; $K_a = 127.6 \cdot 10^3$; $\Lambda_0 = 1.969 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$).

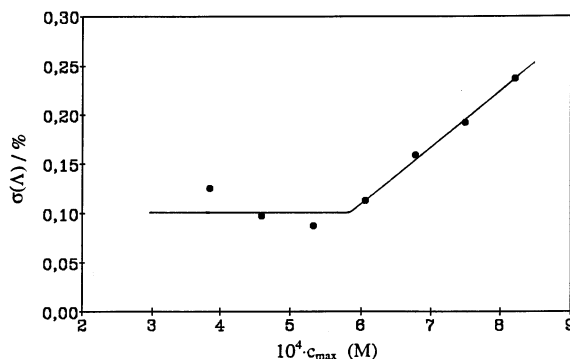


Fig. 3. Dependence of the percentage standard deviation in Λ (same system as in Fig. 1) on the maximum concentration of LidHCl.

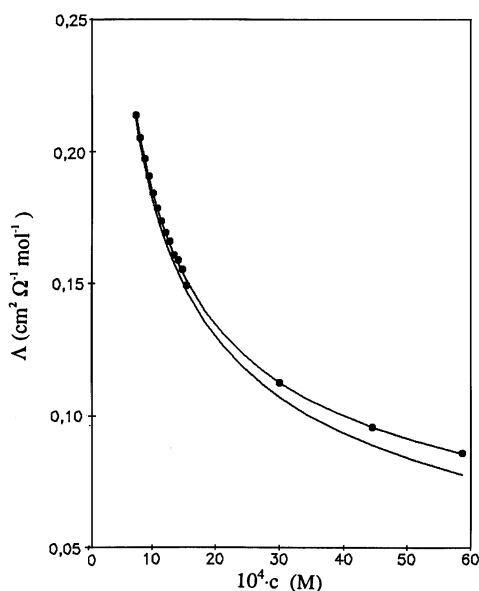


Fig. 4. Relation between molar conductivity of LidHCl in 1-octanol and concentration at 25.0°C. The bottom curve is an extrapolation of Eq. (4) for pair-wise association. The upper curve represents best fit of Eq. (15) including triple ion formation. Experimental points denoted by full circles.

3.2. Higher concentration range: triple-ion formation

In Fig. 4 the experimental values of Λ have been plotted as a function of the analytical concentration of LidHCl. The bottom curve represents an extrapolation of the conductance Eq. (4) for pair-wise association to higher concentrations. In this higher concentration range there is a significant positive deviation between the experimental points and the extrapolated curve. This deviation may be taken as evidence of triple ion formation.

3.2.1. Evaluation of the triple ion association constant

Let us assume that triple ions $(\text{LidH})_2\text{Cl}^+$ and LidHCl_2^- are formed and that the probabilities of formation of the two different kinds of triple ions are equal. In this case we have, in addition to the Equilibrium (2) between ions and ion pairs, to take into account the equilibria,



where K_T is the triple ion association constant, assumed to be identical in Eqs. (9a) and (9b).

Denoting by α_T the fractions of LidHCl present in the form of positively and negatively charged triple ions, respectively, we have the following expressions for the concentrations of single ions, ion pairs, and triple ions,

$$[\text{LidH}^+] = [\text{Cl}^-] = c\alpha \quad (10)$$

$$[\text{LidHCl}] = c(1 - \alpha - 3\alpha_T) \quad (11)$$

$$[(\text{LidH})_2\text{Cl}^+] = [\text{LidHCl}_2^-] = c\alpha_T \quad (12)$$

and, hence, the following expressions for the association constants for ion pair and triple ion formation, respectively:

$$K_a = (1 - \alpha - 3\alpha_T)/(c\gamma^2\alpha^2) \quad (13)$$

$$K_T = \alpha_T/[c\alpha(1 - \alpha - 3\alpha_T)] \quad (14)$$

The molar conductivity,

$$\Lambda = m(\alpha\Lambda_0 + \alpha_T\Lambda_0^T) \quad (15)$$

where m is a mobility correction factor which takes into account ion atmosphere effects and,

$$\Lambda_0^T = \lambda_0\{(\text{LidH})_2\text{Cl}^+\} + \lambda_0\{\text{LidHCl}_2^-\} \quad (16)$$

The mobility correction factor is given by the expression,

$$m = (\Lambda_0 - S c_i^{1/2} + E c_i \log c_i + J_1 c_i - J_2 c_i^{3/2})/\Lambda_0 \quad (17)$$

where the coefficients S , E , J_1 , and J_2 are the same as in Eq. (4) and where,

$$c_i = c(\alpha + \alpha_T) \quad (18)$$

Using a preselected value of K_T , (and of K_a and Λ_0 calculated above) values of α and α_T were iteratively computed for each concentration, c_i , using Eqs. (5), (13) and (14). In the activity coefficient expression (Eq. (5)) the ionic strength is now:

$$I = c(\alpha + \alpha_T) \quad (19)$$

The percentage standard deviation between experimental and calculated Λ -values was then calculated according to the expression,

$$\sigma(\Lambda) = 100 \cdot [\sum (\Delta\Lambda_i/\Lambda_i)^2 / (N - 2)]^{1/2} \quad (20)$$

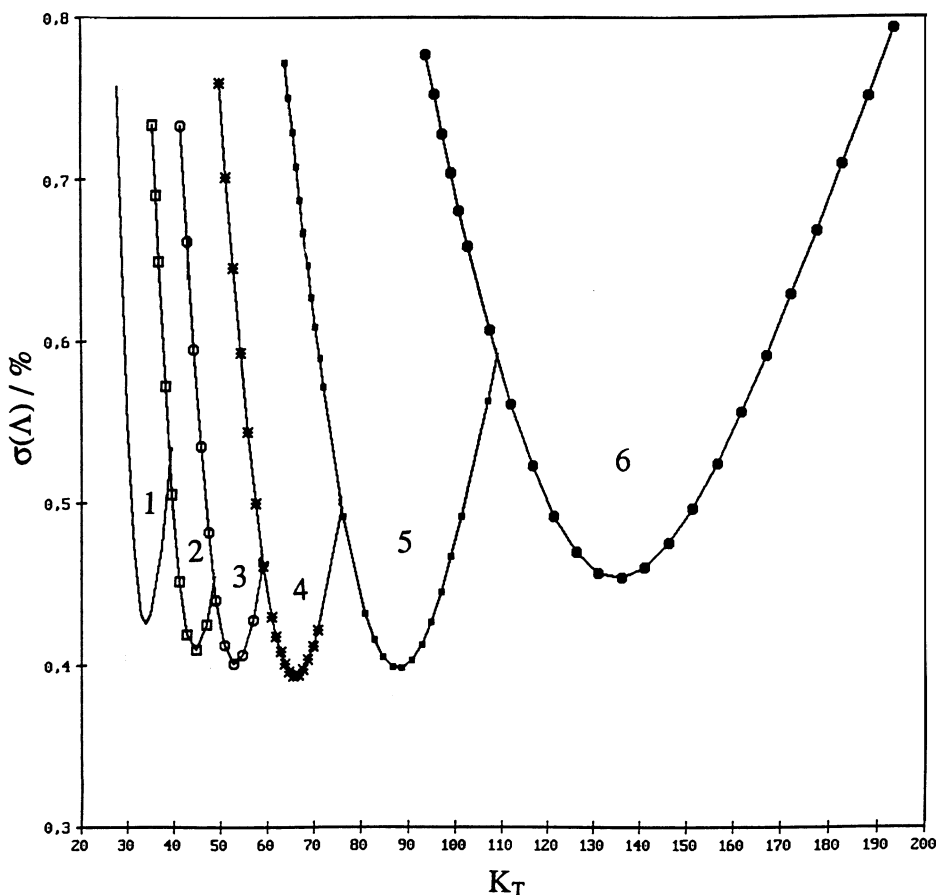


Fig. 5. Dependence of $\sigma(\Lambda)$ on K_T and Λ_0^T (expressed as a fraction of Λ_0) for LidHCl in 1-octanol at 25.0°C. The curves 1–6 refer to $\Lambda_0^T/\Lambda_0 = 0.50, 0.40, 0.35, 0.30, 0.25$, and 0.20 , respectively. Calculations based on Eq. (15).

where $\Delta\Lambda_i = [\Lambda_i(\text{exp}) - \Lambda_i(\text{calc})]$ is the difference between the experimental and the calculated Λ -value for each experimental point ($c_i; \Lambda_i$). This procedure was repeated for different combinations of K_T and Λ_0^T .

Some results of these calculations are shown graphically in Fig. 5, where the percentage standard deviation in Λ has been plotted as a function of the triple ion association constant, K_T , for different values of Λ_0^T expressed as the ratio Λ_0^T/Λ_0 . The curves 1–6 correspond to Λ_0^T/Λ_0 equal to 0.50, 0.40, 0.35, 0.30, 0.25, and 0.20, respectively.

The corresponding 3-D representation is shown in Fig. 6. The 'total' minimum in $\sigma(\Lambda)$ was obtained for $K_T = 65$ (molar scale) and $\Lambda_0^T/\Lambda_0 = 0.30$ indicating a triple ion mobility of about 1/3 of the

mobility of single ions. This result, together with $\Lambda_0 = 1.969 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ obtained above, yields $\Lambda_0^T = 0.59 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ for the limiting molar conductivity of triple ions.

4. Discussion

The excellent fit of Eq. (15) to the conductance data (Table 1) strongly supports our assumption that triple ions, $(\text{LidH})_2\text{Cl}^+$ and LidHCl_2^- , are present in equilibrium with ion pairs, LidH^+Cl^- , and free ions, LidH^+ and Cl^- . Furthermore, the fact that this equation fits the conductance data so well indicates that our initial estimate of negligible dissociation of LidH^+ into Lid and H^+ in the concentration interval studied is correct.

Lidocaine hydrochloride has been previously investigated conductometrically at 25°C using water as solvent medium (Sjöberg et al., 1996). Changing the solvent from water to 1-octanol causes a very strong decrease in mobility of the ions. Compare $\Lambda_0(\text{LidHCl}, 1\text{-octanol}) = 1.969 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ arrived at in this study with $\Lambda_0(\text{LidHCl}) = 94.22 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ for water as solvent medium. The latter Λ_0 -value was obtained using $\lambda_0(\text{LidH}^+, \text{aq.}) = 17.87 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ (Sjöberg et al., 1996) and $\lambda_0(\text{Cl}^-) = 76.35 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ (Robinson and Stokes, 1965). Hence, the change in solvent causes a 48-fold decrease in limiting molar conductivity of LidHCl. This change can be only partly ascribed to the difference in viscosity between these two solvents, which differ by a factor of 12. In this connection it may be of interest to note that the limiting molar conductivity of hydrochloric acid in octanol, $10.04 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ (De Lisi et al., 1979) and water, $426.16 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ (Robinson and Stokes, 1965) differ by a factor 42.

No transport numbers are, to the knowledge of the authors, available to determine single ion conductivities in 1-octanol. To estimate the limiting molar ionic conductivity of the LidH^+ ion in this solvent we shall tentatively use the cation transport number, $t_{\text{LidH}^+} = 0.19$, for LidHCl in aqueous solution derived from the λ_0 -values of

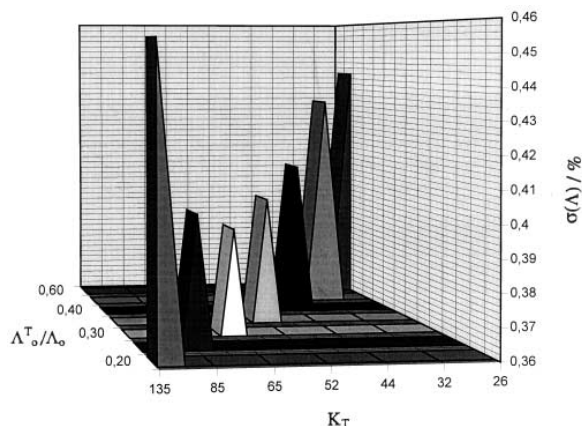


Fig. 6. A three-dimensional representation of the dependence of $\sigma(\Lambda)$ on K_T and Λ_0^T/Λ_0 for the same system as in Fig. 5. The white stack represents best fit parameters of Eq. (15) to the experimental points. $K_T = 65$ (molar scale); $\Lambda_0^T/\Lambda_0 = 0.30$.

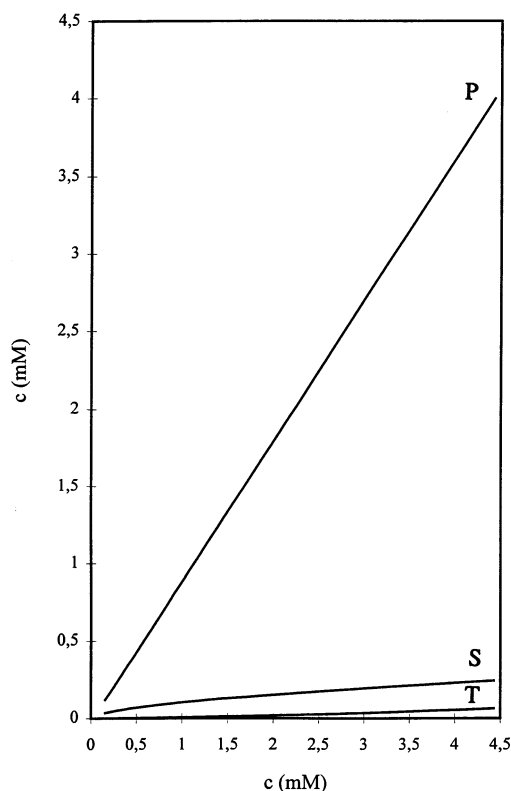


Fig. 7. Concentrations of single ions (S), ion pairs (P), and triple ions (T) as a function of the total LidHCl concentration in 1-octanol at 25°C.

LidH^+ and Cl^- above. This value of the transport number combined with $\Lambda_0(\text{LidHCl}, 1\text{-octanol}) = 1.969 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$ yields $\lambda_0(\text{LidH}^+, 1\text{-octanol}) = 0.37 \text{ cm}^2 \Omega^{-1} \text{ mol}^{-1}$.

The molar conductivity decreases rapidly with increasing LidHCl concentration (Fig. 4). This effect is due to the rapid increase in non-conducting LidH^+Cl^- ion pairs, see Fig. 7, where the concentrations of single ions (S), ion pairs (P) and triple ions (T) have been plotted as a function of the analytical LidHCl concentration. As indicated by this graph there is a strong domination of ion pairs over single ions and triple ions in the concentration interval studied. In this connection it may be of interest to note that drug molecules of local anaesthetics are considered to be transported in unionized form across the continuous cell layer of the perineurium before they combine with the

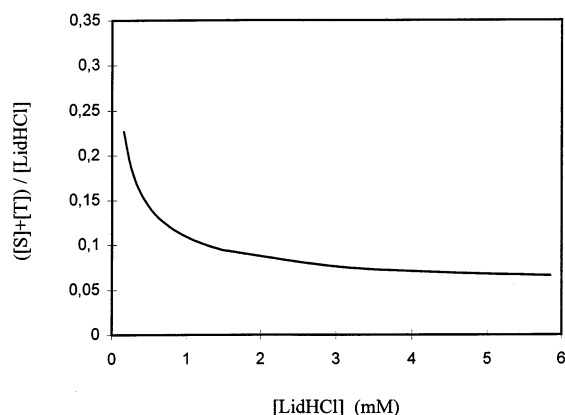


Fig. 8. Fraction of LidHCl in ionic form (free ions and triple ions) as a function of total LidHCl concentration in 1-octanol at 25°C.

receptors in the nerve membrane and give the anaesthetic effect (Rapoport, 1976; Florence and Attwood, 1993).

An alternative representation of the relation between conducting and non-conducting species is shown in Fig. 8, where the total amount of free ions and triple ions, expressed as a fraction of the total amount of lidocaine hydrochloride, is given as a function of the analytical LidHCl concentration. For concentrations below approximately 1–2 mM the fraction of conducting species decreases rapidly with increasing concentration, while above this concentration there is only a slight concentration dependence.

5. Conclusions

In this continued investigation of lidocaine hydrochloride, the purpose of which is to optimize

the conditions in iontophoretic drug delivery, transport properties and aggregation of this anaestheticum has been studied by precision conductometry in 1-octanol as solvent at 25°C.

Analysis of the conductance data, performed at several different concentrations in the interval from 0.2 to 6 mM, indicates that free LidH^+ and Cl^- ions are present in equilibrium with LidH^+Cl^- ion pairs up to a total concentration of about 0.6 mM. Above this concentration there is evidence of formation of measurable quantities of $(\text{LidH})_2\text{Cl}^+$ and LidHCl_2^- triple ions.

The molar conductivity decreases rapidly with increasing concentration. This effect is due to extensive formation of ion pairs dominating over free ions and triple ions. The fraction of the drug present in the form of conducting species decreases rapidly up to a concentration of the order 1–2 mM. Above this level the decrease is less drastic.

The limiting molar conductivity of the LidH^+ ion in 1-octanol is found to be only about 2% of the corresponding value for water as solvent medium.

The compilation in Table 2 clearly illustrates the tremendous effect of the character of the solvent medium on the structure of the electrolyte. In the concentration interval studied LidH^+ and Cl^- ions are the only species common in water and 1-octanol as solvent media.

The drastic change in the ratio between conducting and non-conducting species with the total concentration of the electrolyte in a low dielectric constant solvent, and the very different structure of the electrolyte in solvents of high and low dielectric constants strongly focuses our attention on the importance of considering carefully the conditions in optimizing the iontophoretic process.

Table 2

Measurable amounts of different species present in solutions of LidHCl in the concentration interval 0.2–6 mM at 25°C

1-Octanol	—	—	LidH^+	LidHCl	$(\text{LidH})_2\text{Cl}^+$	LidHCl_2^-	Cl^-
Water	H^+	Lid	LidH^+	—	—	—	Cl^-

Acknowledgements

The authors wish to thank Professor Lars-Olof Sundelöf for most valuable discussions and for his kind support of this research. Financial support from the Swedish Research Council for Engineering Sciences and from the Swedish Natural Science Research Council is gratefully acknowledged.

References

- Ahmed, S., Imai, T., Otagiri, M., 1995. Stereoselective hydrolysis and penetration of propanolol prodrugs: In vitro evaluation using hairless mouse skin. *J. Pharm. Sci.* 84, 877–883.
- Beronius, P., 1975. On the interpretation of conductance data for electrolyte solutions. *Acta Chem. Scand. A* 29, 289–297.
- Beronius, P., 1976. Remarks on the problem of finding best set conductance parameters for electrolyte solutions. *Acta Chem. Scand. A* 30, 115–120.
- Beronius, P., 1978. Properties of sodium iodide in 1-octanol at 25°C. A conductimetric study. *Acta Chem. Scand. A* 32, 469–470.
- Beronius, P., Pataki, L., 1980. On the study of triple ion formation. Sodium iodide in 1-octanol at 25°C. *Acta Chim. Acad. Sci. Hung.* 103, 17–25.
- Cornford, E.M., Braun, L.D., Oldendorf, W.H., Hill, M.A., 1982. Comparison of lipid-mediated blood-brain-barrier penetrability in neonates and adults. *Am. J. Physiol. Cell Physiol.* 12 (243), C161–C168.
- De Lisi, R., Goffredi, M., Livery, V.T., 1979. Effect of water on proton migration in alcoholic solvents. Part 6. Conductance of hydrogen chloride in hexan-1-ol and octan-1-ol. *J. Chem. Soc. Faraday Trans.* 75, 1667–1673.
- Fernandez-Prini, R., 1969. Conductance of electrolyte solutions. A modified expression for its concentration dependence. *Trans. Faraday Soc.* 65, 3311–3313.
- Florence, A.T., Attwood, D., 1993. *Physicochemical Principles of Pharmacy*, 2nd ed. Macmillan, London.
- Fuoss, R.M., Accascina, F., 1959. *Electrolytic Conductance*, Interscience, New York.
- Fuoss, R.M., Hsia, K.-L., 1967. Association of 1-1 salts in water. *Proc. Natl. Acad. Sci. USA* 57, 1550–1557.
- Fuoss, R.M., Hsia, K.-L., 1968. Association of 1-1 salts in water. *Proc. Natl. Acad. Sci. USA* 58, 1818.
- Hasinoff, B.B., Davey, J.P., 1989. The inhibition of a membrane-bound enzyme as a model for anaesthetic action and drug toxicity. *Biochem. J.* 258, 101–107.
- Justice, J.-C., 1971. An interpretation for the distance parameter in the Fuoss-Onsager conductance equation in the case of ionic association. *Electrochim. Acta* 16, 701–712.
- Lindbäck, T., 1984. Aggregation and mobility of electrolytes in solvents of low and intermediate permittivity. Dissertation, University of Umeå.
- Loberg, M.D., Corder, E.H., Fields, A.T., Callery, P.S., 1979. Membrane transport of Tc-99m-labeled radiopharmaceuticals. I. Brain uptake by passive transport. *J. Nucl. Med.* 20, 1181–1188.
- Rapoport, S.I., 1976. *Blood Brain Barrier in Physiology and Medicine*. Raven Press, New York.
- Robinson, R.A., Stokes, R.H., 1965. *Electrolyte Solutions*, 2nd ed. Butterworths, London.
- Shkodin, A.M., Sadovnichaya, L.P., Podolyanko, V.A., 1969. Electrical conductivity of sodium iodide solutions in aliphatic alcohols. *Ukr. Khim. Zh.* 35, 144–147.
- Sjöberg, H., Karami, K., Beronius, P., Sundelöf, L.-O., 1996. Ionization conditions for iontophoretic drug delivery. A revised pK_a of lidocaine hydrochloride in aqueous solution at 25°C established by precision conductometry. *Int. J. Pharm.* 141, 63–70.
- Walter, K., Kurz, H., 1988. Binding of drugs to human skin: Influencing factors and the role of tissue lipids. *J. Pharm. Pharmacol.* 40, 689–693.