International Journal of Pharmaceutics, 30 (1986) 101–109
Elsevier

IJP 01001

The stoichiometric interaction and influence of ionic strength on the organic–aqueous distribution behaviour of a tetrazole ion pair

O. Olejnik * and S.S. Davis

Department of Pharmacy, University of Nottingham, Nottingham (U.K.)

(Received November 13th, 1985)
(Accepted December 6th, 1985)

Key words: ion pair – interaction – distribution behaviour – ionic strength – tetrazole

Summary

Physicochemical measurements have been carried out on drug-pairing ion systems. The stoichiometric solubility product, K_s was used to define the complexation between a novel tetrazole derivative with quaternary ammonium and phosphonium compounds. The stoichiometry of interaction was unity which suggested that the solute transport occurred as a 1 : 1 complex and not as the predicted 2 : 1 species. The behaviour of the ion-pair species was examined by a conditional extraction constant. This constant increased with increasing weight of the interacting cation counterion. However, the presence of an inorganic electrolyte, sodium chloride was shown to inhibit the transfer of the ion pair from an aqueous phase to an organic phase. A salting-in effect was described.

Introduction

The development of drug delivery systems can involve manipulative techniques by which a poorly absorbed but otherwise active compound can be modified to improve its absorption. One approach concerns the concept of ion-pair formation (Wilson et al., 1981). The properties of the altered drug species (e.g. solubility, ionic size, diffusivity, and partitioning behaviour) can differ from those of the respective free drug species. It is the last effect, namely the alteration of the distribution behaviour of the compound which has received much interest. For example, an uncoupler of oxidative phosphorylation, 2,4-dinitrophenol was shown to transfer from an aqueous to an organic environment in three forms: a neutral form, an ion-pair complex, and an anionic form (Terada et al., 1981). It was confirmed, using pH-dependent partitioning that the phenolic compound extracted into the organic phase by the formation of ion pairs with either of the two cations, potassium and *n*-butyltrimethylammonium. Similarly, a preferential distribution of a series of phenothiazines into an organic medium was explained in terms of ion-pairing with various salts (Murthy and Zografi, 1970). This phenomenon was also implicated in the transfer of β-blocking drugs from an aqueous system into 1-octanol, facilitated in the presence of chloride and acetate ions (Dallet et al., 1980). In another study, the sodium cation was considered to act in the process of ion-pair formation with warfarin (Cools and Janssen, 1983). Here a linear relationship between the partition coefficient and the sodium ion concentration was found. An increase in the lipophilicity of proxicromil was

* *Correspondence and current address*: O. Olejnik, CooperVision Inc., 455 E. Middlefield Road, Mountain View, CA 94043, U.S.A.

also thought to result from an ion association effect in the presence of sodium and potassium ions (Davis et al., 1984). Increasing the cation content was reported to have proportionately increased the partitioning of this anti-allergenic compound.

These in vitro observations apparently give credence to the likelihood for promoting the in vivo absorption of drugs as ion pairs. However, a question often ignored is whether the system under study actually involves the formation of these species. Changes in the absorption characteristics could well represent a function of the environment per se and not the ion-pair species themselves. For instance, the distribution behaviour of an organic solute is shown to vary with the ionic strength of an aqueous phase, as described by a modified Setschenow equation (Kojima and Davis, 1984). It follows that the partitioning of organic compounds may not result from an ion-pairing effect but could be influenced by other thermodynamic factors. Therefore, an improperly or poorly defined ion-pair system can lead to an erroneous interpretation regarding the properties of the interacting solutes. This only serves to add to the continuing controversy that surrounds the validity of the hypothesis of ion-pair absorption as a significant factor in drug absorption (Jonkman and Hunt, 1983).

In the present investigation, the stoichiometry of interaction and partition behaviour that occur between large organic species of opposite charge has been studied. The definition of the ion-pair complex is considered an important step in understanding the characteristics of the interacted species. The role of the electrolyte (sodium chloride) on the activity of the organic solutes together with its contribution to ion-pairing has also been examined.

Materials and Methods

Materials

N-(3-acetyl-5-ethyl-2-hydroxyphenyl)-5-carboxamide-1H-tetrazole (MB34903, May and Baker U.K.) was used to prepare ion-associated complexes with cetyltrimethylammonium bromide (Fluka Chemicals) and quaternary phosphonium compounds (Maybridge Chemicals) (Table 1). These compounds were recrystallized from ethanol AR (BDH) prior to use. 1-Octanol 99% (Aldrich Chemicals) was used as supplied, exhibiting a negligible UV absorbance spectrum. Analytical reagent grade chemicals were used throughout. Solutions were freshly prepared with de-ionized, double-distilled water having a conductance of less than 1.0×10^{-6} mho $\cdot$ cm^{-1}, at 25°C.

TABLE 1

QUATERNARY ION-PAIRING AGENTS

Compound	Abbreviation
Cetyltrimethylammonium bromide	C_{16}TAB
m-Chlorobenzyltriphenylphosphonium chloride	Cl-BTPC
p-Methoxybenzyltriphenylphosphonium chloride	CH_3O-BTPC
Benzyltriphenylphosphonium chloride	BTPC
Triphenylallylphosphonium chloride	ATPC

Methods

pK_a determination

(i) Potentiometric titration. An aqueous solution of 1×10^{-4} mol $\cdot$ dm^{-3} MB34903 was prepared in 1×10^{-2} mol $\cdot$ dm^{-3} sodium hydroxide. 100 cm^3 of the solution was titrated with small volumes (1×10^{-1} cm^3) of 1×10^{-1} mol $\cdot$ dm^{-3} acetic acid. To facilitate the titration, an initial amount of 1 mol $\cdot$ dm^{-3} hydrochloric acid was added to neutralize the sodium hydroxide. After reaching pH 5 during the titration procedure, 1×10^{-1} mol $\cdot$ dm^{-3} hydrochloric acid was substituted as the titrant. Triplicate titrations were carried out in a nitrogen atmosphere using solutions previously purged with the nitrogen gas. All solutions were equilibrated at 25°C prior to the titration procedure.

(ii) UV spectroscopy. The method described by Albert and Serjeant (1971) was used. 1×10^{-4} mol $\cdot$ dm^{-3} MB34903 solutions were prepared and adjusted to the required pH. Analysis was carried out at 382 nm at which the absorbances of the non-ionized and ionized species differed appreciably. Solutions were equilibrated to 25°C prior to

use. The pK_a values were calculated according to the equation:

$$pK_a = pH + \log\left[\frac{A_i - A}{A - A_m}\right] \quad (1)$$

where the observed absorbance, A at the analytical wavelength was the summation of the absorbances of the ionized species, A_i and the molecular species, A_m.

Stoichiometric determinations

An ion-selective electrode specific for cetyltrimethylammonium (CTA^+) ions was used as previously described (Davis and Olejnik, 1981). The electrode was further modified to monitor quaternary phosphonium ions using a liquid ion-exchanger containing 4×10^{-3} mol · dm^{-3} *m*-chlorobenzyltriphenylphosphonium chloride (Cl-BTPC) complexed with 5×10^{-3} mol · dm^{-3} MB34903. An internal reference solution consisting of 1×10^{-3} mol · dm^{-3} Cl-BTPC completed the modifications. The electrode was conditioned for 1 h in 1×10^{-2} mol · dm^{-3} Cl-BTPC prior to use.

A titration procedure (Mukhayer et al., 1975) was used to evaluate the interaction between the tetrazole and the cetyltrimethylammonium bromide ($C_{16}TAB$) and the quaternary phosphonium compounds. The interactions were carried out at pH 12.0, ionic strength 0.1, and at 25°C. The complexation end-point was quantitated by determining the stoichiometric solubility product at the equivalence point of the titration.

Assuming additivity of volumes, the stoichiometric molar concentrations of the ion-pairing agent (Q^+) and the tetrazole anion (T^-) at any point in the titration at time, t can be expressed as:

$$C_{Q^+,\,t} = \frac{Q^+}{V_t + V} \quad (2)$$

and

$$C_{T^-,\,t} = \frac{Q^+ V_t}{V_{eq}(V_t + V)} \quad (3)$$

where Q^+ and T^- represents the analytical quantity of the cation and anion in terms of the total amount of the species independent of the form in which it exists. V is the initial volume of the solution, V_t is the volume added at time t, and V_{eq} is the volume of the titrant required for equivalence. From the law of mass balance and considering the definition of the thermodynamic equilibrium constant, K_s^0 (Mukhayer and Davis, 1976) and the activity coefficient $\gamma_\pm$ of the cation and anion, then

$$[Q^+] = \tfrac{1}{2}\left[\left\{(C_{Q^+,\,t} - C_{T^-,\,t})^2 + 4K_s^0/\gamma_\pm^2\right\} - C_{Q^+,\,t} \cdot C_{T^-,\,t}\right] \quad (4)$$

which quantifies the cation concentration at time t in the titration. The limits of Eqn. 4 as K_s^0 tends to zero are denoted as:

$$[Q^+]_{t,\,\lim} = 0$$

and

$$[Q^+]_{t,\,\lim} = C_{Q^+,\,t} - C_{T^-,\,t}$$

and in combination with Eqns. 2 and 3 gives:

$$[Q^+]_{t,\,\lim} = \left(\frac{V_{eq} - V_t}{V_{eq}}\right)\left(\frac{V}{V + V_t}\right)[Q^+]_0 \quad (5)$$

where $[Q^+]_0 = Q^+/V$ and substitution of $[Q^+]_{t,\,\lim} = [Q^+]$ into the Nernst equation defines the relative electrode potential, E as

$$E = E' - N \log[Q^+]_{t,\,\lim} \quad (6)$$

where N is the Nernst constant and $E' = E_0$ (electrode constant) + $N \log(K_s^0/\gamma_\pm)$. A plot of E against $[Q^+]_{t,\,\lim}$ is made possible from which the stoichiometric product can be obtained.

Partition – extraction studies

Solute oil – water partitioning was determined using a filter-probe extractor method (Tomlinson, 1982). The partitioning of MB34903 from an aqueous phase at pH 12.0, ionic strength 0.2 into 1-octanol in the presence of varying concentra-

tions of the quaternary phosphonium compounds was studied. MB34903 was further partitioned with Cl-BTPC at different ionic strengths 0.05–0.7, adjusted with sodium chloride. All phases were equilibrated at 25 ± 0.1°C. A double beam UV spectrophotometer CE505 (Cecil, Cambridge) was used to monitor the aqueous solutions. Mutually saturated solvents were used throughout the experiments.

Results and Discussion

From chemical considerations the MB34903 compound represents a combination of two moieties namely, a substituted tetrazole and a substituted phenol. The ionization constants of related model compounds, tetrazole and 4-aminophenol, have been reported as 4.9 and 10.3, respectively (Albert and Serjeant, 1971) and it is predicted that the MB34903 molecule ionizes at two specific sites (Fig. 1) having comparable pK_a values to these model compounds. The observed pK_a value for the tetrazole moiety was found to be 4.3 determined from a non-linear, least-squares analysis of a plot of pH versus the mol · equivalent of H^+ ions (Fig. 2). In using a spectrophotometric procedure to determine the ionization constant for the weakly ionizing aromatic -O-H group of the phenolic moiety, a pK_a value of 9.7 was calculated (Table 2). The experimental data established that two pK_a values and hence, two ionization sites occur. Under the conditions for complete ionization the MB34903 compound can be expected to behave as a dianion which may have significant implications for ion-pairing interaction studies.

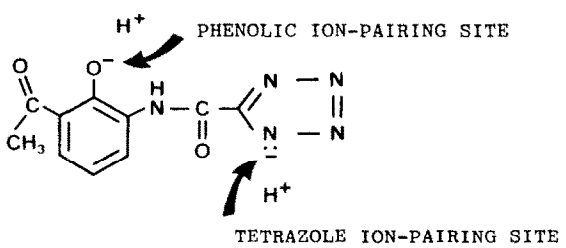

Fig. 1. Ionization sites of MB34903.

TABLE 2

pK_a DETERMINATION OF THE PHENOLIC MOIETY OF MB34903 BY A SPECTROPHOTOMETRIC TECHNIQUE

pH	$\log\left[\frac{A_i - A}{A - A_m}\right]$	pK_a
10.50	−0.73	9.8
10.25	−0.55	9.7
10.00	−0.40	9.6
9.95	−0.32	9.8
9.70	−0.08	9.6
		mean 9.7

The interaction between two large organic ions of opposite charge in water can be characterised by the solubility product (K_s). At concentrations of the solutes where $[Q^+][T^-] < K_s$, the species in solution will be the dissociated ions and the ion-pair species $[Q^+][T^-]$. At higher concentrations (above the complexation point) multiple interactions occur leading to the formation of large complexes and coacervates (Mukhayer and Davis, 1976). The complexation of C_{16}TAB with the tetrazole compound MB34903 can be defined by a solubility product of 1×10^{-8} $(mol \cdot dm^{-3})^2$. This value was obtained from the equivalence value (E) by extrapolation to zero, the linear portion of the

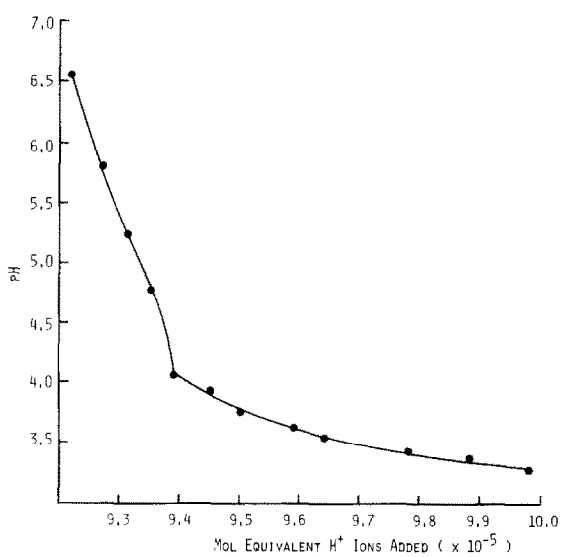

Fig. 2. Potentiometric titration of MB34903.

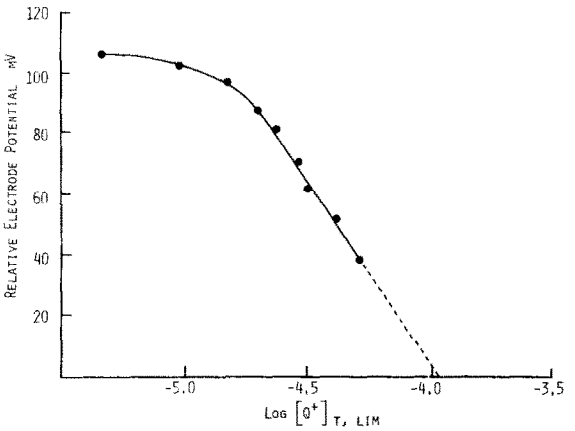

Fig. 3. The ion-selective electrode response to $C_{16}TAB$ in the presence of 1×10^{-3} mol·dm^{-3} MB34903.

E versus log Q_t^+, lim, relationship (Fig. 3). The stoichiometry of interaction was followed by measuring the solubility product for a range of $[Q^+]$ and $[T^-]$ and plotting the appropriate values of log $[Q^+]$ versus log $[T^-]$ (Fig. 4). The good linear relationship (correlation coefficient 0.99) of slope -1.06 indicates a 1 : 1 interaction between the two species $C_{16}TAB$ (Q^+) and MB34903 (T^-). The full dissociation of the tetrazole compound into the dianion form (shown by the presence of the two pK_a values) would be expected to lead to a

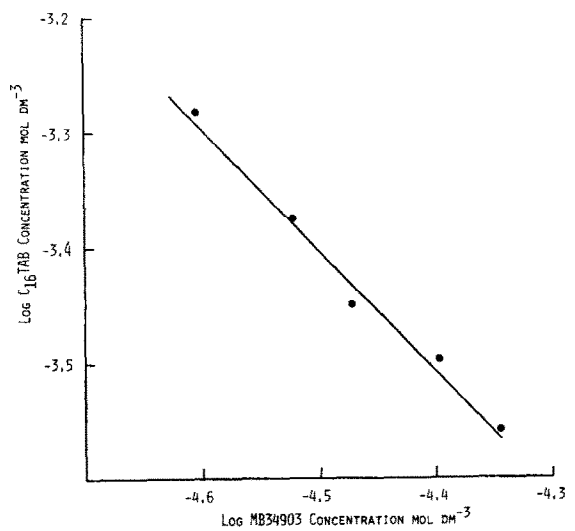

Fig. 4. Complexation end-points for the interaction between different concentrations of $C_{16}TAB$ and MB34903.

TABLE 3

THE EFFECT OF QUATERNARY PHOSPHONIUM COMPOUNDS (Q^+) ON THE STOICHIOMETRY OF INTERACTION WITH MB34903 (T^-)

Quaternary phosphonium compound	log[Q^+] vs log [T^-] gradient	Apparent stoichiometry of interaction
Cl-BTPC	−1.06	1:1
CH_3O-BTPC	−0.98	1:1
BTPC	−1.11	1:1
ATPC	−1.14	1:1

2 : 1 interaction through association of the cation at the tetrazole and phenol anionic sites. The experimentally determined 1 : 1 stoichiometry shows that apparently only one anionic site of the tetrazole is available for interaction. We believe that ion-pairing at the phenolic site is prevented by steric hindrance by the substituent groups at the 20- and 6-ortho position in the benzene ring and that the cation preferentially interacts with the tetrazole anionic moiety. This would appear to be a general effect since a similar 1 : 1 stoichiometry of interaction was found for the complexation of MB34903 with the various quaternary compounds (Table 3). Transfer of the large anion into an organic phase in the presence of large counterions that can participate in ion-pair formation should also follow a 1 : 1 stoichiometry.

The apparent partition coefficient (K′) for the tetrazole anion can be described by the equation:

$$K' = \frac{[QT]_{org}}{[T^-]_{aq}} \tag{7}$$

where [QT] represents the concentration of the ion pair and $[T^-]$ the concentration of the tetrazole anion. The subscripts org and aq denote the organic and aqueous phases, respectively. In the distribution of MB34903 from an aqueous buffered phase to 1-octanol solute transfer to the organic phase was enhanced with increasing concentrations of the ion-pairing agent Cl-BTPC (Fig. 5). An extraction parameter (Shim et al., 1981) characterized the equilibrium process in the following scheme:

$$Q^+_{aq} + T^-_{aq} \rightleftharpoons QT_{org}$$

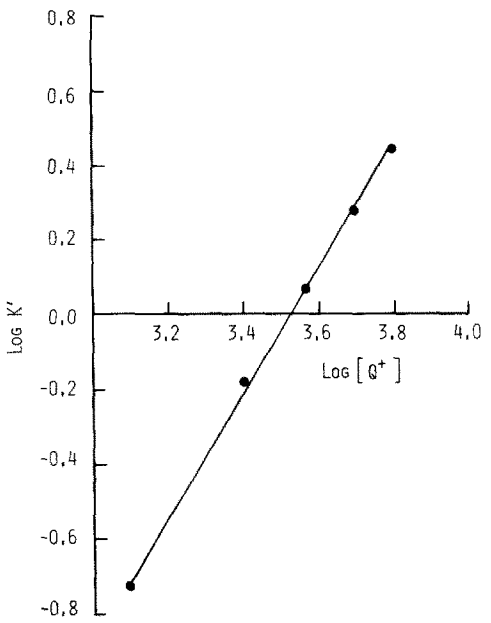

Fig. 5. The effect of Cl-BTPC on the apparent partition coefficient of MB34903.

The ion-pair extraction constant (k_{ip}) can be defined as:

$$k_{ip} = \frac{[QT]_{org}}{[Q^+]_{aq} \cdot [T^-]_{aq}} \quad (8)$$

Assuming that no other interactions occur other than ion-pair formation between the two large ions, K′ can be written as:

$$K' = \frac{[QT]_{org}}{[T^-]_{aq}} = k_{ip}[Q^+]_{aq} \quad (9)$$

This extraction process represents an uncomplicated ion-pairing mechanism. In the presence of additional extraneous ions such as those provided by buffer components, the ion-pairing behaviour can alter (Moser et al., 1975). A conditional extraction constant (k^*_{ip}) was calculated to compensate for the influence of possible side reactions given by:

$$C'T^-(Q^+) = C^0T^- - \bar{C}'T^-(Q^+) \cdot V_r \quad (10)$$

where $C'T^-(Q^+)$ represents part of the total concentration of the tetrazole anion that was not extracted as an ion pair. $\bar{C}'T^-(Q^+)$ is the total concentration of the tetrazole when extracted into the organic phase with the pairing ion (quaternary phosphonium). C^0T^- is the total concentration of the tetrazole in the system and V_r the phase volume ratio. Similarly, the expression applied to Q^+ is shown below:

$$C'Q^+(T^-) = C^0Q^+ - \bar{C}'Q^+(T^-) \cdot Vr \quad (11)$$

The resultant equation for k^*_{ip} is:

$$k^*_{ip} = \bar{C}'T^-(Q^+)[C'T^-(Q^+) \cdot C'Q^+(T^-)]^{-1} \quad (12)$$

The quantity log k^*_{ip} plotted as a function of log C^0Q^+ (Fig. 6) produced a straight line almost parallel to the abscissa confirming the applicability of Eqn. 12. The conditional ion-pair extraction constant described the ion-pair complexation for the solution system and was independent of C^0Q^+. However, at higher solute concentrations a deviation from the constancy of k^*_{ip} heralded a departure from ideal behaviour suggesting a major influence of secondary complex species.

For the more dilute solutions, a correlation between k^*_{ip} and the cation weight of Q^+ was observed (Fig. 7). These results demonstrate a general trend for ion-pair transfer into the organic phase, where the larger the cation the greater the extraction constant. Primarily, this will be a response to the increasing lipophilicity of the cationic species. A similar relationship for the solvent

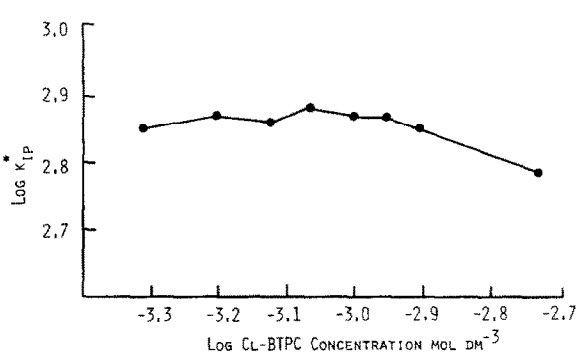

Fig. 6. MB34903 conditional ion-pair extraction constant as a function of Cl-BTPC concentration.

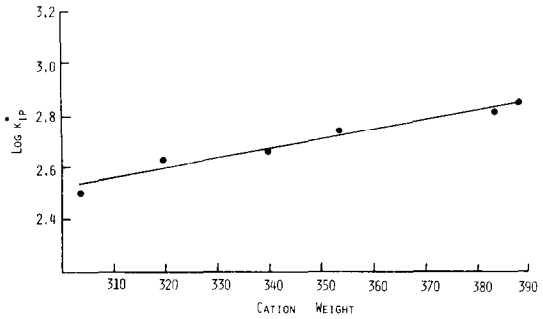

Fig. 7. The influence of the cation weight of a series of quaternary phosphonium compounds on the extraction of MB34903.

extraction of tetraalkylammonium iodides has been reported (Iwamoto et al., 1981).

The extraction behaviour for the ($Cl\text{-}BTP^+ - T^-$) ion pair was found to be dependent upon the concentration of sodium chloride in the aqueous phase. A decrease in k^*_{ip} of approximately 70% occurred with the addition of the inorganic electrolyte (Fig. 8). The extraction was significantly influenced at low ionic strength with k^*_{ip} becoming constant and independent of ionic strengths greater than 0.5. These results are opposite to the reported data of Brandstrom (1977) showing an increase in k^*_{ip} for tetraalkylammonium chloride with increasing ionic strength. This phenomenon was attributed to a salting-out effect due to the 'extraneous solute–solvent interactions', namely a decrease in the free energy of the solvent molecules being compensated by an increase in the apparent partition coefficient of the solutes concerned. Such a salting-out process can be considered as a possible mechanism for the observed enhancement of the partitioning of drug compounds (Cools and Janssen, 1983; Davis et al., 1984) as previously discussed.

In our studies, the decrease in k^*_{ip} for the extraction of the Cl-BTPC–MB34903 complex with increasing salt content indicates a preference of the interacting species for the aqueous phase. This shift in equilibrium favouring an aqueous environment suggests an hydrotropic effect which involves bringing about a high aqueous solubility to a drug species (Saleh and El-Khordagui, 1985). However, this effect is more directed towards a

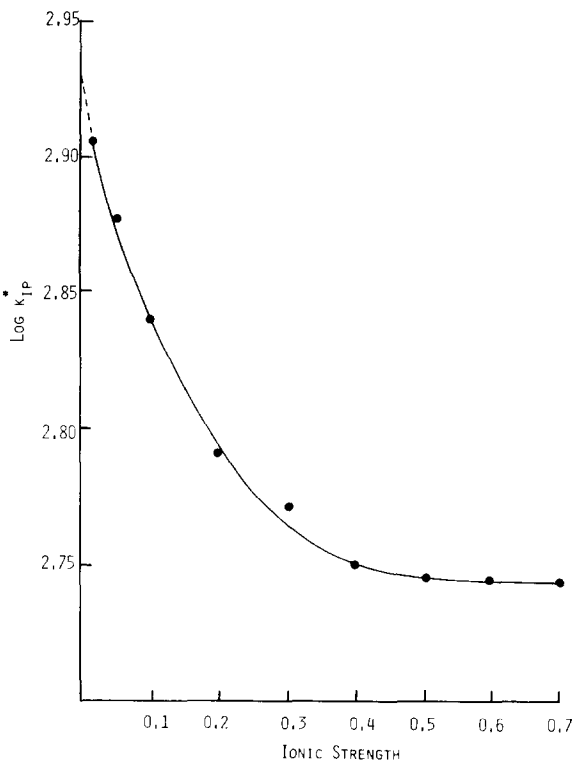

Fig. 8. The effect of ionic strength on the extraction of the MB34903–Cl-BTPC ion pair.

stack-type aggregation of the solute compounds which is assumed not to occur with the ion-associating species used in this study. A more plausible explanation concerns the salting-in effects which have been observed previously for the distribution of cromoglycate ions into chloroform using decybenzyldimethylammonium chloride as the ion-pairing compound (Tomlinson and Davis, 1980). A disturbance of the electrostatic interaction was proposed as the mechanism of reducing the ion-association. Accordingly, the lipophilic characteristics of the drug ion is lost and would account for the lowering of k^*_{ip}. Alternatively, other factors may be considered as having a role in the salting-in effect. The permittivity of an aqueous solvent is known to decrease with the addition of an electrolyte (Hasted et al., 1948) resulting in an increase in the aqueous association constant for the interacting solutes according to the relevant ion association constant equations (Fuoss, 1958; Gordon,

1975). Under these circumstances, it may be expected that the equilibrium for the distribution of the interacting solute species between the aqueous and organic phases shifts in preference for the aqueous phase with the addition of increasing amounts of sodium chloride. A so-called structure enforced ion-pairing mechanism has also been postulated (Diamond, 1963) which would have a stabilizing influence on the ion pairs in water. The effect is thought to lower the ionic free energy of the ion pair thereby facilitating the association of the interacting ions and minimising the disturbance of the solvent water molecules. Such a 'Diamond-type' ion-pairing mechanism could promote the stability of the aqueous associated species achieved by a lowered permittivity. Nevertheless, despite whichever mechanism is acting, the salting-in phenomenon leading to the preferential ion-pair distribution to the aqueous phase denotes a possible limiting role of ion-pair formation and enhanced drug absorption. Recently, Schurgers et al. (1984) have suggested that an 'unfavourable environment' in the rat small intestine led to the non-enhancement of cromoglycate–alkylbenzyldimethylammonium ion pairs. This result can be attributed to the ionic strength of the test solution as indicated by our current observations. It appears then not to be a failure on the part of the ion pair species leading to a lack of drug absorption enhancement but that of the surrounding medium disrupting its activity. Hence, a proper awareness of the relevant physicochemical conditions can contribute towards an understanding of the events that may occur when dealing with complexing species and how transport from aqueous to non-aqueous phases (including biological membranes) can be affected.

Acknowledgements

The authors gratefully acknowledge the support from the Science Research Council (CASE award to O.O.) and May and Baker (Dagenham, U.K.).

References

Albert, A. and Serjeant, E.P., The Determination of Ionization Constants, Chapman and Hall, 2nd ed., 1971.

Brandstrom, A., Principles of phase-transfer catalysis by quaternary ammonium salts. Adv. Phys. Org. Chem., 15 (1977) 267–330.

Cools, A.A. and Janssen, L.H.M., Influence of sodium ion-pair formation on transport kinetics of warfarin through octanol-impregnated membranes. J. Pharm. Pharmacol., 35 (1983) 689–691.

Dallet, P., Colleter, J.C., Audry, E. and Dubost, J.P., Extraction of ion-pairs between beta-blocking agents and chloride or acetate in the water–octanol system. Bull. Soc. Chim. Fr., 11980 (1980) I294–I298.

Davis, M.G., Manners, C.N., Payling, D.W., Smith, D.A. and Wilson, C.A., Gastrointestinal absorption of the strongly acidic drug proxicromil. J. Pharm. Sci., 73 (1984) 949–953.

Davis, S.S. and Olejnik, O., The determination of free long-chain quaternary ammonium species with an ion-selective electrode based on a cetyltrimethylammonium ion pair. Anal. Chim. Acta, 132 (1981) 51–58.

Diamond, R.M., The aqueous solution behaviour of large univalent ions. A new type of ion-pairing. J. Phys. Chem., 67 (1963) 2513–2517.

Fuoss, R.M., Ionic association. III. The equilibrium between ion pairs and free ions. J. Am. Chem. Soc., 80 (1958) 5059–5061.

Gordon, J.E., The Organic Chemistry of Electrolyte Solutions, Wiley-Interscience, New York, Ch. 3, 1975, pp. 371–538.

Hasted, J.B., Ritson, D.M. and Collie, C.H., Dielectric properties of aqueous ionic solutions. J. Chem. Phys., 16 (1948) 1–21.

Iwamoto, E., Ito, K. and Yamamoto, Y., Solute–solvent in ion-pair extraction of tetraalkylammonium iodides. I. A new approach to the extraction constant. J. Phys. Chem., 85 (1981) 894–905.

Jonkman, J.H.G. and Hunt, C.A., Ion pair absorption of ionized drugs — fact or fiction? Pharm. Weekbl. Sci. Ed., 5 (1983) 41–48.

Kojima, I. and Davis, S.S., The effect of salt concentration on the distribution of phenol between aqueous sodium chloride and carbon tetrachloride. Int. J. Pharm., 20 (1984) 203–207.

Moser, P., Jakel, K., Krupp, P., Menasse, R. and Sallmann, A., Structure activity relations of analogs of phenylbutazone. Eur. J. Med. Chem., 10 (1975) 613–617.

Mukhayer, G.I. and Davis, S.S., Interactions between large organic ions of opposite charge. II. The effect of ionic strength, temperature, and urea on the interaction between sodium dodecyl sulphate and benzyltriphenylphosphonium chloride. J. Colloid Interface Sci., 56 (1976) 350–359.

Mukhayer, G.I., Davis, S.S., and Tomlinson, E., Automated conductimetric titrimeter: Use in studying ionic solute–solute interactions. J. Pharm. Sci., 64 (1975) 147–151.

Murthy, K.S. and Zografi, G., Oil–water partitioning of chlorpromazine and other phenothiazine derivatives using dodecane and *n*-octanol. J. Pharm. Sci., 59 (1970) 1281–1285.

Saleh, A.M and El-Khordagui, L.K., Hydrotropic agents: a new definition. Int. J. Pharm., 24 (1985) 231–238.

Schurgers, N., DeBlaey, C.J. and Tomlinson, E., Non-enhance-

ment of sodium cromoglycate intestinal absorption by quaternary ammonium ions. An effect of salt on ion-pair formation? J. Pharm. Pharmacol., 36 (1984) 45.

Shim, C.K., Nishigaki, R., Iga, T. and Hanano, M., Determination of extraction constant, true partition coefficient and formation constant of ion-pair complexes of quaternary ammonium salts, tetrabutylammonium bromide and isopropamide iodide, with some organic anions by a solvent extraction technique. Int. J. Pharm., 8 (1981) 143–151.

Terada, H., Kitagawa, K., Yoshikawa, Y. and Kametani, F., Partition and ion-pair partition of 2,4-dinitrophenol, an uncoupler of oxidative phosphorylation. Chem. Pharm. Bull., 29 (1981) 7–14.

Tomlinson, E., Filter-probe extractor: A tool for the rapid determination of oil–water partition coefficients. J. Pharm. Sci., 71 (1982) 602–604.

Tomlinson, E. and Davis, S.S., Interactions between large organic ions of opposite and unequal charge. II. Ion pair and ion triplet formation. J. Colloid Interface Sci., 74 (1980) 349–359.

Wilson, C.G., Tomlinson, E., Davis, S.S. and Olejnik, O., Altered ocular absorption and disposition of sodium cromoglycate upon ion-pair and complex coacervate formation with dodecylbenzyldimethylammonium chloride. J. Pharm. Pharmacol., 33 (1981) 749–753.