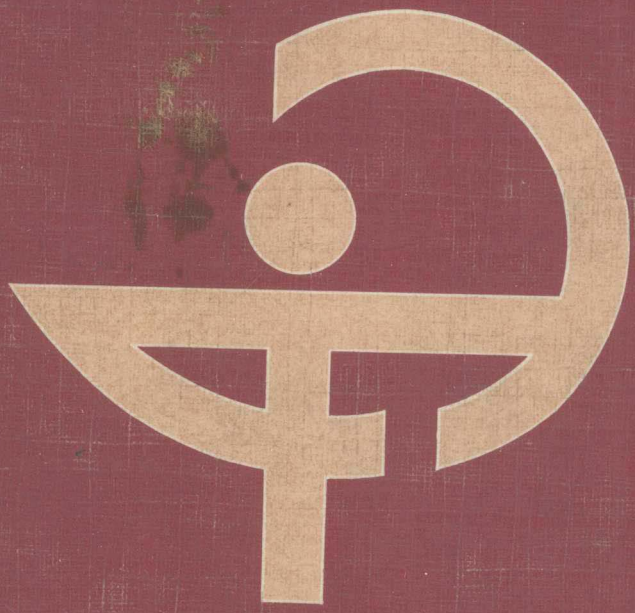
TOPICS IN PHARMACEUTICAL SCIENCES 1983

D. D. BREIMER AND P. SPEISER EDITORS



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TOPICS IN PHARMACEUTICAL SCIENCES 1983

Proceedings of the 43rd International Congress of Pharmaceutical Sciences of F.I.P., held in Montreux, Switzerland, September 5-9, 1983

Editors

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PREFACE

This volume contains the invited papers presented at the 43rd International Congress of Pharmaceutical Sciences of F.I.P. (Fédération Internationale Pharmaceutique or International Pharmaceutical Federation), held in Montreux, Switzerland, 5-9 September, 1983.

The emphasis of this F.I.P.-Congress was on advances in the various fields of pharmaceutical sciences as outlined by 36 invited speakers in 9 specialized symposia. In addition 3 up-date lectures and almost 230 poster and oral communications were presented, which gave the almost 2000 participants ample opportunity to continuously follow the latest developments.

The topics of the nine symposia were selected by the Board of Pharmaceutical Sciences of F.I.P. and associated with the major divisions of pharmaceutical sciences:
pharmaceutical analysis and quality control (*Chemical methods in pharmaceutical analysis*); pharmacokinetics and drug metabolism (*a. Considerations in therapeutic drug monitoring; b. Carrier mediated transport in drug disposition*); pharmaceutical technology (*a. Isotropic and disperse hydrophilic dosage forms; b. Solid drug delivery systems*); biopharmaceutics (*a. Distribution of drug dosage forms in the g.i.-tract; b. Drug targeting*); pharmacognosy (*Potentials and hazards of plant-derived drugs*). In all symposia the state of the art, future perspectives and implications were discussed, which are certainly not restricted to pharmaceutical sciences.

We are grateful to the invited speakers for conforming to the deadline of delivering their manuscripts so promptly. This made it possible to publish these Proceedings very shortly after the congress.

D.D. Breimer and P. Speiser.

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ION-PAIR AND METAL COMPLEX FORMATION IN DRUG ANALYSIS

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INTRODUCTION

The application of the ion-pair concept in pharmaceutical sciences has been increasing rapidly during the last two decades. Especially Higuchi and Schill and their co-workers made large contributions (1,2,3). The concept is now applied in biopharmacy, drug analysis, pharmacology, synthesis, etc. In drug analysis different applications are used, e.g. ion-pair partition chromatography, ion-selective liquid membrane electrodes, isolation of drugs from biological samples, ion-pair extraction titration (4).

The numerous monographs dedicated to ion-pair formation may give the impression that the ion-pair is an isolated phenomenon with its own theoretical background. This is not the case, however. In fact ion-pair formation is a special case of metal complex formation. In this contribution the resemblances and distinctions between ion-pair and metal complex formation will be discussed. Various types of applications of both concepts in drug analysis will be demonstrated.

CHEMICAL EQUILIBRIA IN AQUEOUS SOLUTION

We consider the chemical reaction (ion-pair *or* metal complex formation reaction; charges are omitted):

$$M + L \rightleftharpoons ML \qquad \text{eq. 1}$$

The direction in which the reaction will go, or the point at which equilibrium will be reached, depends on two factors: 1) the tendency to give off energy (the enthalpy change ΔH); exothermic processes are favoured, and 2) the tendency to attain a state that is statistically more probable (the entropy change ΔS); the greater the value of ΔS the more probable (and more disordered) the state. The likelihood of a process occurring thus increases as ΔH becomes more negative or ΔS becomes more positive. These two factors are related by:

$$\Delta G^\circ = \Delta H^\circ - T.\Delta S^\circ \qquad \text{eq. 2}$$

ΔG° stands for the Gibbs free energy and T represents the absolute temperature. The equilibrium of the reaction is reached when ΔG° has reached a minimal value.

Now the thermodynamic stability constant K^T_{ML} is:

$$K^T_{ML} = \frac{a_{ML}}{a_M \cdot a_L} \qquad \text{eq. 3}$$

where a_{ML}, a_M and a_L are the activities of ML, M and L respectively. The relationship between $\Delta G°$ and K^T_{ML} is given in eq. 4:

$$\Delta G° = -RT \ln K^T_{ML} \qquad \text{eq. 4}$$

Thus the more negative $\Delta G°$ the more the reaction (eq. 1) proceeds to the right and the higher the stability constant K^T_{ML} of the complex formed is. An extensive monograph on the thermodynamics of metal complex and ion-pair formation has been written by Nancollas (5). Experimentally the concentration stability constant K^c_{ML} is usually determined (eq. 5) which holds for a given temperature, solvent composition and ionic strength I of the solution. Eq. 6 relates K^T and K^c:

$$K^c_{ML} = \frac{[ML]}{[M][L]} \qquad \text{eq. 5}$$

$$K^T_{ML} = K^c_{ML} \cdot \frac{f_{ML}}{f_M \cdot f_L} \qquad \text{eq. 6}$$

The activity coefficient f_i can be obtained from the Debye-Hückel equation (6).

Experience has shown that the interaction between M and L is more or less affected by competitive side-reactions. These side-reactions are caused by the presence of various substances usually present in the solution analysed, i.e. other ligands like buffer constituents, counter ions, etc. The most significant interference, however, is due to the two species always present in aqueous solution: hydronium and hydroxide ions. In this way a certain amount of the reactants M and L is removed from the main reaction process owing to the formation of various products, e.g. $M(OH)_X$, HL, etc. The extent of these side-reactions is described by α_M and α_L, the (overall) side-reaction coefficients. On the other hand, the formation of mixed complexes of ML increases the yield of the complexation reaction; this process is expressed by α_{ML}. Now the conditional stability constant K'_{ML} is related to K^c_{ML} by

$$K'_{ML} = K^c_{ML} \cdot \frac{\alpha_{ML}}{\alpha_M \cdot \alpha_L} \qquad \text{eq. 7}$$

To get a better insight into the meaning of K'_{ML} in relation to the position of the equilibrium of the reaction (eq. 1), the following is illustrative. In Fig. 1 the relationship between log K'_{ML} and the *degree of dissociation* α for three different concentrations c_M is given ($c_M = [M] + [ML]$ is the total concentration of M species in solution) where

$$K'_{ML} = \frac{1 - \alpha}{\alpha^2 \cdot c_M} \qquad \text{eq. 8}$$

$$\alpha = \frac{[M]}{c_M} \qquad \text{eq. 9}$$

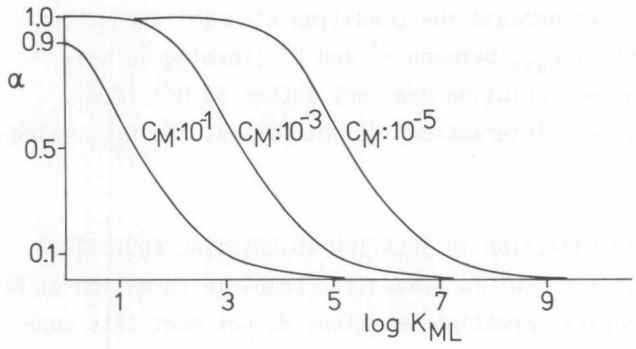

Fig. 1. Relationship between log K'_{ML} and α for three different concentrations (c_M in mol. l^{-1}).

Lowering of c_M results in increase of α for a given K'_{ML} value. To get more than 99% yield of ML ($\alpha \leq 0.01$) the product $K'_{ML} \cdot c_M$ must be larger than 10^4. In a complexometric titration with a precision better than 1% the product $K'_{ML} \cdot c_M$ must be larger than 10^6 (6). Thus, for complexometric titration rather large K'_{ML} values are necessary. This condition is best met by the use of a multidentate (chelating) titrant like EDTA. Most metal ions have thermodynamic log K^T values with EDTA of 10 and higher (e.g. Co(III)EDTA: 36!!). However, the conditional log K' of the metal-EDTA complex strongly depends on the pH of the solution because of protonation of EDTA (side-reaction coefficient $\alpha_{L(H)}$). The dependance of $\alpha_{L(H)}$ on pH forms the basis for the selective determination of Bi(III) with EDTA according to Ph.Eur.Ed. II. The titration is performed at pH = 1.5 and now log $\alpha_{L(H)} = 15.0$. At this pH-value the conditional log K' = log K^T - log $\alpha_{L(H)}$ for Bi(III) is 27.0 - 15.0 = 12.0 and for metals like Cu(II), Pb(II) and Zn(II) lower than 3. Therefore, the last-mentioned metal ions do not interfere with the titration of Bi(III) at this pH-value (6).

Another very illustrative example of the meaning of side-reactions is given by Schubert (7). EDTA is in use as an antidotum for metal poisoning with Pb and Cu but almost useless for Hg poisoning. The log K^T values are Hg(II) : 21.8, Pb(II) : 18.0 and Cu(II) : 18.8. Important side-reaction coefficients of EDTA (=L) and the metal ions in blood plasma (pH = 7.4) are $\alpha_{L(H)}$: 3.0, $\alpha_{L(Ca)}$: 7.6, $\alpha_{Hg(OH)}$: 8.0 and $\alpha_{Pb(OH)} = \alpha_{Cu(OH)}$ = about zero. The resulting conditional log K's are resp. Hg : 3.2, Pb : 7.4 and Cu : 8.2. The actual log K' values will be even lower because of the presence of other endogenous complexing agents such as proteins and citrate.

"Complexometric" titrations based on ion-pair formation are not described

in the literature. This is obvious because the condition $K.c \geq 10^6$ cannot be realized. The association constant K_{ass} between M^+ and L^- (forming an uni-univalent ion-pair $M^+.L^-$) in aqueous solution does not exceed 50 M^{-1} (2,8). Even di-univalent and tri-univalent interactions do not possess log K_{ass} values higher than 2 to 3 (9).

PRECIPITATION AND LIQUID-LIQUID PARTITION IN RELATION TO CHEMICAL EQUILIBRIA

As mentioned before a product $K.c > 10^6$ is needed for complete formation of ML. All ion-pair and most metal complex formation reactions do not meet this condition. However, the equilibrium

$$M + L \rightleftharpoons ML \rightleftharpoons ML_{\downarrow} \text{ or } ML_{org} \qquad \text{eq. 10}$$

can be shifted to the right by removal of ML from the equilibrium, e.g. precipitation or extraction of ML into a water immiscible organic phase (org.).

Precipitation

The thermodynamic equilibrium constant of a sparingly soluble substance ML is expressed by

$$K^T_{sp} = \frac{a_M . a_L}{a_{ML}} \qquad \text{eq. 11}$$

where a_{ML} is unity. In the presence of other electrolytes the concentration constant K^c_{sp} is used:

$$K^c_{sp} = [M][L] = K^T_{sp}/f_M . f_L \qquad \text{eq. 12}$$

The constant K_{sp} is called the solubility product; f_M and f_L are activity coefficients. In case of side-reactions a conditional K'_{sp} is used (eq. 13). The solubility of the compound ML can be

$$K'_{sp} = K_{sp} . \alpha_M . \alpha_L \qquad \text{eq. 13}$$

$$c_{ML} = \sqrt{K_{sp}} \qquad \text{eq. 14}$$

calculated by eq. 14.

Precipitation is the basis of gravimetry and precipitation titration. For a precipitation titration with good precision (1%) the condition $pK'_{sp} + 2 \log c \geq 6$ needs to be fulfilled. The titration reaction can be based on metal complex formation, e.g. titration of halogenides and sulfanilamides with Ag(I), or ion-pair formation, e.g. titration of organic cations with tetraphenylborate (10). The pK'_{sp} values of Cl^- and most sulfanilamides are 9.5 and about 11 respectively. In the hypothetical case that no sparingly soluble Ag(I) compounds were formed, a direct complexometric titration with Ag(I) in water would be impossible. The conditional constants log K_{AgCl} : 2.9 and log $K_{Ag.sulfa}$: about 3.6 (11) are too low for such titration.

A special case of a precipitation titration is the Budde titration of barbiturates (H_2 barb.) with Ag(I) (pH > 11):

I $\quad n\ H_2\ barb. + n\ Ag \longrightarrow [Ag.barb.]_n^{n-} + 2n\ H^+$

II $\quad [Ag.barb.]_n^{n-} + n\ Ag \longrightarrow [Ag.barb.]_n\ Ag_{n\downarrow}$

The titration reaction (I) is based on the formation of an anionic, polymeric water soluble product. The end-point is detected by the formation of an insoluble product (II) (titration to first turbidity) (12).

Anions like $[Cr(SCN)_4(NH_3)_2]^-$, $[Co(SCN)_4]^{2-}$ and $[BiI_4]^-$ form almost quantitatively coloured precipitates with large organic cations (ion-pairs). The isolated precipitates dissolve in a suitable solvent (acetone, methanol) and the colour can be measured spectrophotometrically.

Liquid-liquid partition

Liquid-liquid partition equilibria, commonly called extraction equilibria, usually take place between an aqueous phase (subscript aq) and an organic phase (subscript org) which is immiscible with water. These extraction equilibria are in use both for ion-pair and metal complex formation:

$$M_{aq} + L_{aq} \rightleftharpoons (ML_{aq}) \rightleftharpoons ML_{org} \qquad \text{eq. 15}$$

A thermodynamic treatment of these equilibria is given by Brändström (13). The concentration extraction constant E_{ML} is defined as

$$E_{ML} = \frac{[ML]_{org}}{[M]_{aq} \cdot [L]_{aq}} \qquad \text{eq. 16}$$

The distribution ratios D_M of M and D_L of L are defined as

$$D_M = \frac{[ML]_{org}}{[M]_{aq}} \qquad \text{eq. 17}$$

$$D_L = \frac{[ML]_{org}}{[L]_{aq}} \qquad \text{eq. 18}$$

From eq. 16 and eq. 17 (respectively eq. 16 and eq. 18) follows that

$$D_M = E_{ML} \cdot [L]_{aq} \qquad \text{eq. 19}$$

$$D_L = E_{ML} \cdot [M]_{aq} \qquad \text{eq. 20}$$

In the presence of side-reactions side-reaction coefficients are again introduced and the conditional E'_{ML} is

$$E'_{ML} = E_{ML} \cdot \frac{\alpha_{ML}}{\alpha_M \cdot \alpha_L} \qquad \text{eq. 21}$$

Some types of side-reactions are represented in Fig. 2.

The side-reactions of ML in the organic phase, e.g. dissociation, di(poly)-merization and adduct-formation with an agent S (lipophilic alcohol, etc.) result in an increase of E'_{ML}. On the other hand protolysis of M and L in the

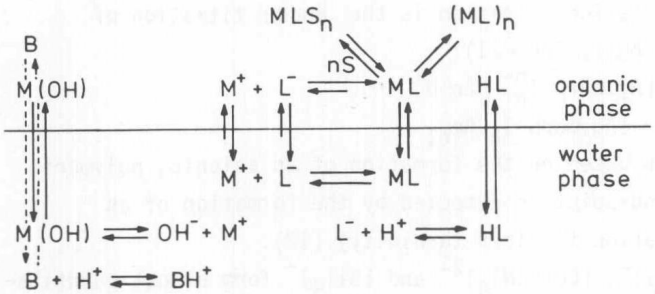

Fig. 2. Side-reactions of the particles in the two-phase system.

aqueous phase and partition result in decrease of E'_{ML}. These processes strongly depend on the pH value. For instance, the cationic acid BH^+ (protonated organic base B) is very sensitive to protolysis and partition of B. Detailed information on side-reactions of ion-pairs is given elsewhere (3, 13).

The degree of extraction of M (as ML) into the organic phase with a single extraction can be calculated from

$$P(\%) = 100 \cdot D_M \cdot q \, (1+q \cdot D_M)^{-1} \qquad \text{eq. 22}$$

where q = phase volume ratio V_{org}/V_{aq}.

The formulas given before are in common use in the treatment of ion-pair theory. The intermediate formation of ML_{aq} is neglected (eq. 15). In case of ion-pair formation with (very) low K_{ass} values this is realistic, especially for lower concentrations (see Fig. 1). In metal complex formation K_{ML} can possess widely divergent values and the formation of ML_{aq} may be of considerable importance. Now, the relationship between E_{ML}, K_{ML} and D_{ML} is given by

$$E_{ML} = K_{ML} \cdot D_{ML} \qquad \text{eq. 23}$$

where

$$D_{ML} = \frac{[ML]_{org}}{[ML]_{aq}} \qquad \text{eq. 24}$$

In drug analysis there are two types of determinations based on the partition of the neutral lipophilic compound ML between the two phases: 1) the extraction of M or L (as ML) into the organic phase followed by direct measurement of ML in that phase, and 2) the two-phase titration. *ad 1)* M or L is extracted from the aqueous solution as a neutral metal complex ML or a neutral ion-pair qx (qx is the common notation for an ion-pair). The quantification of ML (or qx) is performed by spectrometry, fluorimetry or chromatography. For quantitative

extraction ($P > 99.9\%$) a D_M value (D_L, D_q, D_X respectively) of 999 and higher is necessary (eq. 22; $q = 1$). Thus, a product $E' \cdot c \geq 10^3$ is needed (eq. 19). The required E_{ML} (E_{qX}) values can easily be obtained with lipophilic chelates (for M) or lipophilic counterions (for q). Examples of both principles are given below:

Ion-pair. Quaternary N-compounds (R_4N^+) or protonated amines (R_3NH^+) are extracted with anionic dyes like picrate, methyl orange, bromothymol blue, reineckate (spectrophotometric measurement) and anthracene-2-sulfonate (fluorimetric measurement). Anionic compounds (barbiturate, sulfanilamide) can be extracted with a cationic dye like N,N-dimethylprotriptyline (fluorimetric) or neutral red (spectrophotometric). Metal ions also can be extracted as an ion-pair, e.g. Bi^{3+} as BiI_4^- with $N(butyl)_4^+$ (14) and M^{n+} as complex cation of 1,10-phenanthroline: $[M(phen)_2]^{n+}$ with eosin (anion) ($M^{n+} = Ag^+$, Cu^{2+}, Hg^{2+}, Pb^{2+}, Zn^{2+}, etc.) (15).

Metal complex. Well-known extractants for metal ions are xanthate, 8-hydroxyquinoline (oxine), dithizone, etc. (16). There are formed neutral metal complexes. Ph. Eur. Ed. II applies oxine for the selective limit test on Mg^{2+} and dithizone for the limit test on Pb in sugars. In fact, Mg^{2+} is extracted as an ion-pair with the composition $[Mg(oxine)_3]^- \cdot [RNH_3]^+$ (RNH_2 = n-butylamine).

ad 2) Two-phase titrations based on both ion-pair and metal complex formation are known. Examples of both types are given below:

Two-phase ion-pair titration. Quaternary N-compounds (R_4N^+) or protonated amines (R_3NH^+) are titrated with a standardized solution of a lipophilic anionic titrant X^-, e.g. laurylsulphate, dioctyl sulfosuccinate, tetraphenylborate, according to:

$$R_4N_{aq}^+ + X_{aq}^- \longrightarrow R_4N \cdot X_{org} \qquad \text{eq. 25}$$

The end-point detection with indicator dyes is based on two principles:

a) transfer of the indicator dye from one phase to the other at the end-point. With a cationic indicator ($Ind.^+$) like methyl yellow or methylene blue the transfer is based on:

$$Ind._{aq}^+ + X_{aq}^- \longrightarrow Ind.X_{org} \qquad \text{eq. 26}$$

In case of an anionic indicator ($Ind.^-$) like methyl orange or cresol red the transfer is based on:

$$R_4N \cdot Ind._{org} + X_{aq}^- \longrightarrow R_4N \cdot X_{org} + Ind._{aq}^- \qquad \text{eq. 27}$$

b) the colour change solely takes place in one of the phases. A well-known example is the anionic hydrophobic dye tetrabromophenolphthalein ethyl ester ($Ind._{org}^-$). The end-point colour change (blue → yellow) in the organic phase is based on: