

Ion-Pair Extraction of Pharmaceutical Amines IV: Influence of Anion on Enthalpic, Entropic, and Free Energy Changes Resulting from Phase Transfer

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Abstract □ Studies on the influence of temperature on the distribution ratio of pharmaceutical ammonium species paired with various anions and between aqueous and organic phases have permitted determination of thermodynamic parameters associated with these extractive processes. Unlike transfer of uncharged solute molecules, ion-pair transfers involving inorganic anions appear to be largely entropically controlled. The process of movement from water to chloroform of dextromethorphanium halides, for example, involves material increase in ordering. The entropic change associated with the chloride corresponds to -29.7 e.s.u., that for bromide to -17.6 e.s.u. These compare with $+10.7$ e.s.u. for the free base and $+7$ to $+10$ e.s.u. for benzyl alcohol, phenol, and aniline. Less polar organic phases tend to lead to less negative entropic changes. In addition to the halides, data are provided for picrate, trichloroacetate, and several perfluorocarboxylate systems.

Keyphrases □ Ion-pair extraction—amines □ Dextromethorphan—test amine □ Anion effect—phase transfer thermodynamics □ Solvent effect—phase transfer thermodynamics □ Ionic, nonionic solutes—extraction mechanism

As a part of studies on ion-pair extraction of pharmaceutical amines (1–3), the enthalpy, free energy, and entropy changes associated with transfer from aqueous to lipoidal phases of cationic form of dextromethorphan, a typical pharmaceutical amine, paired with various organic and inorganic anions, have been compared with those of neutral solutes. Thermodynamic data on the ion-pair extractive process of this system, it was felt, would shed additional light on the nature of ion-pair formation in the organic phase in general, and permit more rational development of separatory systems for both analytical and isolation purposes. Although these studies have been limited to systems based on the drug cation, it is apparent that the information is applicable to other ion-pair combinations.

Past work of this nature has been relatively sparse. Very little of the literature on the extraction of organic and inorganic compounds has treated the thermodynamics of these systems. Siddall has determined the thermodynamics of the extraction of uranyl nitrate and nitric acid by trialkyl phosphates and dialkylphosphonates (4). Krasnov *et al.* studied the influence of structural factors on the thermodynamic characteristics of the extraction of salts of basic dyes in a series of three papers (5–7). Beyond these few papers little is to be found in the literature concerning these thermodynamic parameters.

These experimental studies are presented in three sections. In the first part, results of an investigation into the effect of the solvating agent concentration in the organic phase on the extractive equilibria as reflected in the enthalpic, entropic, and free energy changes are presented for several ion pairs and organic phases con-

taining varying amounts of chloroform. In the second section, the effect of the nature of the anion on these same thermodynamic parameters for selected halide and halogenated carboxylic anions is analyzed. Finally, the extractive behavior of ion-pair systems is compared with similar data obtained on several neutral organic compounds under comparable conditions.

RESULTS AND DISCUSSION

Effect of Solvent—The distributive tendency of the cationic species used in this study, the protonated form of dextromethorphan, between water and an organic phase has been shown to be markedly influenced by the nature of the organic solvent and that of the pairing anion. As has already been pointed out (1), each ion pair appears to be effectively associated with as many as five proton-donating solvent molecules. For this reason, the thermodynamic behavior of these systems would be expected to be quite sensitive to changes in the concentration of these molecules.

The effect of the composition of the organic phase is evident in Table I where the values of ΔH , ΔF , and ΔS are listed for the transfer from water to oil phases of dextromethorphan paired with three anions at 25° . The enthalpic values were determined directly from the temperature dependencies of the extractive equilibria; the free energy changes were defined as $-RT \ln K_{ex}$, and entropies as being equal to $(\Delta H - \Delta F)/T$.

Since the thermodynamic state in the aqueous phase is essentially unaffected by compositional changes in the organic phase, it is apparent that the large differences in these thermodynamic parameters associated with increasing chloroform concentration for the bromide, trichloroacetate, and picrate ion pairs must be due essentially to thermodynamic differences in the organic solution alone. The relatively large negative entropic changes observed in each instance at higher chloroform concentrations strongly suggest that the presence of ion pairs produces a great deal of ordering or structure formation in these systems, a conclusion consistent with earlier suggestions (1). Correspondingly, the enthalpic changes with chloroform concentration are greater than those observed for the free energy values.

Effect of Nature of Anion—It is evident from the preceding discussion that all comparisons of any anionic influence must take into account the influence of the composition of the organic phase since the thermodynamic values are so highly dependent on this factor. Although it was not possible for experimental reasons to carry out all the studies with a solvent of fixed composition, the general influence of the anion is evident in the data shown in Table II. These thermodynamic values, unlike those induced by variations in solvent composition, represent net effects of differences in the interactions in both phases.

Halides—Comparison of the changes among the halide salts is of some interest. For the chloride, bromide, and iodide salts of dextromethorphan, the extraction process becomes less exothermic, the net ordering as a result of the extractive process decreases, and the net free energy decrease becomes greater in going from the first to the third of the series.

In his work on the selectivity of ion-exchange resins, Chu attributed the order of binding of the halides to the structure of the anions in the water phase and attributed no contribution by the resin phase to the determination of the overall equilibrium (8). The entropies of the three halide ions in water are listed in Table III along with the differences between the ΔS values for the extraction of adjacent members of the series of dextromethorphan halide

Table I—Thermodynamic Values for Extraction Equilibria of Dextromethorphan Ion Pairs from Water to Organic Solvents, 25° — Effect of Solvent

Anion	Organic Solvent, % v/v	ΔH , cal./mole	ΔF , cal./mole	ΔS , cal./mole/deg.
Bromide	100% CHCl ₃	-8,780	-3,520	-17.6
Bromide	80% CHCl ₃ , 20% C ₆ H ₁₂	-6,780	-2,960	-12.8
Bromide	40% CHCl ₃ , 60% C ₆ H ₁₂	-4,000	-1,240	-9.3
Bromide	20% CHCl ₃ , 80% C ₆ H ₁₂	-1,790	+430	-7.4
Trichloroacetate	80% CHCl ₃ , 20% C ₆ H ₁₂	-7,670	-4,460	-10.8
Trichloroacetate	40% CHCl ₃ , 60% C ₆ H ₁₂	-5,160	-3,470	-5.7
Trichloroacetate	20% CHCl ₃ , 80% C ₆ H ₁₂	-2,840	-2,240	-2.0
Picrate	100% CHCl ₃	-12,800	-9,300	-11.7
Picrate	40% CHCl ₃ , 60% CCl ₄	-9,300	-7,630	-5.6
Picrate	100% CCl ₄	-3,700	-5,800	+7.0

salts. It is evident that the difference between the respective observed entropy changes is not approximated by the differences in the entropies of the anions in water. It may be concluded that structuring within the organic phase is probably responsible to a large extent for the net entropy values. These results support the conclusion of the preceding section in that the structure of the organic solvent atmosphere in the vicinity of the ion pair must provide a sizable contribution to the energetics of the extraction process.

It is of some interest at this point to compare the above results with those of Krasnov *et al.*, who studied a similar process using cationic triphenylmethane dyes for the extraction of halide ion pairs from water to chloroform (5). These workers extracted the dye fuchsin and observed differences in thermodynamic values with the several halides in an opposite order to that reported here.

extraction of dextromethorphan and ephedrine are shown in Fig. 1 along with the data of Kato for chlorpheniramine (2). Increasing the chain length by one —CF₂ group resulted in an increase in the observed distribution ratio of approximately 5.3-fold. This corresponds to a decrease in free energy of approximately 1,000 cal./mole. A value of approximately 600 cal./mole was reported by Banks for a series of fatty acids (13). The difference between the observed increase in extracting ability of each —CF₂ and —CH₂ group is probably due to the greater tendency of a —CF₂ group to organize water molecules in their vicinity compared to those of a —CH₂ group. The magnitudes of the interactions of these groups in the less polar organic phase would probably be of the same order.

The structuring influence in the aqueous phase is evident in the

Table II—Thermodynamic Values for Extraction Equilibria of Dextromethorphan Ion Pairs from Water to Organic Solvents, 25° — Effect of Nature of the Anion

Anion	Organic Solvent, % v/v	ΔH , cal./mole	ΔF , cal./mole	ΔS , cal./mole/deg.
Chloride	100% CHCl ₃	-11,300	-2,450	-29.7
Bromide	100% CHCl ₃	-8,780	-3,520	-17.6
Iodide	100% CHCl ₃	-6,150	-4,300	-6.2
Trifluoroacetate	40% CHCl ₃ in CCl ₄	-835	-2,620	+6.0
Perfluoropropionate	40% CHCl ₃ in CCl ₄	-25	-3,600	+12.2
Perfluorobutyrate	40% CHCl ₃ in CCl ₄	+760	-4,530	+17.8
Perfluoropentanoate	40% CHCl ₃ in CCl ₄	+1,570	-5,530	+23.8
Picrate	100% CHCl ₃	-12,800	-9,300	-11.7
Picrate	100% CCl ₄	-3,700	-5,800	+7.0

While it is possible that the cation could make a great difference in the thermodynamic values, it should also be pointed out that while the present data were obtained at a known pH using a buffered system and a relatively stable cationic species this was not the case with these workers' systems.¹

Perfluoroacid Salts—Less hydrophilic ion pairs would be expected to have more favorable free energy changes associated with the extractive process. This is particularly evident in the case of the fluoroacid ion pairs. It would be expected that for a constant cation any increase in the chain length of an organic anion would result in a proportionate decrease in the free energy of the extractive process. Verification of this was obtained using a series of completely fluorinated carboxylic acid anions. Data obtained for the

entropy changes shown in Table II for several fluoroacids paired with dextromethorphan. In all cases the values of the entropy changes were found to be positive. This would indicate a net decrease in ordering within the system for the extraction process. If the only portion of the anion interacting with the water were the carboxylate group and this group interacted with the cation to create the ion pair in the organic phase, then for the series of anions the entropy change would be expected to be quite constant. Since this is not the case, the fluoroalkyl chain must be involved in some

Table III—Comparison of Differences of Entropies for Three Halide Ions to the Corresponding $\Delta\Delta S$ Values Calculated from Experimental Data for the Extraction of Dextromethorphan Salts from Aqueous to Organic Phases, 25°

Anion	$S_{H_2O}^a$	ΔS_{H_2O}	$\Delta S_{ext.}$	$\Delta\Delta S_{ext.}$
Chloride	13.7	+5.6	-29.7	+12.1
Bromide	19.3	+6.8	-17.6	+11.4
Iodide	26.1		-6.2	

^a "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 1956, p. 1734.

¹ It has been shown previously that dextromethorphan, with a pKa of 7.98 at 25° could be extracted as the free base at a pH as low as 4.00 (1). The second pKa of fuchsin has been found to be 7.8 (9) and if pH were not controlled, it would then be possible to extract two forms of the dye, the ratio being highly dependent on the pH at which the extraction was carried out. In addition, fuchsin being a very complex and reactive molecule, could undergo various reactions in solution which the authors did not apparently investigate. For example, self-association has been reported at concentrations as low as 10⁻⁸ M (10), the dyes are known to be light sensitive (11), and reaction with hydroxyl ion gives the corresponding carbinol (12).

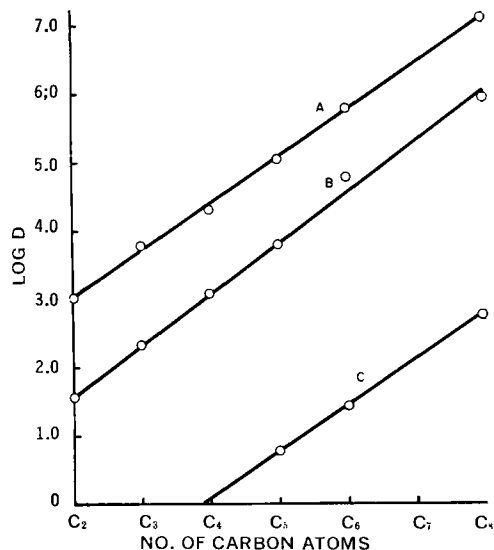


Figure 1—Effect of the number of carbon atoms of fluoroacid anions on the distribution ratio between aqueous and organic phases for several cationic species. Temperature = 25°. Concentrations: 5×10^{-4} M cation, 1.0 M anion, 0.10 M phosphate buffer. Organic phase = 100% CHCl_3 . Higher values extrapolated from data for lower CHCl_3 concentrations. Key: A, dextramethorphan; B, chlorpheniramine; C, ephedrine

manner. Since the chain is considered to interact to only a small extent, if at all, with the water molecules, it would cause the water molecules closest to the alkyl chain to interact with other water molecules farther away from the chain thus creating a tightening of the water structure in the vicinity of the alkyl chain. Extraction of the anion as part of the ion pair would be expected to relax this ordered system of water molecules resulting in a net decrease in order which would be larger for increasing chain lengths. This observation closely parallels that of Diamond who attributed the formation of ion pairs in water between large organic anions and cations to these same solvent-solvent interactions (14). The total energy change for the fluoroacid systems is controlled by the relative sizes of the entropy and free energy changes; the process changing from exothermic to endothermic as the C_4 acid anion is reached.

Picrate—The enthalpy change for dextramethorphan hydrochloride was of the same order as that of the picrate, and consequently it is interesting to examine the picrate values more closely. It was shown earlier that the picrate is a much better anion for the extraction of dextramethorphan than the chloride ion, and also has a lower apparent molecularity. The higher extracting ability of the picrate is seen to result in a more favorable free energy change—a difference of almost 7,000 cal./mole. The lower solvation requirements of the picrate are observed in the entropy change being smaller than that of the chloride. That the value for the picrate is as largely negative as it is can be related to the structure of the picrate ion. With three nitro groups it is likely that the chloroform proton

Table IV—Thermodynamic Values for the Extraction Equilibria of Some Nonionic Solutes from Water to Organic Solvents, 25°

Distributed Compd.	Organic Solvent, % CHCl_3 in CCl_4	ΔH , cal./mole	ΔF , cal./mole	ΔS , e.s.u.
Dextramethorphan	100	-1,890	-5,080	+10.7
Picric acid	100	-1,370	-987	-1.3
Benzyl alcohol	80	+1,270	-1,500	+9.3
Benzyl alcohol	60	+1,300	-1,340	+8.9
Benzyl alcohol	40	+1,495	-1,110	+8.7
Aniline	80	+230	-1,830	+6.9
Aniline	60	+150	-1,570	+5.8
Aniline	40	+385	-1,360	+5.9
Phenol	80	+2,000	-407	+8.1
Phenol	60	+2,500	-224	+9.1
Phenol	40	+2,950	-177	+10.0

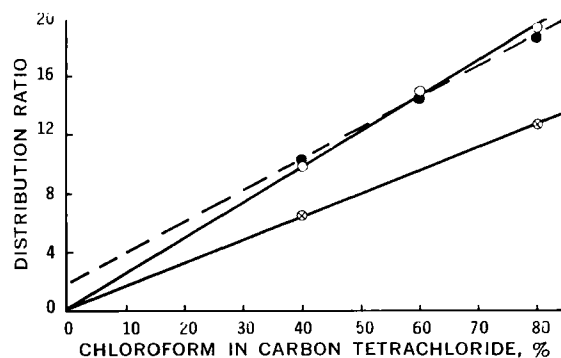


Figure 2—Effect of chloroform concentration in carbon tetrachloride on the distribution ratio of several solutes between water and chloroform. Temperature = 25°. Concentrations: 5×10^{-4} M solute. Key: O, aniline; ●, phenol $\times 10$; □, benzyl alcohol.

exhibits a slight but definite interaction with the electronegative oxygen atoms. In Table II the entropy change for the same ion pair using carbon tetrachloride instead of chloroform as the organic phase is shown to exhibit a positive entropy change—the difference of these values for the two solvent systems being almost 20 entropy units. Since there would be expected to be little if any change in the aqueous phase the observed difference in entropy values is probably related to the structuring in the organic phase caused by the interaction of the nitro groups with chloroform molecules.

Comparison with Some Nonionic Solutes—Results obtained for some nonionic compounds are presented in Table IV. From an overall look at the table it is evident that in all but two cases the extraction process was endothermic and the values were constant for most of the cases studied. The free energy changes were smaller than those for ion-pair systems, and in most cases the entropy changes were positive and fairly constant for most solutes.

Since it would be expected that no specific solvation would be required for the extraction of nonionic solutes, as was shown earlier to be the case with ion pairs, the observed distribution ratios would be expected to be a function of the chloroform concentration in the organic phase as shown by the equation:

$$D_{\text{obs.}} = D_0 + D_0K[M]$$

where $D_{\text{obs.}}$ is the observed distribution ratio, D_0 is the distribution ratio in the pure nonpolar solvent, M is the concentration of chloroform in the organic, and K is the stability constant for the interaction of the solvent and solute in the organic phase (15).

In Fig. 2 the values of $D_{\text{obs.}}$ for the nonionic solutes are plotted as a function of the percent chloroform in carbon tetrachloride. The linear relationship exhibited in all cases verifies the expected interaction between solute and solvent.

The main conclusion obtainable from the comparison of ion-pair and nonionic solutes seems to lie in the entropy terms. In most cases it is evident that the extraction of ion pairs is hindered by entropy while the extraction of most nonionic solutes is aided by the entropy change. From this then it is possible to deduce that the entropy change is a main controlling factor in the extraction of ion pairs. This obviously accounts for the very favorable extraction of nitrogenous cations as ion pairs of the perfluoroacid anions.

EXPERIMENTAL

All procedures and materials used in these studies were essentially as described earlier (1). Where references are to distribution ratios, these are defined as the equilibrium concentration in the organic phase divided by the equilibrium concentration in the aqueous phase. Enthalpic values were calculated from plots of $\log K_{\text{ex}}$ versus $1/T$ and the free energies from $\Delta F = RT \ln K_{\text{ex}}$. In general, the reciprocal temperature plots gave straight lines over temperature ranges of 0–40°, for these particular systems, and are estimated to yield values reproducible to ± 500 cal./mole.

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Solubility of the Parabens in Dioxane-Water Mixtures

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Abstract □ The solubilities of methyl, ethyl, propyl, and butyl parabens have been determined in aqueous solutions of dioxane at 25°. A dielectric requirement of about 8-10 was found for the above materials. Two-phase systems were found for the ethyl, propyl, and butyl derivatives over a given composition range for the binary mixture. Phase separation occurred over a broad range of composition for the butyl derivative, intermediate range for propyl, and a narrow range for the ethyl derivative. The two phases were found to be invariant with respect to the concentration of the components of the ternary system. It is suggested that a solvate between the paraben and a fixed composition of the binary mixture is produced forming a biphasic system in equilibrium.

Keyphrases □ Parabens solubility—dioxane-water mixtures □ Dielectric requirements—parabens solubility □ Dielectric constants—dioxane-water mixtures □ UV spectrophotometry—analysis

The solubility behavior of parabens has been previously reported (1-3) in sucrose solutions and a wide spectrum of pure alcohols. The solubility parameter value for these compounds was found to be about 11.0 by Martin (2). It was also shown that these compounds possessed dielectric requirements (DR) of 14 and possibly another at a dielectric constant of 30 (3). It was thought instructive that solubility studies should be conducted on these compounds over a wide range of dielectric constants produced by a given binary system. Since dioxane-water mixtures encompass the above DR's possessing a dielectric constant span of values from 2 to about 80, this system was chosen. It was expected that a twin-peak array should be evidenced for

the solubility profile having approximate DR values of 14 and 30.

It was further hoped that some sort of delineation of the effect of substituent groups could be found in either the nature of the solubility curves or in the magnitude of the solubility for these compounds.

EXPERIMENTAL

Reagents—Methyl, ethyl, propyl, and butyl parabens were used.¹ Dioxane (stabilized)² and distilled water were the solvents used. All the reagents were used directly as no pretreatment of solutes was considered necessary.

Procedure—Solubilities were determined by a gravimetric procedure at 25 ± 0.1° maintained by a water bath as previously described (4). In the case of two liquid layers, samples were withdrawn from the upper layer first through a pipet fitted with a glass-wool pledget. The vial was tilted and another prepared pipet was quickly introduced into the lower layer and a sample withdrawn. Each paraben was subjected to three solubility runs and average results are given. Several samples of the two liquid systems formed were also checked by analyzing by spectrophotometric means³ at 255 mμ.

RESULTS AND DISCUSSION

In Fig. 1, the solubility of both methyl and ethyl paraben are shown in mg./ml. as a function of the dielectric constants of the binary mixtures. A definite solubility maximum occurs at a dielectric constant value of 10 for both these compounds. In the case of ethyl paraben, two liquid phases are formed over a dielectric

¹ Methyl (No. 5266), ethyl (No. 5082), propyl (No. 5294), butyl (No. 5158), Matheson, Coleman and Bell, East Rutherford, N. J.

² No. 4937, Mallinckrodt, St. Louis, Mo.

³ Cary model 16 spectrophotometer.