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Solubility, melting point and salting-out relationships in a group of secondary amine hydrochloride salts

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Abstract

The solubilites of eight hydrochloride salts of some alpha adrenergic agonists, and beta adrenergic agonist/blocker drugs were determined in water at 25°C. An inverse relationship was observed between log X^+ and the melting points of the salts where X^+ is the mole fraction solubility of drug. The entropy of fusion values were not constant, as suggested by the observed log solubility-melting point correlation, and ranged from 16 to 26 cal K^{-1} mol^{-1}. It is therefore unlikely that crystal forces alone are responsible for the observed relationship between log X^+ and melting point. Setchenow salting-out constants were determined from the solubilities of the hydrochloride salts in sodium chloride-water and were found to be greatest for those compounds that possessed the lowest aqueous solubility and highest melting point. The number of aromatic rings and aromatic ring substituents also appear to have a significant influence on the values of the salting-out constants.

Keywords: Hydrochloride salts; Solubility; Melting point; Salting-out; Common ion effect

Among the FDA-approved commercially marketed salt forms of drugs, the hydrochloride salt makes up almost 43% of the anionic salts used. This is because of the ease of availability of hydrochloric acid and the ease of re-crystallization and physiological acceptability of the Cl− ion (Berge et al., 1977; Miyazaki et al., 1980; Miyazaki et al., 1981). However, it has been demonstrated that hydrochloride salts of cationic drugs may not always provide sufficient increases in solubility compared to other salt forms (Agharkar et al., 1976; Lin et al., 1972).

Because of their prevalence in pharmacy, it is of interest to characterize and understand factors which would help predict the solubility of hydrochloride salts. Previous publications have indicated that solubility-melting point relationships exist for some drug salts (Agharkar et al., 1976; Anderson and Conradi, 1985; Rubino, 1989), while others have found no such correlation (Gu and Strickley, 1987).

In addition, hydrochloride salts may be sensitive to the common ion effect of chloride ions present in biological fluids or intravenous infusion solutions (Miyazaki et al., 1980; Miyazaki et al., 1981). The factors responsible for the magnitude

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of the common ion effect are not completely understood, but Miyazaki observed an inverse relationship between log solubility and the tendency of hydrochloride salts to salt-out in the presence of excess chloride ions.

In the present studies the solubilities of the hydrochloride salts of *d*-phenylephrine, *d,l*-propranolol, labatalol, *d,l*-isoproterenol, isoxuprine, oxprenolol, acebutolol and atenolol were determined in water and sodium chloride solutions at 25°C. All drugs were obtained from Sigma Chemical Co. as the hydrochloride salt, except atenolol. The hydrochloride salt of atenolol was prepared by combining an equimolar quantity of HCl and the free base form (Sigma Chemical Co.) of the drug in 50:50 ethanol:water. The solution was evaporated to a viscous residue under reduced pressure at 35–40°C using a rotary evaporator. Ethanol was added to the remaining viscous residue which resulted in crystallization of the salt form. The material was examined by elemental analysis and the results agreed favorably with theoretical values (C: 55.76% H: 7.70% Cl: 11.64%. Theoretical values = C: 55.53% H: 7.66% Cl: 11.71%).

Solubilities were determined in triplicate at 25 ± 0.2°C by rotating water or sodium chloride solutions with excess solid drug in screw capped vials for 24 h. Preliminary studies indicated that 24 h was sufficient time to reach equilibrium solubility. Samples were filtered through a 0.45-μm filter and assayed by UV spectrophotometry. Samples were protected from light during solubility determinations by wrapping individual vials in aluminum foil. Solubilities were initially determined in molar solubility units and converted to mole fraction units after measurement of the densities of the saturated HCl salt-water solutions. For this study, the mole fraction solubility of drug or the concentration of drug cation at saturation is defined as:

$$X^+ = \frac{[BH^+]}{[BH^+] + [Cl^-] + [H_2O]} \quad (1)$$

where $[BH^+]$ is the molar concentration of drug ion.

In order to determine if hydrate formation or other solid-state changes, including precipitation of the free base form of each drug, had occurred with any of the compounds a sample of the residual solid was recovered at the conclusion of the solubility determination, blotted on filter paper, dried at ambient conditions and examined by differential thermal analysis (Perkin Elmer DSC-2). No evidence of changes in the solid-state form of the salts was observed and there was no evidence that the free base form had precipitated. The pH of the saturated solutions was also examined and ranged from 4.0 to 5.0. In each case the pH was found to be greater than 3 units below the pK_a of the amine group.

Enthalpy of fusion was determined for the compounds using a Perkin Elmer DSC-7. The entropy of fusion of the salts was subsequently calculated by dividing the enthalpy value by the melting point. Isoproterenol HCl was observed to decompose during melting and it is possible that the entropy value obtained may have been influenced by this phenomenon.

Log octanol/water partition coefficients were calculated for each compound using CLOGP (Version 3.54). The values were calculated based on the structure of the unionized form of each compound. pK_a values were obtained from various literature sources.

Salting-out behavior was determined by measuring the solubilities of the various hydrochloride salts in 0–0.512 M sodium chloride solutions. The data were plotted according to the Setchenow equation:

$$\log M_o/M = K_s C \quad (2)$$

where M_o/M is the ratio of the hydrochloride salt solubility in water/sodium chloride solution, C is the molar concentration of sodium chloride and K_s is the salting-out constant. Salting-out was considered significant if the slopes of Setchenow plots had p values less than 0.05 over the entire range of sodium chloride concentrations studied.

Data was analyzed by the aid of Microsoft Excel using a personal computer.

Table 1 lists the log molar solubilities, log X^+, melting points and entropy of fusion values for the eight compounds included in the study. Log mole fraction solubilities of drug ranged from -3.26 to -0.77. Melting points ranged from 385

Table 1
Solubility, entropy of fusion, and melting point data

Name	log S^a	log X^+	Melting point (°K)	ΔS_f (cal deg^{-1} mol^{-1})
Phenylephrine	0.58	−0.77	413	15.9
Oxprenolol	0.38	−0.90	385	23.0
Acebutalol	0.17	−1.31	418	23.8
Isoproterenol	0.14	−1.45	446	18.1[b]
Atenolol	0.04	−1.56	438	18.7
Propranolol	−0.48	−2.19	435	23.5
Labetalol	−1.30	−3.04	468	16.0
Isoxuprine	−1.52	−3.26	488	25.7

[a]Log molar solubility.
[b]Entropy of fusion value most likely influenced by possible decomposition during melting.

to 488 K. Table 2 lists the structures, pK_a values and log octanol/water partition coefficients, log P, of the compounds. In some cases, the pK_a values are listed for the secondary amine group as well as phenolic hydroxyl groups. In the cases of isoproterenol and isoxuprine, the assignments of the pK_a values to the amine or hydroxyl groups were not indicated in the literature, however based on a study of phenylalkanolamines by Riegelman et al. (1962) it is reasonable to assume that the pK_a values for the secondary amine group is close to 10 for each of the compounds.

Previous publications (Agharkar et al., 1976; Anderson and Conradi, 1985; Rubino, 1989) have indicated that the solubilities of certain groups of salts exhibit an inverse relationship with melting point. In the present study an inverse relationship between log solubility and melting point was also observed as illustrated in Fig. 1. Linear regression of log X^+ vs. melting point (T_m, in K) results in the following equation:

$$\log X^+ = -0.026(T_m) + 9.546$$

$$r^2 = 0.807 \quad n = 8 \qquad (3)$$

Fig. 1 and Eq. 3 present a useful general rule regarding the solubilities of the hydrochloride salts included in the present study, in that the higher melting compounds of the group will have relatively low solubilities while low melting compounds generally have higher solubilities.

Fig. 1 at first suggested that the solubilities of the hydrochloride salts are primarily determined by their solid-state properties. Based on the work of others (Yalkowsky, 1981; Shenkin, 1979a; Shenkin, 1979b) a linear relationship between log solubility and melting point would be expected only if the entropy of fusion values of the compounds are relatively constant. The entropy of fusion values for the hydrochloride salts included in the study are presented in Table 1. It can be observed that the values range from approximately 16 to 26 cal deg^{-1} mol^{-1} and are thus not constant. It was also found that inclusion of the entropy of fusion and melting point into the regression equation, in the form $\Delta S_f (T_m - T)$,

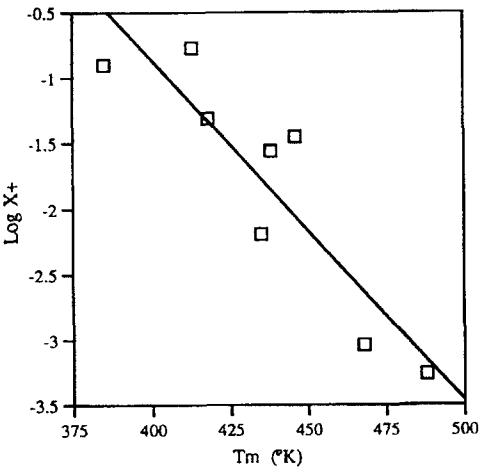
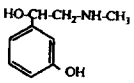
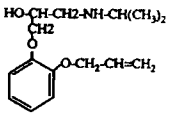
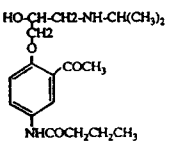
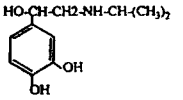
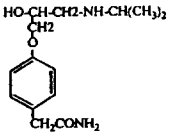
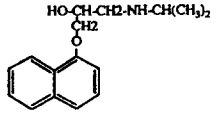
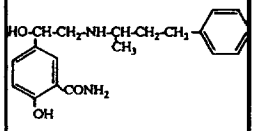
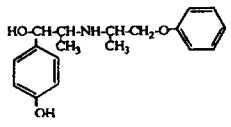


Fig. 1. Log X^+ vs. T_m for various hydrochloride salts in water.

Table 2
Structures, pK_a and log P values of unionized forms of secondary amine drugs

COMPOUND	STRUCTURE	pKa	LOG P
phenylephrine		8.9, 10.1[a]	-0.09
oxprenolol		9.5[b]	1.62
acebutalol		9.6[c]	1.61
isoproterenol		8.6, 10.1, 12.0[d]	0.08
atenolol		9.6[e]	-0.11
propranolol		9.5[a]	2.75
labetalol		9.3[c]	2.18
isoxuprine		8.0, 9.8[b]	2.62

[a]The Pharmaceutical Codex, 1979.
[b]Clarke's Isolation and Identification of Drugs (Clarke, 1986).
[c]AHFS Drug Information, 1994.
[d]Tariq and Al-Badr, 1985.
[e]Caplar et al., 1984.

resulted in a poor correlation with log X^+. These observations suggest that the observed relationship between log solubility and melting point is not solely related to a dependence of the solubilities of the salts on their solid-state properties.

In addition, it has been reported that large differences exist among the abilities of several of the compounds included in the present study to self-associate. Attwood and Agarwal (1979) reported critical micelle concentrations and aggregation numbers for several of the beta-blockers including oxprenolol, acebutalol and propranolol in water and sodium chloride solutions. While propranolol forms relatively large micelles with aggregation numbers of approximately 36, aggregation numbers for oxprenolol and acebutalol were found to be 4 and 3, respectively. Labetalol possesses significant surface activity but, due to its limited solubility, aggregation numbers could not be estimated. It is therefore surprising to find that a single parameter such as melting point can be used to organize the log solubilities of compounds whose self-associating tendencies vary significantly. It is likely that melting point correlates with factors other than solid-state cohesive properties which have an influence on HCl salt solubility. For example, the relatively large, lipophilic compounds, propranolol, labetalol and isoxuprine, possess the highest melting points and lowest solubilities compared to phenylephrine, atenolol and isoproterenol, which are smaller, less lipophilic and possess high solubilities. It would be expected that smaller, less lipophilic compounds can interact more favorably with water, resulting in greater solubilities (Jencks, 1969).

The salting-out behavior of the compounds in the presence of sodium chloride was also examined and the results are plotted in Fig. 2 for those compounds that exhibited significant salting-out. The data were plotted according to Eq. 2. Although Eq. 2 was originally used as a way to characterize and quantitate salting-out for a non-electrolyte solute in the presence of strong electrolytes, Miyazaki et al. (Miyazaki et al., 1980; Miyazaki et al., 1981) illustrated its utility in the analysis of salting-out of a number of

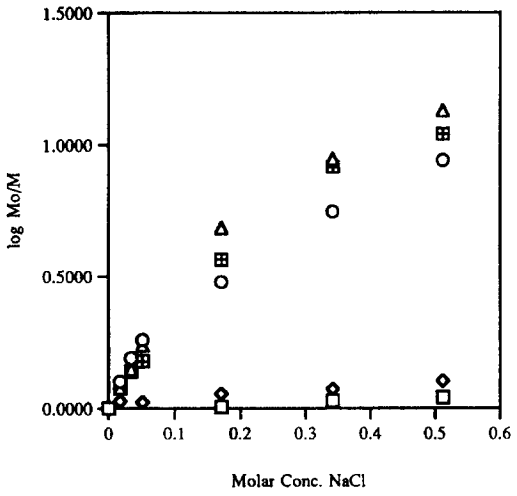


Fig. 2. Setchenow Plots of various hydrochloride salts. Phenylephrine HCl (□); isoproterenol HCl (◇); propranolol HCl (◨); isoxuprine HCl (△); labatalol HCl (○).

hydrochloride salts in the presence of sodium chloride.

In the present study the hydrochloride salts of propranolol, labetalol and isoxuprine all demonstrated relatively large salting-out tendencies in sodium chloride solutions that ranged from 0 to 0.512 mol/l. The hydrochloride salts of phenylephrine and isoproterenol exhibited minor salting-out behavior while oxprenolol, acebutalol and atenolol exhibited no significant salting-out over the range of sodium chloride solutions studied. Values for K_s are listed in Table 3 for each of the compounds. In the cases of propranolol, labetalol and isoxuprine, a negative deviation from linearity or curvature is observed at higher concentrations of sodium chloride, e.g., above 0.2 molar, as seen in Fig. 2. Miyazaki et al. (Miyazaki et al., 1980; Miyazaki et al., 1981) reported a similar phenomenon for some of the compounds included in their study and determined K_s from the slope of the initial, linear portion of the plots. This same approach was used in the present study to determine K_s for these three compounds. It should also be noted that the value of 4.07 for the K_s of isoxuprine hydrochloride reported in Table 3 is less than the value of 6.32 reported by Miyazaki et al. (1981). The difference is most

likely due to differences in the range of sodium chloride concentrations used in the determination of K_s as well as the method of calculation of the slopes of the log S_o/S vs. C plots. There is no indication Miyazaki et al. used a statistical program to calculate the slopes.

For predictive purposes, it is of interest to examine the relationship between the salting-out behavior and the solubility of the individual hydrochloride salts in water. Fig. 3 illustrates a plot of log X^+ vs. K_s. This plot indicates that compounds with relatively high solubilities in water, possess low values of K_s. This is in general agreement with the observations of Miyazaki et al. (1981) who reported an inverse relationship between log K_s and log molar solubility. In the present group of compounds, there appeared to be no advantage to the use of log K_s values in the correlation with log solubility values.

Since, as indicated by Fig. 1, an inverse relationship is observed between melting point and log X^+ it is not surprising to find a correlation between K_s and melting point. In general, higher melting compounds tend to possess larger values of K_s. This relationship is not very quantitative, with linear regression of K_s vs. T_m resulting in $r^2 = 0.5619$.

Table 3
Salting-out constants for hydrochloride salts

Name	K_s	n[a]	Range[b]	r^2[c]
Phenylephrine	0.07	4	0–-0.512	0.91
Oxprenolol	0.00	5	0–-0.512	NS[d]
Acebutalol	0.00	5	0–-0.512	NS[d]
Isoproterenol	0.21	6	0–-0.512	0.89
Atenolol	0.00	5	0–-0.512	NS[d]
Propranolol	3.29	5	0–-0.171	0.9938
Labetalol	5.19	4	0–-0.0512	0.9910
Isoxuprine	4.07	5	0–-0.171	0.9948

[a]Number of points used to determine K_s.
[b]Range of sodium chloride concentration used to determine K_s.
[c]Correlation coefficient of regression using zero intercept.
[d]r^2 could not be estimated using zero intercept regression. Slope was not statistically significant ($p > 0.05$).

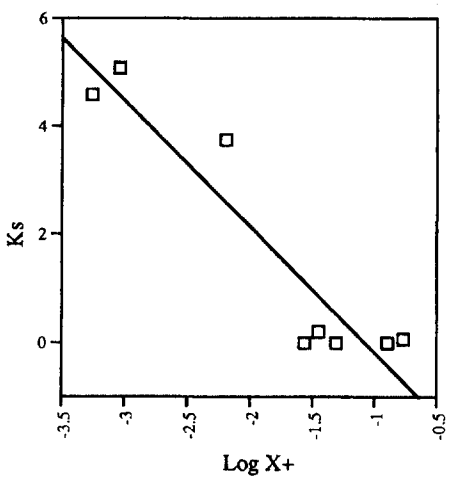


Fig. 3. K_s vs. log X^+.

A comparison of the structures presented in Table 2 with the salting-out constants reported in Table 3 indicates that those compounds with two aromatic rings exhibit the most sensitivity to the common ion effect while those compounds that possess only a single aromatic ring exhibit relatively little or no salting-out. This observation is reflected to a certain extent by the values of log P. For example, log P values for the unionized forms of propranolol, labetalol and isoxuprine range from 2.18 to 2.75 while log P values for phenylephrine, isoproterenol and atenolol range from -0.11 to 0.08. For these six compounds, there appears to be a direct relationship between salting-out constant and log P. However, log P values for acebutolol and oxprenolol are 1.61 and 1.62, respectively, yet do not demonstrate significant salting-out in sodium chloride solutions. It is also unexpected that phenylephrine and isoproterenol demonstrate some sensitivity to added sodium chloride while acebutolol and oxprenolol do not, despite the higher lipophilic character of the latter two compounds.

It is apparent that some structural specificity exists in determining the sensitivity of the compounds to the addition of common ion. The primary structural differences among the compounds

are the type of substituents attached to the phenyl ring(s). The phenyl ring substituents could influence the magnitude of the K_s values via various mechanisms. For example, the distribution of electrons in the phenyl ring would be influenced by the type and position of the ring substituent groups and this could affect both induced and permanent dipole moments of each molecule and influence intra- and intermolecular interactions. It is also interesting to note that the phenyl ring substituents on acebutolol, oxprenolol and atenolol occupy a larger volume compared to those on the other compounds. In the cases of each of the compounds that exhibit salting-out, including phenylephrine, isoproterenol, propranolol, labetalol and isoxuprine, ring substituents, when present, tend to be relatively small and the aromatic rings tend to be more planar. The larger, bulkier groups on acebutolol, oxprenolol and atenolol could hinder close stacking of the planar phenyl groups in solution since they may not lie planar with the phenyl ring (Higuchi and Pisano, 1964). The crystal structures of acebutolol HCl and oxprenolol HCl support the probability that butyramido and the allyloxy groups, respectively, are not co-planar with the phenyl ring (Carpy et al., 1979; Leger and Gadret, 1977). It is possible that hydrophobic ring overlap enhances the stability of the cation-Cl^- complexes, and formation of such complexes may facilitate precipitation of the hydrochloride salts in the presence of excess chloride ion.

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