Common Ion Equilibria of Hydrochloride Salts and the Setschenow Equation

JOSEPH B. BOGARDUS

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Abstract □ A simple equation was derived to describe the relationship between the aqueous solubility of sparingly soluble salts (S_0) and the empirical Setschenow salting-out constant (k): $k = 0.217/S_0$. This relationship and the Setschenow equation were found to be valid only at low concentrations of added salt. This equation agreed with recently published data when compared for the effect of the chloride ion on the solubility of a series of drug hydrochloride salts. The theoretical treatment also predicts the curvature which has been reported in literature Setschenow plots at higher salt concentrations. As the concentration of added salt increases, the apparent k value is not constant but is dependent on solubility and the rate of change of solubility with added salt concentration. It was concluded that the Setschenow treatment is generally inappropriate for description and analysis of common ion equilibria.

Keyphrases □ Hydrochloride salts—relationship of aqueous solubility and Setschenow constant □ Setschenow equation—relationship between solubility of hydrochloride salts □ Common ion equilibria—of hydrochloride salts and Setschenow equation

In several studies the empirical Setschenow equation has been used to describe the effect of the chloride ion on the solubility of drug hydrochloride salts (1–5). Although this equation was originally proposed to describe salting-out phenomena of nonelectrolytes (6), it appeared to adequately describe suppression of solubility by the common ion effect. In other investigations the principles of solubility product equilibrium were used for describing the solubility of drug salts (7, 8). The solubility product treatment was essential in studying the solubility of doxycycline hydrochloride since self-association to form a dimer dominated the aqueous solubility (8).

The present study was initiated to examine the relationship between the empirical Setschenow equation and rigorous solubility product equilibrium theory. The mathematical treatment shows that the apparent Setschenow salting-out constant (k) is not a physical chemical constant. It is related to solubility or the solubility product constant only at low concentrations of added salt. Due to these limitations and the difficulty in detecting self-association of drug, rigorous solubility product relationships should be used to describe common ion equilibria of hydrochloride salts.

THEORY

The solubility product constant (K_{sp}) for the hydrochloride salt of a weak base is defined as:

$$K_{sp} = S\,[Cl^-] \qquad \text{(Eq. 1)}$$

where S is the concentration of the protonated base and $[Cl^-]$ is the chloride ion concentration at equilibrium. The chloride ion concentration is expressed as the sum:

$$[Cl^-] = S + [NaCl] \qquad \text{(Eq. 2)}$$

where [NaCl] is the concentration of added salt (8).

When [NaCl] = 0, $S = S_0 = [Cl^-]$ and the solubility product constant is:

$$K_{sp} = S_0^2 \qquad \text{(Eq. 3)}$$

This equation is valid only when self-association of drug is negligible (8). The Setschenow equation can be written:

$$\log \frac{S_0}{S} = k[NaCl] \qquad \text{(Eq. 4)}$$

where k is the apparent salting-out constant. It is assumed that the salting-out behavior is due only to chloride ion, and specific cation effects are negligible. Literature data using ammonium or sodium chlorides indicate that this assumption is valid (4, 8). The salting-out constant is the slope of a plot of log S_0/S *versus* [NaCl]:

$$k = \frac{d \log \frac{S_0}{S}}{d\,[NaCl]} = \frac{-\frac{dS}{d\,[NaCl]}}{2.303\,S} \qquad \text{(Eq. 5)}$$

This equation indicates that the apparent salting-out constant depends on the solubility and the rate of change of solubility with added salt concentration. The limiting slope at low added salt concentration is:

$$\lim_{[NaCl]\to 0} k = \frac{-\lim_{[NaCl]\to 0}\left(\frac{dS}{d\,[NaCl]}\right)}{2.303\,S_0} \qquad \text{(Eq. 6)}$$

since, as [NaCl] → 0, $S \to S_0$.

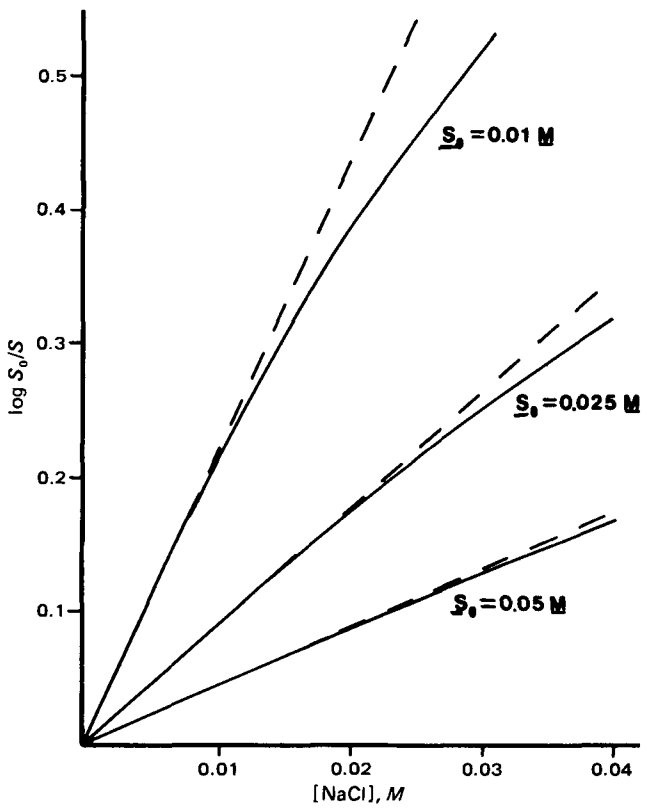

Figure 1—*Hypothetical Setschenow plots at three* S_0 *values according to Eqs. 3 and 7 (—). The initial slopes (- - -) were calculated using Eq. 10.*

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Table I—Comparison of Experimental and Calculated Salting-out Constants

Hydrochloride Salt	25°		37°	
	k^a_{exp}	k^b_{calc}	k^a_{exp}	k^b_{calc}
Phenazopyridine	18.06	16.5	11.57	11.5
Cyproheptadine	21.18	20.9	14.80	13.7
Bromhexine	20.00	21.3	16.78	16.8
Trihexyphenidyl	8.24	12.6	5.66	5.8
Isoxsuprine	6.32	7.4	6.30	5.6
Chlortetracycline	9.60	9.7	6.52	8.9
Methacycline	8.24	5.7	6.36	4.9
Papaverine	5.09	2.3	3.60	1.8
Demeclocycline	3.73	3.1	2.68	2.4
Doxycycline	5.3[c]	1.8[b], 5.1[d]	—	—

[a] From Ref. 1 except as noted. [b] Calculated using Eq. 10. [c] Calculated from the data in Ref. 8. [d] Calculated using Eq. 12 and $K_{sp} = 1.8 \times 10^{-3}\ M^2$ (8).

From Eqs. 1 and 2 and the quadratic formula, the following expression for S is obtained:

$$S = \frac{-[\mathrm{NaCl}] \pm ([\mathrm{NaCl}]^2 + 4K_{sp})^{1/2}}{2} \qquad \text{(Eq. 7)}$$

The derivative with respect to [NaCl] is:

$$\frac{dS}{d\,[\mathrm{NaCl}]} = \frac{-1 \pm [\mathrm{NaCl}]([\mathrm{NaCl}]^2 + 4K_{sp})^{-1/2}}{2} \qquad \text{(Eq. 8)}$$

and the limit of this differential is:

$$\lim_{[\mathrm{NaCl}]\to 0} \left(\frac{dS}{d[\mathrm{NaCl}]}\right) = -1/2 \qquad \text{(Eq. 9)}$$

Therefore, from Eqs. 6 and 9, the limiting value of the salting-out constant has a simple relationship with solubility:

$$k_l = \lim_{[\mathrm{NaCl}]\to 0} k = \frac{1}{4.606\,S_0} = \frac{0.217}{S_0} \qquad \text{(Eq. 10)}$$

or in log form:

$$\log k_l = -\log S_0 - 0.664 \qquad \text{(Eq. 11)}$$

In the absence of self-association, S_0 and K_{sp} are related by Eq. 3, and the limiting value of the salting-out constant can also be written as:

$$k_l = \frac{0.217}{K_{sp}^{1/2}} \qquad \text{(Eq. 12)}$$

DISCUSSION

Figure 1 contains hypothetical Setschenow plots which were generated at solubilities of 0.01, 0.025, and 0.05 M using Eqs. 3 and 7. The range of S_0 and salt concentration were chosen to be similar to that reported previously (1) for several drug salts. At each concentration the lines show downward curvature with increasing salt concentration. With decreasing drug salt solubility the deviations from the initial slope based on Eq. 10 begin to appear at progressively lower concentrations of added salt. Curved Setschenow plots of this type were reported for the hydrochloride salts of phenazopyridine, cyproheptadine, and bromhexine (1). These compounds have solubilities of ~0.01 M, which is consistent with the theoretically generated data. More soluble drug salts, as expected, showed lower slopes and essentially linear relationships.

The experimental salting-out constants at 25 and 37° for several compounds are compared in Table I with values calculated from their solubilities. Good agreement was obtained in most cases with the largest differences appearing with the most soluble salts which have the smallest slopes. Papaverine was approximately two times more sensitive to salt than would be predicted from its solubility. The calculated and experimental values for methacycline differ by 30–40%.

The k_{exp} for doxycycline shows poor agreement with the value calculated from S_0 using Eq. 10. This is not unexpected, since doxycycline is known to form a dimer and higher order complexes in aqueous solution (8). These equilibria cause the apparent solubility product calculated from Eq. 3 ($13.1 \times 10^{-3}\ M^2$) to be larger than the limiting K_{sp} ($1.8 \times 10^{-3}\ M^2$), which was determined under conditions where self-association was negligible. Thus, the k_{calc} from Eq. 10 is incorrect because of the solubility-increasing effect of self-association. Calculations of k using the limiting K_{sp}, which is not influenced by self-association, provides a value similar to the experimental constant.

In view of the known self-association of doxycycline, it is surprising that k_{exp} is so similar to k_{calc}. This appears to be due to compensation of S_0 and dS/d[NaCl] in Eq. 5. The approximately three-fold higher solubility ($S_0/K_{sp}^{1/2}$) caused by self-association is compensated by a three-fold higher salting-out rate estimated from the slope of the plot of S *versus* [NaCl]. The added salt may be decreasing the stability of the associated species.

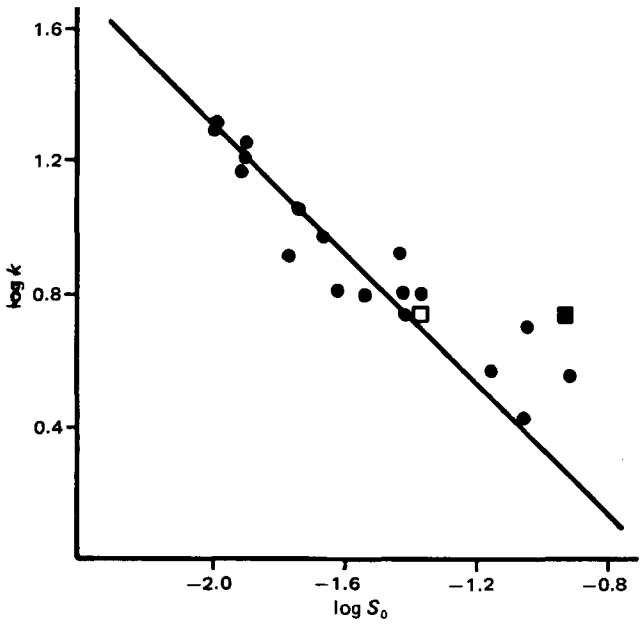

Figure 2—*Relationship between salting-out constant and solubility. Key: (—) Eq. 11; (●) 25 and 37°, data from (1), for the drugs in Table I; (■) observed data for doxycycline hydrochloride; (□) experimental* k *value and* S_0 *calculated from the limiting* K_{sp} *using Eq. 3.*

Since the initial slope is most important in a Setschenow plot, and this region is most susceptible to the effects of self-association, the use of this method may lead to erroneous results. A probable explanation for the poor agreement with papaverine and methacycline hydrochlorides is that the solubilities (S_0) are anomalously high due to self-association. This would be especially likely for methacycline, which is structurally similar to doxycycline. Based on the limited doxycycline data, self-association appears to have a stronger effect on solubility than it does on the apparent salting-out constant.

The solubility product constant is inversely proportional to the square of the salting-out constant (Eq. 12). A doubling in the slope of a Setschenow plot corresponds to a four-fold decrease in K_{sp}. Thus, K_{sp} is a more sensitive indicator of common ion effects than the salting-out constant. A major disadvantage of the use of Setschenow plots is that self-association of the drug cannot be detected. This is not a problem when the data are analyzed according to the principles of solubility product equilibrium since the apparent K_{sp}, calculated as the product of solubility and chloride concentrations, will not be constant (8).

The existence of a linear correlation between log k and log S_0 has been shown (1). More soluble drug salts were found to have smaller salting-out constants. These observations are theoretically predicted by Eq. 11. In Fig. 2 the salting-out constant and solubility of the drug salts in Table I are plotted according to Eq. 11. The experimental data show good agreement with the theoretical line of slope = −1.0. Points for doxycycline, papaverine, and methacycline lie above the line, which is consistent with the proposed self-association of these compounds.

Few of the drugs deviate negatively from the theoretically predicted relationship. Trihexyphenidyl at 25° and chlortetracycline at 37° are below the line, but at the other temperature these compounds show satisfactory agreement. These apparent deviations cannot be explained at present.

The results of this study indicate that the Setschenow treatment, originally proposed to describe salting-out of nonelectrolytes, is inappropriate for description of common ion equilibria of hydrochloride salts. Data analysis based on solubility product equilibrium theory is a more satisfactory approach.

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High-Pressure Liquid Chromatographic Determination of Cimetidine in Plasma and Urine

G. W. MIHALY ˣ, S. COCKBAIN, D. B. JONES, R. G. HANSON, and R. A. SMALLWOOD

Received April 22, 1981, from the *Gastroenterology Unit, Department of Medicine, University of Melbourne, Austin Hospital, Heidelberg, 3084, Victoria, Australia.* Accepted for publication August 26, 1981.

Abstract □ An assay is described for the determination of the H_2-receptor antagonist, cimetidine, in human plasma and urine. Alkalinized plasma or urine was extracted with methylene chloride, the organic phase was evaporated, and the reconstituted residue was analysed by high-pressure liquid chromatography (HPLC) using a reversed-phase prepacked plastic column housed in a radial compression module. The metabolite, cimetidine sulfoxide, was identified but could not be quantitated due to interference from the solvent front. The sensitivity limit of the assay was 25 ng/ml. The assay was applied to the measurement of plasma and urine samples in a pilot pharmacokinetic study. Cimetidine was substantially absorbed and rapidly eliminated (plasma elimination half-life of 112–130 min). Plasma cimetidine concentrations could be measured to 12 hr after a 200-mg dose (iv or oral), but they were below the sensitivity of the assay by 24 hr. Urinary excretion of unmetabolized cimetidine accounted for 40–50% of the administered dose in the first 12 hr. This assay is simpler and more sensitive than those previously described, and it is suitable for the measurement of cimetidine in plasma and urine of subjects receiving doses appropriate for clinical use.

Keyphrases □ Cimetidine—high-pressure liquid chromatographic analysis in plasma and urine □ High-pressure liquid chromatography—analysis, cimetidine, human plasma and urine □ H_2-Receptor antagonists—cimetidine, high-pressure liquid chromatographic analysis in plasma and urine

The H_2-receptor antagonist, cimetidine, profoundly inhibits gastric acid secretion and is effective in the treatment of gastric and duodenal ulcers (1). Studies have shown that the degree of inhibition of gastric acid secretion is related to cimetidine plasma level measurements (2).

Chromatographic assays for the measurement of blood, plasma, and urine concentrations of cimetidine have been published. The sample treatment in these methods is complex and involves multiple extraction steps (3, 4). Moreover, samples are chromatographed on silica-based column packing which is likely to limit the column's efficiency and life under alkaline conditions. A simple micromethod for the estimation of plasma cimetidine has also been reported (5). This method exhibited low precision and sensitivity, as well as lengthy chromatography.

A more sensitive liquid chromatographic method for measuring cimetidine in plasma and urine, using a simple, single extraction step in sample treatment, is reported. Chromatography is rapid and conducted on a column system[1,2] which recently has become commercially available. These columns operate under conditions that produce greater column efficiency and allow longer column life. This method has been applied to a pilot study on a patient with a gastric ulcer, in which the influence of a 6-week course of cimetidine (1 g/day) on its own disposition and elimination is investigated.

EXPERIMENTAL

Instrumentation—A constant flow high-pressure liquid chromatograph[3] was used for all assays. This consisted of a solvent delivery system[4], a universal injector[5], and a variable wavelength UV absorbance detector[6] operating at 228 nm. The plastic column was obtained prepacked[1] (100 mm × 8-mm i.d.) and was housed in a radial compression module[2] which maintained external column pressure at ~2500 psi.

Reagents—Pure samples of cimetidine, cimetidine sulfoxide, and the internal standard, burimamide, were obtained[7]. The HPLC mobile phase contained UV grade acetonitrile[8], triethylamine[9], phosphoric acid[10], and glass-distilled water.

Calibration Standards—A pool of drug-free plasma was spiked with pure cimetidine to a concentration of 5000 ng/ml. By a series of quantitative double dilutions with additional drug-free plasma, standards of 2500, 1250, 625, and 312.5 ng/ml were prepared and stored at −20°. Similarly, drug-free urine was spiked with pure cimetidine to a concentration of 200 μg/ml and diluted to prepare standards of 100, 50, and 25 μg/ml. Calibration curves were prepared by plotting the relationship between the peak height ratios of cimetidine–burimamide and the cimetidine concentration in each sample.

Recoveries of cimetidine and burimamide from plasma or urine were estimated by comparing the peak height of cimetidine obtained after extraction, against that obtained when the same amount of cimetidine from an aqueous stock solution was chromatographed.

Extraction of Plasma—Burimamide (internal standard, 10 μg/ml, 200 μl), NaOH (2 *M*, 0.5 ml), and methylene chloride (20 ml) were added to 1.0 ml of plasma in a 30-ml glass tube. After vortex mixing (60 sec) and centrifugation (3000 rpm, 10 min), the organic layer was carefully transferred into a second tube and evaporated under a gentle stream of

[1] Rad Pak A, Waters Associates, Milford, Mass.
[2] RCM-100, Waters Associates, Milford, Mass.
[3] Waters Associates, Carlton, Melbourne, 3053, Australia.
[4] Waters Associates, Model 6000A.
[5] Waters Associates, Model U6K.
[6] Waters Associates, Model 450.
[7] Smith Kline and French Laboratories Ltd. Hertfordshire, England.
[8] Waters Associates, Carlton, Melbourne, 3053, Australia.
[9] BDH Laboratories, Port Fairy, 3284, Australia.
[10] Merck, Darmstadt, West Germany.

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