THE "SALTING OUT" OF NON-ELECTROLYTES FROM AQUEOUS SOLUTIONS

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The change in the solubility of a non-electrolyte in water which results from the addition of an electrolyte has been known and studied for many years. Since a decrease in the solubility of the non-electrolyte results in many instances from such salt addition the phenomenon has been called the "salting-out" effect, although there are numbers of cases in which the addition of certain salts increases the solubility of particular non-electrolytes causing them to be "salted in."

While the literature abounds with examples of data showing the effect of the addition of one or two salts on the solubility of a given non-electrolyte, comparatively few complete systematic studies of the influence of a series of salts on the solubility of a given non-electrolyte are available. Furthermore, almost no systematic studies of the effect of the molecular structure of the non-electrolyte molecule as determining the extent to which its solubility would be influenced by electrolyte additions have been made. The principal systematic investigations using a series of salts are the older work of Rothmund on phenylthiourea (1), of Hoffman and Langbeck on substituted benzoic acids (2), and of Euler on ether and ethyl acetate (3); also, the more recent investigations of Linderstrom-Lang on hydroquinone, quinone, succinic acid, and boric acid (4), of Glasstone and his coworkers on ethyl acetate and aniline (5), of Larsson on benzoic acid (6), and of Phillip Gross and his students on acetone and hydrocyanic acid (7).

Various equations have been proposed to express the relation between the change in the solubility of the non-electrolyte and the added salt concentration, but that proposed at an early date by Setschenow (8) seems to fit the data most generally and to have been most frequently employed. It is further substantiated by recent carefully determined values for the solubility of benzoic acid in aqueous potassium chloride (9). Setschenow's equation is

$$\log \frac{s_0}{s} = \log f_c = kc_s \tag{1}$$

in which s_0 and s are the solubilities of the non-electrolyte in weight units per unit volume of water and salt solution, respectively, c_s is the salt concentration in moles per liter, k is the "salting-out" constant, and f_c is the activity coefficient of the non-electrolyte expressed in concentration units. This equation is generally valid for values of c_s as high as from 2 to 3 molar, provided s_0 is small. Occasionally it is valid for salt concentrations as high as 4 molar.

The region of dilute salt solutions (below 0.5 molar) has been very little investigated, largely because of the increasing errors in the $\frac{s_0}{s}$ values. While it seems that equation 1 is the only one which will hold over an appreciable range of salt concentrations, there is some evidence that an equation of the form

$$v_a = k_1 c_s \tag{2}$$

holds for solutions of salt concentration below 0.5 molar. Here v_a is the additional volume in liters of solution which would be required to hold 1 mole of the non-electrolyte in solution, in the presence of the added salt concentration c_s, in excess of the volume of water v_0 required for its solution in the absence of the salt. Equation 2 can be shown to be an approximate limiting form of equation 1 in which $k_1 = 2.303\, v_0 k$. Data sufficiently accurate to test equation 2 in dilute solutions are not available except in a few instances. As an example there may be cited the accurate data of Chase and Kilpatrick (9) on the solubility of molecular benzoic acid in potassium chloride solutions. For potassium chloride solutions below 0.7 molar, a straight line whose equation is $v_a = 13.2\, c_s$ satisfactorily represents their data. They use equation

1 to represent the entire range of their data up to 3 molar potassium chloride solutions and calculate a value of $k = 0.138$. From this may be calculated a value for $k_1 = 12.0$ in approximate agreement with the value 13.2 found from their points in the dilute solution range. Whether equation 2 represents a simple relationship true for dilute solutions or whether it is merely an approximation form of equation 1 can only be determined by further tests with accurate data in dilute solutions. If an equation of the form of equation 2 is generally valid, it implies that one of the primary factors in "salting out" is a characteristic constancy of binding of a part of the water by at least some of the ions, the extent of which is directly proportional to the number of ions. The water so bound is probably removed as a shell of oriented water dipoles around the ion. These become unavailable as solvent molecules in which the non-electrolyte could be dispersed, and so it is necessary to add more solution in order to retain a mole of non-electrolyte in molecular dispersion in the salt solution at the temperature concerned.

Probably because of the limited range of solutes investigated, the opinion has at times been held that the "salting-out" effect is not influenced greatly by the character of the non-electrolyte. That this is quite erroneous may be seen when we consider the solubility of a diverse series of non-electrolytes in a given salt solution as in table 1 (10). In this table the weight per cent of non-electrolyte "salted out" (referred to 1000 g. of water in each case) is compared with such measures of its polar character as its dielectric constant D as a liquid, its dipole moment μ, and total polarization P as determined in dilute solution in non-polar solvents.

While there is no consistent correlation shown, there is a well-defined trend in the extent of salting out with polar properties in such direction that those substances which are more polar are least salted out from this electrolyte solution of fixed ion population and kind. This correlation finds recognition in the theory of the "salting-out" phenomena proposed by Debye and McAulay (11) and Debye (12). This theory pictures the "salting-out" effect as a consequence of the aggregation of the water molecules of greater polarity around the ions owing to the field of the latter. The less polar non-electrolyte molecules tend to congregate in the portions of the solution most remote from the field of the ions, with the net result that an enhancement of the water molecules around the ions and of the non-electrolyte in the solution regions away from the ions occurs. A reduction of the solubility of the non-electrolyte, referred to the total water present, thus results, due to the increase of non-electrolyte–water ratio in those regions of the solution containing the non-electrolyte. The criterion of polarity which Debye employs is the dielectric constant of the saturated aqueous solution of the non-electrolyte relative to water at the same temperature. On this basis if the saturated solution has a dielectric constant less than water, "salting out" occurs in the presence of the added salt. If the dielectric constant of the saturated non-electrolyte solution is above that of water, the non-electrolyte becomes more soluble in the salt solution or is

TABLE 1

Salting out by 0.5 molal potassium chloride at 30°C.

	PER CENT SALTED OUT	D	P (Total polarization)	$\mu \times 10^{18}$
p-Nitroaniline	3.0		1080	7.1
m-Dinitrobenzene	3.0		338	3.8
Nitrobenzene	3.1	36.4	346	4.0
Monobromobenzene	4.1	5.3	82	1.50
Monochlorobenzene	5.6	10.9	82	1.56
Bromoform	8.2	4.4	51	1.0
Methylene bromide	9.1	7.0	61	1.4
Chloroform	9.7	5.1	51	1.2
Ethylene chloride	11.3	10.4	93	1.8
Methylene iodide	11.6	5.5	58	1.1
n-Propyl bromide	11.9	7.2	103	1.9
n-Butyl bromide	12.3	6.6	114	1.9
n-Propyl iodide	13.2		102	1.7
Ethyl iodide	13.5	7.4	86	1.7
Ethylene bromide	13.7	4.8	68	1.0
Carbon tetrachloride	16.7	2.23	28	0
Benzene	19.1	2.26	26	0
Toluene	24.3	2.39	36	0

"salted in." This means that the non-electrolyte tends to aggregate around the ions at the expense of the water, and so the non-electrolyte–water ratio in regions removed from the ions is lowered and the total water present can hold more non-electrolyte in solution. A test of this theory involves a knowledge of the dielectric constant of the saturated aqueous non-electrolyte solution,—information which to date is available in but a few instances.

The best test of the theory is provided by the data of Phillip Gross and his coworkers (7) on the solubility of acetone and hydrogen cyanide in aqueous salt solutions. The former lowers while the latter raises the dielectric constant of water. In agreement with the predictions of the theory, acetone is "salted out" whereas hydrogen cyanide is "salted in." The "salting-out" effects calculated from the theory agree in order of magnitude (13) with those found experimentally, although actual values only roughly approximate the observed percentages "salted out" for the different salts. It is clear, however, that such agreement as to order of magnitude would not result unless the Debye picture for the mechanism was essentially correct and represented at least a significant part of the "salting-out" effect. The possibility of other factors also entering into the effect is of course not precluded, as Debye himself clearly points out (14). A study of the recent data on "salting out," particularly in relation to the additive effects of ions, indicates the possible nature of such factors.

It has been generally recognized wherever data on a sufficient number of salts were available for a test that the effects of the positive and negative ions of an electrolyte were at least approximately additive. This is clearly brought out by the data of Larsson for benzoic acid which include a large number of salts (6). Assuming the validity of this additivity principle Larsson writes for equation 1

$$\log f_c = kc_s = (k_c + k_a)c_s \tag{3}$$

in which k_c is the salting-out constant for the cation, and k_a that for the anion. Comparison of his values for a series of chlorides and nitrates of the same metals showed a constant difference due to the difference in the value of k for the chloride and nitrate ion.

In order to evaluate the separate values of k_c and k_a he makes the arbitrary assumption that $k_{K^+} = k_{Cl^-}$ and from the value $k = 0.14$ for potassium chloride thus finds $k_{K^+} = 0.07$. From these values and those for the respective salts he calculates the values for the other ions. These are reproduced in table 2 taken from his paper (6), as they illustrate the range of such values as well as do any other data and they cover a wide variety of salts.

This table further illustrates a general regularity in all "salting-out" data, that of the effect of ionic size. With but rare exceptions the extent of "salting out" by a series of salts of the same valence type containing a common ion is in inverse order to the size of the cation, thus, for example, Li > Na > K > Rb > Cs. The same regularity holds for the simple anions, i.e., Cl > Br > I. This effect of ionic size has been recognized as a necessary and integral part of any theory of "salting out." Thus for the "salting out" of acetone by uni-univalent electrolytes the Debye equation (12) reduces to (13)

TABLE 2

Salting-out constants of individual ions for benzoic acid

ION	k	ION	k	ION	k	ION	k
H^+	0.02	Cs^+	−0.08	Cl^-	0.07	$-OCOCHCl_2$	−0.14
Li^+	0.12	Mg^{++}	0.10	Br^-	0.00	$-OCOCCl_3$	−0.12
Na^+	0.11	Ca^{++}	0.10	I^-	−0.02	$-OCOC_6H_5$	−0.32
K^+	0.07	Sr^{++}	0.09	NO_3^-	0.03	$-OSO_2C_6H_5$	−0.23
Rb^+	0.02	Ba^{++}	0.08	ClO_4^-	0.06	$-OSO_2C_{10}H_7$ (β)	−0.86

$$\frac{1}{fc} = 1 - \frac{0.27}{a} c, \tag{4}$$

where a is the average ionic radius in Ångström units. In this as in other cases there is the difficulty of properly evaluating the radius "a", and as this has to be done from other solution data only an average value is obtained and not the independent contribution of the size of each ion to the total "salting out."

While it is true that there are but few exceptions to the regularities just noted there are a number of cases which involve an anomalous effect of a different kind. These are those instances in which the addition of certain salts to water increases the solubility of the non-electrolyte, whereas others decrease it. Thus Linderstrom-Lang found that whereas sodium and lithium chlorides "salted out" boric acid, potassium, rubidium, and cesium chlorides salted it in. These are not explicable on the basis of the raising of the dielectric constant of water as in the case of the "salting in" of hydrogen cyanide, which is a true inversion of the "salting-out" effect in the sense of the Debye theory previously outlined. The same non-electrolyte cannot both raise and lower the dielectric constant of water at a given concentration. It is therefore clear that these anomalies must originate at least in part from the electrolyte. In general they have been noted and then classified as abnormal and attributable to specific interaction effects, with the non-electrolyte concerned, of the iodides, chlorates, nitrates, and similar ions for which they occur. They show in spite of this anomalous effect the same regularities of the order in which they affect solubility as previously noted. Thus the "salting-in" effect, for instance, in the case of succinic acid decreases in the order $CsCl > RbCl > KCl$. Furthermore it is difficult to conceive of the otherwise normal salts—potassium, rubidium and cesium chlorides—as behaving in some abnormal manner in this particular case. Likewise from Larsson's results we note that cesium chloride shows a slight "salting-in" effect. To indicate that this effect is fairly general and not confined to substances of the type of weak acids whose ionization equilibria might play some part in it, some data for benzene and nitrobenzene are cited here (15). If the values of f_m, the activity coefficient for molalities, are considered for $c_s = 1\ M$, it is found that benzene is "salted out" largely by potassium chloride and very little by cesium chloride, and is "salted in" moderately by potassium benzoate. Nitrobenzene is "salted out" less than half as much as benzene by potassium chloride, slightly "salted in" by cesium chloride, and largely "salted in" by potassium benzoate. By comparison with Larsson's table it will be seen that this is in approximate accord with his results for benzoic acid. This anomalous "salting-in" effect is most evident for salts with large negative ions but is not confined to them alone, as shown by the instances of the three alkali chlorides and succinic acid.

Since this effect occurs in some cases even with such relatively small negative ions as chlorides, its explanation must be more fundamental than that of an abnormal specific interaction. If Larsson's table is used as an illustration and the principle of additivity is assumed, a basis for correlating all the effects is possible. Larsson assumed arbitrarily that $k_{K^+} = k_{Cl^-} = 0.07$ and then calculated that $k_{Cs^+} = -0.08$, because k for cesium chloride was found to be -0.01. If the arbitrary assumption that $k_{K^+} = k_{Cl^-}$ had any significance it would imply that cesium ion was "salting in" the benzoic acid. However, if it is assumed that the slightly increased solubility in cesium chloride is the result of the near balance of two opposite effects, either of the ions could be thought of as responsible for the "salting in." Since the "salting-in" anomaly is more common for salts with large negative ions, it seems reasonable to attribute the "salting-in" effect to the chloride and not to the cesium ion. On this basis the result for cesium chloride is the consequence of the slight inequality in the operation of two practically equal and opposite effects, "salting out" by the cation and "salting in" by the anion.

In the general case these opposite effects will not counterbalance each other, either the "salting out" due to the cation or the "salting in" due to the anion predominating and so determining the direction of the net effect observed for the salt in question. Such an assumption accounts for the anomalies noted above, meets the requirements of the additivity principle, and agrees also with the observed order of increasing "salting out" in a series of salts with a common anion from cesium to lithium. The decreasing "salting out" for a similar series with the anions Cl^-, Br^-, I^- under this assumption is interpreted to mean that the "salting in" by these ions increases with their size. This is in general agreement with the results of Larsson for the large negative organic ions though an additional factor, that of the lack of spherical symmetry, probably also enters in these cases.

An attempt to picture the mechanism underlying such an antagonistic action of cation and anion in their effects on the solubility of non-electrolytes is worth while, though it must be in large degree speculative. The action of the cation is regarded as essentially unaltered from that given by the Debye theory, namely, one of aggregation of water dipoles immediately around the cation and of enhancement of non-electrolyte molecules in regions removed from the cation with the consequent "salting out." In the region around the anion, non-electrolyte molecules must aggregate and water molecules decrease. This does not necessarily imply an absence of binding of water molecules, but does imply a binding of a different order of magnitude than in the case of the cation and one more easily displaced by, or at least shared with, the non-electrolyte. There is an accumulation of related evidence for the existence of such a difference in what is usually termed the "degree of hydration" of cations and anions, the amount of water bound to the former exceeding that bound to the latter. Perhaps the strongest evidence for this is from transference experiments such as those of Washburn (16). These showed that the least hydrated cesium ion carries more water than does the chloride ion. Sugden (17) arrives at the same general conclusion as to the existence of this difference, but goes so far as to say that the anions are unhydrated. This seems doubtful, however, at least in the case of such a small ion as the fluoride ion, for instance.

The reason for aggregation of the non-electrolyte molecules about the anion is more difficult to see, at least for the simple spherical ions such as the halogens. For the complex ions this is not so difficult. An ion like the benzoate ion consists of a large non-polar phenyl group with a small complex carboxyl group of high dipole moment concentrated at one end where the ionic charge resides. The field around such an ion will be highly unsymmetrical, being localized and intense for a small region at one end and low or practically absent at the other. In the space around such ions there would be a small region adjacent to the carboxyl group in which water molecules tended to congregate to some extent. In the proximity of the phenyl group the less polar molecules of the non-electrolyte would tend to accumulate, leaving regions remote from the ion poorer in these and richer in water. The size of the ion and relative distribution of the more and less polar portions of the field about it, together with possibilities for orientation inherent in the non-electrolyte molecule, will result in the highly specific character of the solubility effects which are observed.

Finally it must be emphasized that this assumption of the antagonistic action of the two ions, the cation "salting out" and the anion "salting in," while it seems to fit the observations now extant, may have to be modified in particular cases as the range of ions and non-electrolytes studied is increased. Concerning the behavior in "salting-out" phenomena of complex positive ions of large size but little is known. It seems possible that cases will be found where these, because of their dissymmetry, might tend to orient particular non-electrolytes around them at the expense of water and so "salt in" the non-electrolytes. Furthermore no mention in the foregoing has been made of cases of polyvalent ions as these involve the added problem, in all but the most dilute solutions, of the effect of ionic interaction. The need for data in the dilute solution range is seen to be necessary before much further progress in this direction can be made.

SUMMARY

A survey of the data of the "salting-out" phenomenon has been made and the presence of regularities such as the principle of additivity of individual ionic effects noted. The existence of certain anomalies of general occurrence has also been pointed out.

To explain these a theory of the antagonistic action of cation and anion is proposed and reasons advanced which make it seem probable that the cation is responsible for the "salting-out" portion and the anion for the "salting-in" portion of the effect. According as one or the other predominates, in the case of a given electrolyte, a net observed "salting out" or "salting in" of a given non-electrolyte will result.

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