Effect of Inorganic Additives on Solutions of Nonionic Surfactants II

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Abstract ☐ The effect of electrolytes and urea on the cloud points of the following three nonionic polyoxyethylated surfactants was studied: cetyl, stearyl, and oleyl alcohol adducts containing 10 ethylene oxide units. The results were similar to those obtained previously with polyethylene oxide and with a polyoxyethylated alkylphenol. Nitrates of cations capable of forming stable solid complexes with model ethers like dioxane raised the cloud points in proportion to their concentrations by up to 35°. They salted the surfactants in through complexation with the ether oxygens. The order of effectiveness in raising the cloud points was lead nitrate > hydrochloric acid > cadmium nitrate > sulfuric acid ≃ magnesium nitrate > aluminum nitrate > nickel nitrate > lithium nitrate > calcium nitrate. Only the nitrates of sodium, potassium, ammonium, and cesium lowered the cloud points, salting the surfactants out. These cations do not form complexes with ether oxygens. Urea, sodium perchlorate, and sodium iodide, which break the structure of water, raised the cloud points. This salting-in process is ascribed to increased hydration of the ether groups of the polyoxyethylated surfactants due to depolymerization of water by urea and the perchlorate and iodide anions. The bromide, chloride, and sulfate of sodium lowered the cloud points. The surfactant with the alkylaryl moiety was salted in more extensively but salted out only slightly more than the three surfactants with the linear hydrocarbon chain. The data indicate the need for revising the theories of the effects of salts on the solubility of nonelectrolytes in water. None of the theories takes into account the interaction between electrolytes and nonelectrolytes, even though many nonelectrolytes compete with water as ligands for the cations.

Keyphrases ☐ Surfactants, nonionic—effect of inorganic additives, cloud points, salting-in and salting-out process ☐ Electrolytes—effect on cloud points of nonionic polyoxyethylated surfactants ☐ Urea—effect on cloud points of nonionic polyoxyethylated surfactants ☐ Inorganic additives—effect on solutions of nonionic surfactants ☐ Cloud points—effect of inorganic additives

Aqueous solutions of polyoxyethylated nonionic surfactants, and of polyethylene glycols which constitute their hydrophilic moiety, have an upper consolute temperature called the cloud point. Being more soluble in cold than in hot water leads to reversible phase separation on heating, and the solutions turn quite cloudy at that temperature (1–5).

Cloud points are of practical importance. Suspensions or emulsions stabilized by adsorbed nonionic surfactants tend to coagulate or coalesce, respectively, when the systems are heated to temperatures in the vicinity of the cloud point (5). This may occur, for instance, during sterilization by autoclaving. Subsequent cooling frequently fails to regenerate stable suspensions or emulsions.

Cloud points are independent of surfactant concentration between relatively wide limits (5, 6) but are markedly affected by some additives (7–10). Additives that raise cloud points salt in the polyoxyethylated compounds. By increasing the upper consolute temperature, they extend the temperature range over which homogeneous undersaturated single-phase solutions prevail.
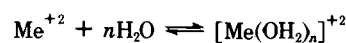
DISCUSSION

The following equilibria are involved in the interactions that occur in the ternary system of water–electrolyte–polyoxyethylated compound, where the latter is represented by the ether linkage R_1—O—R_2:
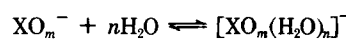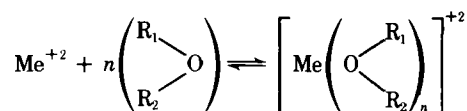
$$(H_2O)_n \rightleftharpoons nH_2O$$
Scheme I

Scheme II

$$Me^{+2} + nH_2O \rightleftharpoons [Me(OH_2)_n]^{+2}$$
Scheme III
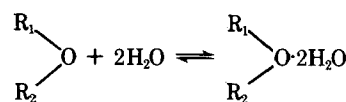
$$XO_m^- + nH_2O \rightleftharpoons [XO_m(H_2O)_n]^-$$
Scheme IV

Scheme V

Most publications on the interaction of inorganic electrolytes with aqueous solutions of polyethylene glycols (2) and polyoxyethylated nonionic surfactants (7–10) report salting out or cloud point lowering via dehydration, as predicted by theory (11, 12). The competition for water of hydration between an electrolyte (Scheme III for a divalent cation and Scheme IV for a monovalent, oxygenated anion) and the polyoxyethylated compound (Scheme V) leads to precipitation of the latter. An ether linkage binds up to two water molecules (13).

The following few instances of salting in or cloud point increases by electrolytes were reported for nonionic polyoxyethylated surfactants prior to publication of Part I of the present series (14). Large anions such as thiocyanate and iodide (9, 15–17), which are polarizable and constitute soft bases in Pearson's nomenclature (18), as well as perchlorate (17), which constitutes a hard base, are effective in destructuring water. They increase the hydration of polyoxyethylated compounds (Scheme II) by promoting the depolymerization of water (Scheme I). Acids (7, 9) and the nitrates of beryllium, magnesium, and calcium (15) also raised the cloud points of a nonionic surfactant, but the mechanism was disputed (15, 19).

A systematic investigation of the effect of cations on the cloud points of aqueous solutions of a branched octylphenol with 10 ethylene oxide units (Surfactant I)[1] and of an ethylene oxide polymer with an average degree of polymerization of 340–455 was made, using mostly nitrates. The nitrate ion has little or no tendency to act as a ligand for the cation, as opposed to the chloride ion. The results showed the importance of complexation of the cations by the ether linkages as represented by Scheme V. All cations that form complexes with model ethers such as dioxane, ethyl ether, and cineole (20–23) salted the two polyoxyethylated compounds in, increasing their cloud points. Included among the complexing

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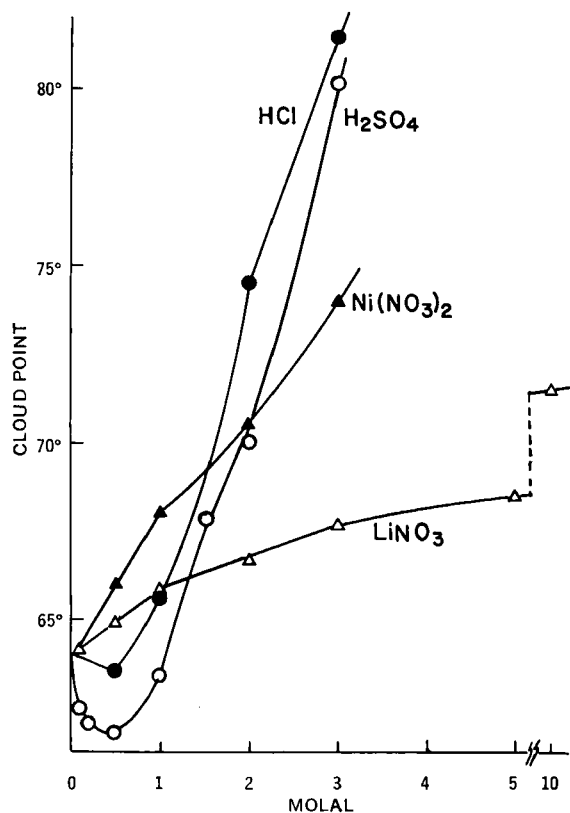
[1] Triton X-100, Rohm and Haas Co.

Figure 1—*Cloud point of a 1.00% solution of Surfactant II as a function of the molal concentrations of added electrolytes.*
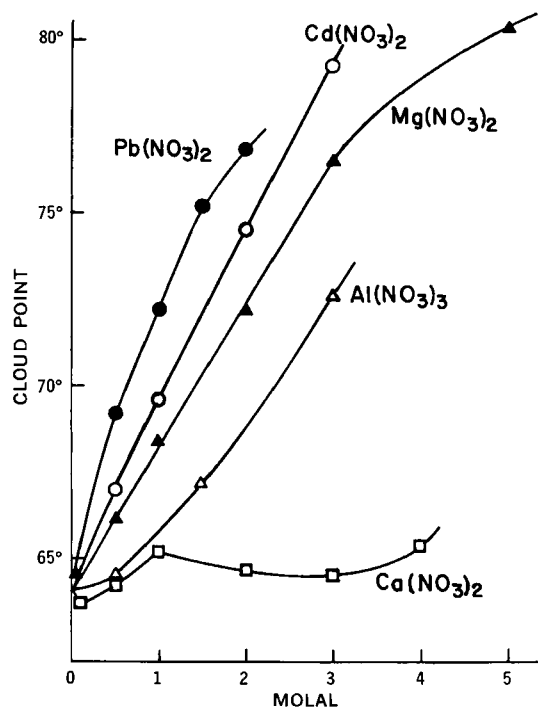

Figure 2—*Cloud point of a 1.00% solution of Surfactant II as a function of the molal concentrations of added electrolytes.*

The surfactant level was 1%. The concentration used for the alkylaryl surfactant in the previous study was 2% (14), but this difference caused only small differences in the cloud point (5, 6).

The methods for assaying the electrolyte content of the concentrated stock solutions, for preparing the ternary mixtures, and for measuring the cloud points are described in Ref. 14 with the following exception. The concentrated stock solutions of sodium bromide, iodide, and sulfate and of potassium and cesium nitrate were analyzed by drying aliquots to constant weight.

RESULTS

The effect of electrolytes on the cloud points of the polyoxyeth-

cations were hydrogen, lithium, and all di- and trivalent cations tested. Only the monovalent cations sodium, potassium, and ammonium, whose salts do not form stable complexes with dioxane and other model ethers, lowered the cloud points of the two polyoxyethylated compounds because the cations could not form complexes with the ether oxygens of the latter. Salting out by electrolytes was found to be the exception rather than the rule, as had previously been thought (1-5, 8-12). Since dioxane can act as a bidentate ligand for cations (23), the flexible polyoxyethylene chains with their many ether linkages probably act as polydentate ligands in the complexation of the cations according to Scheme V (14).

The purpose of the present work was to extend the study of the effect of electrolytes on the cloud points of polyoxyethylated nonionic surfactants whose hydrophobic moiety is a normal alkyl chain rather than a branched alkylaryl group as in Surfactant I. By comparing the behavior of purely aliphatic derivatives with that of an aliphatic–aromatic compound, it is possible to determine whether the aromatic ring produces specific effects in the interaction between electrolytes and nonionic surfactants. Alkali salts of anions capable of breaking and of enhancing the iceberg structure of water were also included. The results for the various compounds can be used to evaluate current theories of salt effects on nonelectrolyte solutions (11, 12).

EXPERIMENTAL

The aliphatic surfactants were ethylene oxide adducts of cetyl, stearyl, and oleyl alcohols containing an average of 10 ethylene oxide units[2]. The stearyl derivative was a waxy solid, and the other two compounds were viscous liquids or semisolids, depending on the room temperature. The properties of the four nonionic surfactants are summarized in Table I. Water was double distilled. Urea was NF grade, and all other chemicals were ACS reagent grade.

The concentrations of the ternary mixtures are expressed as molality or as percent (w/w) based on the amount of water present.
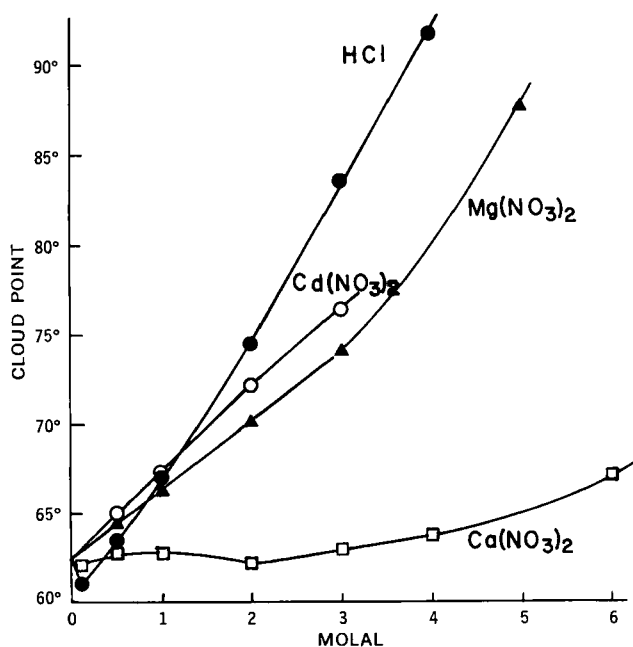

Figure 3—*Cloud point of a 1.00% solution of Surfactant III as a function of the molal concentrations of added electrolytes.*

[2] Supplied by I.C.I. America (formerly Atlas Chemical Co.) as Brij 56, 76, and 96, respectively.

Table I—Properties of Nonionic Surfactants Employed in the Study of Electrolyte Effects

Surfactant Number (and Formula)	Hydrophobic Moiety	Number of Ethylene Oxide Units	HLB	Cloud Point[a]	Critical Micelle Concentration at 25°	
					g/liter	moles/liter × 10⁶
I [C₈H₁₇—C₆H₄O(CH₂CH₂O)₁₀H]	Branched octylphenol	9–10	13.4	65°	0.16	256
II [C₁₆H₃₃O(CH₂CH₂O)₁₀H]	Cetyl alcohol	10	12.9	64°	—	—
III [C₁₈H₃₇O(CH₂CH₂O)₁₀H]	Stearyl alcohol	10	12.4	62.5°	—	—
IV [C₁₈H₃₅O(CH₂CH₂O)₁₀H]	Oleyl alcohol	10	12.4	54°	0.065	92

[a] At 1% (w/w).

Table II—Electrolyte Concentrations Required to Raise the Cloud Points of Surfactant Solutions by 10°, in Order of Decreasing Effectiveness for Salting In

Surfactant I[a]		Surfactant II[b]		Surfactant III[b]		Surfactant IV[b]	
Electrolyte	Molality	Electrolyte	Molality	Electrolyte	Molality	Electrolyte	Molality
Pb(NO₃)₂	0.68	Pb(NO₃)₂	1.30	HCl	1.75	Pb(NO₃)₂	1.72
Cd(NO₃)₂	1.31	Cd(NO₃)₂	1.90	Pb(NO₃)₂	1.78	Cd(NO₃)₂	1.72
HCl	1.47	HCl	1.95	Cd(NO₃)₂	2.09	HCl	1.89
Mg(NO₃)₂	1.55	Mg(NO₃)₂	2.38	Al(NO₃)₃	2.19	H₂SO₄	2.07
H₂SO₄	1.70	H₂SO₄	2.40	H₂SO₄	2.24	Mg(NO₃)₂	2.07
Al(NO₃)₃	1.86	Ni(NO₃)₂	3.00	Mg(NO₃)₂	2.63	Al(NO₃)₃	3.00
Ni(NO₃)₂	2.0	Al(NO₃)₃	3.35	Ni(NO₃)₂	3.06	Ni(NO₃)₂	3.06
LiNO₃	4.6	LiNO₃	>10	LiNO₃	—	LiNO₃	10.7
Ca(NO₃)₂	4.7	Ca(NO₃)₂	—	Ca(NO₃)₂	—	Ca(NO₃)₂	—

[a] At 2% (w/w). [b] At 1% (w/w).

ylated surfactants is presented in two parts. Salts of cations that form coordination compounds with ethers are discussed first, followed by salts of cations that do not form such complexes. Urea is included in the second category.

Salting In by Complexation—Table I of Ref. 14 lists the salts of all polyvalent and of most monovalent cations used in the present study, together with their stable solid complexes in which dioxane or dioxane plus water are the ligands. Dioxane was chosen as the model ether because its adducts are more stable than those of ethyl and other monofunctional ethers (20, 21). Dioxane can act as a bidentate ligand. Hydrogen, lithium, magnesium, calcium,

nickel, cadmium, aluminum, and lead form complexes with ethers. The effect of their nitrates on the cloud points of Surfactants II–IV is shown in Figs. 1–6. Hydrochloric and sulfuric acids were chosen over nitric acid to avoid oxidative degradation of the surfactants.

The effectiveness of the various electrolytes in salting in the four nonionic surfactants is rated according to two criteria. In Table II, the interpolated electrolyte concentrations required to boost the cloud point of the nonionic surfactant solutions by 10° are listed in increasing order. In Table III, the interpolated increases in cloud point achieved by the additives at the 2-molal level are listed in decreasing order. Cloud points in the presence (14) and absence (5, 6, 8) of additives were insensitive to surfactant concentrations between 1 and 4% (w/w). Since some of the cloud point–electrolyte concentration curves cross over one another, the two criteria do
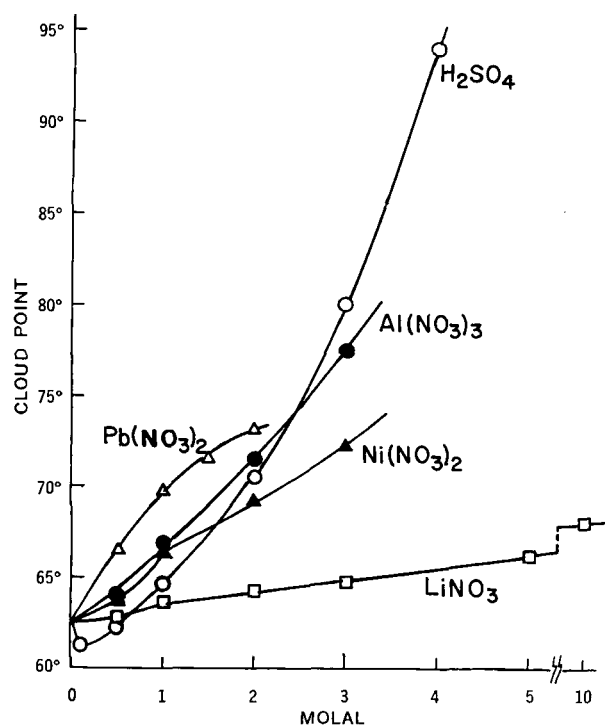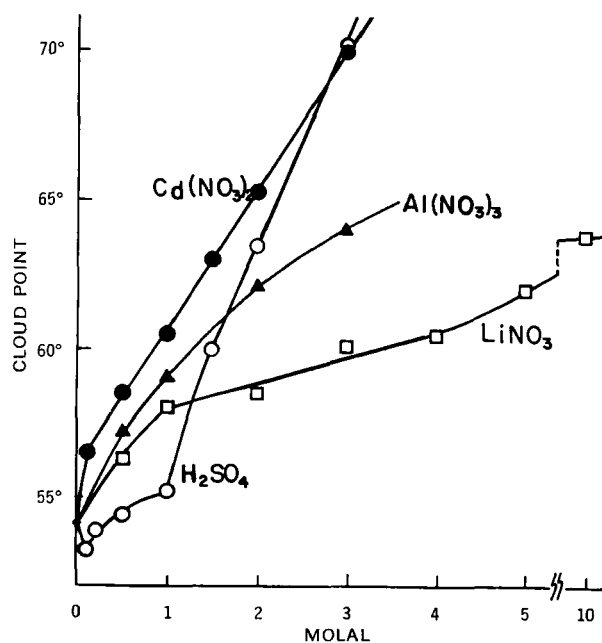

Figure 4—Cloud point of a 1.00% solution of Surfactant III as a function of the molal concentrations of added electrolytes.

Figure 5—Cloud point of a 1.00% solution of Surfactant IV as a function of the molal concentrations of added electrolytes.

Table III—Cloud Point Increases Produced by Salting-In Electrolytes at
2-Molal Concentrations, in Order of Decreasing Effectiveness

Surfactant I[a]		Surfactant II[b]		Surfactant III[b]		Surfactant IV[b]	
Electrolyte	ΔC.P.[c]	Electrolyte	ΔC.P.[c]	Electrolyte	ΔC.P.[c]	Electrolyte	ΔC.P.[c]
HCl	15.0°	$Pb(NO_3)_2$	12.9°	HCl	12.0°	HCl	11.4°
$Pb(NO_3)_2$	14.6°	$Cd(NO_3)_2$	10.5°	$Pb(NO_3)_2$	10.7°	$Cd(NO_3)_2$	11.3°
H_2SO_4	14.5°	HCl	10.5°	$Cd(NO_3)_2$	9.6°	$Pb(NO_3)_2$	11.2°
$Cd(NO_3)_2$	14.3°	$Mg(NO_3)_2$	8.2°	$Al(NO_3)_3$	9.0°	$Mg(NO_3)_2$	9.7°
$Mg(NO_3)_2$	12.5°	$Ni(NO_3)_2$	6.5°	H_2SO_4	8.0°	H_2SO_4	9.5°
$Al(NO_3)_3$	10.4°	H_2SO_4	6.0°	$Mg(NO_3)_2$	8.0°	$Al(NO_3)_3$	8.1°
$Ni(NO_3)_2$	9.9°	$Al(NO_3)_3$	4.8°	$Ni(NO_3)_2$	6.7°	$Ni(NO_3)_2$	7.1°
$LiNO_3$	6.1°	$LiNO_3$	2.7°	$LiNO_3$	1.7°	$LiNO_3$	4.5°
$Ca(NO_3)_2$	2.0°	$Ca(NO_3)_2$	0.7°	$Ca(NO_3)_2$	-0.3°	$Ca(NO_3)_2$	-0.3°

[a] At 2% (w/w). [b] At 1% (w/w). [c] ΔC.P. = cloud point in 2-molal electrolyte solution minus cloud point in water.

not rank all electrolytes in the same order of salting-in efficacy even for a single surfactant. The overall order is lead nitrate > hydrochloric acid > cadmium nitrate > sulfuric acid ≅ magnesium nitrate > aluminum nitrate > nickel nitrate > lithium nitrate > calcium nitrate.

Of the four nonionic surfactants, I was salted in the most extensively and II the least. Surfactant I required less electrolyte for a 10° boost in cloud point than II, and 2-molal electrolytes raised its cloud point more than that of II. Surfactant IV was somewhat more extensively salted in than III. This difference between the four surfactants is not due to differences in the hydrophilic-lipophilic balance (HLB) since Surfactant I has the highest value and III and IV have the lowest. Moreover, the four HLB values differ by one unit only.

Apparently, the presence of the benzene ring enhanced the ability of Surfactant I to be salted in by the electrolytes. This conclusion is tentative because the cloud point of surfactants with a given hydrophobic moiety depends not only on the HLB but on the chain-length distribution of the ethylene oxide moiety as well (6). Since Surfactants I and II–IV were supplied by two different manufacturers, their polyoxyethylene chain-length distribution may well differ due to different ethoxylation conditions. Another differ-

ence is that the alkyl group of Surfactant I is branched while those of Surfactants II–IV are normal. Branching affects the cloud point (6) and may also affect the increase in cloud point by complexation with cations.

Salting In and Out by Noncomplexing Additives—Of the cations studied in Part I (14) and in the present work, only sodium, potassium, ammonium, and cesium do not form stable solid adducts with ethers (20–23). Salts of these cations as a rule salt out nonelectrolytes, except if the anions are effective structure breakers for water such as iodide, thiocyanate, and perchlorate (9, 15–17, 24). The influence of these salts on the cloud points of the nonionic surfactants will be described. Another compound well known for its ability to break the structure of water and to weaken hydrophobic bonds, namely, urea (25), was also included.

The data for Surfactants II–IV are plotted in Figs. 7–9. The effectiveness of the various noncomplexing additives in salting the four surfactants in or out are rated according to the same two criteria used for the salting-in effectiveness of the complexing electrolytes. Table IV lists the additive concentrations required to raise or lower the cloud points by 10°, while Table V lists the increases or decreases in cloud points achieved by the additives at the 2-molal level.

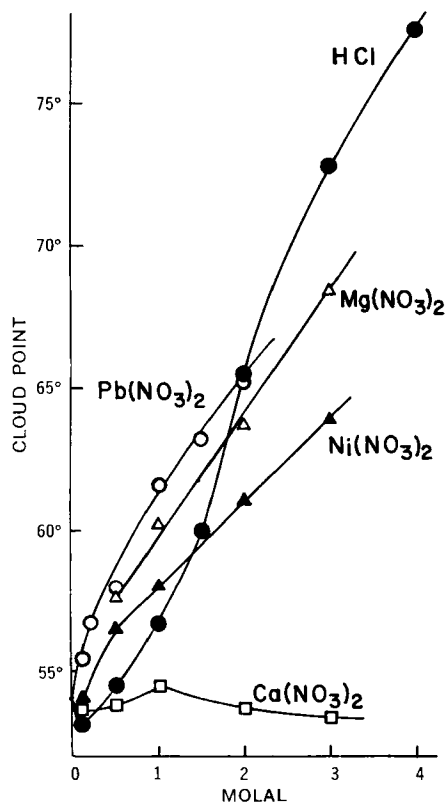Surfactant I was only slightly more susceptible to salting out by

Figure 6—Cloud point of a 1.00% solution of Surfactant IV as a function of the molal concentrations of added electrolytes.
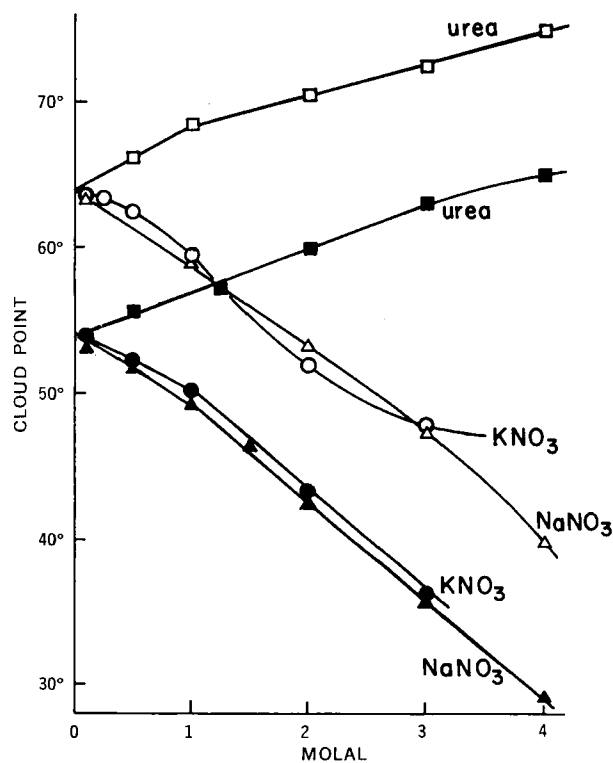
Figure 7—Effect of the concentrations of noncomplexing additives on the cloud point of 1.00% solutions of Surfactant II (open symbols) and Surfactant IV (dark symbols).

Table IV—Additive Concentrations Required to Raise or Lower the Cloud Points of Surfactant Solutions by 10°, in Order of Decreasing Effectiveness for Salting In or Increasing Effectiveness for Salting Out

Surfactant I[a]		Surfactant II[b]		Surfactant III[b]		Surfactant IV[b]	
Additive		Additive	Molality for 10° Increase	Additive	Molality for 10° Increase	Additive	Molality for 10° Increase
—		Urea	3.64	NaClO₄	0.50	Urea	3.41
				NaI	1.87		
				Urea	4.80		
	Molality for 10° Reduction		Molality for 10° Reduction		Molality for 10° Reduction		Molality for 10° Reduction
NaNO₃	1.58	NaNO₃	1.86	CsNO₃	2.13	KNO₃	1.91
		KNO₃	1.65	NaBr	2.00	NaNO₃	1.89
				NaNO₃	1.90		
				KNO₃	1.87		
				NaCl	0.71		
				Na₂SO₄	0.20		
				Na₂SO₄[c]	0.50		

[a] At 2% (w/w). [b] At 1% (w/w). [c] At ionic strength equivalent to 2 molal NaCl.

sodium nitrate than the other three. It required a somewhat lower salt concentration to reduce the cloud point by 10°, and 2-molal sodium nitrate lowered its cloud point by only 1–2° more than those of the other three surfactants.

The differences in the salting-out efficacy among the nitrates of the noncomplexing alkali metals are rather small. The cations are ranked in the order $Na^+ \simeq K^+ > Cs^+$. The differences in the ability of the various anions to salt the nonionic surfactants in or out and the resulting spread in cloud points are far greater than the differences in the ability of the three noncomplexing cations to salt them out. This is shown by comparing the effect of the various sodium salts on the cloud points. The order of decreasing efficacy for salting in or increasing efficacy for salting out is sodium perchlorate > sodium iodide > sodium bromide $\simeq$ sodium nitrate > sodium chloride > sodium sulfate. The spread in the cloud point of

Surfactant III in the presence of these six salts exceeds 50°. The great influence of the anions on the process of salting in or out was also observed by Schick (9) and Saito (17). The order of efficacy of the anions is that of the Hofmeister or lyotropic series (26). The lower the lyotropic numbers of the anions, the greater is their ability to reduce the cloud point (9).

The three noncomplexing cations are also ranked according to the lyotropic series, but lithium and the polyvalent cations, which form complexes with the ether oxygens, are located *ipso facto* at the wrong end of that series. Urea raised the cloud points, as expected in view of its ability to reduce the structure of water.

THEORY

The present study provides a large body of data on the salting in and salting out of four nonelectrolytes by a variety of electrolytes. Each nonelectrolyte consists of a nonpolar hydrocarbon moiety and of a polar polyoxyethylene moiety. It is of interest to use these data to evaluate current theories of the effects of electrolytes on the solubility of nonelectrolytes.

Electrostatic Theories—The electrostatic theories of Debye and McAulay and of Debye (11, 12, 27) describe salting in and out in terms of dielectric effects. They predict that a given nonelectrolyte is salted in by all electrolytes if it raises the dielectric constant of the solvent. If it lowers the dielectric constant, it is salted out by all electrolytes. The electrostatic theories do not cover the present
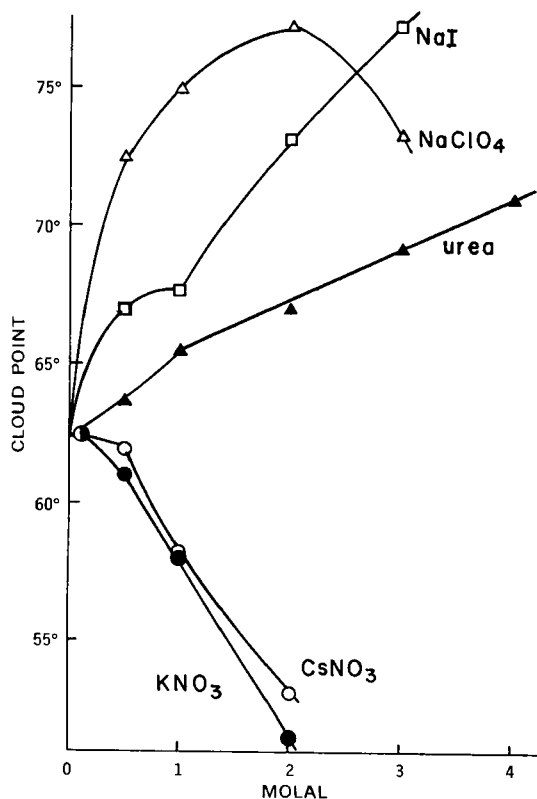
Figure 8—*Effect of the concentrations of noncomplexing additives on the cloud point of a 1.00% solution of Surfactant III.*
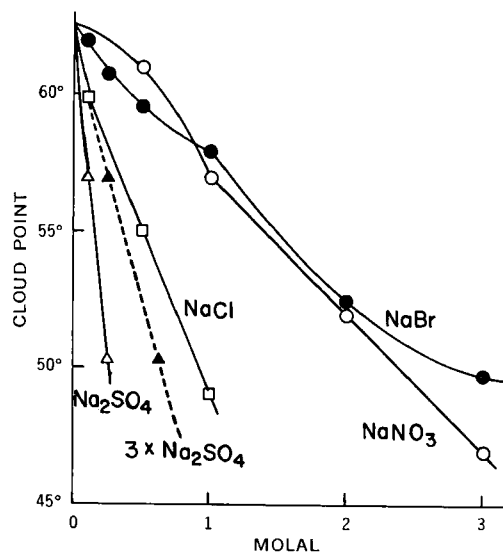
Figure 9—*Effect of the concentrations of noncomplexing electrolytes on the cloud point of a 1.00% solution of Surfactant III.*

Table V—Cloud Point Increases or Decreases Produced by Additives at 2-Molal Concentrations, in Order of Decreasing Effectiveness for Salting In or Increasing Effectivenes for Salting Out

Surfactant I[a]		Surfactant II[b]		Surfactant III[b]		Surfactant IV[b]	
Additive	ΔC.P.[c]	Additive	ΔC.P.[c]	Additive	ΔC.P.[c]	Additive	ΔC.P.[c]
		Urea	6.5°	$NaClO_4$	14.7°	Urea	6.0°
				NaI	10.7°		
				Urea	4.5°		
$NaNO_3$	−13.0°	$NaNO_3$	−10.8°	$CsNO_3$	−9.4°	KNO_3	−11.0
		KNO_3	−12.0°	NaBr	−10.0°	$NaNO_3$	−11.8°
				$NaNO_3$	−10.5°		
				KNO_3	−11.0°		
				NaCl	≈ −25.5°		
				Na_2SO_4	< −55°		
				Na_2SO_4[d]	≈ −37°		

[a] At 2% (w/w). [b] At 1% (w/w). [c] ΔC.P. = cloud point in 2-molal additive minus cloud point in water. [d] At ionic strength equivalent to 2 molal NaCl.

case where some electrolytes raised the cloud points of the polyoxyethylated surfactants, salting them in, whereas other electrolytes of the same valence lowered the cloud points, salting them out. The electrostatic theories are inadequate, because they fail to consider the electrolyte–nonelectrolyte interactions represented by Scheme V, as well as the complex structure of water, which causes certain anions to interfere with the process represented by Scheme I.

Internal Pressure Theories—The internal pressure concept was applied to salting out and in as follows (11, 28). The ion–water interaction of dissolved electrolytes causes electrostriction of water, increasing its internal pressure. When salts are added to the aqueous solution of nonelectrolytes, the increase in internal pressure tends to squeeze out the nonelectrolyte molecules from the solution, reducing their solubility or salting them out. The extent of electrostriction of water by an electrolyte can be represented by the difference between the molal volume of the pure "liquid" electrolyte, V_e, and the partial molal volume of the electrolyte at infinite dilution, $\bar{V}_e^0$.

The relationship derived by McDevit and Long (11, 28) is:

$$\ln \frac{S_n^0}{S_n} = \left[\frac{\bar{V}_n^0 (V_e - \bar{V}_e^0)}{\beta RT} \right] C_e \qquad (Eq.\ 1)$$

where S_n^0 and S_n are the solubilities of the nonelectrolyte in water and in an electrolyte solution, respectively; β is the compressibility of water; C_e is the molar electrolyte concentration: and $\bar{V}_n^0$ is the partial molal volume of the nonelectrolyte at infinite dilution. The nonelectrolyte molecules modify the ion–water interaction merely by occupying volume, and the extent of salting in or out increases with their molecular size. Accordingly, the theory should be applied only to nonpolar solutes, because they have scant affinity toward water and electrolytes, but it was found to hold approximately for polar solutes as well (11).

According to Eq. 1, if $V_e > \bar{V}_e^0$, the solvent medium is compressed by the electrolyte and $S_n^0 > S_n$, i.e., salting out occurs. If $\bar{V}_e^0 > V_e$, the ions loosen the medium and the nonelectrolyte is salted in.

By combining V_e values obtained indirectly with $\bar{V}_e^0$ values, the difference $V_e - \bar{V}_e^0$ was found to be positive for most electrolytes reported, including hydrochloric acid, lithium chloride, lithium iodide, sodium perchlorate, sodium iodide, barium chloride, and cerium (III) chloride (28, 29). Since these salts either raised the cloud points of the nonionic surfactants or are expected to do so in the light of the present results, the internal pressure theory does not have the general application with which it is often credited.

In their review paper on salt effects, Long and McDevit discussed the change in the order of the cations found with basic polar nonelectrolytes like ammonia and trimethylamine as compared to the order for nonpolar nonelectrolytes. They correctly ascribed the inversion in the salting-in and salting-out order observed with the former to chemical interaction between the cations and the nonelectrolytes, specifically, to complex ion formation (11).

Hydration Theories—Hydration theories and theories based on the role of water structure in the salting in and out of nonelec-

trolyes by electrolytes (11, 30, 31) are either not general enough or not explicit enough to describe the present data.

Conclusions—None of the existing theories of salting in and out adequately describes the effects of electrolytes on polyoxyethylated compounds dissolved in water, mainly because they neglect electrolyte–nonelectrolyte interactions. Many nonelectrolytes are capable of acting as ligands for cations in aqueous solution, in competition with water. Thus, a comprehensive theory would have to include all five simultaneous processes represented by Schemes I–V.

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Drug Absorption VII: Influence of Mesenteric Blood Flow on Intestinal Drug Absorption in Dogs

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Abstract □ Intestinal absorption of sulfaethidole and haloperidol was determined using an *in situ* canine intestinal preparation. Intestinal absorption of sulfaethidole was determined at three or four mesenteric blood flow rates in each dog, ranging from unaltered flow (100%) to no flow (0%). A relatively small change in absorption rate occurred when the splanchnic blood flow rate was decreased about 35%. Further reductions in mesenteric blood flow resulted in progressive impairment of sulfaethidole absorption. The simultaneous measurement of sulfaethidole intestinal disappearance and appearance in blood indicates that sulfaethidole disappearance is equivalent to absorption. Haloperidol absorption also decreased with decreased intestinal perfusion but differed from sulfaethidole in that membrane storage of haloperidol appeared to take place during its absorption.

Keyphrases □ Absorption, drug—influence of mesenteric blood flow on intestinal absorption of sulfaethidole and haloperidol, *in situ* canine intestinal preparation □ Drug absorption—influence of mesenteric blood flow on intestinal absorption of sulfaethidole and haloperidol, *in situ* canine intestinal preparation □ Sulfaethidole—influence of mesenteric blood flow on intestinal absorption, *in situ* canine intestinal preparation □ Haloperidol—influence of mesenteric blood flow on intestinal absorption, *in situ* canine intestinal preparation □ Blood flow, mesenteric—influence on intestinal absorption of sulfaethidole and haloperidol, *in situ* canine intestinal preparation

Interest in the influence of blood flow on the GI absorption rate of drugs was stimulated by the observation (1) that periods of fasting greater than 17 hr in rats resulted in decreased rates of drug absorption. This decrease in absorption was accompanied by a concomitant blanching of the intestine, which became more pronounced with longer fasting periods. The observed changes appeared to be due to changes in intestinal blood perfusion (2).

There are many documented cases of pathological conditions leading to decreased intestinal blood perfusion. One study (3) showed that experimentally induced ventricular and supraventricular tachycardias can cause mean superior mesenteric blood flow to drop nearly 40%. Other investigators (4) reported that hemorrhagic necrosis, infarction, and gangrene of the intestinal tract secondary to decreased splanchnic perfusion may result from rapid tachycardia. A high association was reported (5) between congestive heart failure and nonobstructive intestinal ischemia. In one case, intestinal ischemia resulting from congestive heart failure produced digoxin malabsorpion severe enough to make the patient's clinical condition difficult to control (6). Intramuscular administration of digitoxin produced marked improvement in the patient. These reports suggest that the absorption of vital drugs in patients with circulatory pathology may be dangerously reduced.

BACKGROUND

It has long been known that heat and exercise produce a significant reduction in splanchnic blood flow (7–9). A study with five volunteers found that light exercise for 7–8 min decreased splanchnic blood flow by 20% (8). A fall in hepatic and splanchnic blood flow, sometimes in excess of 80%, during severe exertion was clearly demonstrated (9). Thus, it is conceivable that drug absorption following three sets of tennis or during strenuous exercise on the job could be quite different from that encountered under more restful circumstances. In this regard, exercise in a hot environment significantly decreased the absorption of 3-*O*-methylglucose but not D-xylose (10). Thus, exercise or the lack of it during bioavailability studies (studies of drug product performance) could greatly influence the apparent availability and rate of absorption of the product.

The interaction between the circulation and intestinal absorption is complex; blood flow influences absorption, but the reverse also holds true. Digitalis has been shown to be a potent splanchnic vasoconstrictor, and cardiac glycosides have precipitated intestinal necrosis (11). A reduction in splanchnic blood flow of 30–40% was found in human volunteers following a 0.25-mg dose of ouabain (12). The same effect appears to be true for digitalis (12).

The use of oral contraceptives in women also appears to affect significantly the mesenteric blood flow. Numerous reports have appeared in the last 10 years (13–15) linking the use of oral contraceptives in women to decreased intestinal blood flow. Of 24 collected cases of ischemic disease of the colon in younger persons, six were women taking oral contraceptives (13). The role of oral contraceptives in vascular diseases is unclear, and possible associated