

# Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapal (Triton WR-1339)

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The surface-chemical properties, critical micelle concentrations (CMC), and effect of salts on the cloud points (CP) of octoxynol 9 (Triton X-100) and tyloxapal (Triton WR-1339) were compared. The latter nonionic surfactant is essentially a heptamer of the former. Even though the molecular weight of tyloxapal is 7 times larger than that of octoxynol 9, its area per molecule adsorbed at the air–water interface is only twice as large. This suggests an unusual orientation for molecules of tyloxapal at the surface and is in keeping with a plateau that is less horizontal and has a somewhat higher surface tension than the plateaus of most nonionic surfactants. The CMC of octoxynol 9 was 4.4 times larger than that of tyloxapal. Unexpectedly, the CP of dilute aqueous tyloxapal solutions was 28°C higher than that of octoxynol 9 solutions. The salting-out ions Na<sup>+</sup>, Cl<sup>-</sup> and SO<sub>4</sub><sup>2-</sup> lowered the CP of tyloxapal 29% more than that of octoxynol 9. However, because the blank tyloxapal solution started out with a higher CP value, its CPs in the presence of salts were higher than those of octoxynol 9. Pb<sup>2+</sup> and Mg<sup>2+</sup> cations salted both surfactants in, raising their CP, Pb<sup>2+</sup> more extensively than Mg<sup>2+</sup>. © 1998 Academic Press

**Key Words:** cloud points of octoxynol 9 and tyloxapal; critical micelle concentrations of octoxynol 9 and tyloxapal; octoxynol 9; oligomeric nonionic surfactant; salt effects on cloud points of octoxynol 9 and tyloxapal; surface tensions of octoxynol 9 and tyloxapal; Triton X-100; tyloxapal.

## INTRODUCTION

Tyloxapal (Triton WR-1339) is a nonionic surfactant whose study is of practical and theoretical interest. Its practical usefulness stems from the fact that it is official in the USP employed not only as a detergent in preparations for cleaning contact lenses but also as a mucolytic agent in preparations for treating pulmonary diseases (1, 2). It interacts with plasma lipoproteins (3, 4), which rules out its use in injectable preparations.

Tyloxapal is essentially an oligomer of octoxynol 9 (Triton X-100). Comparison with its monomer is of physicochemical importance. The effects of polymerization on the solution properties of monomeric surfactants have not been investigated beyond their dimers (5) and trimers (6),

whereas tyloxapal is essentially a heptamer of octoxynol 9 (see below).

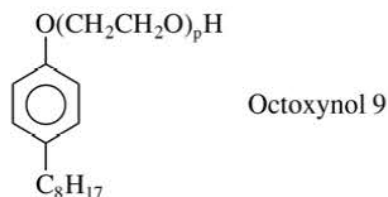
The purpose of the present study is to compare the surface activity and the critical micelle concentration (CMC) of the two nonionic surfactants and their interaction with electrolytes. Such interaction is conveniently investigated by changes in cloud point (CP). Extensive data on the effect of electrolytes on the CP of octoxynol 9 have been published (7). The CP is the lower consolute temperature of nonionic surfactant solutions. It is a sensitive indicator of their interaction with additives.

The practical importance of the CP lies in the fact that suspensions (8), emulsions (9), and ointments and foams (10) stabilized with nonionic surfactants become unstable when heated in the vicinity of the CP, e.g., during manufacturing, steam sterilization, or some end uses. On the other hand, the rate of solubilization by nonionic surfactant solutions increases near their CP (11).

## EXPERIMENTAL

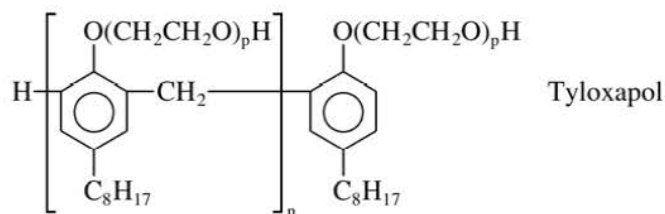
### Materials

Octoxynol 9 NF is *p*-octylphenol ethoxylated to an average *p* value of 9.5. The octyl moiety is 1,1,3,3-tetramethylbutane; i.e., it is an isobutylene dimer:



The molecular weight of octoxynol 9 is  $\cong 625$ . Subsequently, this compound is referred to simply as octoxynol.

Tyloxapal USP is made by treating an excess of octylphenol with formaldehyde in the presence of an acid catalyst, which causes condensation polymerization via methylene bridges in the ortho position. The resulting novolac oligomer is then ethoxylated to an average *p* value of  $9.6 \pm 0.1$  (1, 2):



Its molecular weight of 4500 (4) corresponds to an average  $n$  value of 6: Tyloxapol is a heptamer. Despite the methylene bridges, it has practically the same hydrophilic-lipophilic balance as octoxynol (see Table 1). The tyloxapol sample used, Aldrich Lot No. 05907 TG, had a moisture content of 0.42% determined by drying over  $P_2O_5$ .

Measurements with octoxynol were made with Triton X-100 Lot No. 1S682323, a gift of Union Carbide Corp., except for the previously published values quoted in the tables, which are based on other lots. All other chemicals were ACS grade. The water was double distilled.

#### Surface Tension Measurements

Two tyloxapol stock solutions containing 1.138 and 3.944 g/L, respectively, were equilibrated for  $\geq 24$  h. Volumetric aliquots were diluted to 100 ml in volumetric flasks. To prevent depletion of surfactant from the diluted solutions by adsorption onto the glass surfaces of the volumetric flasks and of the crystallizing dishes used to measure surface tensions, both types of glassware were prerinsed with surfactant solutions of the intended final concentrations. By presaturating the glass surfaces with the equilibrium amount of adsorbed surfactant corresponding to each final concentration, no surfactant was adsorbed onto glass from the final solutions used to measure surface tensions.

TABLE 1  
Comparison of Some Physical Properties  
of Octoxynol 9 and Tyloxapol

Property	Octoxynol 9	Tyloxapol
HLB <sup>a</sup>	13.4	13.2
Molecular weight of monomer	625	4500 <sup>b</sup>
Micellar molecular weight	86,000 <sup>c</sup>	180,000 <sup>b</sup>
$-d\gamma/d \ln c$ at saturation adsorption (dyne/cm) <sup>d</sup>	7.62	3.89
Area per molecule in air-water interface at saturation adsorption ( $\text{\AA}^2$ ) <sup>d</sup>	54	105
Critical micelle concentration (g/L)	0.17	0.038 <sub>s</sub>
Cloud point of 2.00% surfactant solution ( $^{\circ}\text{C}$ )	65.5	93.8

<sup>a</sup> Hydrophilic-lipophilic balance, defined as 1/5 of the weight-percent of ethylene oxide.

<sup>b</sup> Reference (4).

<sup>c</sup> Reference (13).

<sup>d</sup> Defined by Eq. [1].

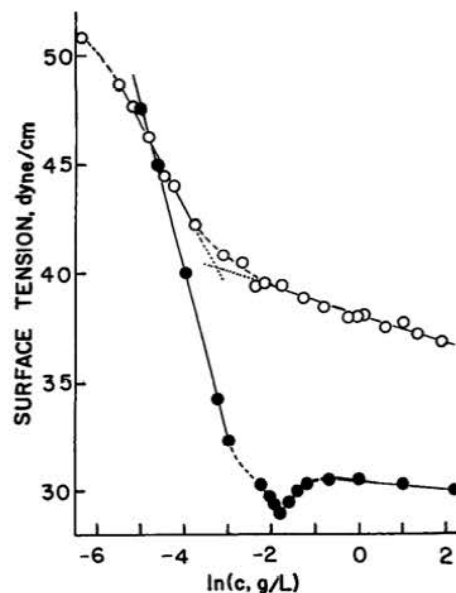


FIG. 1. Surface tension versus the natural logarithm of concentration  $c$  for tyloxapol at  $22 \pm 1^{\circ}\text{C}$  (empty circles) and for octoxynol 9 at  $25.0 \pm 0.2^{\circ}\text{C}$  (full circles). The regions of saturation adsorption and plateau surface tension are shown as solid lines.

This precaution was required by the low CMC value of tyloxapol and the even lower surfactant concentrations in the saturation adsorption region. Without the prerinses, the negative value of the slope of the linear segment of the surface tension versus  $\ln$  concentration curve in Fig. 1 corresponding to the saturation adsorption region would have been increased by  $>10\%$ . This increase would have lowered the CMC by a mere  $\geq 4\%$ . However, it would have lowered the area  $A$  per surfactant molecule adsorbed at surface saturation by  $>10\%$  according to the Gibbs adsorption equation,

$$A = - \frac{RT}{N_{Av}} \frac{1}{d\gamma/d \ln c}, \quad [1]$$

because this area is inversely proportional to  $d\gamma/d \ln c$ . In this equation,  $R$  is the gas constant,  $T = 295^{\circ}\text{K}$ ,  $N_{Av}$  is Avogadro's number,  $\gamma$  is the surface tension in dyne/cm, and  $c$  is the surfactant concentration in g/L.

Prior to measurement of their surface tensions, the surfaces of the diluted solutions were cleaned by suction with glass capillaries, and the solutions were equilibrated for  $\geq 2$  h at  $22 \pm 1^{\circ}\text{C}$ . Surface tensions were measured by means of a Wilhelmy balance (Rosano surface tensiometer, VWR Scientific) equipped with a thin, rectangular, sand-blasted platinum blade. The instrument was calibrated with water and benzene.

### Cloud Point Measurements

The surfactant–salt mixtures used for CP measurements were prepared by adding analyzed, concentrated salt solutions and water to 15.0% stock solutions of surfactant. All liquids were weighed out to the nearest milligram. The final surfactant concentration was 2.00% unless specified otherwise. The percentage is based on the weight of water present. The mixtures were aged  $\geq 24$  h at room temperature in the dark prior to measuring their CP.

CPs were measured visually while the solutions were blanketed with nitrogen, as described recently (7). The temperature interval between incipient and complete phase separation on heating was  $\cong 1^\circ\text{C}$ , as was the interval for the reverse process on cooling. The CP was taken as the temperature at which the immersed portion of the thermometer suddenly became invisible on heating and fully visible on cooling. There was no hysteresis, and the six CP values observed on three successive heating and cooling cycles agreed within  $0.2^\circ\text{C}$ .

## RESULTS AND DISCUSSION

### Surface Tension and Critical Micelle Concentration

The surface tension versus concentration data for tyloxapol and octoxynol are plotted in Fig. 1, where the abscissa represents the natural logarithm of the surfactant concentration expressed as g/L.

The first linear segment, which extends from  $c = 0.004$  to  $0.025$  g/L for tyloxapol, represents saturation adsorption. Its regression equation is

$$\gamma = 27.43 - 3.890_5 \ln c \quad (n = 6, r = -0.998). \quad [2]$$

The intermediate points at  $c = 0.0455$  and  $0.0683$  g/L fall in a transition region that may represent premicellar aggregation.

The regression equation for the saturation adsorption region of octoxynol ( $c \leq 0.05$  g/L, before the shallow surface tension minimum) is

$$\gamma = 9.59 - 7.610 \ln c \quad (n = 5, r = -0.999). \quad [3]$$

For tyloxapol, the regression equation for the second linear segment, which represents the plateau region and begins at  $c = 0.075$  g/L, is

$$\gamma = 38.14 - 0.6022 \ln c \quad (n = 11, r = -0.977). \quad [4]$$

The regression equation for the plateau region of octoxynol after the shallow minimum, i.e., at  $c \geq 0.5$  g/L, is

$$\gamma = 30.44 - 0.176 \ln c \quad (n = 4, r = -0.970). \quad [5]$$

For tyloxapol, the CMC is the concentration at which the

two linear segments intersect and where Eqs. [2] and [4] are simultaneous. The  $22^\circ\text{C}$  value is  $0.038_5$  g/L. The  $25^\circ\text{C}$  value obtained by replotting Fig. 3 of Ref. (4) is  $\cong 0.06$  g/L. The agreement between these two values is only fair.

For octoxynol, the shallow surface tension minimum between the two linear segments requires a different approach (12). Its CMC was taken as the concentration corresponding to the lowest surface tension because the surface tension minimum is caused by traces of a poorly soluble, highly surface-active fraction of low or zero degree of ethoxylation (13). As soon as octoxynol micelles begin to form, they solubilize this impurity, removing it from the air–water interface and thereby causing the surface tension to rise. The surface tension minimum is located at  $0.16$  g/L. This value is in good agreement with the CMC of  $0.18$  g/L determined by light scattering and dye solubilization (13).

The more than fourfold ratio of the CMC values of octoxynol to tyloxapol is in keeping with the general observation that, as the molecular weight of a nonionic surfactant increases at constant hydrophilic–lipophilic balance (HLB), its CMC decreases. This observation is illustrated by comparing the CMC values at  $25^\circ\text{C}$  of two pairs of homogeneous polyoxyethylated normal primary alcohols  $C_nE_p$  having  $n$  carbon atoms in their hydrocarbon moiety,  $p$  oxyethylene units per molecule, and identical HLB values:  $0.072$  M for  $C_6E_4$  (14) and  $(9.0 \pm 1.9) \times 10^{-5}$  M for  $C_{12}E_8$  (15, 16);  $9.9 \times 10^{-3}$  M for  $C_8E_6$  and  $2.3 \times 10^{-6}$  M for  $C_{16}E_{12}$  (17). Doubling of the surfactants' molecular weight decreased their CMC values 800- to 4000-fold.

As expected, this effect is smaller for surfactants of higher molecular weight that are normally distributed, such as octoxynol and tyloxapol. For instance, both  $C_{12}E_{13.77}$  (MW = 792.9) and  $C_{18}E_{20}$  (MW = 1151.5) have HLB = 15.30. Their  $25^\circ\text{C}$  CMC values are  $9 \times 10^{-5}$  M (interpolated) and  $2 \times 10^{-5}$  M, respectively (17): a 45% increase in molecular weight reduced the CMC 4.5-fold.

The surface properties of tyloxapol, illustrated in Fig. 1, have the following three unusual features:

(i) From Eq. [2],  $d\gamma/d \ln c = -3.890_5$  dyne/cm in the saturation adsorption region. According to Eq. [1], the area per tyloxapol molecule in the air–water interface at saturation adsorption is  $105 \text{ \AA}^2$ . This is merely twice the  $54 \text{ \AA}^2$  area of octoxynol calculated from Eq. [3]. The latter value agrees with the  $55 \text{ \AA}^2$  area reported for a nonoxynol with the same degree of ethoxylation ( $p = 9.5$ ) (18).

(ii) The  $22^\circ\text{C}$  surface tension of tyloxapol at the CMC,  $40.1$  dyne/cm, is comparatively high. The  $25^\circ\text{C}$  surface tension of octoxynol beyond the shallow minimum,  $31.5$  dyne/cm, is more typical of the plateau surface tension of nonionic surfactants.

(iii) The negative slope of the plateau surface tension region of tyloxapol is 3.4 times steeper than the more typical slope of octoxynol (compare Eqs. [4] and [5]). The temperature differ-

ence between 22 and 25°C is too small to account for these differences between tyloxapol and the typical nonionic surfactant, octoxynol, to any significant extent.

The comparatively small area per molecule of the oligomeric tyloxapol indicates an unusual molecular orientation at the air–water interface, such as U- or V-shaped instead of extended horizontally. The isooctyl chains would fill the inside of the U or V, squeezing out much of the water and attracting one another (hydrophobic effect), while the polyoxyethylene chains would be on the outside of the U or V in randomly coiled conformations, surrounded by water and fully hydrated.

The proposed surface orientation also explains the other two unusual features in the surface properties of tyloxapol. The relatively high surface tension at the CMC results from a reduction in the interfacial area between water and the isooctane moieties as the molecules adsorbed at the surface bend to assume U or V shapes.

The third unusual feature, namely, the comparatively steep negative slope beyond the CMC, results from a tightening of the U or V shapes. As the bulk surfactant concentration beyond the CMC is increased, the sides of the U- or V-shaped molecules are pushed closer together in order to make room for the adsorption of additional surfactant molecules at the air–water interface, in competition with their inclusion into micelles. This increases the deviation of the surface tension versus log concentration curve beyond the CMC from a horizontal plateau. The increased strain on the apex is partially offset by the increased hydrophobic attraction between opposing isooctane chains across the U or V as more water is squeezed out from inside.

Similar unusual features, even more pronounced than those of tyloxapol, were reported for the surface properties of polyoxyethylene–polyoxypropylene–polyoxyethylene copolymers of low molecular weight (poloxamers or Pluronics) (19). With molecular weights ranging from 1600 to 8000, their areas per molecule at saturation adsorption range from 64 to 146 Å<sup>2</sup>.

Their surface tensions at the inflection points on plots of surface tension versus log concentration are even higher than that of tyloxapol ( $50 \pm 3$  dyne/cm compared to 40 for tyloxapol), and the slopes of the approximately linear segments at higher concentrations are even much steeper than that of tyloxapol ( $-d\gamma/d \ln c = 13\text{--}16$  dyne/cm compared to 0.6 for tyloxapol).

The following conformation was proposed for the poloxamer chains adsorbed at the surface, based on the fact that “increasing the length of the hydrophobic polyoxypropylene segment markedly decreases the area occupied by each molecule. This suggests that the molecules are oriented in the surface in a coiled manner, with the polyoxypropylene segment out of the aqueous phase and the hydrophilic polyoxyethylene groups at both extremities of the molecules anchoring the polymer in the aqueous phase” (19).

Such a conformation is compatible with a U or V shape,

albeit an inverted one, where the coiled polyoxypropylene segment occupies the apex. Because the hydrophilic and hydrophobic moieties of poloxamers are more extensively segregated than those of the tyloxapol molecule and because the poloxamer chains are far more flexible and capable of forming random coils, one would expect their U or V shapes to be less distinct and more poorly defined than that of tyloxapol.

The polyoxypropylene apex of the inverted U- or V-shaped poloxamer molecules may be located above the aqueous phase. However, all of the U- or V-shaped tyloxapol molecules are immersed inside the aqueous phase because the pendent polyoxyethylene chains are spaced evenly along their backbones. This and the greater flexibility of the poloxamer chains and the randomly coiled conformations of their polyoxyethylene and polyoxypropylene segments allow for greater compressibility of the surface layer at concentrations greater than the CMC, resulting in steeper negative slopes on the surface tension versus log concentration plots than that of tyloxapol, which in turn is steeper than those of conventional polyoxyethylated nonionic surfactants.

#### *Cloud Points in Water*

The CPs of 0.50, 2.00, 3.50, and 5.00% tyloxapol solutions are 94.3, 93.8, 93.7, and 93.1°C, respectively. The CPs of 2.00 and 4.00% octoxynol solutions are 65.5 and 65.6°C, respectively.

The following considerations lead to the prediction that tyloxapol should have a lower CP than octoxynol: The CP is the critical temperature of aqueous nonionic surfactant solutions. At the 2.0% use level, both surfactants exist almost entirely in the form of micelles, whose molecular weights are in the range of polymers (see Table 1). Therefore, their solutions should conform to the rules governing the phase equilibria of polymer solutions (20).

Polyoxyethylated nonionic surfactants, like polyethylene oxides, are more water soluble at lower temperatures. Moreover, the micellar molecular weight of tyloxapol at room temperature is twice that of octoxynol. Therefore, on heating their aqueous solutions, the larger tyloxapol micelles should start to precipitate at a lower temperature than the smaller octoxynol micelles. In the case of polyethylene oxides, the CP decreases with increasing molecular weight (21).

However, contrary to the expected behavior, the CP of tyloxapol is 28°C *higher* than the CP of octoxynol. This discrepancy between the precipitation temperature of polymers and the CP of nonionic surfactants is ascribed to the fact that the molecular weights of dissolved polymer molecules are constant while the micellar molecular weights of nonionic surfactants increase with temperature. Apparently, as the temperature is increased, the micellar molecular weight of octoxynol increases faster than that of tyloxapol,

reaching infinity (i.e., precipitating at the CP) at a lower temperature.

#### Cloud Points in Salt Solutions

Salting-out electrolytes lower the CP of nonionic surfactants, shrinking the temperature range on the phase diagram where a surfactant forms undersaturated isotropic solutions (22). Salt effects are quantified by shifts in CP,  $\Delta$ , which represent the difference between the CP of a surfactant solution containing a salt and the CP of a blank solution of the same lot of surfactant at the same concentration. Since the CP of different lots of a given surfactant may differ by a degree or two, it is more convenient to use  $\Delta$  rather than absolute CP values. Furthermore, the effects of a salt on two surfactants are best compared by its  $\Delta$  values. Negative  $\Delta$  values correspond to salting out.

Most plots of  $\Delta$  versus salt molality  $m$  are approximately straight lines passing through the origin:

$$\Delta = hm. \quad [6]$$

The slopes  $b$  are calculated by the method of least squares:

$$b = \frac{\sum \Delta m}{\sum m^2}. \quad [7]$$

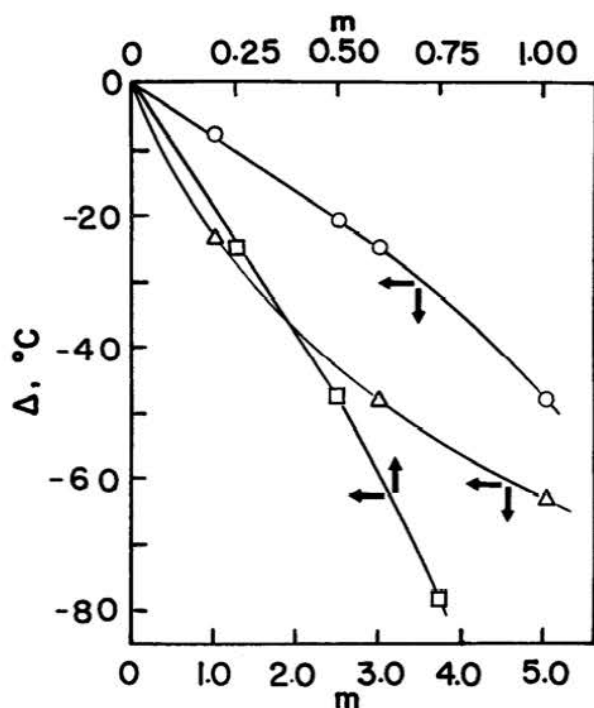


FIG. 2. Cloud point shift values  $\Delta$  of sodium nitrate (circles), chloride (triangles), and sulfate (squares) for 2.00% tyloxapol as a function of salt molality  $m$ .

TABLE 2  
Slopes  $b$  of Figs. 2 and 3 and Ionic Cloud Point Shift Values  $\Delta$  for Octoxynol 9 and Tyloxapol

Salt	$b$ ( $^{\circ}\text{C}/m$ ) <sup>a</sup>	
	Octoxynol 9	Tyloxapol
NaNO <sub>3</sub>	-6.5 <sup>b</sup>	-8.2
NaCl	-16	-21
Na <sub>2</sub> SO <sub>4</sub>	-72.6 <sup>b</sup>	-96.2
Mg(NO <sub>3</sub> ) <sub>2</sub>	6.7 <sup>b</sup>	5.6
Pb(NO <sub>3</sub> ) <sub>2</sub>	23.1	17.0 <sup>c</sup>
$\Delta$ at $W = 2.0$ ( $^{\circ}\text{C}$ )		
Ion	Octoxynol 9	Tyloxapol
NO <sub>3</sub> <sup>-</sup>	0 <sup>d</sup>	0 <sup>d</sup>
Cl <sup>-</sup>	-10.5	-13
SO <sub>4</sub> <sup>2-</sup>	-25.5 <sup>b</sup>	-32
Na <sup>+</sup>	-6 <sup>b</sup>	-8.1
Mg <sup>2+</sup>	4.5 <sup>b</sup>	0.8
Pb <sup>2+</sup>	9	8.5

<sup>a</sup> Defined by Eq. [1].

<sup>b</sup> From Refs. (23, 24). The other values are from the present work.

<sup>c</sup> Extrapolated.

<sup>d</sup> From Ref. (25).

For plots that curve somewhat at higher concentrations,  $b$  is based on the linear portions only.

The change in CP produced by a mixture of two salts is usually the algebraic sum of the changes in CP produced by each salt separately. For instance, the CP of 2.00% tyloxapol in water, 2.0  $m$  Mg(NO<sub>3</sub>)<sub>2</sub>, and 2.5  $m$  NaNO<sub>3</sub> is 93.8, 102.9, and 73.0 $^{\circ}\text{C}$ , respectively. The CP of a 2.00% tyloxapol solution containing 2.0  $m$  Mg(NO<sub>3</sub>)<sub>2</sub> + 2.5  $m$  NaNO<sub>3</sub> is 82.2 $^{\circ}\text{C}$ .  $\Delta$  for 2.0  $m$  Mg(NO<sub>3</sub>)<sub>2</sub> = 102.9 - 93.8 = 9.1 $^{\circ}\text{C}$  and  $\Delta$  for 2.5  $m$  NaNO<sub>3</sub> = 73.0 - 93.8 = -20.8 $^{\circ}\text{C}$ . For the solution containing 2.0  $m$  Mg(NO<sub>3</sub>)<sub>2</sub> + 2.5  $m$  NaNO<sub>3</sub>, the calculated  $\Delta$  is the algebraic sum of the individual  $\Delta$  values, namely, 9.1 - 20.8 = -11.7 $^{\circ}\text{C}$ . The observed  $\Delta$  is 82.2 - 93.8 = -11.6 $^{\circ}\text{C}$ , in excellent agreement with the additive  $\Delta$  value.

The  $\Delta$  values of the anions and cations of individual salts are also additive algebraically. The assignment of  $\Delta$  values to individual ions is made at comparable values of an empirical concentration parameter  $W$  called molal strength (23, 24), defined as

$$W = \sum mz, \quad [8]$$

where  $z$  is the valence of the ions that constitute the salt. Thus,  $W = 2.0$  corresponds to 1.0  $m$  NaNO<sub>3</sub> and to 0.50  $m$  Na<sub>2</sub>SO<sub>4</sub> or Mg(NO<sub>3</sub>)<sub>2</sub>. The reference value is  $\Delta$  NO<sub>3</sub><sup>-</sup> = 0, because the nitrate anion promotes neither salting out nor salting in (25).

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