

specification, but is the result of the interaction of many variables.

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## Preliminary Investigation of the Z-Value Measure of Relative Solvent Polarity in Micellar Solubilization

By STEVEN G. BJAASTAD and NATHAN A. HALL

The Z-value method for determining solvent polarity has been applied to surfactant solutions containing camphor and 2-heptanone. The surfactants used were partially purified polysorbate 80, potassium laurate, and dodecyltrimethylammonium chloride. As the surfactant concentration increased the Z-value decreased, indicating that the solubilized ketones encountered an environment of decreasing polarity. In the polysorbate 80 system 2-heptanone appeared to be solubilized deeper in the micelle interior than camphor. Both ketones in 0.2 M potassium laurate solutions were solubilized in more highly polar environments than in 0.2 M dodecyltrimethylammonium chloride solutions.

**S**URFACTANTS, as agents for making aqueous solutions of poorly water-soluble substances, continue to be of interest in pharmaceutical as well as many other systems. The solute is considered to be solubilized by the less polar micellar pseudophase, and this type of solubilization has been shown to affect the chemical and biological properties of the solubilize. Compounds are thought to be solubilized in various regions of the micelle: on the surface, in the palisade layer, or in the lipophilic micellar core (1, 2). It is logical to assume, therefore, that solubilized molecules would encounter regions of varying polarity.

Riegelman *et al.* (3) have shown that the ultraviolet absorption spectra of solubilized compounds alter upon solubilization and have drawn certain conclusions regarding the micellar region of solubilization from the spectra of solubilized systems. The ultraviolet spectral investigations of Sasaki *et al.* (4) indicated that the micellar interior in solubilized systems does contain some water.

Although polarity is reflected by a number of measurements on bulk liquids, such as dielectric constant and refractive index, the correlation of such measurements with the liquid's solvent

properties has been shown to have many limitations. No single measurement appears to be valid in more than a general way for predicting solubility and the effect of a given solvent on the properties of its solutions. Several investigators have attempted to improve the situation by developing empirical methods to assess the relative polarity of a series of solvents (5-9). One of these, the Z-value method developed by Kosower (9), appeared to be promising enough for use in examining micellar solubilized systems and was the subject of this study.

Based upon the assumption that the first layers of solvent around a molecule or ion will be appreciably different in dielectric constant from that measured for the bulk solution, Kosower originated the Z-value method for measuring the relative polarity of the layer of solvent molecules immediately surrounding the solute molecule (cybotactic region). The Z-value was defined as the energy of electronic transition corresponding to the charge-transfer absorption band of 1-ethyl-4-carbomethoxy pyridinium iodide. The shift of this band to longer wavelengths, occurring with solvents of decreasing polarity, was found to correlate well with other phenomena, such as rates of hydrolysis and keto-enol equilibria, which were known to be sensitive to solvent polarity. Subsequently, many substances were found to exhibit solvent-sensitive absorption spectra and

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were utilizable for  $Z$ -value determinations. In 1961 Kosower showed that the low intensity  $n$  to  $\pi^*$  electronic transitions of cyclic ketones were sensitive to changes in solvent polarity and one, cyclohexanone, could be used as a secondary standard for determining solvent  $Z$ -values (10).

In applying the  $Z$ -value method to solubilized systems it was assumed that the electronic transitions, as reflected by the ultraviolet absorption peak shifts, are due to the same forces of interaction between the solute and its cybotactic region in solubilized systems as in simple binary alcohol-water systems. In absence of information to the contrary, it was further assumed that the electronic transitions in the solute depend only upon the  $Z$ -value of the solvent, thus making the solubilize behavior regular and predictable.

The study reported here involved the application of the  $Z$ -value method to the examination of the environment of several ketones in aqueous surfactant solutions. The surfactants chosen were an anionic agent, potassium laurate; a cationic agent, dodecyltrimethylammonium chloride; and a nonionic agent, polysorbate 80. Two micellarly solubilized ketones, camphor and 2-heptanone, were used and two ketones with appreciable water-solubility, cyclohexanone and norcamphor, were also used for comparison. Subsequent to this investigation, the behavior of camphor in polysorbate 20 solutions was studied (11).

## EXPERIMENTAL

**Materials**—The surfactants, potassium laurate, dodecyltrimethylammonium chloride, and partially purified polysorbate 80, were prepared by a previously described method (12). Norcamphor (Aldrich Chemical Co.) and *D*-camphor (Eastman Organic Chemicals) were purified by sublimation immediately before use. The cyclohexanone and 2-heptanone (Matheson, Coleman and Bell) were purified by preparation of the bisulfites, regeneration with alkali, and fractional distillation. Solvents of reagent grade were not further purified. The *n*-hexanone was fractionally distilled after washing with acid permanganate. Acetonitrile was dried over  $P_2O_5$  and fractionally distilled. Ethanol was redistilled at atmospheric pressure.

Surfactant solutions of the ketones which were saturated were prepared by adding an excess of solute and shaking for 24 to 48 hr. at room temperature. For spectral readings the solutions were filtered into the absorption cells through a Swinney filter adapter (0.45- $\mu$  disk) attached to a hypodermic syringe. Solutions not saturated were made of such concentration that the absorbance maxima could be readily determined.

**Procedure**—Spectral measurements were made in matched cylindrical absorption cells (10 and 1 mm. light path) with a model 14 Cary recording spectrophotometer. The reference cell for each

measurement contained only the solvent or surfactant solution. The absorption maxima were determined by placing the solvent in each of the matched absorption cells and a solvent-solvent base line was recorded between 310  $m\mu$  and 250  $m\mu$ . The cell in the sample compartment was then removed, emptied, and filled with the ketone-containing solution. After the chart paper and wavelength scale were returned to their starting positions and the sample cell replaced, the spectrum between 310  $m\mu$  and 250  $m\mu$  was recorded at a scanning speed of 0.25  $m\mu$ /sec. The location of the spectral peak was noted, and a 10- $m\mu$  spectral recording was made over the region including the peak at a scanning speed of 0.05  $m\mu$ /sec. The slow speed 10- $m\mu$  recording was repeated twice and values of the three determinations were averaged. Repeated observations showed that this method gave maxima of  $\pm 0.4$   $m\mu$  precision.

This procedure gave the following absorption maxima for the ketones in simple aqueous solution: camphor, 284.1  $m\mu$ ; norcamphor, 281.6  $m\mu$ ; 2-heptanone, 272.2  $m\mu$ ; and cyclohexanone, 277.1  $m\mu$ .

The energy of the  $n$ - $\pi^*$  transition ( $E_t$ ) is calculated from the wavelength of the absorption maxima ( $\lambda_{max.}$ ) through the use of the relationship (13):

$$E_t = 2.859 \times 10^4 / \lambda_{max.} \text{ (in } m\mu) \text{ Kcal./mole}$$

Solvent polarity ( $Z$ ) values for the solvents used in this study were obtained from the published works of Kosower (9, 10, 14) or were determined from the measured absorption maximum of dissolved cyclohexanone. The  $Z$ -value of a given solvent could be calculated from the equation expressing its linear relationship with the transition energy of cyclohexanone:

$$E_t = 0.14650 Z + 89.234 \text{ (10)}$$

The solvents used and their  $Z$ -values are listed in Table I.

## RESULTS AND DISCUSSION

**Ketones in Simple Solvent Systems**—For each of the ketones, camphor, norcamphor, and 2-hepta-

TABLE I— $Z$ -VALUES OF SELECTED SOLVENTS

Solvent	$Z$ Value 25°
Water, distilled	94.6 <sup>a</sup>
Methanol	83.6 <sup>a</sup>
Ethanol	79.6 <sup>a</sup>
Isopropanol	76.6 <sup>a</sup>
Acetonitrile	71.3 <sup>a</sup>
Diethylether, water saturated	66.1 <sup>b</sup>
Chloroform	63.2 <sup>a</sup>
<i>n</i> -Hexane	60.4 <sup>b</sup>
56% Methanol	90.9 <sup>a</sup>
75% Methanol	87.8 <sup>a</sup>
80% Methanol	87.1 <sup>a</sup>
90% Methanol	85.5 <sup>a</sup>
92.5% Methanol	84.9 <sup>a</sup>
95% Methanol	84.5 <sup>a</sup>
70% Ethanol	84.4 <sup>a</sup>
80% Ethanol	84.8 <sup>a</sup>
90% Ethanol	82.5 <sup>a</sup>
95% Ethanol	81.2 <sup>a</sup>

<sup>a</sup> Values obtained from References 9, 10, 14. <sup>b</sup> Values experimentally determined.

TABLE II—REGRESSION EQUATIONS  $Z$  Versus  $E_t$ 

D-Camphor	
Aqueous	$E_t = 0.1284 Z + 88.25$ ( $r^a = 0.95$ )
Nonaqueous	$E_t = 0.03805 Z + 95.61$ ( $r = 0.97$ )
Norcamphor	
Aqueous	$E_t = 0.1662 Z + 85.67$ ( $r = 0.98$ )
Nonaqueous	$E_t = 0.1006 Z + 90.96$ ( $r = 0.98$ )
2-Heptanone	$E_t = 0.1071 Z + 94.98$ ( $r = 0.98$ )
Cyclohexanone <sup>b</sup>	$E_t = 0.1465 Z + 89.23$

<sup>a</sup>  $r$  = correlation coefficient. <sup>b</sup> From Reference 10.

none, the absorption maxima in the solvents listed in Table I were carefully measured, and a plot of  $E_t$  versus  $Z$  was made. With 2-heptanone, only a single linear correlation was evident; however, with camphor and norcamphor two linear correlations were found. One line described the correlation in water-containing solvent systems and another the anhydrous systems. Table II indicates the results of the least squares regression analysis of the data for the ketones used in this study.

**Ketones in Aqueous Surfactant Systems**—Initially the absorption maxima for various ketones were measured in partially purified polysorbate 80 solutions to determine whether the method would show lower polarity regions for the solubilized ketones than for those which were water-soluble. Because of their appreciable water-solubilities, norcamphor and cyclohexanone were examined in less than saturated solutions. The plot of  $Z$  versus polysorbate 80 concentration for saturated solutions of camphor and 2-heptanone is shown in Fig. 1.

The  $Z$ -values for norcamphor and cyclohexanone in polysorbate 80 solutions up to 2% showed an environment of essentially the same polarity as water, indicating that significant quantities were not included in the micellar phase. Camphor and 2-heptanone, both possessing low water-solubility, would be expected to be included in the micelles, and the  $Z$ -value of the surfactant system indicates an increasingly less polar environment as the surfactant concentration increased. At low surfactant concentrations both ketones behaved as if in an aqueous environment, however.

The lower polarity of the environment of the ketones may come about through the increased concentration of micelles at higher surfactant concentrations, increased micellar organization, or deeper penetration of the micelles by the ketone molecules. Interpretations of X-ray data (2, 15) suggest that micellar organization does increase with concentration. The relative regions of solubilization in the micelle can be deduced by comparing the changing  $Z$ -values of the two ketones. With increasing concentrations of polysorbate 80, 2-heptanone apparently encounters a less polar environment than camphor, hence it is probably deeper within the micelle. One would expect 2-heptanone, a rather flexible molecule, to be able to penetrate the micellar interior farther than camphor, a bulky molecule of rigid spherical shape. Possible multilayer adsorption or tail-to-tail adsorption following initial adsorption, as described by DeLuca and Kostenbauder (16), also might account for the less polar environment of 2-heptanone, however.

The decrease in  $Z$ -value did not appear to depend

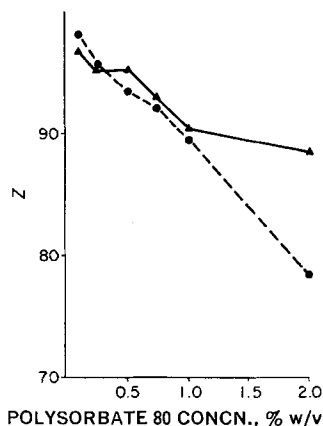


Fig. 1—Solvent polarity ( $Z$ ) versus polysorbate 80 concentration for saturated solutions of D-camphor ( $\blacktriangle$ ) and 2-heptanone ( $\bullet$ ).

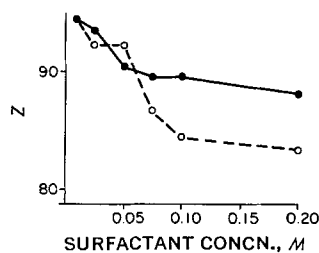


Fig. 2—Solvent polarity ( $Z$ ) versus molar surfactant concentration for D-camphor in potassium laurate solutions ( $\bullet$ ) and in dodecyltrimethylammonium chloride solution ( $\circ$ ).

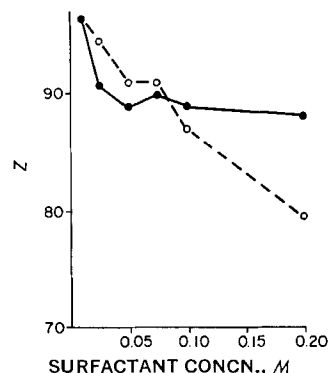


Fig. 3—Solvent polarity ( $Z$ ) versus molar surfactant concentration for 2-heptanone in potassium laurate solutions ( $\bullet$ ) and dodecyltrimethylammonium chloride solutions ( $\circ$ ).

upon the concentration of solubilize, even though the saturated solutions with the lower  $Z$ -values do contain higher solubilize concentrations. When spectra of solutions containing a constant concentration of camphor (1 mg./ml.) were measured, the  $Z$ -values were the same as in the saturated solutions

within experimental error. Bjaastad and Brown (11) also found constant  $Z$ -values for varying camphor concentrations in polysorbate 20 solutions.

The behavior of the  $Z$ -value with concentration was also examined with the anionic surfactant, potassium laurate, and the cationic agent, dodecyltrimethylammonium chloride. The data from saturated camphor solutions were plotted for Fig. 2, and the data for saturated 2-heptanone solutions were plotted for Fig. 3.

Examination of Figs. 2 and 3 shows that the environmental polarity of the solubilized ketones begins to fall off above the CMC of both ionic surfactants (about 0.02  $M$ ). Dodecyltrimethylammonium chloride solutions exhibit the less polar cybotactic regions at high surfactant concentrations. In the potassium laurate solutions, however, the  $Z$ -value appears to attain a plateau. Klevens (2) has reported that potassium laurate achieves "full colloidal form" at about 0.15  $M$ .

The  $Z$ -value method of measuring the polarity of the cybotactic region for micellar systems containing solubilizes appears to show promise. The polarity revealed by the method seems to conform to current micellar theories. Experimental refinements through the use of cells with shorter light

paths may make possible the study of higher surfactant concentrations and solubilizes with higher molar absorptivities. Since the  $Z$ -value is an empirical measure, studies involving its use probably will not have great theoretical significance; however, further investigation of the method is warranted to gain more knowledge of solubilization in complex micellar systems.

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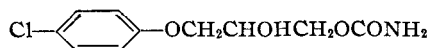
## Preparation of Tritium-Labeled Compounds II

### Chlorphenesin Carbamate by Exposure to Tritium Gas and Determination of Intramolecular Distribution of Tritium

By RICHARD C. THOMAS, DONALD R. BUHLER, and GEORGE J. IKEDA

Incorporation of stably bound tritium in purified chlorphenesin carbamate was 141  $\mu\text{C}$ . per curie-day exposure. The intramolecular distribution of radioactivity was determined by a combination of biological and chemical degradation methods. Aromatic substitution predominated, accounting for 95 per cent of the tritium; two-thirds of this was located *ortho* to the chlorine substituent. The remaining 5 per cent of the radioactivity resided at the number one position of the alkoxy side chain.

CHLORPHENESIN CARBAMATE<sup>1</sup> [3-(*p*-chlorophenoxy)-1,2-propanediol 1-carbamate; I] is a new, centrally acting skeletal muscle relaxant recently discussed by Matthews *et al.* (1).



I

This report describes the preparation of labeled chlorphenesin carbamate by the tri-

tium gas exposure method of Wilzbach (2) and determination of the intramolecular distribution of tritium in the resulting product.

This compound was prepared in a radioactive form to facilitate a study of its metabolism, part of which has recently been reported (3, 4). Exchange labeling by exposure to tritium gas was employed since previous experience (5) in this laboratory, as well as in others, with compounds of comparable structure indicated that incorporation of tritium would be adequate and purification would be feasible.

Advantage was taken of the rather unique pathway for metabolism of chlorphenesin carbamate in the rat (3) (Scheme I) to determine the complete intramolecular distribution of tritium in

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Previous paper: Thomas, R. C., and Ikeda, G. J., *J. Pharm. Sci.*, **55**, 112(1966).

<sup>1</sup> Trademarked as Maolate by The Upjohn Co., Kalamazoo, Mich.