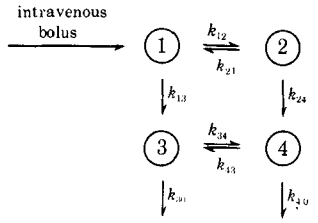

Scheme I—Compartmental model describing the distribution and elimination of a drug injected into Compartment 1. Elimination proceeds from both the central and peripheral compartments, with a metabolite, 3, undergoing analogous disposition.

where:

$E_2 = k_{21} + k_{24}$; $E_4 = k_{43} + k_{40}$; $A_{13} = k_{12}k_{24}k_{40}$

α,β = fast and slow disposition constants describing an intravenous bolus injection of aspirin

γ,δ = fast and slow disposition constants describing an intravenous bolus injection of salicylic acid (3)

A general simplified method for deriving the Laplace transform given in Eq. 7 will be published (4). At present the equation can be derived using determinants, but this derivation is not necessary to demonstrate the method of obtaining inverse Laplace transforms and it is not included here. Since there are no repeated $(s - \lambda_i)$ factors in the denominator of Eq. 7 and since the degree of s is higher in the denominator than in the numerator, the general partial fraction theorem may be used to carry out a one-step solution for the amount of drug in Compartment 3:

$$X_3 = \frac{k_{13}(E_2 - \alpha)(E_4 - \alpha)D + A_{13}D}{(\beta - \alpha)(\gamma - \alpha)(\delta - \alpha)} e^{-\alpha t} + \frac{k_{13}(E_2 - \beta)(E_4 - \beta)D + A_{13}D}{(\alpha - \beta)(\gamma - \beta)(\delta - \beta)} e^{-\beta t} + \frac{k_{13}(E_2 - \gamma)(E_4 - \gamma)D + A_{13}D}{(\alpha - \gamma)(\beta - \gamma)(\delta - \gamma)} e^{-\gamma t} + \frac{k_{13}(E_2 - \delta)(E_4 - \delta)D + A_{13}D}{(\alpha - \delta)(\beta - \delta)(\gamma - \delta)} e^{-\delta t} \quad \text{(Eq. 8)}$$

Let us review the procedure. When the factor $(s + \alpha)$ is omitted from the denominator (that is, when the root $\lambda_1 = -\alpha$ is used), all values of s in Eq. 7 are substituted by $-\alpha$ and this root appears in the exponential term $(e^{-\alpha t})$. Next, the factor $(s + \beta)$ is omitted when the root $\lambda_2 = -\beta$, *etc.* In practice, an easy way to carry out the taking of the anti-Laplace is to cover the factors in the denominator one by one with your finger while substituting the root of the covered factor for all the remaining s terms. If a single s term appears in the denominator, as when zero-order infusion equations are derived, the root for this factor is zero.

The method presented in this work is very easily used, even with complicated Laplace transform equations, so that the investigator may immediately write down the anti-Laplace without taking any derivatives and without breaking down the equation into parts that may reasonably be found in a table. A future publication (4) will contain a more extensive coverage of the method, including ways to solve anti-Laplace operations when the stated conditions of higher degree and nonrepeating factors in the denominator are not met.

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Are There Spherical Micelles?

Keyphrases ☐ Micelles—nonspherical shape surfactants ☐ Surfactants—formation of nonspherical micelles

Sir:

While many shapes have been postulated for micelles in relatively concentrated aqueous surfactant solutions, it is commonly agreed that the small micelles formed at low concentrations (up to a low multiple of the CMC) are spherical (1–8). The generally accepted model for the spherical micelles is that the hydrocarbon chains of the surfactant molecules are randomly arranged in the interior of the micelle, forming a spherical core or oil droplet, and that the hydrophilic headgroups form a concentric external spherical shell surrounding the hydrocarbon core. The headgroups are hydrated and shield the hydrocarbon chains from contact with water. The core is in a liquid-like state of disorder, and the hydrocarbon chains interact with each other by van der Waals forces (1). Despite computations (4, 9) showing that spherical micelles can exist only within a limited range of aggregation numbers, interpretation of viscosity and diffusion measurements of micelles (10–12) are commonly based on a spherical shape.

The combination of simple geometric considerations with the experimentally determined micellar sizes indicates that it is unlikely that surfactants having a single normal alkyl chain as their hydrocarbon moiety form spherical micelles.

Geometric Considerations—The following parameters refer to the core of the micelle formed by the hydrocar-

bon chains of the surfactants, assuming it to be spherical: m = molecular weight of the hydrocarbon moiety of a single surfactant molecule, and v = its volume; s = surface area per hydrocarbon chain on the sphere delimiting the hydrocarbon core; M = molecular weight of the hydrocarbon core of one micelle, V = its volume, S = its surface area, R = its radius, and d = its specific gravity; z = aggregation number or number of surfactant molecules per micelle; and N = Avogadro's number.

Expressing the dimensions in Angstrom units results in:

$$V = 10^{24}zm/dN \qquad \text{(Eq. 1)}$$

and:

$$V = zv = (4\pi R^3)/3 \qquad \text{(Eq. 2)}$$

Combining Eqs. 1 and 2 results in:

$$R = 0.7346\,(zm/d)^{1/3} \qquad \text{(Eq. 3)}$$

If the hydrocarbon moiety is a normal alkyl chain containing n carbon atoms:

$$m = 14.03n + 1.01 \cong 14.03n \qquad \text{(Eq. 4)}$$

Substituting in Eq. 3 yields:

$$R = 1.772\,(zn/d)^{1/3} \qquad \text{(Eq. 5)}$$

For the hydrocarbon core of the micelle to be a sphere of uniform density without a hole in the center, R cannot exceed the extended length of the hydrocarbon chain. This length is $1.27n$ Å, neglecting the length of the C—H bond of the terminal methyl group but including the length of the bond between the carbon atom at the other chain end and the nitrogen, oxygen, or sulfur atom of the headgroup. From Eq. 5:

$$1.772\,(zn/d)^{1/3} \leqslant 1.27n \qquad \text{(Eq. 6)}$$

$$z \leqslant 0.368dn^2 \qquad \text{(Eq. 7)}$$

The values for the specific gravity of the hydrocarbon cores are estimated from the effective molar volumes at 25° of the methyl group (33.3 cm.^{3}) and the methylene group (16.2 cm.^{3}). These volumes were calculated from the densities of liquid n-alkanes (13). The specific gravities were used to calculate the maximum values for z consistent with spherical micelles by means of Eq. 7 (Table I).

Comparison with Experimental Micellar Sizes—Figure 1 shows the experimentally determined aggregation numbers for micelles of surfactants which have a single normal alkyl chain as their hydrocarbon moiety. The values for ionic (6, 7) and nonionic (14, 15) surfactants refer to dilute surfactant solutions in water, with no added electrolytes. The size of ionic micelles is often increased by the addition of salts as the surfactant solubility is lowered (7). Only those nonionic surfactants with cloud points at least 40° above the temperatures of the micellar molecular weight determinations are included, because the size of nonionic micelles increases rapidly with temperature once the temperature approaches the point of macroscopic phase separation (14, 15).

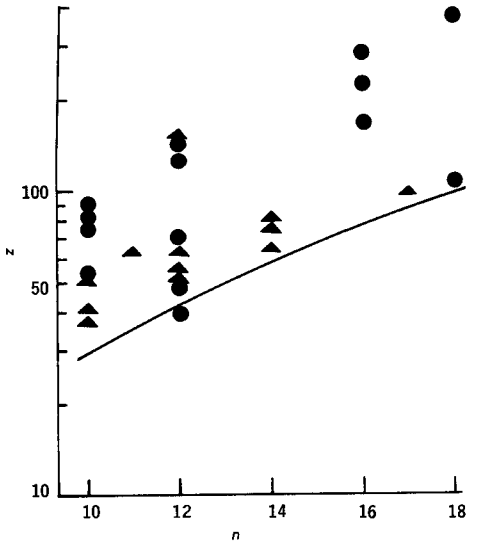

Figure 1—*Aggregation numbers,* z, *of surfactants* versus *the number,* n, *of carbon atoms in the normal alkyl moiety. Key:* ▲, *ionic surfactants; and* ●, *nonionic surfactants. Points above the curve refer to nonspherical micelles.*

Light scattering was frequently employed to determine z. In the case of ionic surfactants without swamping electrolyte, the reported values (7) are probably low (16). Ultracentrifugation, diffusion with viscosity measurements, and osmotic pressure measurements were also employed (6, 7, 14, 15). Only those ultracentrifugation data obtained without supporting electrolyte are included in Fig. 1.

The maximum z values consistent with spherical micelles, calculated according to Eq. 7, are shown in Fig. 1 together with the experimentally observed z values. The observed aggregation numbers are generally larger, indicating that the corresponding micelles should not be spherical. If these micelles were spherical, some of the polar headgroups would have to be buried inside the hydrocarbon core, out of contact with water, which is energetically unfavorable. Alternatively, there would be a hole in the center of the micelle, which is worse.

Further Geometric Considerations—Another way to consider this problem is to calculate the value of s for a spherical micelle:

$$s = S/z = (4\pi R^2)/z \qquad \text{(Eq. 8)}$$

Combining with Eq. 5 gives:

$$s = 39.46(n^2/d^2z)^{1/3} \qquad \text{(Eq. 9}$$

Combining with Eq. 7 gives:

$$55.08/d \leqslant s \qquad \text{(Eq. 10)}$$

The values of the specific gravities of Table I indicate that the area per hydrocarbon chain on the perimeter of the oil droplet exceeds 67–70 Å^2, which is over twice the limiting area per molecule of sodium dodecyl sulfate at the air–water interface. Therefore, in spherical anionic micelles, the polar headgroups shield the hydrocarbon cores only incompletely. This results in an extensive hydrocarbon–water interface, which is energetically unfavorable.

Table I—Maximum Values for the Aggregation Number of Micelles of *n*-Alkyl Surfactants Consistent with Spherical Shape

n	$d_{25°/25°}$[a]	$z_{max.}$[b]
10	0.791	29
12	0.802	42
14	0.811	58
16	0.818	77
18	0.823	98

[a] Of $CH_3(CH_2)_{n-1}$. [b] From Eq. 7.

Effect of Hydrocarbon Compressibility—If micelles have radii greater than the extended hydrocarbon chain length, spherical shape implies that some of the polar headgroups are buried inside the hydrocarbon core or that there is a hole in the center of the micelle, provided that the specific gravity of the core is that listed in Table I for atmospheric pressures. The possibility is now examined that compression of the oil droplet which constitutes the hydrocarbon core, resulting from its small radius of curvature, is capable of closing that hole.

According to the Laplace equation, the pressure within the spherical oil droplet exceeds the external pressure by a difference:

$$\Delta P = 2\gamma/R \qquad \text{(Eq. 11)}$$

where γ is the interfacial tension. The compressibility coefficient is defined as:

$$\beta = -(\Delta V/\Delta P)/V_0 \qquad \text{(Eq. 12)}$$

For surfactants derived from *n*-dodecane, $R_{max.} = (12)(1.27) = 15.24$ Å $= 15.24 \times 10^{-8}$ cm. By setting the oil–water interfacial tension at 50 dynes/cm., $\Delta P = 6.56 \times 10^8$ dynes/cm.[2] according to Eq. 11. For higher *n*-alkanes at low pressure, β is of the order of 100×10^{-6} atm.$^{-1}$ or 10^{-10} cm.[2]/dyne (13). By Eq. 12, $\Delta V/V_0 = -0.0656$; *i.e.*, the volume decreased and the specific gravity increased by 6.56%. The higher specific gravity is (0.802)(1.0656) = 0.855. By Eq. 7, the maximum value of z is now 45. This still falls short of the observed association numbers (7, 14, 15).

These estimates represent the upper limit. Actual compressions are certainly smaller because of the following reasons:

1. In selecting the values of γ and β, the fact that the outer ends of the hydrocarbon chains are connected to hydrophilic groups was neglected.

2. The Laplace equation was derived for the situation where R is large compared to the thickness of the interfacial layer (17). In the present situation, this is not true, so that ΔP is probably smaller.

3. The repulsion between ionized headgroups (18) or the crowding of polyoxyethylene chains reduces the core density somewhat, so that the specific gravity values of Table I are slightly high.

The conclusion for the surfactants examined, namely, those which have a single normal hydrocarbon chain for hydrophobic moiety, is the following: With very few exceptions, experimentally determined aggregation numbers of small micelles are too high to be consistent with spherical shape.

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Structure and Antimalarial Activity o Aminoalcohols and 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

Keyphrases □ Aminoalcohols—structure–antimalarial activity relationships □ 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran—structure–antimalarial activity relationships □ Antimalarial agents—structure–activity relationships of aminoalcohols and 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

Sir:

A series of substituted tetrahydrofuran derivatives synthesized by Marxer (1, 2) showed some interesting antimalarial activity (3, 4). The most active member of this series is 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetra-