Table III—Iron Interference on 100 ppm of Titanium

Iron, ppm	Absorbance Increase, %
25	2
50	4
100	7
300	11
500	13
1000	13
3000	26

samples of placebo-prepared sunscreen product. In all samples, the placebo weight was the same.

Iron in the presence of sulfuric acid concentrations below 1 *N* was reported to depress titanium absorption (5). Iron at 2000 ppm in the presence of 2% HF enhanced titanium absorption, while iron at 200 ppm had no detectable effect (6). A third study indicated no interference on the absorbance of a 100-ppm titanium sample by 50 ppm of iron but a depression of absorbance by iron above 200 ppm (7). Attempts to determine the degree of interference caused by the presence of iron yielded the results in Table III. The iron amount present in the final dilutions varied from 11 to 22 ppm, depending on the shade[8] of the sunscreen. Iron, 16 ppm, was added to the standards to approximate the quantity in the samples to match the matrix and to minimize enhancement.

[8] Neutral and dark shades; iron levels were determined by the atomic absorption spectrophotometric method.

Examination of the effects on titanium absorption caused by a difference in the ammonium sulfate or sulfuric acid levels between the standards and the samples showed that a twofold increase in sulfuric acid produced a 2% enhancement of absorbance while a twofold increase in ammonium sulfate produced a 3% enhancement.

The fuel to oxidizer ratio was verified to be critical (5); when the flow rate of one gas varied slightly, the flame condition and the titanium absorption value changed significantly.

The described atomic absorption spectrophotometric method for the determination of titanium is simple, reliable, and accurate. The procedure, including standard preparation, can be performed in ~3 hr.

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Surface Activities of Barbital, Phenobarbital, and Pentobarbital and Their Interaction Energies with Phospholipid Monolayers

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Abstract □ The adsorption free energies of barbital, phenobarbital, and pentobarbital at the air–water interface were estimated from plots of the surface pressure ($\pi \leq 5$ dynes/cm) against the bulk concentration. Their energies of interaction with dipalmitoylphosphatidylethanolamine and dipalmitoyllecithin monolayers spread at the air–water interface were estimated from the surface pressure increase with increasing concentrations of the subphase-injected barbituric acid derivatives. Adsorption free energies and interaction energies were barbital < phenobarbital < pentobarbital, which correlate with their nerve blocking concentration.

Keyphrases □ Barbiturates—adsorption free energy, phospholipid monolayers, barbital, phenobarbital, pentobarbital □ Free energy—adsorption, barbital, phenobarbital, pentobarbital, phospholipid monolayers □ Phospholipid monolayers—adsorption free energy, barbital, phenobarbital, pentobarbital □ Surface activity—barbital, phenobarbital, pentobarbital, interaction with phospholipid monolayers

The interaction energies of procaine, lidocaine, and tetracaine with phospholipid monolayers were correlated recently with their anesthetic and nerve conduction blocking potencies (1).

The present work concerned the surface activities of barbital, phenobarbital, and pentobarbital at the air–water interface and their interaction energies with dipalmitoylphosphatidylethanolamine and dipalmitoyllecithin monolayers spread at the air–water interface.

EXPERIMENTAL

Reagents—Sodium salts of barbital[1], phenobarbital[1], and pentobarbital[1] were used without further purification. Dipalmitoyllecithin[2], dipalmitoylphosphatidylethanolamine[3], the hexane[4] used to prepare the phospholipid spreading solutions, and the water used to prepare the solutions fulfilled the requirements previously specified (2, 3). Analytical reagent grade sodium chloride[1] was roasted for 6 hr at 700° prior to preparation of the aqueous solutions to remove surface-active impurities.

Instruments and Methods—The instruments and methods for the measurement of the surface tension of aqueous solutions (γ) and of the surface pressure change ($\Delta\pi$) of the phospholipid monolayer after drug injection in the subphase already were described (2, 3). The experiments reported here were performed in 0.15 *M* NaCl at 20 ± 1°. In the injection experiments, the initial surface pressure of the phospholipid monolayer was 5 dynes/cm (±0.1 dyne/cm). Surface pressures (π) of the 0.15 *M* NaCl drug solutions were fitted to a function of the logarithm of the drug concentration, *C*, by digital-computerized, nonlinear regression (1, 4). Drug solution densities were determined using 10-ml specific gravity bottles.

RESULTS

Adsorption at Air–Aqueous Interface—Typical plots of the surface pressure (π) against the logarithm of the concentration (*C*, moles per liter)

[1] Mallinckrodt Chemical Works, St. Louis, Mo.
[2] Applied Science Laboratories, State College, Pa.
[3] Schwarz-Mann Research Laboratories, Orangeburg, N.Y.
[4] J. T. Baker Chemical Co., Phillipsburg, N.J.

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Table I—Adsorption Free Energies at the Air–Water Interface (ΔG_{ad}), Interaction Energies with Phospholipid Monolayers (Ψ), and Free Energies of Transfer (ΔG_{tr}) to Erythrocyte Membranes and to Octanol of Barbital, Phenobarbital, and Pentobarbital

Barbiturate	Air–0.15 *M* NaCl, ΔG_{ad}, kcal/mole	Dipalmitoyllecithin–0.15 *M* NaCl, Ψ, kcal/mole	Dipalmitoylphosphatidylethanolamine–0.15 *M* NaCl, Ψ, kcal/mole	Erythrocyte[a] Membrane–Buffer Solution, ΔG_{tr}, kcal/mole	Octanol[b]–Water, ΔG_{tr}, kcal/mole	Nerve Blocking[c] Concentration (Frog, Sciatic), mole/liter
Barbital	−4.0	−3.2	−4.0	+0.2	+0.2	28×10^{-3}
Phenobarbital	−4.6	−4.2	−5.2	−1.1	−0.2	5.7×10^{-3}
Pentobarbital	−6.4	−6.0	−5.7	−1.3	−0.4	1.7×10^{-3}

[a] Calculated from Ref. 10. [b] Calculated from Ref. 9. [c] From Ref. 10.

for barbital, phenobarbital, and pentobarbital in 0.15 *M* NaCl are given in Fig. 1.

The adsorption free energy at the air–aqueous solution interface can be estimated from (1, 4, 5):

$$\Delta G = -RT \ln \frac{\pi}{X_2^*} \qquad \text{(Eq. 1)}$$

where ΔG is the standard free energy change associated with solute adsorption at the air–water interface, π is the surface pressure, X_2^* is the solute activity, R is the universal gas constant, and T is the absolute temperature.

The ΔG value can be calculated from the slope (π/X_2^*) of a linear plot of the surface pressure (π) against the solute mole fraction (X_2) in the bulk solution when $X_2 \rightarrow 0$ and $X_2 \rightarrow X_2^*$ at low mole fractions. Plots of the surface pressure (π) against the mole fraction (X_2) for barbital, phenobarbital, and pentobarbital were linear in the region $\pi \leq 5$ dynes/cm (regression coefficients of 0.9988, 0.9918, and 0.9975, respectively). The estimated ΔG values from such plots are given in Table I and were barbital < phenobarbital < pentobarbital.

Interaction with Phospholipid Monolayers—The interaction of the subphase-injected drugs with dipalmitoylphosphatidylethanolamine and dipalmitoyllecithin was virtually completed in the first 15–25 min. The equilibrium criterion was the constancy (±0.1 dyne/cm) of the surface pressure increment ($\Delta\pi$) during 30 min. The interaction energies (Ψ) were estimated (1–4, 6) from the slopes of the linear plots of the reciprocals of the equilibrium surface pressures ($\Delta\pi_{eq}$) against the reciprocals of the final concentrations (n, molecules per cubic centimeter) of the subphase-injected drug. Such energies (Table I) were barbital < phenobarbital < pentobarbital for both monolayers.

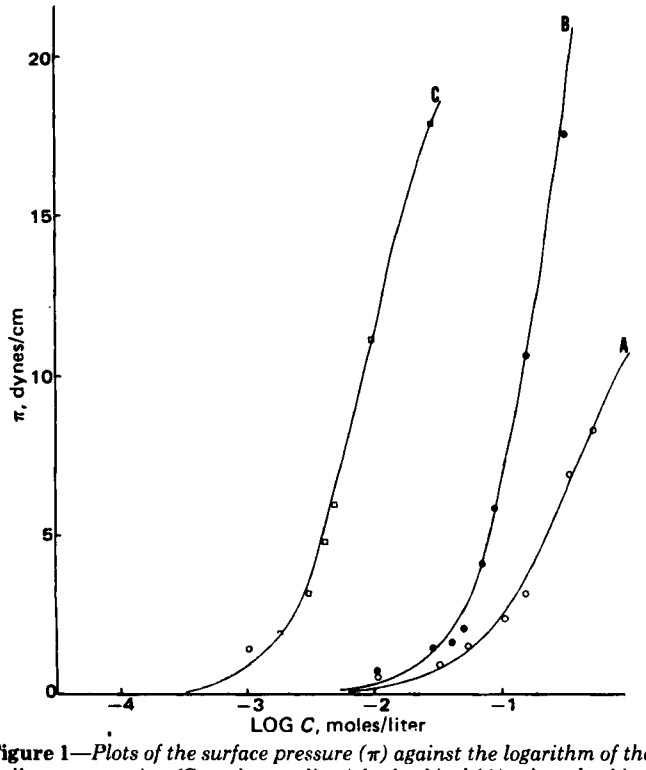

Figure 1—*Plots of the surface pressure (π) against the logarithm of the bulk concentration (C, moles per liter) for barbital (A), phenobarbital (B), and pentobarbital (C). The lines drawn through the experimental points were the best fit obtained from the computer.*

DISCUSSION

The amount of surfactant ions in an adsorbed monolayer at the air–water interface can be estimated directly from measurements of the surface tension variation with surfactant bulk concentration at a constant counterion concentration (1, 7):

$$\Gamma_2^m = \left(\frac{1}{RT}\right)\left(\frac{d\pi}{d \ln m_2}\right)_{m_3} \qquad \text{(Eq. 2)}$$

where Γ_2^m is the monolayer surface concentration of surfactant (moles per square centimeter), R is the universal gas constant (ergs per degree per mole), T is the absolute temperature (degrees Kelvin), π is the surface pressure (dynes per centimeter), and m_2 and m_3 are the molalities (moles per kilogram) of the surfactant ion and the counterion in the bulk solution.

The computed derivative ($d\pi/d \ln m_2$) of the exponential equation that characterized the surface pressure dependence on the concentration permitted (1–4, 6) calculation of the surfactant ion amount in the monolayer (Γ_2^m, moles per square centimeter) at any bulk concentration. Apparent molecular volume calculations performed using crystal density values (8) and space-filling molecular models indicate that the molecular dimensions of these barbituric acid derivatives can be accommodated into a thin interfacial region 8–12 Å thick. On the premises that the barbituric acid derivatives that form the adsorbed monolayer at the air–aqueous interface are immersed completely in the aqueous phase and that the average thickness is 10 Å, the volume, V_s, of the interfacial region that contains the amount of barbituric acid derivative, Γ_2^m (moles per square centimeter), can be estimated reasonably for comparison.

Concentration plots in such a thin interfacial region ($\Gamma'_2 = \Gamma_2^m/V_s$, in moles per liter) estimated from these volumes and from the surface concentration (Γ_2^m, mole per square centimeter) against the bulk concentration C (moles per liter) are given in Fig. 2 for barbital, phenobarbital, and pentobarbital and indicate that the adsorbed pentobarbital concentration at the thin interfacial region could be up to 500 times

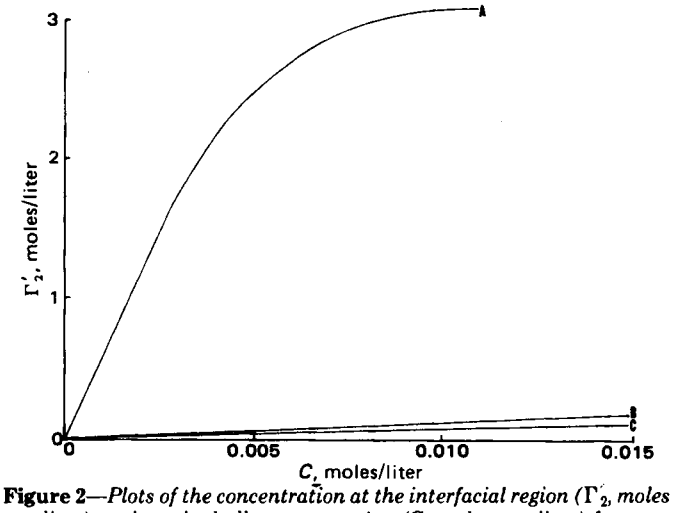

Figure 2—*Plots of the concentration at the interfacial region (Γ'_2, moles per liter) against the bulk concentration (C, moles per liter) for pentobarbital (A), phenobarbital (B), and barbital (C).*

greater than that of phenobarbital and barbital at the same conditions.

Partition coefficients have been measured between octanol–aqueous solution (9) and between erythrocyte membrane–buffer solution (10) for barbital, phenobarbital, and pentobarbital. With the assumptions that the numerical values of the interaction energies of barbital, phenobarbital, and pentobarbital are valid estimates (*i.e.*, the entropies are invariant) and that the same energies are operative for comparative purposes under the conditions in which partition coefficients were measured, the corresponding changes in free energies of transfer to the nonaqueous phase were calculated from literature data (9):

$$\Delta G_{tr} = RT \ln P \qquad \text{(Eq. 3)}$$

where P is the partition coefficient and ΔG_{tr} is the standard free energy associated with solute transfer from the aqueous to the nonaqueous phase. The order of such energies (ΔG_{tr}) (Table I) correlates with the interaction energies of barbital, phenobarbital, and pentobarbital with dipalmitoylphosphatidylethanolamine and with dipalmitoyllecithin monolayers and with their blocking concentrations.

These results show that the interaction energies of pentobarbital with the phospholipid monolayers are higher than those of barbital and phenobarbital and seem to indicate that its increased nerve blocking potency may be due to the comparatively greater interfacial concentration.

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Rationalization of Drug Complexation in Aqueous Solution by Use of Hückel Frontier Molecular Orbitals

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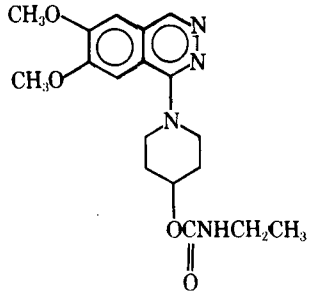
Abstract □ The complexation of certain drug molecules with niacinamide in aqueous solution was explained by the application of Hückel frontier molecular orbital calculations. A linear relationship was observed between the association constants derived from phase solubility studies and the interaction energy predicted by frontier molecular orbital calculations.

Keyphrases □ Niacinamide—complexation with drug molecules, aqueous solution, frontier molecular orbital calculations □ Complexation—of niacinamide with drug molecules, aqueous solution, frontier molecular orbital calculations □ Solubility—modification, niacinamide complexation with drug molecules, aqueous solution, frontier molecular orbital calculations

The solubility of drug substances often is modified by the use of additives. The discovery of the solubilizing (or solubility inhibiting) action of these additives frequently is made empirically; but in many cases, the system can be described by specific interactions between the drug and additive molecules. The use of phase solubility techniques to derive the association constants that quantitatively define the extent of interaction between the species involved was established (1). The nature of the specific interaction often is well understood.

Many potential interactions can be exploited to modify drug solubility. The present work concerns the use of Hückel frontier molecular orbital (FMO) calculations to confirm a π-donor–π-acceptor mechanism for the interaction of 6,7-dimethoxy-1-[4-(ethylcarbamoyloxy)piperidino]phthalazine (I), 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (II), 4-(4-amino-6,7,8-trimethoxyquinazolin-2-yl)piperazine-1-carboxylic acid 2-methyl-2-hydroxypropyl ester (III), and 6,7-dime-



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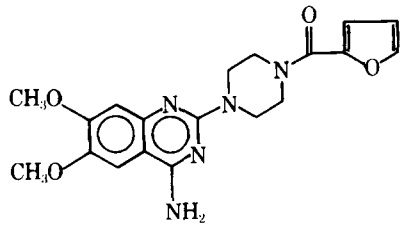

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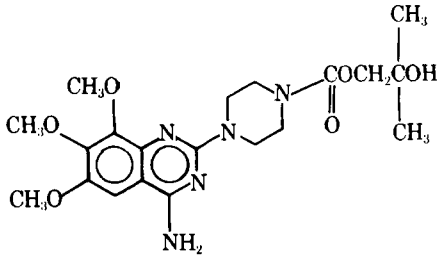

III

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