

and, from Eqs. 4 and 7:

$$\lim (k_{app}) = \frac{k_2}{B} \quad (\text{Eq. 8})$$

where $B = 1 + (P/K_d)$.
Substituting in Eq. 5:

$$\int_0^\infty C_f dt = \frac{D}{BV_1 \lim (k_{app})} \quad (\text{Eq. 9})$$

and, again, the area under the free drug concentration-time curve may be related to measurable pharmacokinetic parameters.

Equation 9 gives rise to an interesting observation on the effect of competitive binding inhibition. If a competitive inhibitor of drug-protein binding is present, C_f/C_f is decreased since more free drug is present. Thus, values of k_{app} increase as long as the inhibitor is present. However, if the inhibitor is itself eliminated rapidly enough that measurements of total drug concentration can be made after the inhibitor has disappeared, the observed value of $\lim (k_{app})$ is obtained in the absence of inhibitor. Since the value of B refers to the binding parameters effective at the time the measurement of

$\lim (k_{app})$ is made, this value is also unchanged. Therefore, according to Eq. 9, the area under the free drug curve is unchanged.

Simply stated, the effect of displacement of bound drug on the area under the plasma free drug concentration-time curve depends on the pharmacokinetics of the displacing agent. In particular, if the displacing agent is eliminated much more rapidly than the drug, there is no effect on the area under the free drug curve.

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Solvation of Montmorillonite

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Abstract □ It is known that polar solvents penetrate the montmorillonite lattice and that multiple layers of solvent can exist between the silicate layers. It is shown here that the number of layers in the interlaminar spacing is different when the clay is equilibrated with liquid than when it is equilibrated with vapor. A method for calculating the number is presented, and a generally usable experimental approach is suggested. Acetonitrile, ethanol, and methanol form 11, 5, and 7 layers, respectively, when equilibrated with montmorillonite as liquids but form only 3, 2, and 2 layers, respectively, when equilibrated with vapors.

Keyphrases □ Montmorillonite—solvation, comparison of liquid and vapor, number of layers in interlaminar spacing □ Solvation—montmorillonite, comparison of number of layers in interlaminar spacing when equilibrated with liquid and vapor

The degree of solvation of montmorillonite has received some attention in the past. Norrish (1) showed that the hydration occurs in two stages: (a) adsorption, and (b) penetration of water molecules into the crystal lattice. Packter (2) showed that the rate of gelation increases with the sixth power of the montmorillonite concentration. Mering (3) reported that the solvation of montmorillonite is one by which solvent molecules penetrate the clay lattice and that one or more solvent layers are present between the silicate layers, and MacEwan (4) and MacEwan and Talib-Uddin (5) reported the increase in lattice spacing per layer added in between the silicate layers.

These latter studies were conducted by equilibrating the clay with solvent vapor. Quite different phenomena might occur in the (pharmaceutically) more applicable situation of solid-liquid equilibria.

EXPERIMENTAL

Since the solvents with high dielectric constants are the ones liable to form multilayers between the silicate layers (4, 5), the following solvents were checked: acetonitrile, ethanol, and methanol; mixed solvents were avoided. The solute (adsorbate) employed was diazepam, since the diazepam-montmorillonite system has been well elucidated (6). Due to the poor water solubility of diazepam, water could not be included as a solvent in this study. The montmorillonite used was the hydrogen form of the clay and was a micropulverized grade¹; it was dehydrated under high vacuum

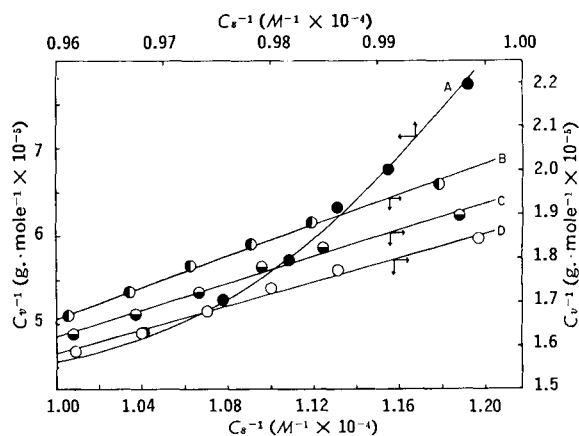


Figure 1—Adsorption isotherms of diazepam on montmorillonite from acetonitrile. Curve A is the conventionally treated curve, where no allowance is made for solvent intercalation. Curves B, C, and D are curves where allowance is made for 12, 12.5, and 13 layers, respectively, of acetonitrile between silicate layers.

¹ Veegum neutral micronized, R. T. Vanderbilt Co., Inc., New York, NY 10017.

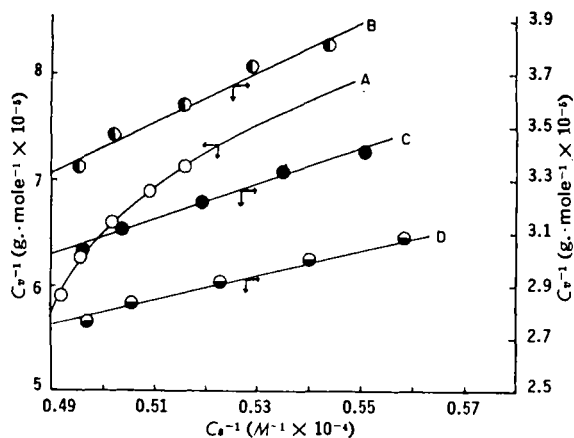


Figure 2—Adsorption isotherms of diazepam on montmorillonite from ethanol. Curve A is the conventionally treated curve, where no allowance is made for solvent intercalation. Curves B, C, and D are curves where allowance is made for 4, 5, and 6 layers, respectively, of ethanol.

(less than 0.1 millitorr) for 3 weeks and had an equilibrium moisture vapor pressure of 10-20 millitorr.

Adsorption isotherms were conducted as described in an earlier publication (7). Dielectric constants were determined as outlined in an article to be published from this laboratory (6).

RESULTS AND DISCUSSION

It was pointed out in another publication (6) that diazepam adsorbs on montmorillonite externally (not by intercalation) and that Langmuir isotherms are obtained in a series of solvents of dielectric constants less than 25.

In solvents of higher dielectric constants, reciprocal linearity is lost. Examples of this are lines A in Figs. 1-3. The distance (l) between silicate layers was given by Mering (3) to be 9.3 Å; the increase caused by one solvent layer (Δl) was reported by MacEwan and Talib-Uddin (5) to be 3.4 Å for the three solvents tested. The data can be treated with the assumption that n layers of solvent are formed between each silicate layer and that these solvent layers have the same density, ρ g./ml., as the bulk density. If each montmorillonite particle has cross-sectional area A and height l , then N such particles would have a volume of $N \cdot A \cdot l = w/d$ before addition of solvent; w is here the weight of the N particles, and d is the absolute density of montmorillonite. After addition of solvent, n layers (each of thickness Δl) will be formed between each silicate layer, so that the swell volume will be $w/d \cdot [(9.3 + n \Delta l)/(9.3)]$. The number of layers is assumed to be large so that edge effects are negligible. This, in turn, means that $w/d \cdot [(9.3 + n \Delta l)/(9.3)]$

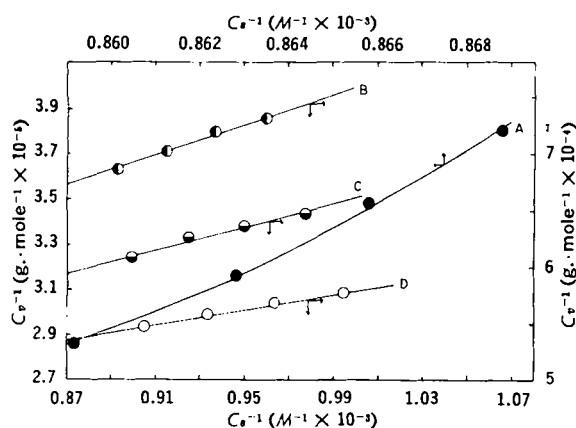


Figure 3—Adsorption isotherms of diazepam on montmorillonite from methanol. Curve A is the conventionally treated curve, where no allowance is made for solvent intercalation. Curves B, C, and D are curves where allowance is made for 6, 7, and 8 layers, respectively, of methanol.

Table I—Comparison of Parameters Obtained in This Study with Conventionally Obtained Parameter Values

| Solvent | Number of Sites | Number of Layers ^a | log k_+/k_- (Reference 6) (Theoretical) | log k_+/k_- (This Work) |
|-----------------------|-------------------|-------------------------------|-------------------------------------------|---------------------------|
| Acetonitrile | $6 \cdot 10^{19}$ | 11 | 2.38 | 2.86 |
| Methanol | $4 \cdot 10^{19}$ | 7 | 2.96 | 2.40 |
| Ethanol | $1 \cdot 10^{19}$ | 5 | 3.23 | 3.18 |
| Reference 6 (average) | $7 \cdot 10^{19}$ | — | — | — |

^a Density adjustment is accounted for in this column.

$- 1] = (w \cdot n \cdot \Delta l)/(9.3d)$ ml. of solvent no longer are in the external phase.

The amount of solute adsorbed is obtained by adding 100 ml. of a solution of molarity C_0 (i.e., $0.1 \cdot C_0$ moles of solute) to w g. or w/d ml. of montmorillonite and then determining the molarity, M , of the solute after adsorption equilibrium is established. The total amount of moles present in the external phase is, however, not $(M/1000) \cdot 100$, since 100 ml. external phase is no longer present but rather $(M/1000) \cdot [100 - (w \cdot n \cdot \Delta l)/(9.3d)]$ moles.

By inserting various values of n , a situation is reached where the plot is linear. To evaluate the point of best linearity, least-squares fits were calculated and the residual sums of squares: $s_{y,z}^2 = \sum (y_i - \bar{y}_i)^2 / (\nu - 2)$ was plotted in Fig. 4. Here ν is the number of determinations, y_i is the observed quantity [$1/C_p$, where C_p is the (adjusted) concentration on the montmorillonite], and \bar{y}_i is the quantity calculated by inserting x_i ($1/C_s$, where C_s is the concentration in solution) into the least-squares equation. It appears that 12-13 layers are involved in the acetonitrile intercalation, six layers in the case of ethanol, and six layers in the case of methanol.

These computations assume that the density of the "liquid" between the silicate layers is the same as that of the bulk liquid. This, of course, is not necessarily likely; in the cited cases, the error introduced by this assumption is, however, not serious. If one solvent molecule is attached to each lattice point per layer, then it can be shown geometrically that each solvent molecule occupies $2^3 \cdot 2^2 \text{ Å}^2$ and, hence, a volume of $23 \cdot 3.4 = 78 \text{ Å}^3$, i.e., in the case of acetonitrile, 1 mole (41 g.) occupies $78 \cdot 10^{-24} \cdot 6 \cdot 10^{23} = 46.8$ ml. This is equivalent to a density of 0.875 g./ml. as opposed to 0.78 g./ml. for bulk acetonitrile. The number of layers is, therefore, $(0.78/0.875) \cdot 12.5 = 11$ rather than 12-13. For methanol and ethanol, the spacings are about the same as for acetonitrile (4) (and the available surface at each lattice point also remains the same), so the densities of the solvents in the crystal are $32/46.8 = 0.68$ and $46/46.8 = 0.97$ g./ml., respectively, as opposed to bulk densities of 0.80 and 0.79 g./ml. The adjusted number of layers is, therefore, seven for methanol and

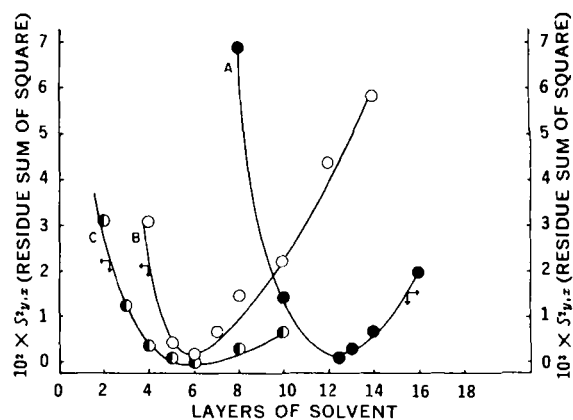


Figure 4—Residual sums of squares for least-squares fits of data allowing for various numbers of layers of intercalation. Key: A, acetonitrile (right ordinate); B, methanol (left scale); and C, ethanol (left scale)

² Based on lattice parameters of 5 and 9 Å in hexagonal array (3).

five for ethanol. In the liquid–solid equilibria, the rule of the number of layers being the larger the larger the dielectric constant is even more predominant than in vapor–solid equilibria.

The number of sites calculated from the three optimum curves, as well as the value of the slope, corresponds very closely with those obtained in different circumstances using conventional techniques (6). In the cited references, the ratio of adsorption to desorption rate (k_+/k_-) was related to the dielectric constant by a log reciprocal relationship; i.e., $\log [k_+/k_-] = \alpha \cdot (1/\epsilon) + \beta$. Comparison of $\log [k_+/k_-]$ calculated by inserting the dielectric constants for ethanol, methanol, and acetonitrile into the equation of Reference 6 with values obtained in this study gives good correlation, as shown in the last two columns of Table I. The number of sites obtained in Reference 6 also agrees with those found in this study to within an order of magnitude (10^{19} – $6 \cdot 10^{19}$ sites/g. vis-a-vis $7 \cdot 10^{19}$ sites/g.).

The value of the described approach is not only that of establishing the number of layers of solvent in the montmorillonite but, from an experimental point of view, also of pointing out the necessity of volume adjustment in establishing adsorption isotherms in solutions where solvent intercalation into the adsorbing species is a possibility.

SUMMARY

The effect of solvent intercalation in adsorption isotherms of montmorillonite from solvents with a high dielectric constant was

described, and it was shown that the number of solvent layers in the interlaminar spacing is higher than when montmorillonite is equilibrated with the vapor. The utility of this point in establishing isotherms was described.

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New Compounds: Convenient Preparation of Nicotinoyl Glycine Derivatives

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Abstract □ A simple preparation of nicotinoyl glycine derivatives by the anhydride method is reported.

Keyphrases □ Nicotinoyl glycine derivatives—convenient preparation, anhydride method □ Nicotinic anhydride and methyl glycinate—convenient preparation of nicotinoyl glycine derivatives

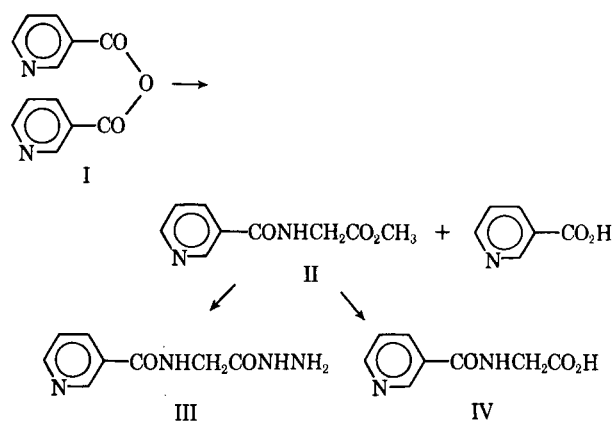
A new convenient preparation of nicotinoyl glycine derivatives, consisting of treatment of nicotinic anhydride (I) (1) with methyl glycinate, was developed. Since I and the amino acid esters are soluble in nonpolar solvents while the nicotinic acid formed in the reaction is insoluble, the product can be isolated conveniently.

Nicotinoyl glycine methyl ester (II) was obtained in good yield by treatment of I with equivalent amounts of methyl glycinate in chloroform and dioxane at room temperature. The by-product, nicotinic acid, was removed by filtration. Compound II was then treated with hydrazine hydrate in ethanol to give nicotinoyl glycine hydrazide (III) (2) in 81% yield (Scheme I).

Saponification of II with aqueous sodium hydroxide, followed by acidification, yielded nicotinoyl glycine (IV) (3) in 75% yield. The IR spectrum was identical with an authentic sample of IV and a mixed melting point gave no depression.

EXPERIMENTAL

Nicotinoyl Glycine Hydrazide (III)—Compound I (1.14 g., 0.005 mole) was dissolved in 30 ml. of chloroform with the aid of 20 ml. of dioxane. The solution was added with stirring to a solution prepared from methyl glycinate hydrochloride (0.63 g., 0.005 mole) and triethylamine (0.75 ml.) in chloroform (20 ml.). After 1 hr., the nicotinic acid was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 10 ml. of ethanol containing 1 ml. of 85% hydrazine hydrate and



Scheme I