it is used for a prolonged period of time and over a large body surface area, due to the extensive percutaneous absorption and the well-recognized toxicity of the drug.

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In Vitro Adsorption–Desorption of Phenethylamines and Phenylimidazoles by a Bentonite and a Resin

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Abstract □ The adsorption of phenethylamines (dextroamphetamine, phentermine, mephentermine, diethylpropion), choline, and phenylimidazoles (levamisole and imazalil) was examined *in vitro* in aqueous solutions on bentonite and on lewatite at 25°C. An ion-exchange mechanism prevails for lewatite and for bentonite up to 0.8 mEq·g^{-1}. The organic cations are more strongly adsorbed on bentonite than on lewatite. On bentonite, the selectivity of adsorption follows the order: primary < secondary < tertiary phenethylamines. An interlamellar monolayer is formed. All drugs, except choline and imazalil, are adsorbed in excess of the cation exchange capacity of bentonite without observable Cl^- adsorption and pH changes. Desorption is reversible for lewatite and partially irreversible for bentonite.

Keyphrases □ Phenethylamines—*in vitro* adsorption-desorption by a bentonite and a resin □ Phenylimidazoles—*in vitro* adsorption-desorption by a bentonite and a resin

The prolonged action of drugs in the GI tract with a peak-and-valley pattern of the drug in the blood (1) is realized by binding, *e.g.*, phenethylamines as diethylpropion, to an ion-exchange resin. The same effect was also observed for an oral dose of a mixture of clay-drug compared to the pure drug [*e.g.*, amphetamine, (2)]. Clindamycine, tetracycline (3), and chlorpheniramine (4) are adsorbed by cation exchange under pH conditions favoring the cationic form of the drugs, and they penetrate into the interlayer spaces of montmorillonite, producing an increase in the basal distance.

There are many important clay-organic interactions, *i.e.*, some animal feed additives are adsorbed on vegetable carriers such as maize or soy starch or on resins; bentonites are used as binder and caloric extender for poultry (5); fungicides such as imazalil, used in the foliar treatment of bananas, contaminate the soil. Clay minerals constitute an interesting commercial alternative to resin. Therefore, the adsorption of phenethylamines, choline, a quaternary amine, and two imidazoles on bentonite and lewatite were investigated as model *in vitro* systems. Desorption behavior was tested with simulated gastric and intestinal fluids.

EXPERIMENTAL SECTION

The macroporous (100–200 mesh) sodium lewatite[1] and bentonite[2] were used as adsorbents. Air-dried resin was equilibrated for 2 weeks with an at-

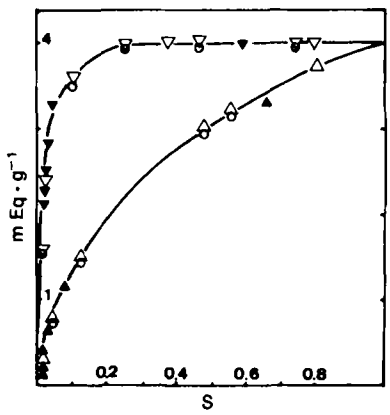


Figure 1—*Adsorption of diethylpropion (△) and imazalil (▽), and sodium desorption (○) on lewatite at pH 4 and 25°C versus S, the equivalent fraction of the organic cation in the equilibrium solution. Filled symbols refer to the desorption of the organic cation with a simulated gastric fluid (0.1 M NaCl, pH 2).*

[1] Resin SP 1080 (analytical grade); Merck, F.R.G.
[2] Wyoming bentonite (Volclay); American Colloid Co., U.S.A.

0022-3549/84/1000-1372$01.00/0

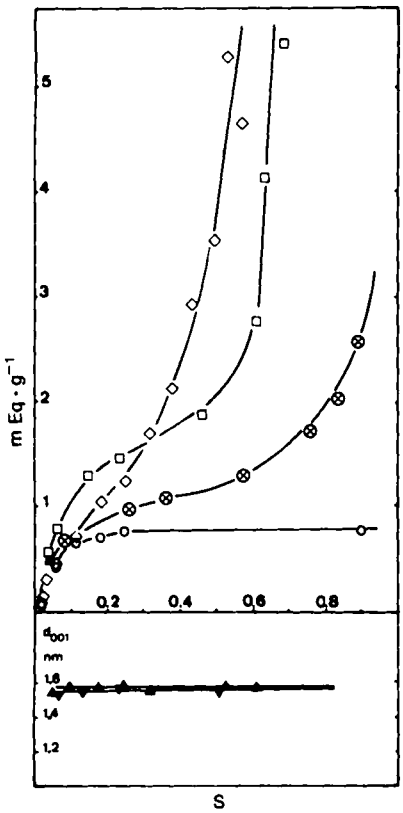


Figure 2—*Adsorption of amphetamine (◇), phentermine (□), and mephentermine (⊗) and sodium desorption (○) on bentonite at pH 5. Basal distances of the amphetamine-bentonite complexes in solution (▲) or dried in 1.333 × 10⁻⁴ Pa vacuum for 1 d at 25°C (▼). S is the equivalent fraction of the organic cation in the equilibrium solution.*

mosphere of 40% relative humidity. The cation exchange capacity (CEC), measured by isotopic dilution of ^{22}Na, was 4 mEq·g^{-1} dry resin. The bentonite fraction, under 0.5 μm, was separated by centrifugation, washed with acidified (pH = 3.5) and neutral NaCl (1 M) solutions for removal of hydroxy-aluminum compounds, and stored in the dark as a 1% suspension. The CEC of the bentonite was 0.7 and 0.8 mEq·g^{-1} clay at pH 4 and 5, respectively.

The adsorbates were the organic cations dextroamphetamine[3], phentermine[4], mephentermine[5], diethylpropion[6], choline[7], levamisole[7], and imazalil[7]. All of these have Cl^- as the anion, except for mephentermine which was purchased as the sulfate. Amphetamine and imazalil were obtained as bases and titrated to the equivalence point with HCl.

Exchanges were carried out in polyethylene tubes by end-over-end shaking for 48 h at 25°C and 0.01 M. For lewatite, 30–50 mg of resin were equilibrated with 30–40 mL of mixed Na-organic cation solutions containing different proportions of the two ions. The lewatite was separated by centrifuging for 5 min at 14,000 rpm. In the case of bentonite, 10-mL portions of a 1% clay suspension, enclosed in dialysis tubing, were equilibrated with 20 mL of mixed Na-organic cation solution.

All adsorptions were carried out at pH 5, except for imazalil and diethylpropion, in order to minimize hydrolysis of the clay. The low pK_a of 6.53 for imazalil necessitated experiments carried out at pH 4 to ascertain the presence of the cation. In the case of diethylpropion, the decomposition of the molecule was minimized by exchange at pH 4. The extent of adsorption was determined by radiometric analyses using: ^{14}C-labeled amphetamine[8], choline[8], and diethylpropion[9]; ^{3}H-labeled imazalil[7] and levamisole[8]; ^{22}Na; ^{36}Cl[10]. Countings were performed on 5-mL aliquots of the supernatant solutions, using a liquid-scintillation counter[11] and a γ-scintillation counter[12]. The concentrations

[3] C.E.R.T.A., 5050 Eghezée, Belgium.
[4] Troponwerke, 5000 Köln 80, F.R.G.
[5] Wyeth, Taflon, Maidenhead, U.K.
[6] Trenker, 1180 Brussels, Belgium.
[7] Janssen Pharmaceutica, 2340 Beerse, Belgium.
[8] C.E.A. Saclay; 91190 Gif-sur-Yvette, France.
[9] Laboratory of Medical Chemistry and Toxicology, University of Liège, Belgium.
[10] I.R.E., 6220 Fleurus, Belgium.
[11] Tricarb 460 C; Packard.
[12] PDG Auto-gamma; Packard.

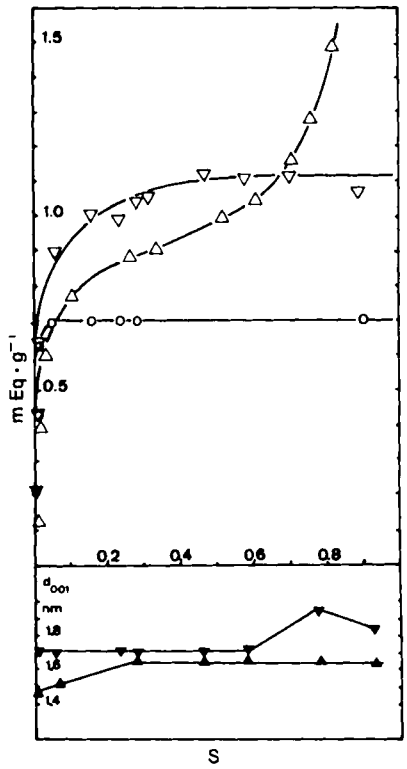


Figure 3—*Adsorption of imazalil (▽) and sodium desorption (○), adsorption of diethylpropion (△) on bentonite at pH 4. Basal distances of the imazalil-bentonite complexes in solution (▼) or dried in 1.333 × 10⁻⁴ Pa vacuum for 1 d at 25°C (▲). S is the equivalent fraction of the organic cation in the equilibrium solution.*

of phentermine and mephentermine were determined by UV absorption at 252 nm[13].

The swelling of the clay was studied by X-ray diffraction. For this purpose the sediment, obtained after centrifuging for 5 min at 14,000 rpm, was transferred into a Lindemann capillary, which was sealed, transferred to a Debye-Scherrer camera, and irradiated with CuK_α. The remainder of the sediment was rinsed with distilled H_2O, centrifuged, air-dried, and dried under high vacuum for 1 d at 25°C before X-ray measurement.

Desorption experiments were carried out on the fully exchanged resins, prepared by mixing 50-mg resin and 40-mL (0.01 M) organic cation. In the case of the clay, the desorption was studied on samples containing a low and a high organic cation content. These were obtained by equilibrating 10 mL

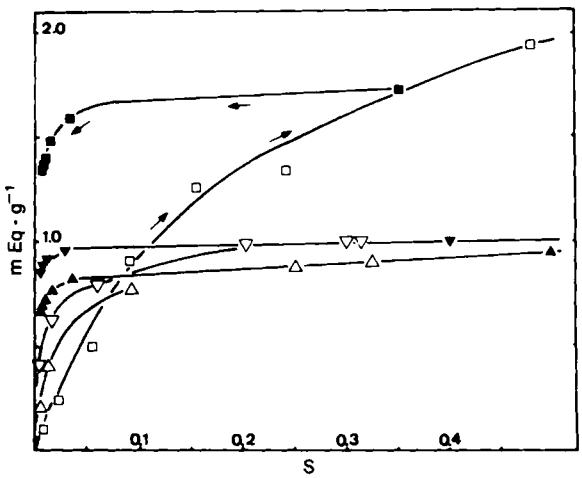
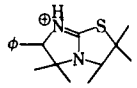
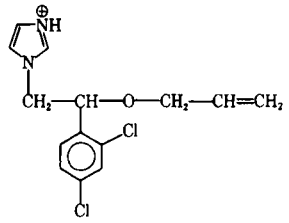


Figure 4—*Release pattern* in vitro *at 25°C by a simulated gastric fluid (0.1 M NaCl, pH 2) from bentonite of phentermine (■), diethylpropion (▲), and imazalil (▼). Open symbols refer to the adsorption isotherm. S is the equivalent fraction of the organic cation in the equilibrium solution.*

[13] Shimadzu QV-50 Spectrophotometer; Kyoto, Japan.

Table I—Natural Log of the Mean Selectivity Coefficient for the Exchange of Na by the Organic Cation on Lewatite and Bentonite at 298 K

	pK_a	Formula	$\ln \overline{K}_c$ (lewatite)	$\ln \overline{K}_c$ (bentonite)
Amphetamine	9.6	$PhCH_2CH(CH_3)NH_3^+$	—	3.35
Phentermine	9.84	$PhCH_2C(CH_3)_2NH_3^+$	1.67	3.39
Mephentermine	10.11	$PhCH_2C(CH_3)_2NH_2CH_3^+$	—	4.63
Diethylpropion	8.78	$PhCOCH(CH_3)NH(C_2H_5)_2^+$	1.45	5.40
Choline		$HO—CH_2—CH_2—N(CH_3)_3^+$	—	3.26
Levamisole	8.00		—	6.39
Imazalil	6.53		3.9	7.56

of a 1% clay suspension with 30 mL 0.01 M and 30 mL 0.025 M solutions of the organic cation, respectively. The desorption procedure was as follows: after 5 min of centrifugation at 14,000 rpm, 30 mL of the supernatant was removed and used for radioassay. The addition and removal of 20-mL portions of the supernatant was performed every hour thereafter. The amount desorbed was obtained from the radioassay of the successive supernatants and was expressed as a fraction of the initially adsorbed amount. The desorbing agent used was part of a simulated gastric fluid (NaCl 0.1 M, pH 2). The drug release pattern, as a function of time, was followed for a simulated intestinal fluid [122 mmol NaCl, 5 mmol KCl, 1 mmol KH_2PO_4, and 26 mmol $NaHCO_3$/L, *i.e.*, a buffer solution of pH 8, (6)].

RESULTS

Figure 1 shows the adsorption isotherms for diethylpropion and imazalil on lewatite; phentermine follows the same pattern as diethylpropion. In all cases the maximum loading equals the CEC. The adsorption occurs by ion exchange because, at every loading, the Na^+ ion release equals the amount of adsorbed organic cation.

The adsorption isotherms for amphetamine, phentermine, mephentermine, diethylpropion, and imazalil on bentonite, together with basal spacings, are presented in Figs. 2 and 3, respectively. They have two characteristic features: (*a*) a stoichiometric ion-exchange process wherein the Na^+ ion release equals the amount of adsorbed organic cation, and (*b*) adsorption in excess of the CEC. The latter is more pronounced for amphetamine followed by phentermine, mephentermine, and diethylpropion. The excess adsorption is not accompanied by simultaneous adsorption of Cl^- or by pH changes.

The basal spacing of 1.56 nm is independent of the loading and of the type of phenethylammonium cation. For choline and imazalil they are 1.50 and 1.72, respectively. The thickness of a clay plate was 0.96 nm. The differences

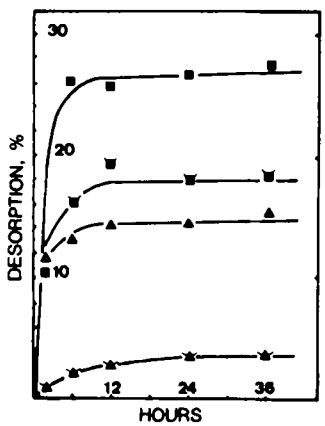


Figure 5—*Kinetic desorption profile with a buffer solution at pH 8 of: (■) phentermine-bentonite (1.06 mEq·g^{-1}), (▣) phentermine-bentonite (2.95 mEq·g^{-1}), (▲) diethylpropion-bentonite (1.14 mEq·g^{-1}), and (▲) diethylpropion-bentonite (1.78 mEq·g^{-1}).*

(*e.g.*, 1.56 − 0.96 nm = 0.60 nm) were indicative of a monolayer of organic cations on the surface.

Lewatite desorption of diethylpropion and imazalil was the reverse of the ion-exchange reaction as verified by the overlap of desorption and adsorption isotherms (Fig. 1). This is also the case for bentonite up to a loading with organic cations of ~0.7 mEq·g^{-1}. It should, however, be mentioned that since the H^+ concentration is much higher during desorption (but still 10 times smaller than the Na concentration), adsorption and desorption isotherms are not fully comparable.

When the loading on bentonite exceeds the CEC, adsorption and desorption curves are not superimposed, Fig. 4. The desorption experiments at pH 8 are presented in Fig. 5; 12 h were required to reach equilibrium. A smaller relative amount was desorbed for high loadings of organic cations as illustrated for phentermine and diethylpropion. Imazalil could not be desorbed at pH 8 because of the pK_a value and the limited solubility of the base (0.3 g·L^{-1}).

DISCUSSION

For lewatite, ion exchange was the only adsorption mechanism, whereas, for bentonite, ion exchange was followed by an excess adsorption process of the organic cations. From molecular models we estimated that 1.49 mEq·g^{-1} amphetamine and 0.9 mEq·g^{-1} diethylpropion can be adsorbed as monolayers in the interlamellar space of bentonite (700 m^2·g^{-1}) (7). Therefore, excess adsorption occurs to a large extent on the external surface, but the mechanism of adsorption is unclear.

For the exchange reaction between a solid exchanger (z) and a solution (s):

$$Na_z + B_s^+ \rightleftharpoons B_z + Na_s^+ \qquad \text{(Eq. 1)}$$

The selectivity coefficient, K_c, is defined as:

$${}^{B}_{Na}K_c = \frac{Z_B \cdot M_{Na}}{Z_{Na} \cdot M_B} \qquad \text{(Eq. 2)}$$

where Z and M refer to the equivalent fraction for the surface phase and the molality for the solution phase concentration. The latter can also be expressed in S units, *i.e.*, the equivalent fraction of the ion under consideration in the equilibrium solutions (8). The dependency of the selectivity coefficient on the organic loading is shown in Fig. 6. The mean $\overline{K}_c$ value is:

$$\ln {}^{B}_{Na}\overline{K}_c = \frac{1}{x_2 - x_1} \int_{x_1}^{x_2} \ln K_c dZ_B \qquad \text{(Eq. 3)}$$

Table II—Total Charge and Charge Density of the Ammonium Group of the Organic Cations [a]

	$-NH_xR_{(3-x)}$	$\sum_i$ (Charge/Volume)$_i$
$PhCH_2CH(CH_3)NH_3^+$	0.6239	0.1166
$PhCH_2C(CH_3)_2NH_3^+$	0.5994	0.1127
$PhCH_2C(CH_3)_2NH_2CH_3^+$	0.6300	0.0765
$PhCOCH(CH_3)NH(C_2H_5)_2^+$	0.7217	0.0494
$HO—CH_2—CH_2—N(CH_3)_3^+$	0.7506	0.0252

[a] Obtained from CNDO/2 calculations.

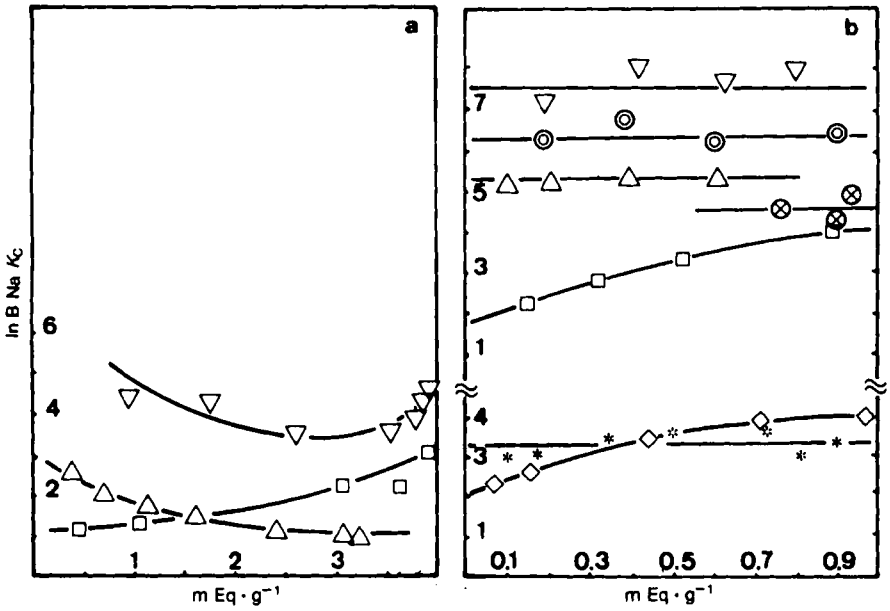


Figure 6—*Surface composition dependence of the selectivity coefficient for the exchange of Na by organic cation B at 25°C on (a) lewatite: phentermine (□), diethylpropion (△), and imazalil (▽) and, (b) bentonite: choline (*), d-amphetamine (◇), phentermine (□); mephentermine (⊗), diethylpropion (△), levamisole (◎), and imazalil (▽).*

The lower limit is necessary for the inaccuracy of the measurements at very small loadings, and the upper limit eliminates the excess adsorption. The mean selectivity coefficients are given in Table I. The data show that the organic cations are more strongly adsorbed on bentonite than on lewatite.

The selectivity order on bentonite was found to be: choline < amphetamine < phentermine < mephentermine < diethylpropion < levamisole < imazalil. This selectivity order is explained by the charge delocalization principle, which is also operative in the case of alkylammonium ions (9–11), histammonium, and ethyldiammonium ions (12). This principle states that selectivity increases with the increasing delocalization of the positive charge over a molecule.

We have calculated the charge on the N and the groups directly attached to it by CNDO/2 (13). This charge divided by the van der Waals volume is a measure of the charge density, as shown in Table II. Figure 7 shows that there is a linear correlation between the charge density and the average exchange selectivity coefficient of the organic cations investigated. There is a deviation for choline, but this is probably due to the absence of a phenyl ring.

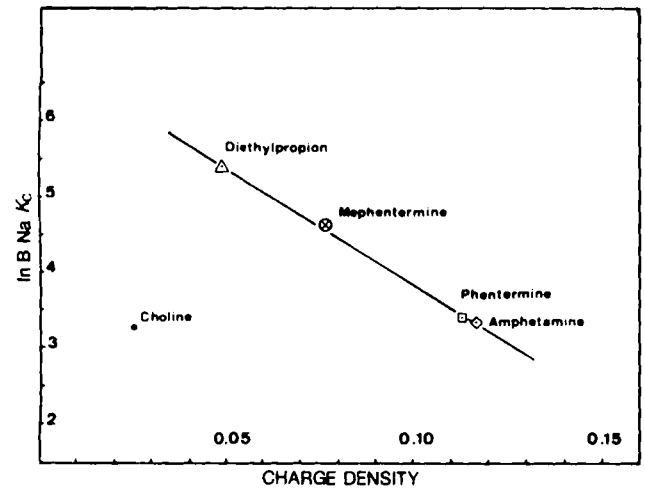


Figure 7—*The selectivity coefficient of exchange as a function of the charge density of the ammonium group.*

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