Molecular Orbital Calculations for Parabens: A Possible Mechanism of Action

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Abstract □ Molecular orbital calculations were carried out on the series benzoic acid, *p*-hydroxybenzoic acid, methylparaben, and ethylparaben. The characteristic trends of this entire series of preservatives are demonstrated by these members. The computer program used was Iterated Extended Hückel Theory. These systems were characterized in terms of atomic charge distributions, effect of hydroxyl and ester groups (both sterically and electronically), preferred molecular conformations, and distinguishing features of molecular orbitals. Through this approach, it was hoped that a common mode of action for all members of this series could be detected and that the trend(s) in this feature would correlate with known trends in activity of members of this series.

Keyphrases □ Orbitals, molecular—calculations for substituted benzoic acid series, atomic charge distributions, effect of hydroxyl and ester groups, preferred conformations, pharmacokinetics, structure–activity relationships □ Benzoic acids, substituted—molecular orbital calculations, pharmacokinetics, structure–activity relationships □ Pharmacokinetics—substituted benzoic acids, related to molecular orbital calculations □ Structure–activity relationships—substituted benzoic acids, molecular orbital calculations related to mechanism of action □ Preservatives—substituted benzoic acids, molecular orbital calculations, pharmacokinetics, structure–activity relationships

During the past 10 years, the mechanics of interaction between drugs and receptor sites have been intensively scrutinized in the hope of describing these interactions and their nature, rate, and steric dependence in terms of chemical and physical parameters. Several investigators (1–10) attempted to relate molecular parameters such as bond lengths, acid–base character, energy levels, and orbital types to drug action (activity).

Because drug systems are extremely complex, a simplistic correlation between activity and some scaling factor of molecular parameters has not often been found. The mechanism of action of phenol-type disinfectants has been discussed from the point of view that phenol interrupts cellular transport and permits "leakage" of essential cell constituents into the extracellular fluids (11–13).

Various organic acids have been shown to elicit different antibacterial mechanisms of action depending on their molecular structure. It is the molecular structure of these acids that influences the ease with which they penetrate the cell, the part of the cell they attack, or the chemical nature of their attack (14).

The possible mode of action of benzoic acid has been postulated to be membrane action and competition with coenzymes (15). To date, the esters of *p*-hydroxybenzoic acid and vanillic acid are thought to act in the same manner as benzoic acid; however, further study is required to clarify or substantiate this hypothesis.

EXPERIMENTAL

The Iterated Extended Hückel Theory molecular orbital calculations were carried out by computer[1]. The program, a modification of Hoffmann's Extended Hückel Theory (EHT) program (16), was designed to iterate until charge consistency was attained. Input parameters were chosen that have been widely used in the application of semiempirical LCAO methods. This choice gave the calculations a relevance not obtainable with other, less well-recognized parameters. These input parameters included the molecular cartesian coordinates, Slater-type orbital exponents, a rough guess at atomic charges, valence state ionization potentials, a test limit of 0.002 (in units of charge distribution) to define a converged distribution, a weighing factor of 9/10 to control the charge correction with each iteration, and the maximum number of iterations to be carried out.

Cartesian coordinates were calculated by use of the CORCAL computer program (17), for which the input data included the molecular geometry in terms of bond angles, bond lengths, bond attachments, and dihedral angles. The molecules were situated with the phenyl ring in the x–y-plane, with the x-axis in the direction of the ester fragment. Upon rotation of the carbonyl fragment out of this plane, the carbonyl oxygen was directed in the positive z-direction.

The crystal-morphological X-ray data used to generate these coordinates were obtained for benzoic acid from the work of Sim *et al.* (18). Estimates of corresponding data for esters of *p*-hydroxybenzoic acid were based upon previously established crystallographic work for esters of various types, such that bond angles and bond lengths represent typical values (19–24).

Values for the orbital exponents, derived from Slater's rules, were as follows: carbon 2*s* and 2*p*, 1.625; nitrogen 2*s* and 2*p*, 1.95; oxygen 2*s* and 2*p*, 2.275; and hydrogen 1*s*, 1.2. The value of 1.2 for the hydrogen 1*s* orbital has been found to produce better results in several applications than the traditional value of 1.0.

Valence state ionization potentials given previously, (25, 26) were used as coulomb integrals, which, in turn, were used to obtain resonance integrals by use of the Cusachs formula (27).

All calculations were carried out with iteration to charge consistency. In this procedure, coulomb integrals were adjusted for atomic charge after each iteration, and the calculation was repeated until input and output charges matched within the present limit of 0.002 unit of charge.

RESULTS AND DISCUSSION

If one accepts the premise that a pattern of essential atoms and groups in a drug molecule must bear some distinct relationship to complimentary features on a receptor molecule, then it follows that the spatial relationships of these essential moieties must be identified in order to relate structure to biological activity. Therefore, an understanding of the electron density distributions within the various fragments of the drug moiety and an understanding of the drug molecule stereochemistry are critical to a deduction of the nature and/or topology of the receptor.

Important also is the relationship among the molecular orbital-calculated conformation, the X-ray crystallographic-determined conformation, and the conformation of a substance in solution. To this end, it must be remembered that molecular orbital calculations are carried out on a single isolated molecule, without considering the perturbations introduced by a neighboring molecule(s) or solvent, and crystal studies are done on a molecule frozen into an array of its kind. The solution-derived conformations are those of a molecule surrounded by solvent.

A recent question regarding molecular orbital-calculated conformations has been raised as to whether drug molecules treated in

[1] IBM 360/50.

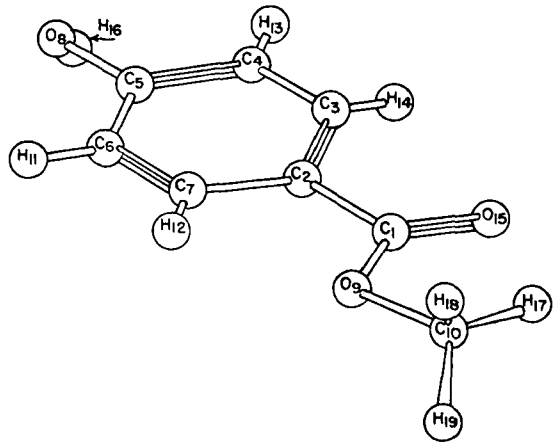


Figure 1—*Illustration of methylparaben in the planar,* cis-*conformation. See* Discussion *and Table I.*

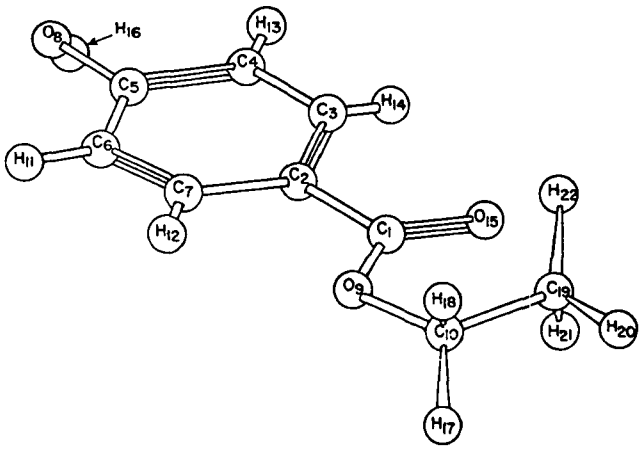


Figure 3—*Illustration of ethylparaben in the planar,* cis-*conformation. See* Discussion *and Table I.*

such a manner can be used to map complementary features of a receptor (28). Two working hypotheses have evolved in an effort to answer this question. One hypothesis, used in molecular orbital studies, is that these molecules engage the receptor in their preferred conformations. An alternative hypothesis is that the receptor is capable of a significant perturbation influence on a drug molecule within its vicinity and that a nonpreferred conformation engages the receptor. This hypothesis is not in violation of the concept that optimum stereochemistry maximizes efficacy, since the perturbed conformation could arise from the initial presentation of the drug molecule in its preferred conformation (29–32).

The graphic representation of several configurations considered in this study are given in Figs. 1–4. In Fig. 1, the methyl ester fragment of methylparaben is shown coplanar with the ring and the methyl group is directed toward the carbonyl oxygen. This arrangement can be called the "planar, *cis*"-conformation ("*cis*" implying that the carbonyl oxygen and methyl carbon are *cis* with respect to the C-1—O-9 axis). A rotation of 90° about the C-1—C-2 bond axis produces a "perpendicular, *cis*"-conformation. Subsequent rotation by 180° about the C-1—O-9 bond axis yields the "perpendicular, *trans*"-conformation (Fig. 2).

A planar, *cis*-conformation of ethylparaben is given in Fig. 3. A 180° rotation about the O-9—C-10 bond axis yields the planar, *trans*-conformation. Three perpendicular conformations were studied. A perpendicular, *cis*-conformation is obtained by a 90° rotation of the ethyl ester fragment about the C-1—C-2 axis of the planar, *cis*-conformation. A perpendicular, *trans*-conformation (perpendicular, *trans* A in Tables I and II) is obtained by an analogous rotation about the C-1—C-2 axis in the planar, *trans*-conformation. Subsequent 180° rotation about the C-1—O-9 bond axis in the planar, *trans*-conformation yields the conformation shown in Fig. 4 (perpendicular, *trans* B in Table II).

Other conformations not shown in this series are the "planar" configurations of benzoic acid and *p*-hydroxybenzoic acid in which the carboxyl group is coplanar with the ring (carboxyl hydrogen *cis* to carbonyl group), and the "perpendicular" configurations of these two systems in which the carboxyl group lies in a plane perpendicular ring. Table I illustrates the charge distributions within the various compounds and conformations studied. Table II shows the total molecular energy as well as that of the Highest Filled Molecular Orbital (HFMO) and Lowest Empty Molecular Orbital (LEMO).

From resonance arguments, it can be said that *p*-hydroxybenzoic acid as well as its esters forms stable resonance structures when the carboxyl group is coplanar with the ring. Therefore, it is expected that molecular conformers that tend to retain these configurations would be more stable than conformers that restrict this resonance. However, the relationship of molecular orbital theory, X-ray crystallography, and solution and biological conformers must be kept in mind as the analysis of the data progresses.

The following analysis of the data uses a charge/HFMO/LEMO/configurational energy approach to study effects of various substituents and conformers, both by trends and by discontinuities within these trends.

The analysis can best be carried out by considering the compounds as they relate to each other by a common parameter.

Energies—From the total energies given in Table II, it can be

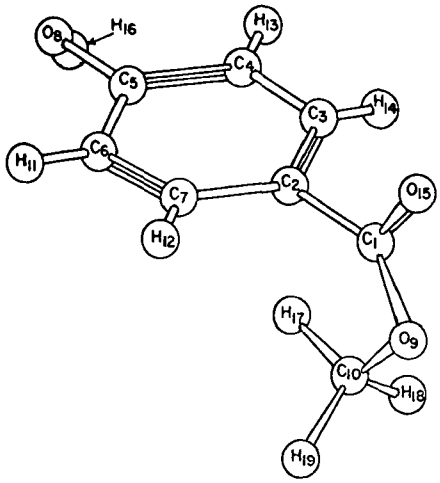


Figure 2—*Illustration of methylparaben in the perpendicular,* trans-*conformation. See* Discussion *and Table I.*

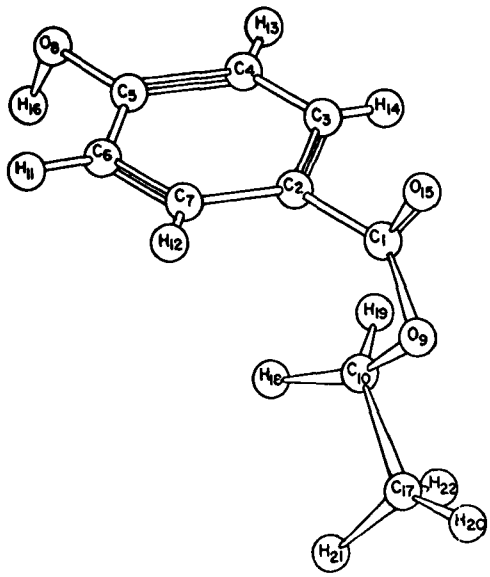


Figure 4—*Illustration of ethylparaben in the perpendicular,* trans-*conformation. See* Discussion *and Table I.*

Table I—Net Molecular Fragment[a] or Atomic Charge Distributions

Compound	Figure or Conformation	H—O	C-5	[b]	C-2—C-1	O-15	—C(=O)—O—R	O-9	R
Benzoic acid	Planar	—	0.004	0.050	0.183	−0.285	−0.183	−0.172	0.125
Benzoic acid	Perpendicular	—	0.0006	0.048	0.184	−0.286	−0.180	−0.171	0.128
p-Hydroxybenzoic acid	Planar	−0.132	0.088	0.189	0.178	−0.286	−0.195	−0.178	0.125
p-Hydroxybenzoic acid	Perpendicular	−0.176	0.084	0.205	0.194	−0.281	−0.168	−0.170	0.129
Methylparaben	1	−0.172	0.086	0.192	0.170	−0.293	−0.156	−0.208	0.210
Methylparaben	Perpendicular, *cis*	−0.186	0.081	0.184	0.166	−0.296	−0.157	−0.213	0.220
Methylparaben	2	−0.186	0.077	0.201	0.192	−0.299	−0.146	−0.207	0.220
Ethylparaben	3	−0.157	0.087	0.184	0.167	−0.278	−0.142	−0.217	0.218
Ethylparaben	Perpendicular, *cis*	−0.180	0.080	0.180	0.178	−0.274	−0.131	−0.210	0.207
Ethylparaben	Planar, *trans*	−0.158	0.086	0.180	0.159	−0.299	−0.153	−0.218	0.236
Ethylparaben	Perpendicular, *trans* A	−0.180	0.083	0.198	0.184	−0.291	−0.154	−0.206	0.196
Ethylparaben	4	−0.184	0.077	0.182	0.176	−0.300	−0.128	−0.210	0.247

[a] Entries in each column are the sum of the net atomic charges for each atom indicated in the column headings. [b] The hydrogens attached to the ring have been ignored.

seen that the most stable conformations are exhibited in compounds that have a planar and linear configuration, as expected; the next most stable conformation in the ester series is the perpendicular dangling chain (under the ring and down). Conformational changes are also reflected in changes in the LEMO energies but not to a great extent in the HFMO energies.

All planar conformations exhibit a LEMO energy of 8.6 ± 0.2 ev, and all perpendicular conformations exhibit a LEMO energy of 7.7 ± 0.2 ev. With only the exception of the planar and perpendicular, *cis*-conformation of ethylparaben, all esters as well as the parent acid and hydroxy derivative exhibit HFMO energy of 10.3 ± 0.2 ev.

Several additional comparisons can be made in terms of the total energies within the ethyl ester series:

1. The destabilization exhibited in the total energy and in the LEMO energy caused by rotating the ester group out of the plane of the phenyl ring (planar *versus* perpendicular, *cis* or planar *versus* perpendicular, *trans*) parallels the change in the methyl ester series and in *p*-hydroxybenzoic acid itself.

2. Of the two cases where there is a linear extension of the ethyl group away from the ring (planar and perpendicular, *trans*), the planar case is again more stable.

3. In the two planar cases, hooked and linear (planar, *cis versus* planar, *trans*), there is an increase in stabilization when going from the hooked to the linear configuration.

4. In the perpendicular-and-under-the-ring-and-down configuration (Fig. 4), the molecule is quite comparable to the most stable conformation (planar, *trans*); in this orientation, the whole ester substituent cannot participate in resonance stabilization or hydrogen-bonding stabilization, as is possible in the planar, *cis* molecule.

These comparisons lead to the conclusions that the molecule will tend to resonance stabilize if given a chance [this is also evident throughout the whole series (Table II) and is primarily reflected in the more stable energy of the LEMO as well as in the total energy] and that there is no significant evidence that intramolecular hydrogen bonding exists or plays an important role in molecular stabilization.

Charge Distribution—It is expected that absence of a *para*-substituent would markedly decrease the tendency for resonance stabilization and minimize charge redistribution with conformational changes. This result is shown in Table I in the case of benzoic acid. In *p*-hydroxybenzoic acid, however, where such stabilization can take place, there is a significant redistribution of charge with conformational change.

As the carboxyl group is moved from a position perpendicular to the plane of the phenyl ring to a coplanar position, there is a generalized redistribution of charge, notably involving a more negative charge on the hydroxyl fragment in the perpendicular case, when resonance is prevented. A maximum or near maximum negative charge is also observed in the ester cases when resonance is prevented, *i.e.*, when the ester fragment is perpendicular to the phenyl ring.

LEMO and HFMO Character—When considering possible charge-transfer or Lewis acid–base mechanisms of action, consideration is generally given to the HFMO and LEMO of a molecule as a result of energy matching criteria. In this instance, HFMO energies are significantly higher than the energy of the next highest filled molecular orbital, as expected, but the first *two* empty molecular orbitals are nearly degenerate in cases where the ester fragment is perpendicular to the phenyl ring. In the planar conformations, the second empty molecular orbital is significantly higher in energy than the first and need not be considered.

Comparisons show that when the members of this series are held in a planar conformation in which the alkyl portion of the ester fragment is directed away from the carbonyl oxygen (*trans*), the

Table II—Total Molecular, HFMO, and LEMO Energies[a]

Compound	Conformation	Figure	Total	HFMO	LEMO
Benzoic acid	Planar	—	−748	−10.453	−8.796
Benzoic acid	Perpendicular	—	−748	−10.416	−7.925
p-Hydroxybenzoic acid	Planar	—	−862	−10.394	−8.610
p-Hydroxybenzoic acid	Perpendicular	—	−861	−10.449	−7.801
Methylparaben	Planar, *cis*	1	−953	−10.203	−8.598
Methylparaben	Perpendicular, *cis*	—	−946	−10.117	−7.658
Methylparaben	Perpendicular, *trans*	2	−951	−10.158	−7.597
Ethylparaben	Planar, *cis*	3	−1045	−8.642	−8.590
Ethylparaben	Perpendicular, *cis*	—	−1042	−8.680	−7.722
Ethylparaben	Planar, *trans*	—	−1049	−10.157	−8.521
Ethylparaben	Perpendicular, *trans* A	—	−1044	−10.146	−7.694
Ethylparaben	Perpendicular, *trans* B	4	−1045	−10.124	−7.636

[a] All energies are given in electron volts (ev).

HFMO's are all very similar. When the alkyl group of the ethyl ester is oriented in close proximity to the carbonyl groups (*cis*) in either the planar or perpendicular orientation, the HFMO contains antibonding contributions from the methyl fragment and the energy of this orbital is destabilized with respect to the HFMO's of other members of the series.

The LEMO character falls into two categories, either a delocalized π-type or an antibonding carbonyl π-interaction. When planar, the LEMO's of all members of this series are delocalized orbitals over the ring and carbonyl group. When the ester fragment is perpendicular to the ring, the LEMO and second empty molecular orbital form a near degenerate set of molecular orbitals in which one is an antibonding carbonyl π-orbital and the other is a delocalized π-orbital different from those in the planar cases.

While these characteristics cannot substantiate a specific mechanism of action for members of this series, the use of these results for formulations of possible modes of action is possible. In this hypothesis, it is assumed that all members of the series function in a similar fashion; that is, the known increase in biological activity with alkyl group length is assumed to result from an increasingly facilitated mode of action as the chain is lengthened.

In two conformations, there is a series-wide similarity in several properties. First, when the molecules are held in a planar configuration in which the ester fragment is extended at the maximum distance from the carbonyl group and also in the planar configuration of benzoic acid, the energies are all at the configurational minimum for each member. The charge distribution (Table I) also shows a minimum charge on the hydroxyl group (corresponding to resonance stabilization, which is maximized in this orientation), and the HFMO and LEMO characters and energies are all very similar.

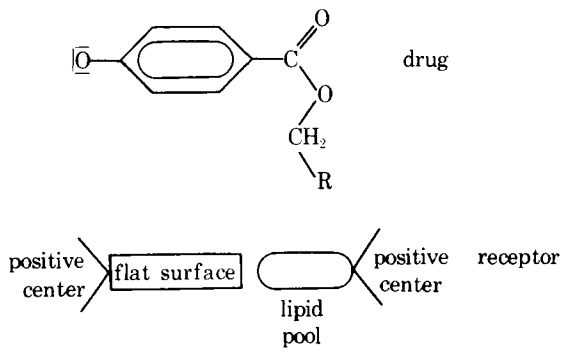
Second, when the next most stable conformer is examined, the perpendicular, *trans*-conformer of methylparaben and the ethylparaben conformation shown in Fig. 4, as well as the perpendicular conformation of *p*-hydroxybenzoic acid, are included. In this series, the negative charge is maximized on the hydroxyl group (resonance is prevented), the HFMO energy and character is very similar for all members, and the first two empty molecular orbitals form a near degenerate set, which is virtually identical in both cases.

The remaining conformers have fewer similar characteristics and/or are higher in energy.

While it is entirely possible for the biological activity of the parabens to be associated with the most stable configuration of each member of the series, it is also possible that it is related to the ability of these molecules and/or receptor sites to be mutually perturbed. Hence, hypotheses of action could be based on either ground-state geometry or the next most preferred geometry. This latter possibility and the similar characteristics of all members of the series and proposed receptor site (discussed later) when in this geometry suggest a mechanism in which the alkyl group of the ester fragment is directed downward from the ring. In this conformation, all of these compounds may react with a similar sized receptor site on a bacterial cell wall or membrane, for example.

Since these conformations of the perpendicular methyl and ethyl esters differ only by the length of the ester chain, lengthening of this chain could serve to increase still further the lipid solubility or site stability of the compound (discussed later). Previous solubility studies (23) substantiated this idea. In comparing the spatial requirements of this conformation with that of the most stable conformer, it also should be noted that the receptor site geometry would be required to change with the increasing alkyl group size of the ester in its most stable geometry (planar, with the alkyl group extending away from the carbonyl group). With this working hypothesis, a reasonable receptor site would be one consisting of a lipid area or areas in which alkyl groups of varying lengths for the ester chain are solubilized, sites of positive or negative charge resulting from ionic or ion–dipole interactions with protein functional groups, and relatively uncharged areas composed of hydrocarbon fragments. Such a general model utilizing these features is given in Scheme I. This scheme suggests an interaction of these intact esters with the site such that their alkyl ester group would be buried in the lipid pool, the phenyl group would be in the vicinity of a relatively nonreactive hydrocarbon fragment, and the hydroxyl fragment would be attached to a center of positive charge.

As indicated previously, the negative charge on the hydroxyl



Scheme I—Theoretical receptor for the postulated active form of the paraben preservatives

group is maximized in the perpendicular conformation. With such a model, it is not unreasonable that all paraben esters would present a −10.4-ev lone-pair molecular orbital primarily localized on the carbonyl oxygen and a pair of nearly degenerate empty molecular orbitals of carbonyl antibonding π^* and delocalized ring π symmetries at −7.6 ev, which could interact by a charge-transfer or an acid–base interaction with molecules and thereby prevent normal cell membrane transport. Notably, all parabens could operate in a similar fashion at the molecular level, and the increase in effectiveness as a series is ascended would be directly proportional to the solubility of the compound. Therefore, solubility (at a receptor site and in transport) could become a primary factor in determining the amount of drug reaching the receptor site and interacting with the site, superseding the factor of chemical reaction whose characteristics change with alkyl chain lengthening.

Such a mechanism easily rationalizes the observed trend in activity from phenol < benzoic acid < *p*-hydroxybenzoic acid < ester and in the ester series from methyl < ethyl < propyl < butyl. *p*-Hydroxybenzoic acid would not be as lipid soluble as the methyl ester and may not readily be at such a site. Phenol and benzoic acid, while they may engage in the same mechanism of action, do not have the same functional groups to act in precisely the same manner as the later members of the series.

According to this hypothesis, the activity of these compounds should increase as the lipid portion of the molecule, the ester chain, becomes larger, since it may act as an anchor to retain the molecule at the site for a longer period. If sufficient sites are filled, cell function may be interrupted, causing the observed biological effect. As noted, biological activity does indeed increase as the ester chain increases.

In conclusion, Iterated Extended Hückel Theory molecular orbital calculations were carried out on a series of parabens. By use of characteristics common to all members of the series when each is held in a configurationally similar geometry, a working hypothesis was constructed for a mode of action for members of this series. In this proposed model, each member interacts with a receptor site through dipole–dipole interactions at the hydroxyl group and lipid solubilization of the ester alkyl fragment when the ester fragment is perpendicular to the ring plane. Each member also presents a -10.4 ± 0.2 ev HFMO of lone-pair symmetry on the carbonyl oxygen and a pair of nearly degenerate empty molecular orbitals of delocalized ring π and carbonyl antibonding π^* symmetries at −7.6 ev, which can interact with other portions of a receptor site or possibly restrict the activity of another molecular system through an acid–base or charge-transfer mechanism.

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ACKNOWLEDGMENTS AND ADDRESSES

Received March 15, 1974, from the *College of Pharmacy, University of Rhode Island, Kingston, RI 02881*

Accepted for publication August 8, 1975.

Abstracted in part from a dissertation submitted by K. S. Alexander to the Graduate School, University of Rhode Island, in partial fulfillment of the Doctor of Philosophy degree requirements.

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Controlled Flocculation of Coarse Suspensions by Colloidally Dispersed Solids I: Interaction of Bismuth Subnitrate with Bentonite

HANS SCHOTT

Abstract □ Deflocculated suspensions of coarse powders tend to cake as the individual particles settle out and form compact, cohesive sediments. Limited flocculation results in looser sediments because the settled-out flocs incorporate large amounts of the liquid suspending medium. Controlled flocculation of bismuth subnitrate suspensions was achieved by the addition of small amounts of bentonite. The interaction of the coarse, positively charged bismuth subnitrate particles in aqueous suspension with negatively charged, colloidally dispersed bentonite was investigated by measuring electrophoretic mobility, sedimentation volume, and viscosity. Gradual addition of bentonite dispersion to bismuth subnitrate suspensions first reduced the ζ-potential of the bismuth subnitrate particles from +28 mv to zero, then inverted it, and finally caused it to level off at −20 mv for bismuth subnitrate–bentonite weight ratios below 200. Owing to the much greater specific surface area of bentonite, the surface of the bismuth subnitrate lath-shaped crystals was completely covered by 0.5% of its weight in clay platelets. Adhesion was promoted by electrovalences between surface bismuthyl ions and cation-exchange sites of the clay and by secondary valences. The charge neutralization of bismuth subnitrate by bentonite was a heterocoagulation process: the addition of small amounts of the clay flocculated the bismuth subnitrate suspensions and eliminated caking. While the ζ-potential of the bismuth subnitrate particles leveled off when their surface was saturated with bentonite platelets, sedimentation volume and viscosity continued to increase when the clay concentration was increased further while maintaining the bismuth subnitrate concentration constant. The excess, nonadsorbed bentonite formed the characteristic house-of-cards structure, incorporating the bentonite-coated bismuth subnitrate particles as cornerstones.

Keyphrases □ Flocculation, controlled—coarse suspensions by colloidally dispersed solids, interaction of bismuth subnitrate with bentonite □ Suspensions, coarse—controlled flocculation by colloidally dispersed solids, interaction of bismuth subnitrate with bentonite □ Colloidal dispersions—controlled flocculation of coarse suspensions, interaction of bismuth subnitrate with bentonite □ Bismuth subnitrate—coarse suspension, controlled flocculation by colloidally dispersed bentonite □ Bentonite—colloidal dispersion, controlled flocculation of coarse suspension of bismuth subnitrate

The kinetic units in extensively deflocculated suspensions are primary particles or small aggregates. When approaching the bottom of the container during sedimentation, these particles can slip past one another, each seeking the lowest possible point, and settle down next to each other. They pack efficiently to produce compact, dense solid layers. The interparticle attraction in such compact sediments is high because the interparticle distances are small and the London–van der Waals forces, which decrease approximately with the seventh power of the distance, are consequently appreciable. Such conditions frequently lead to caking or claying, an undesirable phenomenon because it produces sediments that require extensive agitation for redispersion (1).

The kinetic units in flocculated suspensions are larger aggregates or flocs. They bridge easily when settling out and produce loose, voluminous sediments containing large amounts of trapped liquid suspending medium. Such sediments are easily redispersed into the original