# APPLICATION OF QUANTUM CHEMISTRY TO DRUGS AND THEIR INTERACTIONS

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## INTRODUCTION

Whether or not quantum mechanics is the supreme intellectual accomplishment of man—an allegation that appears less of a conceit as one reads its history (1–3)—it has certainly fostered philosophical speculation (1, 4–7) and a great deal of very practical achievements. It is reassuring to learn that quantum mechanics does not exclude life (8) and at the same time that it can account for laboratory observations that otherwise elude explanation. Molecular orbital (MO) methods, which have been more widely applied than the other method of quantum mechanics (the valence-bond or resonance method), have explained many of the physical and chemical properties of molecules of interest to the chemist (9–15). Evidence is accumulating that MO methods can also explain the physical and chemical properties of large biomolecules and, by inference, their biological activities (16–18). The relative ionization potentials and dipole moments of a series of purines (18, 19) were consistent with those predicted ten years earlier in the Pullmans' laboratory by MO theory. MO calculations on biomolecules have yielded information in agreement with that obtained by nuclear magnetic resonance spectroscopy (20–23), infrared spectroscopy (20), X-ray diffraction analysis (21, 24, 25) and, reasonably, with circular dichroic spectra (26). In most of this work, the results of the calculations have clear biological implications even to enzymatic mechanisms (16, 17, 27–32). Many of the inferences from MO calculations have been supported by subsequent experiment, a surprising number in consideration of the simple methods available when this work began and the inherent shortcomings of even modern MO techniques.

Despite these successes in accounting for the biological *properties* of molecules, there has been much less effort to use quantum-mechanical methods to account for the biological *effects* of molecules. This relative lack is strange, because the first application of quantum mechanics in biology was to analyze carcinogenic hydrocar-

bons. This work, begun by the Pullmans in the mid-forties (16, 33, 34), showed electronic correlates of carcinogenicity that have in large part been sustained (16, 35–42) even though the techniques they were obliged to use in this early work were primitive. It was in fact this success with the carcinogens that stimulated the use of quantum mechanics in biochemistry (16). Applications to pharmacology were sparse (43) even into the late fifties and early sixties. At a symposium in 1965, a review and some calculations of indoles were presented, but the paper was mainly a hortative plea that quantum mechanics be applied to pharmacology (44). Enough work has since been done to have impelled several reviews (45–50).

It has become clear that an understanding of the reactions of drugs with tissues or tissue components must rest on an understanding of the fundamental particles that control these events, the electrons and atomic nuclei that comprise the drug and its receptor. Such understanding requires information about the structural features of the molecules, the energies and distribution of the electrons, and the spatial arrangement of the atomic cores. Quantum mechanics provides such a description of matter, and molecular orbital theory is a quantum mechanical approach conveniently adapted to large molecules. It can yield quantitative information on electronic structure and on the geometry of molecules. Excellent texts and reviews of molecular orbital theory and methods are available at varying levels of formalism (9–13, 16, 20, 51–67). For the purposes of this article in this short space, it is sufficient to describe the information that these methods yield, particularly that which is germane to this article.

Theoretically, all the properties of the molecule are described in the wave equation. But existing techniques fall considerably short of that goal. Until recently, MO methods were confined to Hückel (H) method which considers only the $\pi$-electrons, i.e. the delocalized electrons that are usually pictured as contributing to double or triple bonds but that are extended over the whole conjugated part of the molecule. This highly approximative method has accounted for some of the chemical and biological behavior of aromatic compounds, probably because the $\pi$-electrons are the determinants of activity in many of these compounds. From the H method was developed the $\omega$ modification and then the Parr-Pariser-Pople (PPP) method which unlike the H procedure, includes an approximation to interelectron repulsion. The Del Re method was developed to include the localized $\sigma$ electrons. A major step was taken with the simultaneous inclusion of both $\sigma$ and $\pi$ electrons: the extended Hückel (EH); CNDO (complete neglect of differential overlap) and modifications, e.g. CNDO/2; INDO (intermediate neglect of differential overlap); and the modified INDO (MINDO). Another approximate total valence technique is PCILO (Perturbative Configuration Interaction Using Localized Orbitals). Most recently various *ab initio* techniques have been applied to biologically interesting compounds (68–74). Not always do the all-valence and *ab initio* methods give a better account of aromatic properties than does the simple H (14, 60, 75–77), but the availability of these more sophisticated methods provides a means of studying saturated substances, saturated side-chains, conformation of molecules, and molecular interactions (73). The applications of these different methods to biomolecules has been reviewed (24, 73, 78), and their successes and failures in accounting for the proper-

ties of chemicals have been compared (14, 79–81). The enormous amount of work done with these methods on many different types of molecules vitiates any generality on their respective advantages. However, it is beginning to appear that the PCILO method gives a more realistic picture of molecular conformation than do other methods (21, 82). The CNDO/2 and INDO methods may best describe charge distributions, as they give dipole moments that most nearly correspond with measured ones, and the calculated electron densities correlate with the chemical shifts as measured by NMR spectroscopy (13).

In the development of these methods, the results of the calculations are compared with experimental facts; and in the semi-empirical methods, the method is adjusted to fit the laboratory results from, say, X-ray diffraction analysis, various spectroscopies, measurements of ionization potential, dipole moments, etc (14, 79–81). When results show agreement with laboratory findings in groups of molecules, the method is extended to other molecules. Although these methods evolve from abstract, inductive reasoning which historically was necessitated by anomalous laboratory findings that could not be explained by existing theories, they are rooted, as quantum mechanics has always been, in laboratory data. If the quantum chemical view of an electron is imaginary, then it is, like Marianne Moore's definition of a poem, "an imaginary garden with real toads in it."

As so much effort in quantum mechanics is directed to devise methods that reflect empirical laboratory findings, one may ask why not forego the computations and get on with the measurements. There are several practical reasons for using quantum mechanics. First, there is the hope, however wistful, that methodological advances will eventually provide a proper solution to the wave equation that will then yield all the properties of a molecule. Meantime the existing methods produce correct relative values of physicochemical measurements that can be determined by experiment either with great difficulty or not at all: resonance energies, dipole moments, ionization potentials, electron affinities, charges on atoms, transition states. And the studies can be carried out on molecules not yet available, the results of which can suggest what compounds to synthesize.

MO studies of molecular conformation proceed much more rapidly than by X-ray diffraction analysis and NMR spectroscopy. The conformation obtained by X-ray diffraction analysis is influenced by the free energy of crystal packing, which is not a consideration in a biological system. Crystal structure is influenced by intramolecular and intermolecular forces that may not occur in a biological system. Intramolecular forces, which are determinant of the conformation of large molecules like proteins, are less important in the conformation of molecules of pharmacological interest in a biological milieu; and intermolecular associations between two identical molecules are even less likely in a biological milieu. Also X-ray studies must often be done on salts of the compound of interest, e.g. acetylcholine chloride or bromide, which may not reflect the conformation of the free cation. Of great advantage in conformational studies is that MO calculations reveal the relative likelihood of occurrence of all possible conformers. At the very least, MO theory can account for the unmeasurable events that give rise to the observed ones, and in helping to interpret experiments it can suggest new ones. This assertion of the

value and purpose of molecular orbital studies in no way denigrates the value of other methods. Information from all sources will have to be used to infer the conformation of molecules at a biological site and the forces controlling their biological activities.

Studies of molecular conformation or geometry are carried out by calculating the energies of a series of possible configurations of the rotatable bonds. For example, the atoms of the side-chain of an aromatic biogenic amine, $-CH_2-CH_2-NH_2$, are rotated with respect to each other and with respect to the aromatic ring (the geometries of all aromatic rings are virtually planar and fixed). For each rotamer, the energies are calculated to determine the relative likelihood of existence of the various conformations.

Electronic characteristics are expressed as reactivity indices. The energy of the highest occupied molecular orbital ($E_H$) correlates with ionization potential and indicates ability of a molecule to donate an electron. It contributes to charge transfer complexation. The energy of the lowest empty molecular orbital ($E_L$) correlates with electron affinities and polarigraphic reduction potentials and indicates ability of a molecule to accept an electron. Also it contributes to charge transfer complexes. The electron density of atom r, $q_r$, describes the electronic charge in the region of the atom; it can be used to calculate dipole moments. The net charge of atom r, $q^n_r$, is obtained by subtracting from $q_r$ the number of electrons considered as contributed by that atom to the molecule. Frontier electron density in the case of an electron-donating reaction, $f^e_r$, is the electronic density in the $E_H$ associated with atom r. For an electron-accepting reaction, $f^n_r$, is the electronic density in $E_L$ associated with atom r.

Frontier density is associated with electron transfer rather than electrostatic interaction. Superdelocalizability ($S_r$) indicates the stabilization energy in the formation of a complex with another molecule; for an electron-donating reaction it is large when the electron density in the highest occupied orbital is large. The approximate superdelocalizability ($S'_r$) reflects the degree of contribution of the frontier orbitals to $S$: if the frontier electrons play a more significant role in the course of reaction than do the other $\pi$-electrons, the $S'_r$ would be a better index of reactivity than is $S_r$, for the latter, by including the other electrons, can obscure the contribution of the frontier electrons. These indices are relatively simple to calculate and are formally similar to other indices that have been described: $S_r$ to Wheland's localization energy, and $S'_r$ to Dewar's approximate localization energy (57, 61, 62).

Static indices such as $q_r$ have been surprisingly successful in correlating with chemical reactivity, probably because they mimic what is happening in the transition state: in the application of static indices, especially to a series of similar compounds, it is assumed that relative electronic structures are altered in a similar way or that the initial and transitional states are similar especially for very reactive molecules (83, 84). But it cannot be presumed that the electronic properties in the initial and transitional state are similar. Relative reactivity varies with the magnitude of the perturbation of the molecule by another (83, 84). $S$ and localization energy (and the formally equivalent indices) are dynamic indices that reflect the transition state during a chemical reaction. Perturbation theory has been expanded

(83–85) and considered in drug-receptor interactions (46). In another method (86) a transition state for the enzymatic reduction of acetophenone was approximated by calculating the interaction energy as a hydride ion approached the carbonyl group of the acetophenone. In addition the energy difference between the ground state and the approach to a transition state was calculated. Others have calculated the electrostatic energy generated around the molecule by the approach of a charge and applied these methods to biomolecules (73, 87, 88) and to cholinergic agents (89, 90). It is likely that these approaches will have wide application in pharmacology.



## SCOPE AND LIMITATIONS

Quantum mechanics is used as a tool to learn the molecular forces determining drug activity. This information can be used to infer the nature of the biological substances with which the drug reacts and hopefully as a guide to the synthesis of useful new agents. Like any other tool or any laboratory procedure, quantum mechanics can give rise to spurious or misleading information, and its use requires the same critical sense in resisting a too facile conclusion that one needs in evaluating data from ultraviolet spectroscopy, X-ray diffraction analysis, or from any other source.

MO theory has been used to study the conformation of drugs with the hypothesis that the results are applicable to the conformation of drugs at the receptor site and that the results can also help in the understanding of the structure of the active site of the receptor or enzyme reacting with the drug. In this work, the total energy of the molecule is calculated as a function of bond rotation with bond lengths and bond angles being held constant to avoid an impractical computing problem. It is clear, however, that the conformational energies are influenced by bond lengths and angles: the *ab initio* calculation (91) of acetylcholine (ACh) based on the bond lengths and angles from X-ray studies of ACh chloride showed the *gauche* form to be 3.2 kcal/mole more stable than the *trans,* whereas with the standard geometric input the *trans* form is 3.4 kcal/mole more stable than the *gauche* (91). Analogously, PCILO calculations based on geometric input from X-ray studies of ACh chloride or ACh bromide produced different preferred conformers of ACh (92). A similar ambiguity was found in studies of acetyl-α(R)-methylcholine (92), based on two geometric inputs derived from the same crystal. However, the differences are small (about 5 kcal/mole) and do not invalidate the conclusion that the most stable conformer is found in the vicinity of the theoretically calculated lowest conformation. Implicit in all this is the fact that X-ray studies present similar ambiguities, the salt form influencing conformation; and even in a single unit cell, one compound can have more than one conformation.

As it is unlikely that the conformation calculated to have the lowest energy is necessarily the conformer at the receptor, or the only important conformer, it is necessary to decide from the energy map what conformers are allowable. A consideration of 20 kcal/mole as an upper limit is high (93), for it often includes all possible conformers, i.e. the entire energy contour of mescaline is less than 10 kcal/mole (94). It is reasonable to suggest that all conformers within 6 kcal/mole

of the conformer of lowest energy be considered allowable. Within this falls hydrogen bonding energy, electrostatic forces, van der Waals forces, and usually charge-transfer energy. This range of energy minima could encompass environmental effects. MO studies do not otherwise consider the environment, a fault shared by laboratory studies of conformation carried out on crystals or simple aqueous solutions. Also, the probability of finding conformers in various energy minima depends not only on the differences in energy but also on the width of the energy minima.

Some MO methods like X-ray studies suggest important conformers with intramolecular interactions that may not occur in a solvent. The CNDO and INDO methods especially overestimate nonbonded attractive forces; the EH method underestimates them. The PCILO method gives conformations of drugs (95) more nearly like those found in crystals than do the other methods. The relative energies of specific rotamers vary with different methods, as has been shown for ACh (91–93, 96–98), but in this example, all methods showed the *gauche* form to be more stable than the *trans,* in agreement with experiment (99–104). Whatever ambiguities evolve from MO studies on conformation can be reduced by studying series of similar compounds, as pharmacologists and medicinal chemists and crystallographers have always done.

The other objective in MO calculations on drugs is to account for the relationship between chemical structure and biological activity. In this work, studies are made on a series of structurally related substances differing in potency but appearing to act on the same receptor. Environmental effects are not considered, as it is assumed that they would alter the relative electronic structures of similar compounds in a consistent way. Attempts are made to find electronic indices of reactivity that correlate, preferably in a quantitative way, with potency. From the correlation, one attempts to deduce some information about the receptor. Implicit in the correlation are predictions of the activities of compounds not yet tested, the synthesis and examination of which not only tests the initial inference but could result in interesting and useful new compounds.

MO theory considers the molecule as a unit, not simply its specific atoms or groups. For example, putting a substituent on an aromatic ring, e.g. a hydroxyl group on the ring of tryptamine, influences the whole ring system. The $\pi$-electron cloud now has a different shape, and the distortion results in the alteration of the reactivity of other atoms in the ring. A hydroxyl group in different positions of the ring (e.g. 4-, 5-, or 6-hydroxytryptamine) alters the electronic characteristics in different ways in atoms far removed from the hydroxy group (44). Each molecule has properties different from its component system. In some instances, particularly for saturated portions of a molecule, substitution leads to only small changes in the electronic properties of atoms remote from the site of substitution. This circumstance raises a question about the significance of these indices in regressions analysis programs. Examination of this question in a series of molecules led to the conclusion (105) that both CNDO and *ab initio* methods are probably adequate for predicting qualitative charge variations in atoms separated from a molecular modification by as many as three saturated bonds. In general, EH charges correlated with CNDO charges but were exaggerated approximately threefold. For atoms far removed from

the modification site, EHT predicted essentially random charge variations with respect to the CNDO results; therefore EH should be used with caution in structure-activity studies. This type of analysis indicates only that the CNDO and *ab initio* methods are reasonably self-consistent. The fact that these methods also yield quantitatively realistic estimates of certain experimentally measurable quantities, such as dipole moments, suggests that the calculated charge densities may be physically meaningful, although correlation of a charge term (or any other index) with biological activity does not imply a cause–effect relationship.

One of the hypotheses in this work is that the indices do in fact relate to chemical reactivity. Although many correlations between these indices and different types of chemical and biological activity have been found, there is no assurance that the indices describe reaction mechanisms. As noted above, the static properties of a molecule are probably different from those of the molecule when it is perturbed by a receptor or a chemical reagent, and the examples where MO theory correctly predicted chemical properties could be fortuitous, the ground state reflecting the perturbed state while still differing from it. Nevertheless, with the correlation is a testable prediction that depends on the assumption that the new compound(s) differ only quantitatively from the others. If it is found to differ qualitatively, the new finding may be more interesting than the correlation. If the quantitative activity is correctly predicted and with enough compounds, the inferences are supported, although it would be difficult to hold that the molecular mechanisms are truly understood (Ptolemaic astronomy accurately predicted eclipses) without independent chemical evidence.

Extrapolating from the electronic correlate of pharmacological activity to mechanism is less risky if the pharmacological activity is relatively free of competing reactions. A drug given to a whole animal is subject to many independent processes, all of which should have an independent correlate (44): absorption, distribution, binding to plasma proteins and other sites of loss ("silent receptors"), penetration through special membranes (e.g. the blood–brain barrier), enzymatic metabolism (sometimes to an active compound), and excretion. At the site of action, the compounds must have the same mechanism of action (drugs may cause the same gross effect by different mechanisms) and must act at the same site. At the site of action, potency is a function of both affinity for the receptor and intrinsic activity (106–108). The correlate is mechanistically more meaningful when the number of intervening biological steps are reduced to a minimum, e.g. intrinsic activity or $K_1$ for an enzyme inhibitor. When the biological measurement requires many intervening steps, e.g. the potency of hallucinogens, the hope for a simple correlate diminishes. One becomes dependent on the assumption that all compounds are similarly susceptible to the intervening reactions, e.g. metabolic destruction; one can use multiple regression analysis to find the independent variables that account for activity. Work reviewed below shows that more than one variable is often needed to account for the relative potencies of similar compounds. For even in an isolated system, e.g. a muscle in a bath, the relative potency of congeners in causing contraction is influenced by the activity of the metabolizing enzyme (109) and ability to penetrate the tissue (110).

In most studies trying to relate chemical structure to biological activity, it is assumed that agonists and competitive antagonists act at the same receptor, the latter having affinity but no intrinsic activity. This assumption may not hold for all compounds. For example, it has been suggested that the receptors for agonist and antagonist opioids differ (111). The nonselectivity of many antagonists, their faint structural similarity to their agonists, and their large size suggest that antagonists may not neatly fit the receptor but react with sites adjoining the receptor (106). Other experiments have shown the exquisite selectivity of some receptors, e.g. the muscarinic and nicotinic receptors (106), even in particulate material (112).

In view of all these complexities it is appropriate that studies attempting to account for pharmacological activity not be confined to one approach. As noted below, MO methods can be fruitfully combined with empirical methods (113) that account for properties, e.g. lipid solubility, imperfectly handled by MO methods (114). This eclectic approach could yield inferences about receptor mechanisms complementing those obtained by isolation techniques (112, 115).



## APPLICATIONS TO SPECIFIC SUBSTANCES

### *Cholinergic Substances*

On the basis of EH calculations (96, 116) the nature of the cholinergic receptor was suggested, the difference between nicotinic and muscarinic activity being determined by the conformation of the $-C-O-C-CH_3$ portion of ACh, 120° for the nicotinic site and 180° for the muscarinic site (96, 117). The interatomic distances for muscarinic activity were suggested to be: $N-O_1 = 3.0–3.4$ Å, $N-O_2 = 5.4–5.8$ Å [or 4.4–5.6 Å in a later paper (118)], and $O_1–O_2 = 2.2–3.4$ Å. Neither X-ray studies (119) nor INDO (93) CNDO (120) PCILO calculations (92) support such flexibility of $-C-O-C-CH_3$; all show this angle to be 180°. A similar model had been proposed (121, 122) without the aid of MO theory which also tried to explain the different activities of enantiomers: L(+)-muscarine is 700 times more potent than the D(–)-enantiomer, and D(–)-muscarone is three times more potent than the L(+)-enantiomer. The interheteroatomic distances of the enantiomers are the same. The deduction (96, 117) that the $N-O_1$ distance is 3.0–3.4 Å is not supported by the activities of rigid muscarinic compounds such as arecoline, pilocarpine, and others (123), in all of which the $N-O_1$ distance is 4.4 Å. Also, a model requiring three heteroatoms cannot account for the muscarinic activity of meprochol (123) which lacks a carbonyl oxygen or any analogous atom. Finally, the proposed model is a *gauche* form; the studies on three different types of rigid muscarinic agonists show that the *trans* form is active (124–126). It is interesting that preference of a *gauche* form is suggested by all MO calculations (although the *trans* form is not ruled out) and by X-ray (119) and NMR (99, 127–129) studies; yet work on rigid molecules show the *trans* form to be active at the muscarinic site.

All the MO calculations show that the positive charge of the onium head is spread out over the attached methyl groups, the nitrogen itself being electronegative as had been shown in another quaternary nitrogen compound (130).

The electronic structure of muscarine (131), nicotine (131), 3-acetoxyquinuclidine (132), and phencyclidines (89, 90) show clear analogies to that of ACh. Both the CNDO/2 and EH calculations (133) yield a relatively greater net negative charge on the carbonyl oxygen of carbamylcholine than that of ACh, a difference that fits with the suggestion (134) that the magnitude of this charge is a determinant of nicotinic activity.

The nicotinic activity of a series of nine compounds, mostly phenyl choline ethers, paralleled the H $E_H$ (135). The search for an atom-localized correlate of the activities of phenyl choline ethers showed that $S^E_{\frac{1}{2}}$ (135–138), $S^E_{\frac{1}{4}}$ (135), and $f^E$ of the ether oxygen (138) inexactly paralleled activity. These results could imply that these compounds may interact with the nicotinic receptor through a charge-transfer reaction involving electron donation from the phenyl ring or the ether oxygen or both. EH calculations of phenyl choline ether (139) showed that the distance separating the 2-position of the ring from the onium group is nearly the same as that between the carbonyl oxygen and the onium group in ACh.

All calculations on ACh show a positively charged carbon of the carbonyl group, which Wilson had suggested (140) reacts with a nucleophilic site on cholinesterase, and a positively charged onium head that reacts with the anionic site. All-valence electron calculations suggest that the enzymatic hydrolysis of acetylcholine is an exception to the postulate that hydrolysis usually occurs at a bond between atoms that both carry net positive charges (16). PCILO calculations showed that acetylthiocholine, which is a good substrate for acetylcholinesterase, is exclusively in the *trans* form (141) in agreement with X-ray (142) and NMR (127) studies.

The rate of hydrolysis of a series of nine phenyl acetates by butyrylcholinesterase, though not by acetylcholinesterase, correlated with $f^E_1$ (136, 137), suggesting that the carbon at the 1-position of the phenyl ring is involved in binding to the active site of the enzyme through electron donation. The positive $\pi$-charge, derived from the H method, on the phosphorus atom of three organophosphate congeners paralleled their potencies as inhibitors of cholinesterase, a relationship that was also obtained with diisopropyl phosphofluoridate and mepafox (143), in agreement with the idea that inhibitory potency depends on the affinity of the phosphorus atom for an electron-rich site of the enzyme. The potency of four nicotinic acid derivatives in inhibiting acetylcholinesterase correlated with $f^N$ of the carbonyl carbon (137), implying that this atom is the acceptor for electron transfer from a nucleophilic site in the enzyme, presumably the same site that attacks the carbonyl carbon of ACh. It was also suggested that the ring nitrogen binds to the anionic site of the esterase. One factor that tended to reflect cholinesterase inhibition in five carbamoylpiperidines was the net charge on the amide nitrogen, activity increasing as the nitrogen becomes more positive (144, 145). It was suggested that this circumstance increases the electrostatic attraction between the amide nitrogen and the serine hydroxyl group of the enzyme (146). The inference that a hydrogen bond is involved in the interaction of 3-hydroxyphenyltrimethylammonium derivatives with cholinesterase (147) was supported by $\sigma$-$\pi$ calculations on six of these derivatives (148). An EH calculation on the cholinesterase reactivator, pralidoxime (i.e. 2-PAM), showed that the oxygen atom is strongly electronegative (130) which could account for its serving

as a nucleophile in reactivating phosphorylated cholinesterase according to the mechanism proposed by Wilson (140).

Factors contributing to the potencies of 21 aryl-substituted styrylpyridines in inhibiting rat brain choline acetyltransferase correlated (149) with the sums of the $S^E$ and the sums of the total charges of all atoms on the aryl portion of the molecule (H method). These sums had been shown to correlate with partition coefficient (150).

Other MO calculations have been done on cholinergic agonists and cholinesterase inhibitors (151–158).

### *Adrenergic Substances*

Based on an EH study of ephedrine and ψ-ephedrine, a model for the alpha adrenergic receptor pharmacophore was proposed involving a *trans* arrangement of phenyl and amino groups and a β-OH to amino nitrogen distance of 2.9 Å (159). Favorable and unfavorable arrangements of the phenyl ring and α-methyl groups were proposed to explain the rank order of potency of the four ephedrine isomers. This model was supported by the X-ray crystallographic study of (–) norepinephrine (160) and a subsequent EH study of the same molecule (161). The distance of the β-OH to center of the ring was shown as 2.5 Å (158) and changed to 3.6 Å (162).

An INDO calculation on norepinephrine showed that the *gauche* arrangement of phenyl and amino groups was 2.5 kcal/mole more stable than the *trans* form, a difference that would not exclude either form as possible receptor pharmacophores (163). The O–N distance in either the *trans* or *gauche* conformations would be the same, 2.9 Å. PCILO calculations (164) on phenylethylamines as well as naphazoline, an α-adrenergic agent of significantly different structure, suggested a similar model for the α-receptor pharmacophore, a N to β-O distance of 2.8 Å, a N to ring center distance of 5.1 Å, and a N to ring plane distance of 1.3 Å. Some support for this model was provided by PCILO calculations (165) on α-sympatholytics having the molecular structure ϕ-O-C-C-N (e.g. piperoxan). The calculations showed preferred conformations for these antagonists that give interatomic distances like those noted above. It has been suggested that the selectivity for α- or β-receptors observed in norepinephrine or isoproterenol was due either to an effect of the N-alkyl group on *gauche/trans* conformational preference (166) or to changes in the charge of the onium group with substitution (167). Neither of these theories was verified by EH conformational studies or by CNDO and *ab initio* charge calculations (168). It was suggested that α-activity requires an unhindered onium hydrogen atom whereas β-activity depends on the presence of an alkyl substituent capable of dispersion interaction with the receptor, this interaction being optimal with the isopropyl group. Studies on rigid analogs of the phenylethanolamines (3-amino-2-phenyl-*trans*-2-decalols) cast considerable doubt on the significance of the MO preferred conformations: four isomers, one *trans* and three *gauche* arrangements of the β-OH and amino groups, were equipotent on α-receptors in the rat vas deferens (169).

CNDO calculations on norepinephrine and dopamine showed that the *gauche* forms were slightly more stable than the *trans*; it was suggested that an interatomic distance between two heteroatoms of about 6 Å was required for the uptake process

at adrenergic nerve terminals (170). In a related CNDO study of polyhydroxyphenylethylamines the following requirements for activity in long-term reduction of cardiac norepinephrine uptake were proposed: an interatomic distance between two heteroatoms of about 6 Å, ease of oxidation to 1,4-quinones by anion-radical mechanisms when a third hydroxyl group is present in the ring, and adequate uptake at the active site (171).

Other H calculations on adrenergic substances have been published (172, 173).

### *Dopaminergic Substances*

EH calculations (174) suggested that dopamine, unlike norepinephrine and ephedrine, could exist only in a *gauche* conformation, results allegedly supported by NMR data. These observations were used as evidence for dissimilarity in the adrenergic and dopaminergic receptors. Other EH calculations (175, 176) as well as NMR (175) and X-ray studies (177) showed the *trans* form of dopamine to be only slightly more stable than the *gauche* forms. A PCILO calculation also indicated that the *trans* and *gauche* forms had about the same energy (164).

A comparison of the two N–O interatomic distances in one of the *gauche* conformations of dopamine and the N–N and N–O distances in the EH preferred conformation of oxotremorine (178) led to the proposal that tremorogenic compounds react with the same receptor. To test this idea, 18 drugs, as different as possible from dopamine and oxotremorine yet with the appropriate heteroatom distances fixed in a rigid molecule, were examined for dopaminergic properties. The results were negative (179).

Inhibition of synaptosomal dopamine uptake by six antihistaminic pheniramines was correlated with the $E_H$ values from $\omega$-Hückel calculations (180). It is confusing that this is an inverse correlation: the greater the electron-donating capacity of the molecule, the poorer the inhibitory activity. The significance of the $E_H$ values in this study is not clear since both electron donating and withdrawing groups change $E_H$ in the same direction, and the $E_H$ orbital appears as an anti-bonding orbital, probably in artifact of the method of calculation.

### *Serotonergic Substances*

Based on EH calculations of 5-hydroxytryptamine (5-HT), which showed only one preferred conformation (extended), a model was proposed (181) for the serotonergic pharmacophore consisting of three heteroatoms separated by specific distances: hydroxyl to alkylamine of 7.0 Å, hydroxyl to indole nitrogen of 5.7 Å, and indole nitrogen to alkylamine of 5.8 Å. There appears to be little justification for including the hydroxyl group as a part of the model pharmacophore, because other tryptamine derivatives without this function are active at 5-HT receptors. The prediction that only the extended conformation is energetically allowed was not confirmed by a more extensive EH calculation (182). The extended conformation was only slightly more stable then the folded conformations. INDO (183) and PCILO (184) calculations indicated that the folded forms were more stable than the extended. However, the few kcal/mole differences in the energies of the various low-energy conformers did not warrant exclusion of any of them as pharmacophore models (182, 185, 186).

Both extended and folded forms have been observed experimentally (187–189). The fact that the extended form of 5-HT and the rigid LSD molecule have a somewhat similar arrangement of heteroatoms and the fact that LSD acts on the 5-HT receptors in many pharmacological systems were offered (181) as support for the postulated pharmacophoric pattern (also see section on hallucinogens).

The potencies of 5-substituted tryptamines in contracting the rat fundus strip correlated with the resonance contribution of the substituents to the indole ring (190) as estimated by the empirical resonance parameters. This result suggested that the effect of the substituent group on potency was related to an effect on the $\pi$-electron density of the indole ring. INDO calculations on a larger number of derivatives supported this hypothesis and demonstrated several correlations of potency with charge densities and frontier electron densities at the C-4 and C-5 positions of the ring (191). It was suggested that the greater potency of 5-HT was mainly due to the influence of the hydroxy group on the electronic structure of the indole ring.

In an effort to explain the neuroleptic activities of chlorpromazine and haloperidol, the EH-preferred conformations (192) of these compounds were compared with those of dopamine and 5-HT obtained in previous EH studies. The pattern of heteroatom distances in the neuroleptics was not consistent with the predicted conformations of dopamine but was stated to be similar to the serotonergic pharmacophore. The amine to hydroxy distance in 5-HT was stated to be 5.6 Å in this paper, whereas in the original study (181) and subsequent reviews (117, 193) this distance was given as 6.96 Å.

## *Histaminergic Substances*

Histamine has dual receptor activity: stimulation of $H_1$ receptors (e.g. guinea pig ileum) which is blocked by the conventional antihistamines, and stimulation of $H_2$ receptors (e.g. gastric secretion) which is blocked by burimamide (194). EH calculations on histamine showed two equally stable conformations with amino nitrogen–imino nitrogen interatomic distances of 4.55 and 3.60 Å (195). From molecular models of a potent $H_1$-antihistamine, triprolidine, an amino nitrogen-pyridyl nitrogen distance of 4.8 $\pm$ 0.2 Å was obtained, suggesting that the conformation of histamine relevant to $H_1$ receptor activity had a N–N distance of 4.55 Å; the second conformation with N–N of 3.6 Å was proposed as the $H_2$-receptor pharmacophore (195). NMR studies supported the EH conformations (196–198) but not those from other methods (199, 200). Only the extended form (equivalent to the postulated $H_1$ pharmacophore) was observed in crystals of histamine free base and histamine dication (201–203). Support for the extended form of histamine as the $H_1$ pharmacophore has also been provided by X-ray crystallography on the $H_1$-antihistamines, methapyrilene • HCl (204), and brompheniramine maleate (205). However, in the latter study the N–N distance was found to be 5.3 Å, considerably larger than the 4.6 Å predicted for the histamine pharmacophore. This comparison of histamine and antihistamine structures may be misleading because many of the latter do not have a nitrogen in a position analogous to the ring nitrogen of histamine. It is also questionable to assume that an aryl carbon atom could act as a ring nitrogen.

Comparison of EH calculations on histamine and molecular models of anti-ulcer compounds (which may not be appropriate) suggested a model for the $H_2$ pharmacophore involving two heteroatoms, 3.7 ± 0.2 Å apart, one with lone pair electrons in a $\sigma$-type hybrid orbital and the other involved in a $\pi$-electron system (206). It was stated that the model is supported by EH calculations of the preferred conformations of two anti-ulcer drugs, 2-phenyl-2-(2-pyridyl)thioacetamide (206) and prostaglandin $E_1$ (207). The rigid structures of two other anti-ulcer drugs give N–N or N–O distances of 3.8 Å in agreement with the model.

Several experimental studies argue against the proposed $H_1$ and $H_2$ pharmacophore models (195). N,N-dimethylhistamine, in which the *trans* isomer is preferred over *gauche* forms, is more active as a gastric stimulant than histamine and is less active than histamine on $H_1$ receptors (197). *trans*-2-(4-Imidazolyl)cyclopropylamine has weak but significant activity at $H_2$ receptors (208). EH calculated *trans/gauche* ratios for $\alpha$- and $\beta$-methyl- and N,N-dimethylhistamines are quite different, yet none of these compounds shows selectivity for $H_1$ or $H_2$ receptors; 2- and 4-methylhistamines, on the other hand, have very similar conformer ratios but show a marked difference in receptor selectivity (198).

The relatively high activity of 4-methylhistamine on $H_2$ receptors and very weak activity on $H_1$ receptors and the observation that the 4-methyl group precludes a planar extended conformation has led to a new model for the $H_1$ pharmacophore in which the ethylamine side chain is coplanar with the imadazole ring in a *trans* conformation with N–N distance of 5.1 Å (209).

### *Hallucinogens*

Early H calculations (210) on LSD suggested that its unusually high $E_H$ might account for the activity of this drug. In a series of seven hallucinogens (including LSD, tryptamines, and methoxyamphetamines) a good correlation was found between activity and H $E_H$ values (44, 211). These results were confirmed and extended by INDO calculations to 12 hallucinogenic methoxyamphetamines and to a series of N,N-dimethyltryptamines (212, 213). INDO calculations showed that $E_H$ values do not correlate with potency among structurally different hallucinogens (213). It is also worth noting that since $E_H$ values are sensitive to the conformation of aromatic ring substituents such as methoxy groups, care should be taken in interpretation of correlations based on calculations of molecules of uncertain geometry. $E_H$ values do not adequately explain the presence of hallucinogenic activity in dialkyl-substituted tryptamines as opposed to the lack of activity in the nonalkylated analogs. Recent INDO calculation (186) and modified H calculations (214) on some LSD analogs failed to uncover any relationship between hallucinogenic potency and $E_H$. Thus, it is not clear that $E_H$ is a realistic correlate of hallucinogen potency. This question can only be answered by testing the predictions stemming from apparent correlations with $E_H$ (212, 213). One such prediction, that 7-hydroxy-2-aminotetralin would be mescaline-like (213) has been experimentally verified in animals (215).

The question of whether a charge-transfer reaction is involved in the mechanism of action of these psychotomimetics as implied by the $E_H$ correlations has been approached experimentally by spectroscopic studies of donor-acceptor complexes.

Only moderate electron donating power among indoles and methylsergate was found, suggesting that LSD is not as good an electron donor as indicated by H calculations (216). A correlation was observed between hallucinogenic potency of eight methoxylated amphetamines and ability to form a molecular complex with the electron acceptor, 1,4-dinitrobenzene; three other amphetamines did not fit the correlation (217). It was suggested that the lack of correlation of $E_H$ values among the different hallucinogens (LSD, tryptamines, and amphetamines) and the relatively low potency of the latter two groups of drugs may rest on the fact that only a small proportion of a dose of these hallucinogens exists in the correct conformation for binding to the LSD receptor (94, 186). It has also been emphasized (44) that such a molecularly gross characteristic as high $E_H$, possessed by many substances, cannot explain so specific a biological activity, and that $E_H$ is probably correlated with a more subtle molecular characteristic.

It was suggested that the conformations of the hallucinogenic tryptamines (e.g. psilocin) and phenylalkylamines (e.g. methoxyamphetamines) at the receptor were such that their six-membered aromatic rings were congruent with the A ring of LSD, and their alkylamino nitrogens were congruent with the amino nitrogen of LSD (213). The stereochemical arguments upon which this model was based are supported by NMR studies (218) and biological experiments including the mescaline-like activity of rigid structures related to mescaline (215, 219). The proposed conformations of psilocin and mescaline are congruent with LSD within 3 kcal/mole of the global minimum (94). PCILO calculations on phenylethylamine (164) showed similar results. Thus only small energy barriers—less than the energy of a hydrogen bond—need to be overcome in order to attain close congruency. These energy barriers, however, could be sufficient to result in a relatively small amount of the appropriate conformer being available to the receptor, a circumstance that could partly account for the relatively low potencies of these compounds compared with LSD.

If LSD interacts with 5-HT receptors it is possible that a close congruence of the amines and aromatic rings is required for binding to the receptor. INDO calculations showed that the conformation of 5-HT having *closest* congruence to LSD was about 10 kcal/mole above the global minimum and 4 kcal/mole above a nearby local minimum (182, 183). A point should be made concerning this comparison of the energy of a particular conformation to an energy minimum. It is obvious that an energy minimum occurs due to specific stabilizing effects. In some cases, the stabilizing effects may be observed in the isolated molecule, but their presence in solution may be unlikely because of solvent effects. This may well be the situation for the global minimum in the 5-HT map because this conformation appears to be stabilized by N–H—$\pi$-electron hydrogen bonding (83). It is probably more reasonable in this case to compare the congruent conformation to the nearby local minimum.

EH calculations have also been made on cannabinoids (220).

## *Neuroleptics*

The phenothiazines have been a subject of interest since H calculations suggested (16, 210) that they could function as electron donors, which was supported by other

calculations (221–225) and, importantly, by measurements of ionization potentials (see 16, 223) and charge-transfer complexation (226, 227). There was no correlation between potency of neuroleptics (phenothiazines, butyrophenones, and others) and stabilization energies of their complexes with chloranil (227).

PCILO calculations (228) on promazine showed that it is folded along the N–S axis, the angle between the two planes being 140°. X-ray studies (229, 230) showed that chlorpromazine and two other phenothiazine tranquilizers are folded to the same degree. The degree of folding influenced the conformation of the side-chain, a finding supported by the PCILO calculations (228). EH calculations (192) on chlorpromazine and haloperidol showed similar distances between two heteroatoms, a conclusion not supported by the PCILO and crystallographic studies.



### *Other Neurally Active Substances*

PCILO calculations (231) indicated that three local anesthetics, with side-chains of different lengths, have allowable conformers in which the distance between the carbonyl oxygen and amino groups is about 4.1 Å. In other local anesthetics this distance was significantly less than 4.1 Å, and in cocaine the distance between these groups is large, about 5.7 Å. In cocaine the distance between the ester oxygen near the phenyl ring and the carbonyl oxygen of the other ester group is about 4.1 Å (231), and the possibility was raised that the cabonyl oxygen of cocaine is positioned similarly to the amino group of the other local anesthetics (231). The functional implication of this positioning is not clear. It is unlikely that an oxygen in cocaine functions as the amino group in other local anesthetics through their lone pair electrons. Quaternary amines, which lack a lone pair, are effective local anesthetics, and further, an amino group is not required for activity, e.g. benzocaine (232, 233). In the PCILO calculations (231) it was assumed that a *trans* relationship exists between the carbonyl oxygen and the amino group in both ethanolamino and propanolamino local anesthetics; studies on cyclic analogs suggest that a *trans* configuration is important in the ethanolamine derivative, whereas a *gauche* configuration is important in the propanolamine (234). Dreiding models of these cyclic compounds show that despite these different configurations, the distance between the ester oxygen and nitrogen atoms is 3.6–3.7 Å; in two other cyclic derivatives with activity this distance was 4.2 and 2.9 Å (234).

In one attempt to account for the relative potency of eight anilide local anesthetics, the interaction between each compound and the electron-acceptor thiamine was considered (235) because spectroscopic observations showed that local anesthetics form complexes with thiamine. Each compound was sterically oriented to the pyrimidine ring of thiamine to maximize the electrostatic attactions. Stabilization energy, calculated by the H method, tended to correlate with local anesthetic potency (235).

In a large and heterogeneous group of substances, ranging from methyl alcohol to tricyclic compounds, the ability to block excitation of a frog nerve was a function of the polarizability and the H $E_H$ (236). Examination of the data suggests that polarizability is a sufficient correlate of potency, the introduction of $E_H$ not significantly improving the correlation.

The conformations of five barbiturates obtained by the PCILO method agreed well with available crystallographic studies. Noncyclic aliphatic substituents tend to fold toward the barbiturate ring, whereas cyclohexanyl and phenyl substituents eclipse the bonds attached to C-5 of the barbiturate ring. The substituents had little effect on the atomic charges of the ring (237). EH and CNDO/2 calculations of 19 compounds, barbiturates, and related anticonvulsants, failed to reveal any electronic correlate with biological activity (105).

A correlation between the analgesic activity of six aryl ethers of imidazolinyl methanol, substituted on the benzene ring, could be accounted for by a combination of $E_H$ (Huckel) and the lipophilic substituent (238), suggesting that both charge-transfer and hydrophobic bonding are important in determining activity.

Other calculations of local anesthetics have appeared (239, 240). Morphine has been calculated by two methods (225, 241) and acetanilide (242) and salicylic acid (243) by the CNDO/2 method. Iproniazid was calculated by the PCILO method (244) and $\alpha$-aminobutyric acid by the EH method (245).



## *Metabolism*

MO calculations have been applied to the oxidation, reduction, and conjugation of pharmacological substances. Correlations with MO indices have sometimes been obtained.

The results of MO calculations on hydroxylation and oxidation allow no generality on mechanisms to emerge, and the conclusion of ten years ago, that metabolic hydroxylation is difficult to explain on the basis of the electronic properties of the ground state, appears valid today (246). Enzymatic hydroxylation of aromatic heterocycles occurs on electronegative sites, implicating electrophilic species like $OH^+$. No evidence for the occurrence of a hydroxyl cation has been found (247). It has been postulated that in some enzymatic oxygenations the attack is made by an oxygen with an oxenoid structure, defined as an electrophilic particle with six valence electrons (247), but it is not known how this could be formed from molecular oxygen. Hydroxylation of proline and lysine in collagen synthesis occurs on the carbons with the most negative EH charge, also suggesting an electrophilic mechanism (248). The rate of oxidative N-demethylation of six derivatives of 4-dimethylaminoazobenzenes, some of which are carcinogens, correlated with the H $\pi$-electron density on the amino nitrogen (249). The rate of O-demethylation seemed to depend on the net positive charge of the oxygen (250). The site of oxidation of purines by xanthine oxidase was suggested to be nucleophilic with $OH^-$ serving as a nucleophilic agent (251, cf 252). For oxidation by ceruloplasmin, amines seemed to require a high $E_H$, as deduced from the H method (253).

Four possible mechanisms were considered for dechlorination of chlorethanes by the microsomal oxidase system (254): (*a*) radical or anionic displacement of a H by an OH group; (*b*) insertion of an O between a C–H bond; (*c*) radical cleavage of either a C–H or C–Cl bond; (*d*) anionic displacement of a Cl by an OH group. Nine compounds were calculated by the iterative EH method. The rate of dechlorination did not correlate with the C–Cl bond order, the carbon charge, or the Cl charge, suggesting that C–Cl bond cleavage was not the initial rate-determining step. Simi-

larly, dechlorination did not correlate with C–H bond order, the carbon charge, or the H charge, suggesting that C–H bond cleavage, including insertion of an O in the C–H bond, was not the initial reaction. However, dechlorination did correlate rather well with the degree of electron deficiency in the most electron-deficient carbon valence orbital (the orbital involved exclusively in bonding to the Cl atom), which indicates that anionic attack by an $OH^-$ group might occur at this orbital. A fair correlation was noted between dechlorination and the number of nonbonding electrons on the Cl atom, suggesting that C–Cl cleavage may be by C–Cl—H–R bond formation with a proton of the enzyme. Preliminary results with $OH^-$ approach and $Cl^-$ loss indicate that initial bonding overlap of the approaching $OH^-$ group is indeed with the electron-deficient carbon orbital noted above and that C–Cl bond order (a measure of the strength of the bond) rapidly and preferentially drops as the $OH^-$ group approaches.

Among antimetabolites that inhibit dihydrofolate reductase studied by the H method, both the 2-amino group and N–1 in the antimetabolites were, by these calculations, shown to be more basic than the corresponding groups in folic acid (255, 256). Basicity was calculated by a method (257) that has been criticized (258) but which gave values that correlated with measured $pK_a$'s (259) and with potency in inhibiting the enzyme (260, 261). It was also suggested that for compounds to be active as substrates, the 4-substituent must have a positive charge greater than 0.1, which is reduced to a lower value by the enzyme, and are thereby displaced easily from the enzyme by other substrate molecules. In a challenge of these inferences, it was observed (262) that the *p*-aminobenzoylglutamic acid portion of the molecules was ignored in the calculations, that alkylation of the 2,4-diamino groups results in inhibitors with low activity, that insertion of phenyl groups in the pyrazine ring increases activity, and that the atom deduced to be most basic from calculations is not the one that is alkylated. It should be noted that ignoring the *p*-aminobenzoylglutamic does not imply that it is inconsequential; it is a necessary portion of the molecules, but, as it occurs in all analogs its contribution to the varied potencies of the molecules is constant and it would have a slight and consistent effect on the electronic characteristics of the pyrimidine portion of the ring. The fall in activity with alkylation could be attributable to a steric effect. Increased activity of phenyl derivatives could be accounted for by increased van der Waals or hydrophobic binding. The fact that the apparently most basic atom is not alkylated could be explained by factors other than basicity determining alkylation; also, the electronic correlate that seems to imply basicity may in fact indicate a more subtle kind of reactivity.

Inhibition of enzymatic conversion of orotic acid into uridine monophosphate by five orotic acid analogs correlated with $f_i^e$ by the H method (263).

Both the EH and CNDO/2 methods were applied to the analysis of ten acetophenones that are substrates for a reductase (86). In this work, attempts were made to mimic the reduction of the compounds by studying the effect on the carbonyl carbon of an approaching hydride ion and to calculate the energy differences between the approach to a transition state with the hydride ion and the ground state of the molecules. Although the correlations of substrate reactivity with the MO indices

were not quite as good as those obtained with the empirical constants, i.e. Hammett and Hansch, a significant correlation was found between charge density near the carbonyl carbon atom and $V_{max}$. Similar results were obtained with $E_L$ or incipient-transition state energy difference, which is the difference between the ground state energy and the energy in the presence of a hydride ion near the carbonyl carbon. The meaning of the correlation with the transition state energy difference is hard to understand, because the energy difference is greater with a greater $V_{max}$. The values for the electron density for the carbonyl group (0.3 Å above the carbon) do not vary much with substitution: less than 0.002 electron by CNDO. A further confusion is that the EH and CNDO/2 values are quite different in magnitude and sign.

With the PPP method, the rate of phosphorylation of 15 adenosine analogs tended to correlate with $f^c$ of N–3 (264). It was suggested that a magnesium chelate may form among this nitrogen, the 5'-hydroxyl group, and adenosine kinase. No evidence for such a chelate has appeared.

Data are not strong in supporting the idea that the rate of enzymatic acetylation of amines is reflected in $\pi$-electronic charge of the nitrogen atom (265). It was suggested that the rate of deacetylation reflected the dispositivity of the dissociable bond (265), but the data supporting this idea are also inconclusive. A dipositive bond is not required for deacetylation of acetylcholine (see above).

The H electronic charge on the hydroxyl oxygen of a series of coumarins seemed to reflect the extent to which they are conjugated in vivo (43), and H $E_H$ reflected the inhibition of histamine methyltransferase (222). The potency of ten coumarins in inducing hepatic drug-metabolizing enzymes could be accounted for by several regression equations (266): in one equation, the lipophilic component, $E_H$, and the net charges on the carbonyl carbon and oxygen while in another, the lipophilic component, $E_H$, and the net charges on the ring oxygen and the carbonyl carbon. The third and best correlation was the electronic transition energy (the difference between $E_H$ and $E_L$) and the net charges at the ring oxygen and carbonyl carbon. These and the other correlations, all obtained with the EH method, implicate in enzyme induction the –O-C–O portion of the molecule, perhaps as a site of electron transfer or of H-bonding. It was suggested that the electronic transition, indicating the excitation energy of the molecule, may reflect the free energy of reaction or activation. It may be interesting that inclusion of the electronic transition term made inclusion of the lipophilic term gratuitous.

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