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Quantum Organic Chemistry

Recent work has brought chemistry closer to its ultimate role as a branch of applied mathematics.

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Nearly 50 years ago Dirac remarked that the development of quantum theory had turned chemistry into a branch of applied mathematics. While this was true in the sense that exact solution of the appropriate Schrödinger equation would make it possible to predict in detail the behavior of any system, such exact solutions had at that time been obtained only for the simplest atoms and ions, composed of a nucleus and a single electron (H, He^+, Li^{2+}, and so forth), and even now direct solutions of the Schrödinger equation are still limited to the simplest of molecules (H_2^+, H_3^+, H_3). While Dirac's goal of replacing chemical experiments by calculations is therefore still very remote, quantum theory has nevertheless had a revolutionary effect on chemistry. The whole of current chemical theory is indeed based on a picture derived from approximate quantum mechanical treatments, and in recent years these have been refined to a point where quantitative calculations of chemical behavior are becoming possible.

Calculation of Atomic Energies

The primary objective of chemistry is to explain the way in which atoms combine to form molecules, to predict the reactions that atoms and molecules undergo, and to predict the rates of such reactions. All these objectives depend on an ability to calculate the energy of a collection of atoms as a function of their geometrical arrangement in space. If we plot the energy as a contour map in a many dimensional space—the dimensions corresponding to the variables needed to define the geometry—the minima will correspond to possible stable species (molecules) that can be formed from our collection of atoms. A possible chemical reaction will correspond to a crossing from one minimum to another. The ease of such a process will depend on the height of the energy barrier separating them.

If our object is to provide information of this kind in a manner useful to chemists, two major conditions must be met. First, the calculations must be accurate enough for the results to be chemically significant; in other words, they must be of "chemical" accuracy. Ideally, we should be able to predict the relative energies at different parts of our potential surface to within 1 kilocalorie per mole, and our molecular geometries should be accurate to 0.02 angstrom in bond lengths and 2 degrees in bond angles. Second, the calculations must not cost more than their chemical worth. How much this is will, of course, depend on their accuracy and reliability. If we could achieve chemical accuracy, the calculation for a reaction would be worth as much as we would be willing to pay for an experimental study. In the case of a really important reaction this might amount to several hundred thousand dollars. A less accurate treatment might still be of value as an adjunct to experiment, but in this case it would be worth only the saving in the cost of experiment due to the additional information provided by the calculations.

The cost factor is vital because the amount of computation required can be very great. The trouble is that we cannot calculate the geometry of a molecule directly. We can only infer it by interpolation from calculations of the energy for a number of geometries around the corresponding minimum in the potential surface. The cost of studying the rate of a chemical reaction is even greater. Here we have to find the minimum amount of energy (activation energy) needed for the system to cross from one minimum in the potential surface (corresponding to the reactants) to another (corresponding to the products). In general the two depressions will be separated by a ridge, like two valleys in a mountain range, and the easiest crossing point will be the lowest point in this ridge (the transition state). To deduce the rate of reaction, we have to locate the transition state and so find how much energy we need to supply to make it possible to cross it. Finding the transition state is often quite a difficult task, involving the calculation of thousands of points on the potential surface, and each point involves calculating the energy for the entire collection of atoms in some particular geometry. Unless each such calculation can be carried out in a matter of seconds rather than hours or days, the cost will become excessive. It must be remembered that the cost of operating a large digital computer is around $500 per hour. Even if the theoretician is fortunate enough not to have to pay this himself, someone does, and the money so spent may come from funds that could otherwise be used to support experimental work. Therefore if quantum theory is to serve as a genuine chemical tool rather than a subsidized luxury, it must do so on a basis of rigorous cost-effectiveness.

There is no prospect of obtaining accurate solutions of the Schrödinger equation in the foreseeable future for molecules large enough to be of interest to chemists. Current attempts to calculate chemical behavior have consequently followed two less rigorous paths.

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Ab Initio Approach

The first approach, known as the ab initio approach, relies on the closest approximations that can be made to the true solutions of the Schrödinger equation, the approximations to the equation being carried out in a rigorous manner. The errors in the resulting energies of atoms and molecules, while small on a percentage basis, are enormous in chemical terms, amounting to thousands of kilocalories per mole for a molecule of quite moderate size. The hope is that the errors may cancel in comparisons of related systems so that the relative energies of the systems may be reproduced with sufficient accuracy. Since chemistry is concerned only with relative energies, not absolute ones, this would be quite sufficient. It is true that there is no theoretical reason for expecting such a cancellation to occur, at any rate to the required degree of accuracy. However, it might be possible to establish its existence empirically by comparison with experiment. The procedure could then be used in areas where it had been tested. Such an approach will, of course, be purely empirical, a point which needs to be emphasized because the term ab initio has proved very misleading to chemists. However, for chemical purposes this would not matter; all we are concerned with is finding a procedure that will give us chemically useful information regardless of its basis.

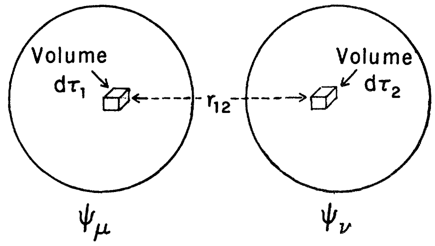


Fig. 1. Illustrating the calculation of the Coulomb integral $J_{\mu\nu}$ between two MO's Ψ_μ and Ψ_ν.

Most ab initio calculations have been based on the orbital approximation (Hartree-Fock method), the orbitals in turn being approximated by linear combinations of hydrogen-like (Slater) or Gaussian atomic orbitals (AO's). The results approach the ideal Hartree-Fock limit more closely the larger the number of AO's, that is, the larger the basis set. The simplest treatments use a minimum basis set, corresponding to the inner and valence shell AO's of simple molecular orbital (MO) theory.

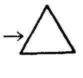
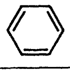
Pople and co-workers (*1, 2*) have carried out fairly extensive tests of these methods. From their results, and those of other workers, the following conclusions now seem clear.

1) The Hartree-Fock method is inherently incapable of giving heats of atomization, the error for a typical organic molecule being of the order of 100 kcal/mole per atom. Expedients such as the introduction of configuration interaction (CI) reduce the errors somewhat but not nearly enough.

2) Heats of reaction are, in general, very poorly reproduced if a minimum basis set is used. The situation seems to improve if the basis set is increased, but the degree of possible improvement is uncertain because the cost of such calculations has limited their testing. Table 1 shows some examples. For comparison, values calculated by our MINDO/3 procedure are also listed.

3) The one situation where good results are obtained is in the comparison of systems that contain not only the same number of bonds but the same number of bonds of each type. In the case of such bond separation reactions even a limited basis set can be used successfully.

Table 1. Comparison of calculated and observed heats of reaction; calculated values are for optimized geometries of reactants and products. The STO-3G and 4-31G results are from (*1*). STO-3G and 4-31G are two of the basis sets used by Pople and co-workers in ab initio calculations; the former is a minimum basis set and the latter a basis set of double zeta type.

Reaction	Heat of reaction (kcal/mole)			
	Observed	STO-3G	4-31G	MINDO/3
$CH_3C\equiv CH \rightarrow CH_2{=}C{=}CH_2$	1.6	17.1	0.8	7.0
$CH_2{=}C{=}CH_2 \rightarrow$ 	20.2	12.9	34.8	17.4
$CH_3{-}CH{=}CH_2 \rightarrow$ 	7.8	−3.7	12.5	2.1
$H_2C{=}CH_2 + H_2 \rightarrow H_3CCH_3$	32.7	72.0	42.0	39.0
$H_2C{\equiv}CH + 2H_2 \rightarrow H_3CCH_3$	74.6	134.9	94.7	77.6
$3HC{\equiv}CH \rightarrow$ 	−143.2	−209.8	−152.5*	−144.6

* Calculated by A. Komornicki.

These results are not very encouraging, for the intermediate phases of reactions involve species which differ in bonding from both the reactants and the products and moreover contain weakened bonds. If a procedure fails to predict the energy required to break a bond, it is unlikely to give good estimates of the energy needed to weaken it. In the few cases where meaningful ab initio self-consistent field (SCF) calculations for organic reactions have been reported, the calculated activation energies have been seriously in error. There are also strong indications that serious errors arise, for similar reasons, in comparisons of isomeric ions where one contains three-center bonds (*3*).

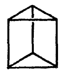
The main barrier to this approach is, however, cost. We know that calculations with a minimum basis set are too inaccurate to be chemically useful, yet the cost of even these becomes prohibitive for systems that are still small in a chemical sense. To use a larger basis set would be quite out of the question, and one cannot be sure that the results would even then be accurate, since such procedures have not been tested adequately because of cost.

Consider, for example, a rather simple problem, the barriers to interconversion of the four $(CH)_6$ isomers, benzene (**1**), benzvalene (**2**), Dewar benzene (**3**), and prismane (**4**).


1


2


3


4

We have studied this system in detail, using a procedure which will be described presently, completely optimizing the geometry throughout and locating the transition states unambiguously by checking that each has one and only one negative force constant. We have also carried out an ab initio SCF (4-31G) calculation for benzene, assuming D_{6h} symmetry but otherwise optimizing the geometry. The presence of symmetry, of course, enormously simplified the problem; it would be quite impracticable to carry out a similar calculation for **2** → **4**. However it is clear from the time taken for benzene, and our experience of the potential surface, that a very conservative estimate of the cost of a correspondingly complete 4-31G study of the potential surface would be $1 billion, that is, at least five orders of magnitude more than the possible chemical value of the results obtained. This ratio is far too large to be countered by any foreseeable developments in computers. (For comparison, our calculation for benzene cost $5000.)

Semiempirical Approach

The second line of approach follows an entirely different philosophy. We start off with the premise that our calculations must be economically feasible. We therefore limit ourselves not to the best available approximate solution of the Schrödinger equation but rather to the best that can be carried out at reasonable cost. Since the accuracy of even the best treatments is suspect, that of our simple one will naturally be terrible. Our object is to try to remedy this situation by introducing parameters into our treatment which we can adjust to fit suitable experimental data. In this way we hope to achieve our goal of developing a procedure which is both cheap and accurate. This approach has been termed semiempirical, in contrast to the ab initio approach which involves no parameters; it should, however, be clear that for chemical purposes both approaches are, in fact, entirely empirical, and a choice between them must be made solely on grounds of practical success. This situation would change only if an ab initio method became available that reproduced absolute energies with chemical accuracy.

Most workers in this field have been skeptical concerning the potential of a semiempirical approach and have therefore concentrated mostly on ab initio SCF procedures. It is true that current semiempirical treatments, other than ours, have led to very poor results; this, however, is because they were parameterized to mimic the results of minimum basis set ab initio SCF calculations rather than to reproduce the observed properties of molecules. Since ab initio SCF methods are themselves unsatisfactory unless an extended basis set is used, the failure of treatments such as CNDO and INDO (discussed below) is not in any way surprising. It should be pointed out that Pople *et al.* developed these treatments with the object of obtaining approximations to ab initio calculations cheaply (*4*). They were never intended to give estimates of molecular energetics, nor have Pople *et al.* used them in this way. However, before our work, no one had tried to parameterize CNDO or INDO in any other manner, probably because of the general belief that no semiempirical approach could equal, let alone exceed, the accuracy of ab initio ones. The proper parameterization of such treatments, in fact, presents a very difficult problem; and it needed much perseverance on our part to solve it. While we still have a long way to go, we do already have a procedure which seems to be in general more accurate than available ab initio ones and which can be applied to chemical problems at one-hundred-thousandth of the cost.

In order to understand our approach, it is necessary to know something of the basic principles of SCF-MO theory.

SCF-MO Theory

In our orbital approximation, we assume that the electrons in a molecule occupy a set of MO's, two in each according to the Pauli principle. Each MO Ψ_μ is in turn expressed as a combination of our basis set of AO's ϕ_i

$$\Psi_\mu = \sum_i a_{\mu i}\phi_i \tag{1}$$

If we know the MO's in a molecule, we can then calculate its total energy, this appearing in the form of an expression involving the coefficients $a_{\mu i}$ and various integrals involving the basis set functions. The best MO's, that is, those that lead to the best approximation to the actual state of the molecule, are then given by choosing the coefficients $a_{\mu i}$ to minimize the total energy (variation principle).

The total energy in turn appears as a sum of terms representing (i) the kinetic energy of the electrons; (ii) the attractions between the electrons and nuclei; (iii) the repulsions between the electrons; and (iv) the repulsions between the nuclei.

Consider for example the Coulombic energy of repulsion $J_{\mu\nu}$ between two electrons, one in the MO Ψ_μ and the other in the MO Ψ_ν. In our orbital picture, we can treat this as a repulsion between two clouds of negative charge, the densities of which vary as $\Psi_\mu(1)^2$ and $\Psi_\nu(2)^2$. The fraction of the total charge e in a small volume element $d\tau$ of the first cloud is then given by

$$\frac{\Psi_\mu(1)^2 d\tau_1}{\Sigma\Psi_\mu(1)^2 d\tau_1}e = \frac{\Psi_\mu(1)^2 d\tau_1}{\int\Psi_\mu(1)^2 d\tau_1}e \tag{2}$$

where the sum is over all the infinitesimal volume elements $d\tau_1$, a quanity equal by definition to the indicated integral. Likewise the amount of charge in a volume element $d\tau_2$ of the second cloud is given by

$$\frac{\Psi_\nu(2)^2 d\tau_2}{\Sigma\Psi_\nu(2)^2 d\tau_2} = \frac{\Psi_\nu(2)^2 d\tau_2}{\int\Psi_\nu(2)^2 d\tau_2} \tag{3}$$

If the two volume elements are at a distance r_{12} apart (see Fig. 1), the repulsion between the two small charges will be

$$\frac{\Psi_\mu(1)^2 d\tau_1 e}{\int\Psi_\mu(1)^2 d\tau_1} \times \frac{\Psi_\nu(2)^2 d\tau_2 e}{\int\Psi_\nu(2)^2 d\tau_2} \times \frac{1}{r_{12}} \tag{4}$$

The total repulsion between the two electrons is given by summing these contributions over all volume elements $d\tau_1$ and $d\tau_2$; this is equivalent to a double integration, that is

$$\begin{aligned} J_{\mu\nu} &= \int\int \left\{ \frac{\Psi_\mu(1)^2 d\tau_1 e}{\int\Psi_\mu(1)^2 d\tau_1} \times \frac{\Psi_\nu(2)^2 d\tau_2 e}{\int\Psi_\nu(2)^2 d\tau_2} \times \frac{1}{r_{12}} \right\} d\tau_1 d\tau_2 \\ &= \frac{\int\int \Psi_\mu(1)^2 \frac{e^2}{r_{12}} \Psi_\nu(2)^2 d\tau_1 d\tau_2}{\int\int \Psi_\mu(1)^2 \Psi_\nu(2)^2 d\tau_1 d\tau_2} \end{aligned} \tag{5}$$

If we now express Ψ_μ and Ψ_ν in terms of our basis set AO's (Eq. 1), this becomes:

$$J_{\mu\nu} = \frac{\sum_i\sum_j\sum_k\sum_l a_{\mu i}a_{\mu j}a_{\nu k}a_{\nu l}(ij,kl)}{\sum_i\sum_j\sum_k\sum_l a_{\mu i}a_{\mu j}a_{\nu k}a_{\nu l}S_{ij}S_{kl}} \tag{6}$$

where

$$(ij,kl) = \int\int \phi_i(1)\phi_j(1)\frac{e^2}{r_{12}} \times \phi_k(2)\phi_l(2)\,d\tau_1 d\tau_2 \tag{7}$$

$$S_{ij} = \int \phi_i\phi_j d\tau \tag{8}$$

We can thus find $J_{\mu\nu}$ in terms of the coefficients $a_{\mu i}$ and integrals (ij,kl) and S_{ij}, which can be calculated since we know the functions ϕ_i that compose our basis set.

The problem facing us is now apparent. The integrals (ij,kl) are not only rather difficult to evaluate but are excessive in number. Their number varies as the fourth power of the number of AO's in our basis set. The cost of computations following this course indeed arises entirely from the time taken to evaluate these electron repulsion integrals and the problems involved in storing and handling such huge numbers of integrals during subsequent calculations.

Our object is to try to simplify this general approach in order to reduce the amount of computation required. To do this we must somehow reduce the number of electron repulsion integrals to manageable proportions.

1) We will of course use a minimum basis set.

2) We can reasonably assume that there is no interaction between the inner shell electrons and valence shell electrons; for the inner shell electrons are very tightly bound and occupy very tiny AO's near the nucleus. This intuition is moreover supported by ab initio calculations. We can then assume that the valence shell electrons move in the field of a fixed core composed of the nuclei and inner shell electrons. Our basis set need then contain only valence shell AO's of the atoms in question. This reduces considerably the size of our basis set.

However, even with these simplifications, the amount of computation still remains excessive. Our final approximation is a rather cavalier one that enables us to reduce enormously the number of electron repulsion integrals that have to be calculated.

Neglect of Orbital Overlap

Consider the numerator of Eq. 6. If we expand the density function $\Psi_{\mu}(1)^2$ for an electron occupying the MO Ψ_{μ}, we find

$$\Psi_{\mu}(1)^2 = \sum_{i}\sum_{j} a_{\mu i}a_{\mu j}\phi_i(1)\phi_j(1) \qquad (9)$$

Likewise for the electron occupying Ψ_{ν}

$$\Psi_{\nu}(2)^2 = \sum_{k}\sum_{l} a_{\nu k}a_{\nu l}\phi_k(2)\phi_l(2) \qquad (10)$$

Each of the distributions is thus dissected into regions corresponding to AO's (ϕ_i^2) and overlap clouds between AO's($\phi_i\phi_j$). The quadruple sum in the numerator of Eq. 6 thus represents a dissection of the repulsion between the two clouds of charge, Ψ_{μ}^2 and Ψ_{ν}^2, into repulsions between the regions (ϕ_i^2,ϕ_i,ϕ_j, and so forth) into which we have dissected Ψ_{μ}^2 and Ψ_{ν}^2.

Now the density of the overlap cloud between the AO's ϕ_i and ϕ_j is given by the product $\phi_i\phi_j$; the total magnitude of the cloud is therefore given by the overlap integral S_{ij} in Eq. 8. The total charge in the cloud is thus eS_{ij}. Likewise the total charge in the overlap cloud between AO's k and l is equal to eS_{kl}. The repulsion between the two overlap clouds must thus be proportional to the product S_{ij} S_{kl}. We can see therefore that in Eq. 6 the numerator and denominator consist of parallel terms, $a_{\mu i}a_{\mu j}a_{\nu k}a_{\nu l}(ij,kl)$ and $a_{\mu i}a_{\mu j}a_{\nu k}a_{\nu l}$ $S_{ij}S_{kl}$, which are roughly proportional to one another. This suggests that the total value of $J_{\mu\nu}$ may not be much affected if we neglect all terms involving overlap between different AO's, both in the numerator and in the denominator, because both will change by comparable percentage amounts. Löwdin (*5*) has indeed shown that this is true, to a first approximation. With this simplifying assumption

$$J_{\mu\nu} = \frac{\sum_{i}\sum_{j} a_{\mu i}^2 a_{\nu k}^2 (ii,kk)}{\sum_{i}\sum_{k} a_{\mu i}^2 a_{\mu k}^2 \int \phi_i^2 d\tau \int \phi_k^2 d\tau}$$
$$= \frac{\sum_{i}\sum_{k} a_{\mu i}^2 a_{\nu k}^2 (ii,kk)}{\sum_{i}\sum_{k} a_{\mu i}^2 a_{\nu k}^2} \qquad (11)$$

(since we normally use basis set functions that are normalized, that is, $\int \phi_i^2 d\tau = 1$).

This is clearly an enormous simplification since the number of electron repulsion integrals now varies as the square of the number of basis set functions instead of the fourth power. There is, however, a complication. Our argument works perfectly so long as we neglect overlap only between AO's of different atoms. In the case of two different AO's of the same atom, however, the overlap integral vanishes through symmetry, while at the same time the corresponding term in the numerator of Eq. 6 need not vanish (*6*). It is therefore incorrect to neglect repulsion integrals involving overlap if the overlap is between two AO's of the same atom. Including such overlap, and making the other approximations indicated above, leads to the approximation termed NDDO (neglect of diatomic differential overlap) by Pople *et al.*, who were the first to suggest it (*4*).

The NDDO approximation still requires a fair amount of computation, however, and Pople *et al.* accordingly suggested that adequate results might be given in practice by treatments in which all repulsion integrals are neglected, even those involving one-center overlap (*4*). This is the CNDO (complete neglect of differential overlap) approximation. They also suggested a third compromise treatment (INDO, intermediate neglect of differential overlap) which differs from CNDO in that one-center overlap is retained in one-center integrals, that is, those in which ϕ_i, ϕ_j, ϕ_k, and ϕ_l are all AO's of a single atom. In fact, because of symmetry, all such integrals vanish anyway except those of type (ij,ij).

Pople *et al.* developed these procedures as ways of getting approximations to Hartree-Fock wave functions. They therefore parameterized them to reproduce as closely as possible the best available ab initio SCF results, these being confined to small molecules. Since the Hartree-Fock method itself is of dubious accuracy, it is not surprising to find that the simplified approximations to it give terrible results, and much of the current prejudice against semiempirical procedures is based on their failure.

MINDO Approach

Our own goal has been much more ambitious. We have chosen the parameters in our treatments to reproduce experimentally measured properties of molecules, in particular heats of atomization and geometries, rather than to mimic the results of ab initio calculations. Our object has been not merely to produce results comparable in accuracy to ab initio ones; we hope to surpass them by a wide margin. Most of our work so far has been based on the INDO approximation since this is much simpler to parameterize than NDDO and requires less computation. We have termed these procedures MINDO (modified INDO) to distinguish them from the standard Pople INDO treatment. Our present treatment (MINDO/3) is the third and latest version, and we suspect that it represents about the limit for an INDO-based treatment. The principles that guided us in developing it are as follows.

First, we need to consider only relative energies, in particular the changes in energy when atoms combine to form molecules, for the absolute energies of atoms and molecules are without chemical significance. These changes are only a very small fraction (about 1 percent) of the total energies involved; if we try to calculate them by difference between the energies of atoms and molecules, very small errors in the latter will produce large errors in the difference. Clearly, as Moffitt (*7*) pointed out some time ago, it must be better to use some kind of perturbation treatment to estimate the differences directly.

The SCF expression for the total energy of a molecule appears in terms of a number of integrals involving MO's (for example, Eq. 5) and these can in turn be expressed in terms of integrals involving our basis set (Eq. 6). The latter in turn consist of one-center integrals and multicenter integrals. Now the one-center integrals also appear in analogous orbital treatments of the various individual atoms. If we choose these in such a way as to reproduce the experimental properties of atoms and use the same values for calculations of molecules, we should compensate for all errors introduced in our treatment so far as atoms are concerned, and so we should in effect be calculating only the differences in energy between atoms and molecules. There are, of course, a number of one-center integrals to be determined for each atom; however we can fit them to the energies of the atom in various states and also to the energies of ions derived from it. Enough experimental data for these are available to enable us to determine our one-center integrals.

Errors in the heats of atomization calculated by the usual SCF procedures arise partly from the approximations inherent in the orbital representation and partly because the use of inadequate basis sets leads to orbitals that only approximate the Hartree-Fock ones. Our purpose is to compensate for both of these errors by judicious introduction of carefully chosen parameters.

In the orbital approximation, the electrons in an atom or molecule are assumed to move independently of one another. In actual fact, the electrons try to synchronize their motions so as to increase the distances between them and so reduce the corresponding Coulombic repulsions. Thus in helium, where two electrons circle a single nucleus, the electrons are more likely, at any instant, to be on opposite sides of the nucleus than on the same side of it. However, electron correlation does not significantly alter the way in which individual electrons move; it only requires them to move in concert. (A good analogy is provided by a battalion of infantry marching; each soldier marches in the same way he would if none of the others were there, but they all keep in step.) As a result, the orbital approximation gives a good account of the overall electron distribution in an atom or molecule, electron correlation reducing the interelectronic interactions without significantly altering the overall electron distribution. This suggests that we should be able to allow for the effects of electron correlation in our semiempirical orbital treatment by simply reducing the electron repulsion integrals by an appropriate amount.

In our treatment the only surviving electron repulsion integrals are two-center ones. Each of these will be a function of the corresponding internuclear distance (R_{mn}). As $R_{mn} \rightarrow 0$, the repulsion integral must approach a corresponding one-center integral, that is, one of those whose values have been determined from atomic data. Also as $R_{mn} \rightarrow \infty$, the integral must approach e^2/R_{mn}; for correlation effects become unimportant for large values of R_{mn} and the repulsion energy also becomes independent of the shapes of the AO's involved. If then we equate the integral to a suitable function of R_{mn} with the right boundary conditions (at $R_{mn} = 0, \infty$), we should automatically not only allow for electron correlation between pairs of electrons at different points in the molecule but also avoid the errors that would arise if we calculated the integrals using an inadequate basis set. This idea, due to Pariser and Parr (*8*) is used in MINDO/3.

Table 2. Comparison of calculated and observed ^{14}N nuclear quadrupole coupling constants.

Molecule	Nuclear quadrupole coupling constant (megahertz)	
	Observed	MINDO/3
N_2	−5.55	−6.18
NH_3	−4.08	−4.70
HCN	−4.58	−3.77
CH_3CN	−4.21	−3.81
$(CH_3)_3CN$	−3.85	−3.58
NC−CN	−4.27	−4.19
$HC{\equiv}CCN$	−4.20	−4.04
$CH_3C{\equiv}CCN$	−4.40	−3.67
CH_3NC	+0.50	−0.41
$H\underline{N}{=}\overset{+}{N}{=}\overset{-}{N}$*	+4.85	+3.11
$HN{=}\overset{+}{N}{=}\underline{\overset{-}{N}}$*	−1.35	−0.60
Pyridine	−4.58	−4.65
Pyrazine	−4.85	−5.11
Benzonitrile	−3.64	−3.72

* The results refer to the underlined nitrogen.

The remaining terms in the expression for the energy represent the kinetic energy of the electrons, the attractions between the electrons and the nuclei, and the core-core repulsions.

The electronic terms can again be divided into contributions by the AO's and overlap clouds into which we dissect our MO's. Consider first an overlap cloud such as $\phi_i\phi_j$. These terms are a measure of the interference effects between adjacent AO's in a molecule; a positive contribution implies that electron density will be high in the region between the two nuclei m and n, of which ϕ_i and ϕ_j are AO's, and this concentration of negative charge will then tend to hold the two nuclei together. This indeed is the main factor involved in the formation of covalent bonds in molecules; the corresponding terms in the expression for the energy represent the bonding interactions between them.

We denote the contribution of the overlap cloud $\phi_i\phi_j$ (that is, its contribution to the kinetic energy and the core-electron attractions) by β^c_{ij} and call it the corresponding core resonance integral. In principle these integrals might be calculated, but there are two good reasons for not doing so. First, our neglect of differential overlap makes the definition of the β^c_{ij} a bit obscure; second, since we know that ab initio SCF calculations with a minimum basis set are too inaccurate, and since we are using a subminimum basis set (valence shell AO's only), it would represent surrender to calculate our β^c_{ij} with it. We have to try to do better than that if our results are to be of real chemical value. We have already followed this principle in our approach to the electron repulsion integrals; we must try to do the same here—that is, develop a suitable empirical function of R_{mn} to represent the corresponding ideal values of β^c_{ij}.

Trying to find a suitable function without any guidance would be a hopeless undertaking. What we have tried to do is to guess from physical intuition what the general form of the function should be, this providing a first approximation which will then, we hope, need only minor modification. Indeed, as Mulliken *et al.* (*9*) pointed out, β^c_{ij} should be proportional to S_{ij} (the magnitude of the overlap cloud); it should also be proportional to an average of the bonding energies of electrons in the AO's ϕ_i and ϕ_j (J_i and J_j) because the potential energy of an electron in the overlap region $\phi_i\phi_j$ should be related to the average of that in the regions of the two AO's. This suggests that we should write β^c_{ij} in the form

$$\beta^c_{ij} = S_{ij}(J_i + J_j)f_1(R_{mn}) \qquad (12)$$

where f_1 is a function of the internuclear distance R_{mn}. We will try to use a single function for atoms of all kinds; this will correspond to the potential function having the same general shape for all bonds. To allow it to be fitted to bonds between specific pairs of atoms, we will include in it an adjustable parameter B_{mn}, characteristic of the pairs of atoms involved.

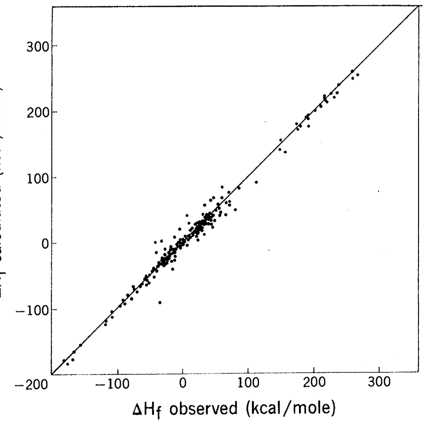
The remaining electronic terms represent the contributions of individual AO's to the kinetic energy and to the core-electron attractions. The kinetic energy term and the term representing attraction to the core corresponding to the AO appear in the analogous description of atoms and so have already been estimated (from atomic data). The remaining terms contribute to the net Coulombic interactions between pairs of different atoms.

The net Coulombic interaction between two atoms m and n is a sum of four parts: the electron-electron repulsion, the core-core repulsion, the attraction between the electrons in atom m and the core of atom n, and the attraction between the electrons in atom n and the core of atom m. The net effect is a repulsion; this indeed is what keeps the molecule from collapsing under the influence of the attractions corresponding to the β^c_{ij}. Now while the four contributing terms are very large, their net effect is small, for since two represent repulsions and two attractions, they almost cancel. If we try to calculate the four interactions separately, it will be very difficult to maintain the necessary balance between them. One of them of course is known—the interelectronic repulsion—for we already have estimates of the contributing integrals (*ii*, *kk*). How are we to deal with the rest? Our approach is to choose the attractions and repulsions in such a way that they cancel if the atoms are neutral and then to add to the corresponding core-core repulsion a function of R_{mn} that represents the net repulsion. Since the total interelectronic repulsion (EE_{mn}) is known, we choose the core-electron attractions in such a way as to make the total attraction between the electrons on atom m and the core of atom n, and the total attraction between the electrons on atom n and the core of atom m, each equal to $-EE_{mn}$. The core repulsion (CR_{mn}) is then given by

$$CR_{mn} = EE_{mn} + f_2(R_{mn}) \qquad (13)$$

where f_2 is another function of R_{mn}. We will try to use the same function in all cases; it will contain a second parameter (α_{mn}) to enable us to fit it to specific atom pairs.

Our final problem is to determine the best forms of the functions f_1 and f_2 in Eqs. 12 and 13 and the best values of the parameters in them. We have found no easy way of doing this; we were forced to an extremely laborious trial-and-error procedure. For any given choice of likely functions f_1 and f_2, the parameters are found by fitting the heats of atomization and geometries of a set of standard molecules, chosen to represent as wide a variety of types of structures and bonding as possible. Well over 500 combinations of functions were tested in this way during the development of MINDO/3.



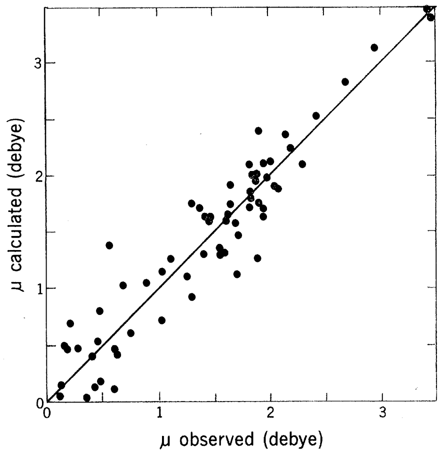
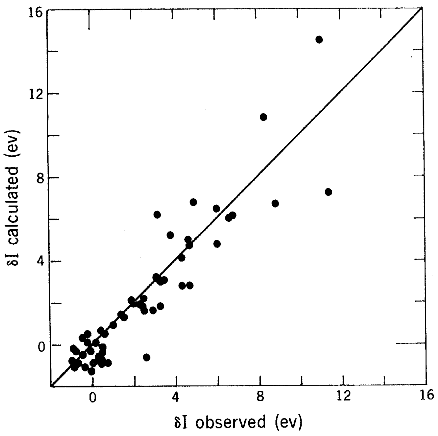


Fig. 2 (left). Plot of calculated against observed heats of formation of 193 compounds derived from H, C, N, O, F, Si, P, S, and Cl. The line is the theoretical line of unit slope, not one drawn through the points. Fig. 3 (right). Plot of calculated against observed dipole moments (μ) for 65 compounds derived from H, C, N, O, F, Si, P, S, and Cl. The line is the theoretical line of unit slope.



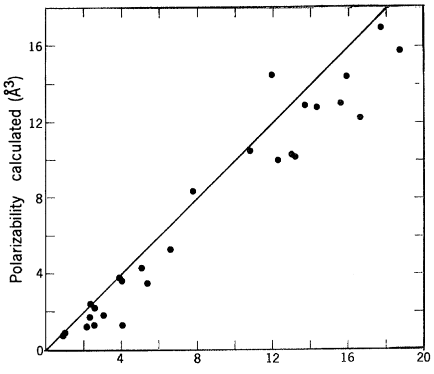


Fig. 4 (left). Plot of calculated against observed ESCA chemical shifts (δI) of 31 compounds of carbon (relative to CH_4), 14 compounds of nitrogen (relative to NH_3), and 10 compounds of oxygen (relative to H_2O). The line is the theoretical line of unit slope. Fig. 5 (right). Plot of calculated against observed polarizabilities for 27 compounds derived from H, C, N, and O. The line is the theoretical line of unit slope.

Results with MINDO/3

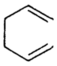
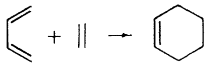
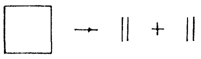
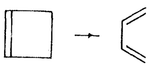
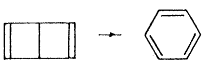
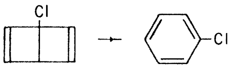
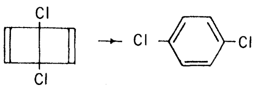
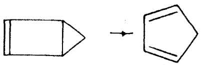
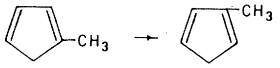
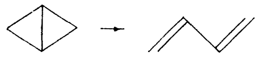
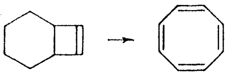
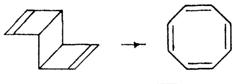
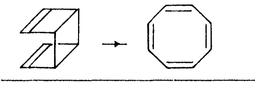
The theory of MINDO/3 was outlined in the preceding section; now what about the results? When it became clear that we had at last a procedure that seemed to have more or less overcome the difficulties met in earlier versions, we set about testing it by calculations for a large number of molecules of all kinds, derived from the elements for which we had parameters (H, B, C, N, O, F, Si, P, S, and Cl). It should be added at this point that we have parameterized MINDO/3 to reproduce experimental heats of atomization at 25°C. For convenience, however, we convert the calculated heats of atomization to heats of formation, using experimental values for the heats of formation of gaseous atoms. Thus the comparison of calculated (*10*) and observed heats of formation for nearly 200 molecules in Fig. 2 really refers to a comparison of heats of atomization. The agreement is seen to be quite good, most of the compounds lying within ± 5 kcal/mole of the line (which incidentally is the theoretical line of unit slope, not one drawn through the points). It would be impossible to include points for analogous ab initio calculations on the same diagram because they would lie far off the page, the errors being hundreds or thousands of times greater than those for MINDO/3. It should be added that the compounds plotted on Fig. 2 also include free radicals and carbonium ions. It has been commonly stated in the past that semiempirical treatments can be applied only to narrow ranges of compounds, by using parameters specifically chosen for them. Figure 2 shows that to be false, provided the parameterization is carried out properly.

Indeed MINDO/3 seems to reproduce all ground state properties in an equally satisfactory manner. This is not surprising for bond lengths and bond angles (*11*) since MINDO/3 was parameterized to fit energies and geometries; however, as Figs. 3 to 5 show, it also gives good results for dipole moments, polarizabilities, and ESCA (electron spectroscopy for chemical analysis) chemical shifts. The errors in dipole moments are comparable with those given by ab initio methods, at any rate those using minimum basis sets, while the ESCA values are better than those given by previous treatments. No one before has calculated polarizabilities for any but the simplest molecules; we can calculate not only polarizabilities but also hyperpolarizabilities (*12*) for quite large molecules, and our preliminary results again look encouraging. Such calculations should be useful in the search for materials with specified optical properties, needed in laser technology. First ionization potentials are also quite well reproduced (usually to ± 0.3 electron volt), and Table 2 shows a comparison of calculated and observed ^{14}N nuclear quadrupole coupling constants. Here again our results are superior to any previously reported for any but the very simplest molecules.

It should be added that all our calculations refer to geometries found by minimizing the total energy with respect to all geometrical parameters without any assumptions whatsoever. One of the major advantages of treatments based on INDO or NDDO approximations is that it is very easy indeed to calculate derivatives of the energy with respect to the geometrical variables. The procedures for finding the minimum value of a function of variables fall into two groups. In the first, one uses only values of the function calculated for various values of the variables; in the case of a molecule, such procedures need $\sim n^2$ function evaluations (in our case, SCF calculations) to optimize n variables. The second type of procedure needs not only values of the function but also its derivatives with respect to the variables; here the number of SCF calculations seems to be almost independent of the size of the molecule, being 30 to 40 for molecules with up to 30 atoms. Since calculation of the derivatives is trivial in MINDO, procedures of the latter kind can be used. We have indeed carried out such a calculation for lysergic acid diethylamide (LSD), a molecule with 49 atoms and hence requiring optimization of 141 independent geometrical variables. While 122 cycles were carried out, each cycle involving an SCF calculation, convergence was complete to within 1 kcal/mole after 90 cycles. In the case of ab initio SCF methods, the calculation of derivatives takes so much computation that any advantage of using one of the more efficient geometry procedures would be lost. One shudders to think what a 4-31G calculation for LSD would cost, using one of the less effective geometry programs such as Simplex.

Having thus shown that MINDO/3 gives good results for various ground state properties of a wide range of molecules, we next set out to study a number of chemical reactions. If they could be trusted, the results of such calculations would be of major chemical interest because the intermediate phases of reactions cannot be studied experimentally, the time involved in a chemical

Table 3. Comparison of calculated and observed activation energies of reactions.

Reaction	Activation energy (kcal/mole)		
	Observed	MINDO/3	Error
Rotation about C=C bond in $H_2C=CH_2$	65.0	63.9	−1.1
Rotation about C=C bond in $H_2C=C=CH_2$	47	46.9	0
$H_3C\cdot + H-CH_3 \rightarrow H_3C-H + \cdot CH_3$	11.5	14.8	3.3
Cope rearrangement of 			
Via "chair" transition state	33.5	35.1	1.6
Via "boat" transition state	44.7 ± 2	41.4	−3.3
Diels-Alder reaction			
	28.2	27.5	−0.7
	62.5	62.0	−0.5
	32.4	48.9	16.5
	23.0	27.3	4.3
	19.1	24.9	5.8
	30.5	24.9	−5.6
	26.9	27.1	0.2
H migration in 	23.0	28.3	5.3
	24.6	28.3	3.7
	40.3	40.6	0.3
	18.7	22.8	4.1
	31.1	39.3	8.2
	28.8	36.0	8.2

reaction being so short ($\sim 10^{-13}$ second). We can at most determine the thermodynamic properties of the transition state of a reaction, not even its geometry.

Our procedure here is to use as a reaction coordinate some interatomic distance or angle that seems to vary monotonically during a reaction, and to minimize the energy with respect to all other geometrical variables for various values of the reaction coordinate. If the potential surface for the system consists of two minima (corresponding to the reactants and products) linked by a simple valley, the points we calculate should then correspond to points at the bottom of this valley. A plot of energy against the reaction coordinate should then give a section of the potential surface along the bottom of the valley, and the highest point in this should correspond to the transition state. In practice, problems often arise because multidimensional potential surfaces tend to have complicated shapes, full of lumps, dents, and grooves, so one may not find the best path from reactant to product by using an arbitrary reaction coordinate. We have developed various techniques for detecting and overcoming such difficulties; as one might expect, these involve a lot of extra computation, but fortunately the time involved in MINDO/3 calculations is short enough for this to be possible.

One major development, due to McIver and Komornicki (*13*), is a method for locating and identifying transition states, based on the fact that a transition state, being a point of equilibrium on the potential surface, has a zero gradient. By minimizing the function $\Sigma_i(\partial E/\partial q_i)^2$, where the q_i are the geometrical variables and E is the total energy, we can find points with zero gradient directly. Since, morever, the derivatives $\partial E/\partial q_i$ are easily found, we can also get estimates of the second derivatives and hence the force constants. Since a transition state is a species stable to deformations along all directions other than the reaction path, it has one and only one negative force constant. Thus, once we have located the position of a transition state on the potential surface approximately, we can find its exact location directly and also confirm that it really is a transition state, rather than the top of a hill or the bottom of a hole (that is, a stable intermediate rather than a transition state).

Table 3 shows a comparison of calculated and observed activation energies for a number of reactions. The calculated values are nearly all correct to ± 5 kcal/mole. Evidently MINDO/3 provides estimates of the energies of transition states that are as accurate as those for normal molecules, and it is certainly reasonable to suppose that our calculated geometries for transition states are correspondingly accurate. On this basis our results have already led to some interesting and important conclusions, in particular to major revisions of current views concerning pericyclic reactions and their mechanisms (*14*). Recent work seems moreover to suggest that MINDO/3 also gives good estimates of the energies of lowest singlet and triplet excited states. If confirmed, this should open up the whole area of organic photochemistry, where satisfactory theories have been sadly lacking. We have already made some interesting contributions to the theory of chemiluminescent processes (*15*).

MINDO/3 thus represents a quantum jump in theoretical organic chemistry, providing for the first time an apparently reliable and thoroughly tested procedure that can be applied at reasonable cost to real chemical problems. It is true that numerous other calculations of the course of chemical reactions have appeared, and are appearing. These, however, have used untested methods of dubious accuracy, and nearly all of them have been based on assumptions concerning the geometries of reaction intermediates (*16*). Such calculations are worthless in principle, and our own studies indicate that they have led in many cases to erroneous conclusions.

MINDO/3 can thus be regarded as a new kind of experimental technique, for studying the otherwise inaccessible area of reaction intermediates. The experimental accuracy is admittedly not very high; one could say it has a resolving power of about 5 kcal/mole. In other words, if there are two possible modes of reaction in a system, MINDO/3 can distinguish between them with reasonable assurance if their calculated activation energies differ by this amount. The structures of transition states are probably reproduced to a few hundredths of an angstrom in bond lengths and a few degrees in angles. This again is sufficient to be useful and informative in many connections.

It should of course be emphasized that MINDO/3 is only the first procedure of its kind, based on a very crude approximation (INDO). In fact we already have a breadboard version of NDDO which looks as though it will be a good deal better when it is developed. Also the field we have so far studied is one where calculations of this kind are least valuable, for organic chemistry is a relatively simple and very well explained area where no great surprises are to be expected. If even MINDO can be extended to photochemistry, or to organometallic chemistry (*17*), the results could be of major importance, for these are areas where no acceptable quantitative theory exists.

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4. See J. A. Pople and D. L. Beveridge, *Approximate Molecular Orbital Theory* (McGraw-Hill, New York, 1970).
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6. This is because the overlap integral S_{ij} vanishes through cancellation of regions where $\phi_i\phi_j$ is positive and regions where it is negative. However, the repulsions between the two regions and an outside charge are not, as a rule, the same. Hence integrals of the type (*ij,kk*) do not vanish if ϕ_i and ϕ_j are AO's of the same atom.
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10. The MINDO/3 method, and results for several hundred molecules, are reported in a series of papers by R. C. Bingham, M. J. S. Dewar, and D. H. Lo (*J. Am. Chem. Soc.*, in press).
11. These are usually reproduced to ± 0.02 Å and ± 4°. It is difficult to show the agreement in a simple pictorial manner.
12. The polarizability of a molecule is the derivative of the dipole moment with respect to an electric field, that is, the second derivative of the energy. The hyperpolarizability is the corresponding third derivative. The polarizability and hyperpolarizability are represented by second and third rank tensors, respectively. Our treatment gives all the elements in these.
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16. Our own studies, using earlier versions of MINDO, were confined to areas where the procedures used had been tested and shown to work. However, we were forced in many cases to make geometrical assumptions since we had not at that time an efficient procedure for calculating geometries. Our later work has shown that several of our earlier conclusions were incorrect as a result of these assumptions.
17. The main problem here is the dearth of thermochemical data needed for parameterization. It could be of more value to chemistry to support research in this direction than in many others that are being currently explored.
18. Our work in this area has been made possible by generous support from the Air Force Office of Scientific Research and the Robert A. Welch Foundation.