

Application of semi-empirical and ab initio quantum mechanical calculations

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Computer-aided molecular modeling requires programs which relate the energies to the structures of molecules as accurately as possible. Three basic approaches, molecular mechanics, semi-empirical and ab initio calculations, are well represented by the most widely distributed programs: the MM2/MMP2 series of Allinger, MOPAC and AMPAC (including MINDO/3, MNDO, and AM1) of Dewar and the Gaussian ab initio series of Pople [1]. Such standard and easy-to-use programs are attractive to the researcher interested primarily in applications, rather than in developing his own algorithms. The strengths and limitations of these three methods will be compared and possible future developments anticipated.

Molecular mechanics employs empirically derived force fields parameterized from experimental data to fit chemical properties as closely as possible. These programs are fastest by far and can be applied to large chemical systems. While high accuracy is achieved for classical molecules (where good experimental data are available for parameterization), the reliability of extrapolated results or those involving other systems is questionable. There is a strong tendency towards overparameterization and the results become increasingly difficult to interpret with any rigor. Semi-empirical quantum mechanical calculations are applicable to a wider range of chemical elements, but these are still largely confined to the main groups. Since only the valence shell electrons are treated explicitly, parameterization in order to fit good experimental data also is needed. Even so, high accuracy does not appear to be achievable (average AM1 errors in energy are about 5 kcal/mol). Nevertheless, these programs are invaluable for chemists. They provide a practical way to obtain information about the actual molecules being investigated experimentally. Such programs (as well as molecular mechanics) run on personal computers, and can be vectorized efficiently for the fastest machines, e.g., MNDO is up to 30 times faster on our Erlangen CONVEX C120 than on a VAX 11/780.

Partly through the availability of efficient programs and partly due to the continuing advances in computer hardware technology, ab initio calculations are coming of age as a tool for general chemical applications. Considerable further progress can be anticipated in future when the programs are reconstructed to take full advantage of vector (rather than scalar) architecture. Although ever larger molecules can be examined, such calculations are currently limited to medium-size systems. Chemical accuracy (± 1 kcal/mol in energy and nearly perfect geometries) can be achieved, often quite readily for classical molecules. Transition states and species difficult or impossible to study experimentally can be examined with confidence. Ab initio theory increasingly

challenges experiment; when there is a discrepancy, it is far more likely that the experimental result is in error. The chief practical drawbacks of *ab initio* theory are the large amount of computer time demanded and the complexities involved. Although the method is non-empirical, the operator of a program like Gaussian 82/86 must make choices, e.g., concerning the basis set (both for the geometry optimization and for the final point calculations), whether or not to include electron correlation (and, if so, at what degree of sophistication), and whether to carry out frequency analyses. The latter provides vibrational frequencies, zero point energies, entropies, and a full thermochemical analysis, but is quite costly in computer time. Fortunately, the performance of standard levels of *ab initio* theory has been evaluated in a recent book [2] so that a chemist can choose the appropriate type of calculation for the problem of interest.

What developments can be expected in the next decade? For large molecular systems, modeling will be based on methods involving empirical potentials. However, the necessary parameters will be increasingly derived from results of *ab initio* calculations on small model systems. 'Stochastic' searches, e.g. that of Saunders [3], will allow the exploration of complex potential energy surfaces with many minima automatically. Semi-empirical methods, at least as presently conceived, seem to have reached a plateau of development. AM1 results are only marginally better than MNDO. More elements will be included. Jug's SINDO/1 program has shown that d-orbitals for second-row elements can be incorporated successfully in semi-empirical treatments. Pseudopotential methods, intermediate between semi-empirical and full *ab initio* treatments, offer much promise. Rather than calculating the inner shell electrons explicitly, effective core potentials are employed. The valence shell electrons can be treated with any of the usual *ab initio* basis sets and electron correlation treatments, so that high accuracy appears to be achievable. In this manner, it may be possible to study compounds of the heaviest elements efficiently. In part, the future developments of *ab initio* programs will be strongly related to computer architecture. Many developments are foreseeable: better use of vector and parallel processors and advanced computer designs, specialized chips (e.g. for integral evaluations), more efficient electron correlation algorithms, etc. Not only the largest computers get faster, but also their smaller cousins, so that every chemist will have access to machines fast enough to carry out meaningful *ab initio* calculations.

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