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Quantum Organic Chemistry: An Alternative View

In "Quantum organic chemistry" Dewar (*1*) rightly emphasizes the use of quantum chemical calculations as cost-effective alternatives to experiment, but errs in suggesting this as being the ultimate goal of quantum chemistry. Calculations also serve to illuminate experiment. By rigorously treating particular physical models, ab initio methods enable us to evaluate critically and, if necessary, ultimately improve the models themselves. In contrast, parameterization schemes employed in semiempirical methods, such as Dewar's MINDO/3, inevitably obscure the physical bases for success (however striking) and failure alike, thereby limiting the prospects for learning why the results are as they are. No simple cost accounting of the type Dewar proposes can be meaningful for ab initio studies which are intended not so much to predict a given experimental result as to examine what that result can tell us. By way of illustration, Parr's elegant recent account (*2*) which we recommend highly, includes several examples of computational tasks to which semiempirical techniques could not meaningfully have been applied.

Moreover, Dewar misstates the relative costs of MINDO/3 and ab initio calculations when he cites \$1 billion versus \$5000 as estimates for ab initio 4-31G and MINDO/3 studies of the barriers to interconversion of the benzene valence isomers, $(CH)_6$. In particular, the relative costs for individual 4-31G and comparable INDO calculations are ~400 : 1 for our computers. Although large, this figure falls considerably short of the factor of ~200,000 : 1 Dewar advances. Moreover, we estimate that we could conclude 4-31G studies for these processes for approximately the lower figure of \$5000 by coupling an efficient new technique for potential surface investigations (*3*) with a rapid approximate ab initio procedure (*4*) for the initial calculations. Key structures obtained in this way would then be reassessed by 4-31G calculations. Such a dual usage of minimum and extended basis set calculations greatly reduces the overall costs and is by now an accepted practice.

In summary, the difference in the motivations for doing ab initio and semiempirical calculations needs to be considered alongside the question of relative costs when judging the merits of these approaches for a given problem. At bottom, neither approach can be the method of choice for all computational problems, and surely each will have a vital role to play in the continuing development of quantum chemistry.

THOMAS A. HALGREN
DANIEL A. KLEIER
WILLIAM N. LIPSCOMB
Department of Chemistry,
Harvard University,
Cambridge, Massachusetts 02138

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I am all in favor of rigorous quantum mechanical calculations—that is, ones leading to results that are accurate in an absolute sense—and entirely agree that these provide information of a different order of value to that given by empirical procedures such as ours. If such calculations could be carried out for complex chemical systems, I would be their most ardent champion. However, the only reasonably accurate methods currently available are limited to atoms and small molecules, systems of interest more to astronomers and physicists than to chemists. As I pointed out in my article, the best ab initio methods that can be applied to complex chemical systems are inaccurate. If they lead to results that agree with experiment, this can be due only to errors canceling with quite unexpected precision, so such treatments can be used only empirically. My criticisms were directed at those who try to attribute to these essentially empirical procedures the same aura of illumination and meaningfulness that applies to the rigorous ones.

As regards cost, the cost of a single 4-31G calculation for C_6H_6 is indeed about 400 times that for MINDO/3 (3/4 hour versus 7 seconds on our computer). However a full geometry optimization requires the equivalent of far more such calculations in the case of 4-31G than MINDO/3 and the location of a transition state far more again. No one has attempted such a calculation for a system as large as C_6H_6; indeed, no one until recently had even optimized the (4-31G) geometry of benzene, although this is trivial if D_{6h} symmetry is assumed. Needing this value we calculated it ourselves; the calculation took 4 hours, which at \$500 per hour (the rate I assumed) would have cost \$2000. A single optimization for an unsymmetrical C_6H_6 species would have cost many times more than this, so it seems clear that the figure of \$5000 quoted by Lipscomb *et al.* is somewhat unrealistic.

My objection is not to ab initio calculations but to their misuse. What is needed in chemistry in the ab initio area is some better approach than those currently available, not vast and very expensive calculations for problems that can be treated at least equally effectively in other ways at far less cost.

MICHAEL J. S. DEWAR
Department of Chemistry,
University of Texas, Austin 78712

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Model for Differentiation Based on DNA Modifying Enzymes

The theory by Holliday and Pugh (*1*) of differentiation controlled by modifying enzymes of DNA relies on several assumptions, some of which can be readily refuted by existing biochemical data.

If DNA adenine deaminase, which deaminates adenine at the polymer level, were operative, then its product whether deoxyribohypoxanthine (not inosine!) or hypoxanthine, should be detectable in DNA hydrolyzates. Neither was ever found. Inosine is found in hydrolyzates of transfer RNA (tRNA).

The deamination of 5-methylcytosine in the polynucleotide to yield thymine in situ proposed by Scarano had some evidence in its favor, but a new interpretation of the data may cast doubt on the mechanism of that phenomenon as well. The methylation of DNA in eukaryotes is achieved by the transfer of an intact methyl group from *S*-adenosylmethionine (SAM) to cytosine