CC/NUMBER 47
NOVEMBER 19, 1984

This Week's Citation Classic™

Engler E M, Andose J D & Schleyer P V R. Critical evaluation of molecular mechanics. *J. Amer. Chem. Soc.* 95:8005-25, 1973.
[Department of Chemistry, Princeton University, NJ]

This paper critically assessed the ability of molecular mechanics to accurately calculate the structures and enthalpies of large organic molecules. Through extensive calculations on a wide variety of structurally diverse alkanes using two force-field models, most of the available data were reproduced with an accuracy rivaling that achieved by experimental methods. [The *SCI*® indicates that this paper has been cited in over 520 publications since 1973.]

Edward M. Engler
IBM Research Laboratory
5600 Cottle Road
San Jose, CA 95193

March 27, 1984

"Westheimer[1] first outlined the molecular mechanics approach in 1946, in which a molecule was viewed as a collection of particles held together by simple harmonic or elastic forces such as stretching, bending, or torsion. Over the years, this method[2] has grown considerably in its value to chemists who apply it to a wide variety of chemical problems in areas such as reaction rates, conformational analysis, and thermodynamics. Interest in this computational technique is due in part to its conceptual simplicity, which enables it to calculate accurately the structures and enthalpies of large, complex organic molecules. The study of polymers and biomol-ecules are areas actively employing this tec-nique.[3]

"During m- graduate thesis work at Princeton, we -e interested in approaching molecular me-anics as users; that is, experimentalists who wanted a simple, fast, and cheap computational technique for treating the 'real' molecules that we were studying in the lab. We therefore set out to collect all of the available data on the structures and energies of alkanes, especially polycyclic and highly strained molecules, and compared the ability of molecular mechanics to reproduce these data. Since the constants for the force-field parameterization are arrived at empirically, we were interested in knowing the smallest number of parameters that could accurately reproduce the data and, also, how sensitive the results were to the particular choice of parameters.

"A variety of force fields developed by us and outside groups were critically examined to determine their strengths and weaknesses, although we principally compared results with a force field developed by Allinger.[4] Our basic findings were that both structures and enthalpies were calculated with an accuracy rivaling that achieved by experimental methods. Further, the calculated results were not a sensitive function of the choice of parameters for the force field within reasonable limits. Our conclusion was that molecular mechanics is a valuable tool not only for quantitative interpretation of experimental results, but also (and more importantly) as a means of leading the experimentalist to interesting problems.

"With all the papers on molecular mechanics, why is this one so highly cited? There obviously are many reasons. The paper was exhaustive in its inclusion of data and also well referenced, which I am sure contributed a lot. However, I believe another reason is that we offered a challenge to the experimentalist by 'predicting' the enthalpies for a large number of unknown and exotic polycyclic hydrocarbons, including such molecules as dodecahedrane and hexaprismane. Perhaps, by sticking our necks out, we may have stirred some interest. With the passage of a decade, I think our conclusions and predictions have held reasonably well, and I would hope that this paper continues to serve as a useful contribution to the field of molecular mechanics."

CONTINUED

1. **Westheimer F H & Mayer J E.** The theory of the racemization of optically active derivatives of diphenyl. *J. Chem. Phys.* 14:733-8, 1946. (Cited 70 times since 1955.)
2. **Burkert U & Allinger N L.** *Molecular mechanics.* Washington, DC: American Chemical Society, 1982. 339 p.
3. **Scheraga H A.** Theoretical and experimental studies of conformations of polypeptides. *Chem. Rev.* 71:195-217, 1971.
4. **Allinger N L, Tribble M T, Miller M A & Wertz D H.** Conformational analysis. LXIX. An improved force field for the calculation of the structures and energies of hydrocarbons. *J. Amer. Chem. Soc.* 93:1637-49, 1971. (Cited 425 times.)

