

Klopman G. Chemical reactivity and the concept of charge- and frontier-controlled reactions. *J. Amer. Chem. Soc.* 90:223-34, 1968.
[Cyanamid European Research Institute, Cologny-Geneva, Switzerland]

A treatment of chemical reactivity was described, based on a general perturbation theory involving both the reactants and the solvent. It emphasized the importance of charge- and orbital-controlled effects in the transition state. The treatment provided a unifying and quantitative base for the concept of hard and soft Lewis acids and bases, of nucleophilic order, of conservation of orbital symmetry, and other reactivity indexes. [The SCJ® indicates that this paper has been cited in over 510 publications since 1968.]

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"Considerable interest, and controversy, was generated in 1963, when Pearson^{1,2} introduced the concept of hard and soft acids and bases (HSAB). At the time, I was a research associate at the Cyanamid European Research Institute in Geneva, and my boss, Robert F. Hudson, in conjunction with C.K. Jorgensen, decided to convene a mini-symposium on the subject. I personally did not believe in the concept, but being interested in chemical reactivity, I decided to look at this idea from a more fundamental standpoint. Perturbation theory had been around for a number of years, but nobody thought of using it for anything other than approximating the solution of Huckel type matrices of complicated molecules. Encouraged by Hudson, I started to work on the subject and published with him some of our preliminary results.³

"I was also interested, at the time, in the possibility of developing a self-consistent method that would be suitable to calculate molecular orbitals and heats of formation of saturated molecules. I succeeded in doing so and published the results in a series of papers in 1964.^{4,5} My major problem, at the time, was that I did not have access to a computer, and I had to solve the self-consistent field (SCF) matrix by hand. Needless to say, I immediately accepted when Michael Dewar offered me the opportunity to join him in Texas and have access to his computer to implement my methodology. The result of this 1965 stay in Texas was the development of the partial neglect of differential overlap (PNDO) method, later modified and

renamed modified intermediate neglect of differential overlap (MINDO).

"When I returned to Geneva, I was again without access to a computer and painfully aware that I could not compete with those who had access to the code of the PNDO. At that point, though, I accepted a position at Case Western Reserve University.

"I had a year before me, and decided to spend it reevaluating the results we had obtained from our perturbation method. I started by using the method to calculate the properties of specific electrophiles and nucleophiles, and found that the quantitative scales of reactivity that I was obtaining were actually excellent indexes of hardness and softness. Thus, my results, rather than refuting the HSAB concept as I had originally set out to do, provided it with a theoretical and quantitative basis.

"From there on, everything was pretty easy and I rapidly noticed that my approach provided a unifying method of studying chemical reactivity which not only encompassed ambidexterity, and nucleophilic and electrophilic orders, but also the then newly developed concept of orbital symmetry. Actually, in the last paragraph of the paper, I stated that the Woodward-Hoffmann rules and the orientation in Diels-Alder reactions of asymmetric molecules can easily be explained by this methodology. To me, that was the end of it, and I never anticipated that some people would make a career illustrating that point.

"Many papers on the subject have followed this Citation Classic, mostly by other authors.⁶ I personally did not receive much support for continuing this work after I came to the US. Nevertheless, I accumulated enough material that I was able to edit a book on this subject in 1974.⁷

"I knew when I wrote this paper that it would attract a lot of attention, and I am gratified to see that, indeed, it did. I think that the paper's success is due to the fact that it provided a simple and unifying method of evaluating many aspects of chemical reactivity on a semiquantitative basis. There were many empirical methods of assessing the importance of various factors in determining the outcome of a reaction, and the perturbational approach that I described in this Citation Classic provided a theoretical basis for assessing the importance of these factors."

1. Pearson R G. Hard and soft acids and bases. *J. Amer. Chem. Soc.* 85:3533-9, 1963.
2. ----- Citation Classic. Commentary on *J. Amer. Chem. Soc.* 85:3533-9, 1963.
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3. Klopman G & Hudson R F. Polyelectronic perturbation treatment of chemical reactivity. *Theor. Chim. Acta* 8:165-74, 1967. (Cited 110 times.)
4. Klopman G. A semiempirical treatment of molecular structures. I. Electronegativity and atomic terms. *J. Amer. Chem. Soc.* 86:1463-9, 1964. (Cited 80 times.)
5. ----- A semiempirical treatment of molecular structures. II. Molecular terms and application to diatomic molecules. *J. Amer. Chem. Soc.* 86:4550-7, 1964. (Cited 140 times.)
6. Fleming I. *Frontier orbitals and organic chemical reactions*. London: Wiley, 1976. 249 p.
7. Klopman G, ed. *Chemical reactivity and reaction paths*. New York: Wiley, 1974. 369 p.