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Theoretical
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*Perspective*

# Perspective on "Theoretical interpretation of 1-2 asymmetric induction. The importance of antiperiplanarity"

## Anh NT, Eisenstein O (1977) Nouv J Chim 1: 61–70

**K.N. Houk**

Department of Chemistry and Biochemistry, University of California at Los Angeles, 405 Hilgard Avenue,
Los Angeles, CA 90095-1569, USA

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**Abstract.** This paper describes how Anh and Eisenstein's publication in 1977 solved a classic problem in organic stereochemistry and simultaneously provided the impetus and a model for the use of quantum mechanics to understand a wide range of organic chemical phenomena in a style accessible to experimental chemists.

**Key words:** Stereoselectivity – Transition state – Ab initio quantum mechanics

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In the century-old development of synthetic organic chemistry, a myriad of methods have been discovered and developed for the formation of new bonds between carbons and for the manipulation of functionality. To do so with control of the three-dimensional arrangement of atoms about the transformed bond is a central goal of organic synthesis. Control of stereoselectivity continues to be a challenging goal of synthesis and one of increasing practical significance as regulations controlling the use of stereoisomers as pharmaceuticals are created. Quantum mechanics has a surprisingly large role in this development, and the origins of this can be traced to the Anh–Eisenstein paper described here.

The 1950s saw the beginning of empirical generalizations about the stereochemistry of nucleophilic additions to chiral carbonyl compounds. The reaction in Fig. 1 is an example of such a process.

In the 1950s, Cram and Cornforth proposed models to rationalize results of this kind, invoking ideas about steric effects and their influence on transition-state conformations [1]. In the 1960s, Karabatsos and Felkin proposed alternatives to the Cram model, shown in Fig. 2. About the same time, mathematical formulations of stereoselectivity issues were formulated by Ruch and Ugi (1969) and by Salem (1973).

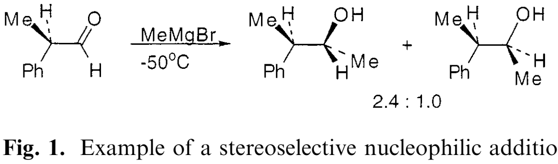
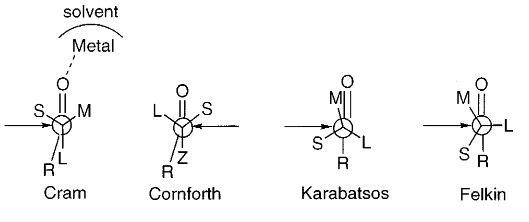


**Fig. 1.** Example of a stereoselective nucleophilic addition

Anh and Eisenstein used quantum mechanics to determine which of these models most accurately reflected the actual transition state of the reaction. These were large systems for quantum mechanics calculations of the time, and many conformations had to be studied. STO-3G calculations on assumed model geometries were used. The tests reported in the paper are demonstrated in Fig. 3 (reprinted from Fig. 1 of the original paper). The figure shows the energies of different rotamers of the transition-state model for attack of hydride on the right-hand (solid line) or left-hand (dashed line) side of the carbonyl group. The dotted line near the bottom of the figure is the energy of rotamers of the aldehyde reactant.

For this case and many others, the Felkin model was established unequivocally to be energetically preferred, and a variety of details and interpretations were provided. In addition to the role of torsional and steric effects, Anh and Eisenstein found that the most electronegative substituent–that with the lowest-lying $\sigma^*_{CX}$LUMO–would take the conformation anti to the attacking nucleophile. This model and its rationale are now universally known as the Felkin–Anh model. A variety of refinements and extensions occurred in following decades, such as the location of actual transition



Cram Cornforth Karabatsos Felkin

**Fig. 2.** Cram, Cornforth, Karabatsos, and Felkin models for nucleophilic addition stereoselectivity (*S*, *M*, *L*, *Z* – small, medium, large, electronegative)

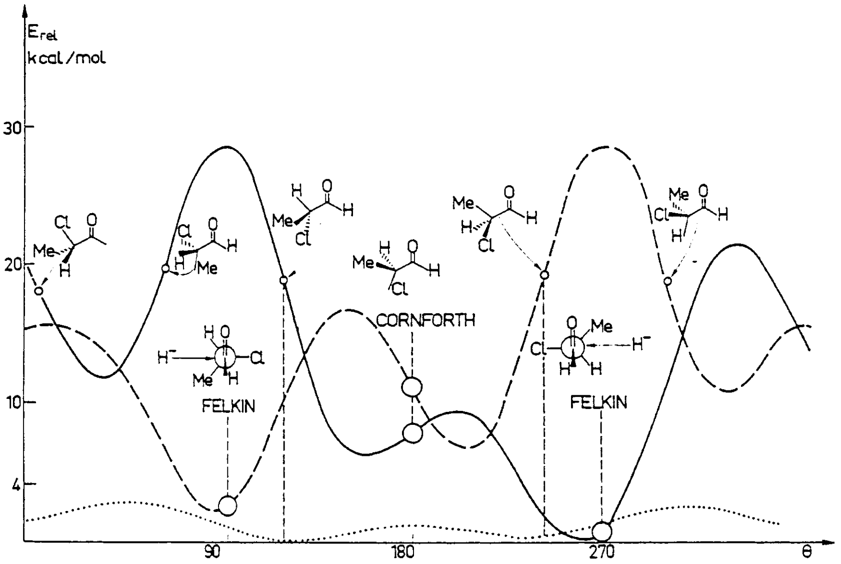


**Fig. 3.** An example of the results in Felkin and Anh's 1977 paper

states for model reactions of this type with larger basis sets, organometallic reagents, and full optimizations [2], as well as extensions to radical and electrophilic reactions [3]. Alternative explanations have been proposed [4], but alternatives to the Felkin–Anh model have not been generally accepted [5].

The publication of a quantum mechanical investigation of this reaction in 1977 was important not only because it solved an important general problem in stereoselectivity, but because it demonstrated the power of quantum mechanical calculations to solve important problems on real organic systems. This style of reasoning, and the tests of stereoselectivity postulates through quantum mechanics, have set the style for theoretical studies relevant to synthetic organic chemistry research.

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