Number 11 March 13, 1978

Citation Classics

Cram D J & Elhafez F A A. Studies in stereochemistry. 10. The rule of ‘steric control of asymmetric induction’ in the synthesis of acyclic systems. *J. Amer. Chem. Soc*. **74**:5825-35, 1952.

A rule was formulated that correlates and predicts, on the basis of steric effects, the direction of stereochemical bias in addition reactions of aldehydes and ketones in which one chiral carbon is generated in the presence of an attached chiral carbon. [The *SCI*® indicates that this paper was cited 265 times in the period 1961-1976.]

Professor Donald J. Cram
Department of Chemistry
University of California
Los Angeles, California 90024

December 2, 1977

“In 1952 we published ‘The Rule of “Steric Control of Asymmetric Induction” in the Syntheses of Acylic Systems.’ This hypothesis resulted from our syntheses of organic chemical systems needed to investigate our newly discovered ‘phenonium ion.’ Our rule evolved from earlier observations of the Frenchman, M. Tiffeneau, and the Scot, A. McKenzie. These early 20th century investigators observed a pattern in addition reactions where one chiral (handed) carbon center was constructed while attached directly to a second chiral carbon. Two diastereomerically related compounds were produced. These authors found that the predominant isomer depended on the order in which substituents were introduced into the products.

“A simple analogy illustrates the evolution of our rule. Imagine that Tiffeneau and McKenzie were assembling diads of N or $$$ letters out of parts, $$$, turned in any direction. Assume that two three-quarter finished assemblies, N $$ and N $$, were in hand which needed one part to complete the diads. These early authors noticed that addition of one part to one assembly gave predominantly one diad, and addition of another part to the other assembly gave predominantly a different diad. The diads had the structure, N N and N $$, but Tiffeneau and McKenzie did not know which was which. They were unable to correlate the patterns obtained in one set of reactions with the patterns observed in other sets of reactions.

“Our contribution consolidated the many patterns into a single rule with predictive power. In effect, we found that adding $$ to N $$ gave mainly N N, and adding $$ to N $$’gave N $$. We correlated the structures of the stereoisomeric products in terms of steric effects in the transition states leading to these products. We suggested a reaction mechanism as an explanation for the rule. Our explanation stimulated controversy! My co-workers and colleague-competitors the world over joyously suggested alternative explanations for why the rule worked.

“Our first manuscript on the rule, a Communication to the Editor, was rejected, but our full paper was accepted. At about the same time, V. Prelog in Switzerland investigated a similar problem, except that the chiral centers were 1,4 rather than 1,2 to one another. His and our results were similar in form, as were our rationalizations. Special exceptions to our rule were designed by J.W. Cornforth in Britain and by H. Felkin in France.

“Our publication is much quoted for several reasons. It deals with a problem encountered in many syntheses. The rule is useful in designing synthetic sequences. The explanation offered is reasonable, arbitrary, unprovable, and provocative. It has therefore stimulated experiments, alternative explanations, calculations, and even semiquantitative expression in algebraic language. In my judgment, the reason why the rule works is still not understood. Probably it works in different systems for different reasons which, by chance, can be summarized in terms of our single generalization.”