

Kinetics, Thermodynamics, and the Problem of Selectivity: The Maturation of an Idea

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This Essay examines the response of organic chemists to the need for application of the principles of physical chemistry to competing reactions. Both mechanistic investigations and multistep chemical synthesis benefited through the eventual establishment of those principles.

1. Understanding Selectivity Requires Physical Chemistry

New ideas in science typically develop on the basis of previous theories and observations. There is much we can learn by examining that process. This Essay examines the problem of selectivity in organic chemistry and how chemists' awareness of it grew over decades. That advance required the incorporation of some important theoretical ideas from physical chemistry, namely the concepts of reaction rate and equilibrium that control the ratios of products in competing reactions. Thus, the selectivity may be determined either by competing rates (if under kinetic control) or by the position of the equilibrium among the products (if under thermodynamic control). The concept is commonplace today and one that every student in organic chemistry is required to learn.

However, that was emphatically not the case even as late as my student years

in the 1940s. Many undergraduate and even graduate textbooks of that period, although concerned with the problem of selectivity, make no mention of this critically important distinction. Although one can point to instances in which a kind of rough-and-ready perception of kinetic versus thermodynamic control was helpful in the work of a few chemists, the organic chemistry community on the whole did not alert itself to the broad reach of these ideas until the late 1950s. This left chemists with only dim insights into the physical and chemical consequences of the interrelationships of energy, rate, and equilibrium. Of course, it would be the height of condescension to claim on behalf of today's chemists that we are more able than our predecessors to handle issues on the forward edge of discovery. Accordingly, I believe that we can be instructed by imagining ourselves in the surroundings of that time.

2. From Affinity to Rate and Free Energy

During the first half of the 19th century, chemists used the rather vague and highly controversial concept of affinity to explain the course of reactions.^[1,2] The malleability of the idea lent it a spurious utility in systematizing experimental facts, but because the underlying physical basis was unknown the concept was not suited to make quantitative conclusions and was open to a variety of oppositional arguments.

The modern formulation of rates and equilibria began to emerge as early as the 1860s and continued well into the next century. These advances were thor-

oughly reviewed, publicized, and employed by some of the founders of modern physical chemistry, notably van't Hoff,^[3-5] Arrhenius,^[6] and Ostwald,^[7] who acted as advocates for the new ideas by virtue of their positions among the leading researchers in the field. Among the most significant developments were the differential formulation of the rate equation and the subsequent quantitative expression of the relationships of rate, temperature, and activation energy. These equations provided the means to compare reaction rates on a common basis. Similarly, the thermodynamic driving force of a reaction, that is, the physical reason why some reactants are transformed to products essentially completely whereas others reach equilibrium short of completion, could be explained by the concept of free energy.

3. Kinetic or Thermodynamic Control of Selectivity?

The fundamental laws of physical chemistry led to a number of statements, some of which will be of particular relevance in our examination of selectivity:

Corollary 1

If the competing reactions are each essentially irreversible, the products will be formed in the same ratios as the ratios of the respective rate constants, provided that Corollary 2 is fulfilled and provided that the products are not differentially consumed by other side reactions.

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Corollary 2

Those relative rates, however, will only be time-independent if the competing reactions are all of the same kinetic order. To my knowledge, this idea was first stated by Ingold et al. in 1931.^[8] If the rates are of different orders, the product ratio in general will change with time, as not all of the concentration terms in the rate equations for the competition will cancel.

Corollary 3

If the reactions are reversible, a channel exists through which products can interconvert with each other by reverting to starting materials.

a) If this interconversion process is fast compared to the initial reaction, the product ratio will be the same as the equilibrium ratio.

b) If the interconversion is only moderately fast, the product ratio will change with time.

Corollary 4

However, the products may interconvert by some other independent process, even if the reactions by which they are formed are essentially irreversible.

a) If this other process is fast compared to the initial reaction, the product ratio will be the same as the equilibrium ratio.

b) If the interconversion is only moderately fast, the product ratio will change with time.

Corollaries 1 and 2 are the basis of kinetically controlled reactions, whereas corollaries 3 and 4 come into play for thermodynamically controlled (3a and 4a) or thermodynamically influenced (3b and 4b) reactions. These corollaries were not set out in detail in the early reports, but they were implied by the basic theory. In the following years, chemists sometimes invoked one or another of the corollaries to justify their procedures. However, it is difficult to find a statement of the complete set of corollaries in books or journal articles of the time.

4. A Slow Learning Process

Thus, whether chemists were aware of it or not, they had proper intellectual tools at hand since about 1900 or even earlier to think clearly about these concepts. Looking back on the subsequent developments, one asks why then did another half-century have to pass for them to diffuse broadly throughout the organic chemical community. We return to this question later. First, we address how slow the learning process was.

The basis for a (very crude) estimate of how slowly the process occurred can be derived from *Chemical Abstracts*, which covers the period from 1907 to the present. A search therein for the term “kinetic control” during the period 1907–1930 gleans only one hit, whereas for the term “thermodynamic control” no hits are obtained. These results increase only to two and 18, respectively, during 1930–1950, but by 1950–1970 an exponential growth is apparent, with 65 and 124 references, respectively. Of course, too much cannot be read into this data; the apparent increase in hits may overestimate the true extent of cognitive growth if some of them simply reflect an autocatalytic expansion of the community’s familiarity with the specific identifying terms “kinetic control” and “thermodynamic control.” On the other hand, there would be a countervailing deficiency of the search for those terms if there were instances (as we will discuss later) in which the investigators were fully aware of the concept but used other nomenclature or simply did not include the term in the abstract.

With the exception of Walter Hückel, no author of textbooks before about 1940 seems to have incorporated any systematic discussion of the corollaries. Even Hückel’s treatment in the 1935 version (2nd edition) of his *Theoretische Grundlagen der Organischen Chemie*^[9] is fragmentary, as he states that the ratio of the rates of two competing reactions is given by the ratio of the products, provided that the reactions are irreversible. The statement is literally correct, but it is incomplete in defining the selectivity because it overlooks the proviso of Corollary 2. In the postwar translation^[10] of the *Grundlagen*, this flaw was pointed out by the translator, Rathmann. Such important pedagogical texts

as Hammett’s *Physical Organic Chemistry*^[11] and Frost and Pearson’s *Kinetics and Mechanism*^[12] do not treat competitive reactions as a general category at all, although Hammett does give a very brief mention of one group of them in a discussion of the Friedel–Crafts reaction (see Section 6).

5. Kinetically Controlled Aromatic Substitutions

Holleman at the University of Amsterdam was one of the first organic chemists to incorporate the new concepts. He made important progress in determining product ratios in aromatic substitutions, mostly through the construction and use of Gibb’s phase diagrams.^[13,14] His strength in physical chemistry, probably gained in his experience as an assistant in the laboratory of van’t Hoff,^[15] led him to adopt the working principle that the product ratios were measures of the *relative rates* of the competing reactions. This idea, which now seems obvious to the modern chemist, apparently was a substantial intellectual leap in the first decade of the 20th century. Following on from the earlier work of van’t Hoff^[4] and Lapworth,^[16] it was one of the first applications of the new quantitative concept of reaction velocity to organic chemical phenomena. Beginning in about 1910, Holleman and co-workers studied the absolute reaction rates of various substitutions to make quantitative the generalizations that *meta*-directing groups deactivate the ring (decrease the rate of substitution), whereas *ortho/para*-directing groups activate the ring (increase the rate of substitution). Subsequently, Holleman and Caland^[17] showed that the sulfonation of toluene is kinetically controlled. It was a rare and perhaps unprecedented instance in which the explicit attention of the investigators to the central issue of selectivity was clearly manifested.

Note, however, that the experiments by Holleman and Caland did not come to grips with the requirement of identity of kinetic order of the competing reactions (Corollary 2). Also, a modern chemist might be concerned about the sensitivity of Holleman’s analytical method for determining the product

ratios by phase diagrams. Nevertheless, the sophisticated level of reasoning in this early mechanistic study is impressive; very few other experiments of comparable quality were to be found during that era. Despite that, the insights reported by Holleman did not seem to make much impact on organic chemists for many years to come.

6. Thermodynamically Controlled Aromatic Substitutions

Not all aromatic substitutions are kinetically controlled, as can be seen in the literature regarding Friedel–Crafts alkylation of aromatic compounds^[18–20] which provides compelling examples of thermodynamically controlled systems. The reaction of benzene with chloromethane in the presence of aluminum chloride is difficult to stop at the stage of monomethylation to toluene because the product is quickly alkylated further to dimethylbenzenes (xylenes) and higher alkylation products.^[21,20] However, the significant point in the present context is that the distribution of the three xylene products (*ortho*, *meta*, and *para*) changes during the time they are allowed to remain in contact with the aluminum chloride. Similarly, in the methylation of toluene, the three products initially comprise mostly *ortho*- and *para*-xylene, together with small amounts of *meta*-xylene, but over time the amount of the *meta* product increases, mainly at the expense of the *ortho* derivative.

It was only in 1939 that the Lewis acid facilitated interconversion of the isomeric xylenes was examined in some detail by Norris and co-workers. Their work had an empirical and preparative motivation, not a mechanistic one.^[22,23] The papers by Norris and co-workers report the influence of time, temperature, and other variables on the ratio of xylene isomers but do not attempt to discuss the results in kinetic or thermodynamic terms. Even later (1946) in a review article on Friedel–Crafts reactions,^[19] Price gives no discussion in terms of physical chemistry principles and describes the variations in product composition by the following statement: “[...] in general, the more vigorous the conditions with respect to the activity of

the catalyst or the alkylating agent or the severity of the time and temperature factors, the greater is the tendency for the formation of the abnormal m-derivatives.”

This terminology invoking the “vigour” of the conditions was quite widespread, even if not universal,^[24] during that period, but it is seen to be lacking a precise physical foundation. The review by Price even omits any mention of the landmark study by Pitzer and Scott in 1943^[25] which definitively showed that some of the Norris–Vaala^[23] xylene mixtures corresponded closely in composition to the *equilibrium mixture* predicted directly from the measured thermodynamic properties of the individual components.

Despite the clearly laggard pace of adoption of the underlying physical principles of selectivity in aromatic substitutions, it should not be assumed that the entire community of chemists failed to recognize the importance of those ideas. A few early examples may be found in which one or more of the concepts were fully understood. Among these were several studies of allylic rearrangements.^[26,8,27–30] In the interest of brevity, we omit a detailed description of those important results in order to focus on a stereochemical issue of broad significance (Section 7).

7. Kinetics versus Thermodynamics in Other Systems: The Puzzle of the Walden Inversion

Walden’s astonishing discoveries, which were reviewed in 1911,^[31] of stereochemical inversion of configuration in several substitution reactions (for example, OH replacing Cl or vice versa) of aliphatic compounds are now well understood, as a result of studies carried out by Phillips, Kenyon, Hughes, and Ingold, among others.^[32] Modern chemists therefore must exert some imagination to reproduce the widespread confusion that prevailed when the results were new. In both his review^[31] and book,^[33] Walden considers several now-abandoned theories proposed by his contemporaries, some of which were imaginative but none of which survived further examination.

From the point of view of this Essay, the most interesting of those abandoned theories was a proposal by Noyes and Potter^[34] in 1912 which was essentially a restatement of a hypothesis that Walden had already considered and rejected. Noyes and Potter stated: “*The rational view seems to be that the Walden inversion is merely a limiting case of ordinary rearrangements, where the interatomic forces are such that the equilibrium in the formation of two possible forms lies far on the side toward the formation of one of these.*”

Walden criticized this proposal on the following grounds: “*This conclusion of Noyes, however, is only another formulation of the facts as those which Walden first established and has presented as inexplicably opposed to theory. The question of course remains open as to what kind of force must exist by which this extreme case of equilibrium, which defies kinetic and thermodynamic considerations, can be kept in place when otherwise it should strive to exit from this state and lead to a true equilibrium.*”^[35]

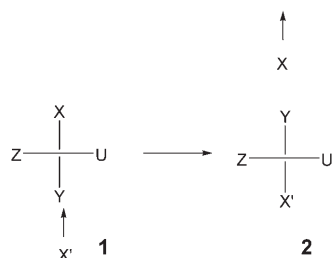
Apparently, the idea that “direct” displacement of one group by another could be accompanied by clean inversion of configuration was so strange that Walden could not conceptualize it and therefore thought that it amounted to a complete overshoot of the equilibrium position, which of course was a thermodynamic impossibility.

Walden ended his review^[31] with a comparison of the views of two of the leaders of physical chemistry. Ostwald,^[35] Walden’s postdoctoral mentor, asserted that “[...] *this phenomenon appears to me in opposition to the fundamental principles of stereochemistry. One cannot invoke here the assistance of a transposition, which in principle, always gives only the racemic combination but not the optical inverse. Obviously, one cannot pretend that the problem does not permit of a solution, but each worthy solution actually considered shakes or modified the bases of stereochemistry.*”

In contrast, Arrhenius was not ready to abandon the fundamentals, as he put it in his book:^[6] “*It is even more probable that from the consequences of more extensive research, a new hypothesis in agreement with the principles of stereochemistry will explain the Walden*

inversion [...] allowing for the formation of intermediate products, this singular result will no longer remain inexplicable.”

A direct challenge to Walden’s pessimistic position of 1911 on the inversion phenomenon appeared later that same year, when Le Bel wrote a short note^[36] based on a private letter sent earlier from Le Bel to Walden, proposing what turned out to be a prescient explanation. Le Bel began by saying that the phenomenon of Walden inversion “[...] astonished me like everyone by its novelty, but I do not believe that one must see it as being in disagreement with the principles of stereochemistry.” He imagined that in certain cases the attacking reagent, X’, could approach the asymmetric carbon center which bears the groups X, Y, Z, and U (**1**, Scheme 1)



Scheme 1. The Walden inversion according to Le Bel.

from the direction opposite to the position occupied by the leaving group X, rather than from the same side. In effect, if X’ pushes Y in front of itself with sufficient force, racemization need not result but instead the restoration of the tetrahedral structure may take place, with Y occupying the place originally held by X and with X’ occupying the original place of Y, as in **2**. A similar argument appeared in a paper by Emil Fischer in the same year.^[37]

Le Bel and Fischer both went on to consider, as a plausible but not obligatory possibility, that the actual mechanism may involve a “product of addition” as an intermediate stage. Although neither of them used the specific term, the context of their remarks seem to point to a pentavalent carbon atom as the key structural feature of the intermediate. Le Bel ended his discussion, “I therefore conclude that the Walden in-

version [...] does not modify the bases of stereochemistry.”

Eight years later, in his book^[33] Walden still held to his doubts that his inversions could be reconciled with fundamental physical theory. Regarding Le Bel’s idea, he remarked that “[...] it has the merit of simplicity which is inherent in the chosen mechanical picture. One can hardly claim that it also possesses the characteristic of completeness.”

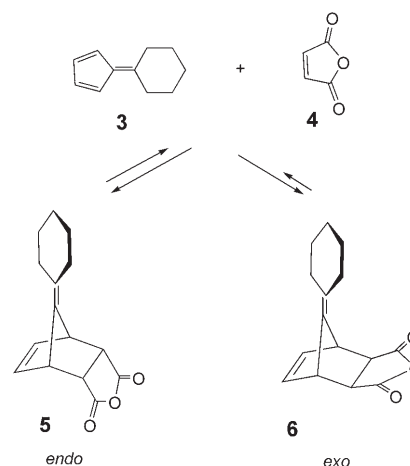
Missing from the theory, according to Walden, was an explanation of why some substitutions at asymmetric centers gave largely retention, others gave inversion, and still others gave some of each or even a near-racemic mixture, even when after-the-fact racemization could be shown to be absent.

To the present-day chemist, the Le Bel–Fischer hypothesis bears a strong resemblance to the later ideas about Walden inversion pioneered primarily by Ingold and the English school during the period 1920–1940.^[32] What was the insight that Walden needed to grasp in order to accept the Le Bel–Fischer hypothesis as the basis for further progress in elucidating the mechanism of inversion? In my view, it was precisely the necessity to distinguish between kinetic and thermodynamic factors. Walden met an impasse at the point in his argument when he could not understand how one could overshoot equilibrium. Possibly he was influenced by his former mentor Ostwald, who also was confused by the problem. What both of them apparently failed to recognize was that the substitution reactions are under kinetic control. If the product ratio is determined by the ratio of competing rates, one does not reach equilibrium. This point had been made, notably by Holleman for aromatic substitutions (Section 5), but Walden did not make the conceptual connection of that work to his own.

8. The Pedagogy of Selectivity

Scattered evidence of awareness of the kinetics versus thermodynamics problem in selectivity is evident during the period up to 1940, notably in several papers on allylic rearrangements from several different laboratories.^[26, 38, 8, 27–30]

However, formal attempts to communicate the general principles in a concise way were rare until the appearance of a paper on the Diels–Alder reaction by Woodward and Baer,^[39] who reported in 1944 that the addition of pentamethylenefulvene **3** to maleic anhydride **4** (Scheme 2) gives both *endo* and *exo* ad-



Scheme 2. Addition of pentamethylenefulvene (**3**) to maleic anhydride (**4**) to give the *endo* adduct **5** and *exo* adduct **6**.

ducts (**5** and **6**, respectively). The *endo* adduct **5** is formed in greater amount at low temperature, but the product composition gives increasing proportions of *exo* product at higher temperatures. Furthermore, even in cold solution, the *endo* adduct, but not the *exo* product, dissociates to the addends—a reaction that is readily visible because of the yellow color of the fulvene. They proposed that the rate of formation of the *endo* adduct is faster than that of the *exo* adduct at low temperature, but the *exo* adduct is more stable than the *endo* adduct and therefore accumulates at equilibrium. Woodward and Baer summarized their proposal in the energy diagram shown in Figure 1.

Alder and Trimborn had made similar observations and interpretations, perhaps as early as 1943, during the war in Germany, but apparently they were unaware of Woodward and Baer’s paper. Eventually a referee called it to Alder’s attention,^[40] and Alder and Trimborn finally published in 1950, after the end of the war, the results of Trimborn’s dissertation from 1943.^[41] They

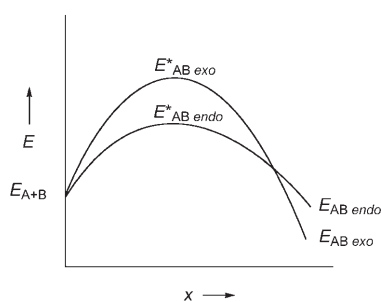


Figure 1. Diagram of energy versus reaction coordinate for the reaction of pentamethylene-fulvene (A) and maleic anhydride (B). Adapted from Ref. [39] with permission of the American Chemical Society.

reported essential agreement with Woodward and Baer in all of the relevant experimental and interpretive points.

Obviously, these events raise a question of priority for the discovery of the temperature dependence of the Diels–Alder reactions of fulvenes, but of greater interest here is the appearance of the energy diagram shown in **Figure 1**. This diagram is one of the first—perhaps the very first—pictorial aid expressing the problem of kinetic versus thermodynamic control in chemical selectivity.

Although the Woodward–Baer diagram preceded by four years a paper on allylic rearrangements by Catchpole, Hughes, and Ingold,^[42] the latter authors were apparently unaware of the earlier work and presented an essentially equivalent diagram representing selectivity in allylic rearrangements. A number of chemists had mastered the basic concepts of the selectivity problem, but it is curious that, as far as I can determine, the actual terms themselves did not make an appearance until the paper by Ingold in 1948.^[42] By then, Ingold apparently was concerned to teach chemists the basic ideas in a pedagogically compelling way. The abstract of that paper contains the statement, “the distinctions between the kinetic and thermodynamic control of the rearrangement are emphasized.” Still later, Zimmerman used essentially the same kind of graphic illustration to display the energy relationships that control the stereochemistry of ketonization of enols, again with no mention of either of the previous published diagrams.^[43]

I believe that the repeated presentations plausibly represent the urgency the authors felt to disseminate the basics of kinetic–thermodynamic principles to the community. This illustrates how spotty they must have seen the recognition of these principles to be at that time.

9. Why so Slow?

One of the reasons for the slow learning curve may have been sociological. Segregation of organic and physical chemistry was endemic during the 19th century, especially in Germany, where the traditional academic organization of chemistry into separate institutes for each disciplinary unit prevailed. A more practical issue before 1950 was the difficulty of analyzing product mixtures to obtain accurate product ratios. Although solutions to this problem ultimately could be found in carefully chosen cases (see Section 5), there were no accurate analytical methods of general applicability until the advent of sophisticated chromatographic methods and of nuclear magnetic resonance spectroscopy, among other powerful tools. Still another stimulus to productive thinking about kinetic and thermodynamic issues after 1950 was the tremendous flowering of multistep organic synthesis, a discipline for which control of selectivity is required at every step. Examples of successful regioselective applications abound in the recent literature on synthetic organic chemistry, but also worthy of mention are the numerous enantiospecific syntheses now appearing in response to government requirements that a chiral drug be enantiomerically pure. Satisfaction of this requirement can be achieved only by the choice of conditions that avoid the thermodynamic trap of racemization.

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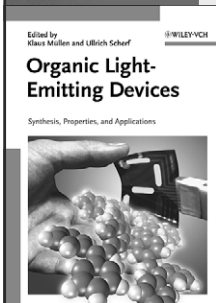
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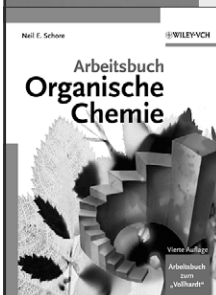


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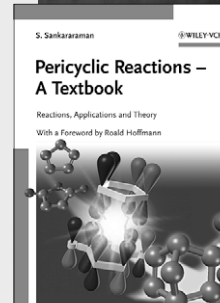
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