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# Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin–Hammett/Winstein–Holness Kinetics

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> "It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..." David Y. Curtin (1954)[1]
>
> "Because Curtin is very generous in attributing credit, this is sometimes referred to as the Curtin–Hammett Principle [rather than] the Curtin Principle." Lewis Plack Hammett (1970)[2]

## *I. Introduction*

The importance of conformation to chemical reactivity has stimulated many organic chemists to focus considerable attention on the impact of conformational concepts on almost all facets of modern organic chemical investigations. Some of the ultimate goals of conformational analysis are the experimental determination, evaluation, and prediction of the relative stability of conformational isomers, their rates of interconversion, and their rates of reaction. Examination of the literature indicates that far more effort has been employed to understand and predict the relative stabilities of conformations than to evaluate the chemical and physical properties of these conformations.[3]

What is the relationship between a molecule's many possible conformations and its properties? Consider, for simplicity, a molecule which can exist in only two conformations $A_2$ and $A_3$ (Scheme I).[4] Intuitively, we know that a property of the molecule must in some way be related to the corresponding physical properties of both $A_2$ and $A_3$. An immediate question arises: to what extent, if any, will the magnitude of the rate constants $k_{23}$ and $k_{32}$ affect a molecular property? Either a measured property will be a weighted average of the properties of the two conformations *or* it will not be; the time constant of the measurement must be known relative to the interconversion rates in order to distinguish between these two possibilities.

SCHEME I

$$A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3$$

The simplest situation which examines the relationship between a molecule's conformations and its chemical reactivity is illustrated by Scheme II[4] which is the basic Curtin–Hammett (C–H)/Winstein–Holness (W–H) kinetic system. It reflects the reactivity of a molecule which exists in two interconverting forms, each of which gives a different product. Scheme II is also valid for any two molecules, $A_2$ and $A_3$, not solely for conformational isomers of a single compound. We will focus considerable attention on the consequences of Scheme II kinetics. We will also examine the chemical implications of the related Schemes III and IV and focus attention on the relationships between these three schemes and a number of related chemical systems. Ultimately, the effect of conformation on reactivity can be answered only through a knowledge of $k_{21}$ and $k_{34}$; i.e., by knowing the reactivity of each of the molecule's conformations. Once the rate constants for product formation are known, the evaluation of conformational effects[3a] on reactivity can be assessed.

SCHEME II

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$

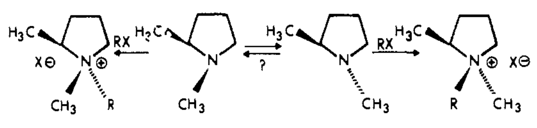
SCHEME III

$$A_1 \xleftarrow{k_{21}} A_2 + R \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} R + A_3 \xrightarrow{k_{34}} A_4$$

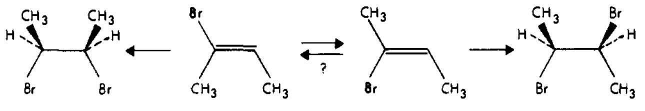
SCHEME IV

$$\begin{tikzcd} & A_0 \arrow[d, "k_0"] & & \\ A_1 & A_2 \arrow[l, "k_{21}"'] \arrow[r, shift left, "k_{23}"] & A_3 \arrow[l, shift left, "k_{32}"] \arrow[r, "k_{34}"] & A_4 \end{tikzcd}$$

Consider, for example, the alkylation chemistry of 1,2-dimethylpyrrolidine (1) which can exist in two isomeric forms, one (**1c**) in which the two methyl groups are cis and the second (**1t**) in which the two methyl groups are trans. Alkylation of **1c** leads to the product in which the alkylating group enters trans to the 2-methyl group; the converse is true for **1t**. This is a stereospecific reaction in that the stereoisomerically different starting materials **1c** and **1t** lead to stereoisomerically *different* products, **2** and **3** respectively.



2 1c 1t 3



5 4c 4t 6

Another example of a stereospecific reaction is the free-radical addition of hydrogen bromide to the *cis*- and *trans*-2-bromo-2-butenes (**4c** and **4t**) to form **5** and **6**, respectively.[5] It is instructive to compare the stereochemical consequences of the alkylation of **1c** and **1t** with the hydrohalogenation of **4c** and **4t**. Questions of interest include: (a) What are the rates of product formation for each conformation in these reactions? (b) What factors influence these rates? (c) What is the ground state distribution of the reactants (**1c** and **1t**; **4c** and **4t**)? (d) Does reactant ratio change as a function of time? (e) What are their rates of interconversion?

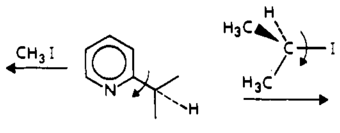
One might well suggest that the reactivity of **1c** and **1t** and **4c** and **4t** are not analogous in that **4c** and **4t** do not interconvert under the reaction conditions while **1c** and **1t** do. Yet the questions (a)–(e) asked above are valid for both systems. Chemical concepts involved with Scheme II do not change simply because the in-

TABLE I. Major Developments in the Study of Conformational Effects on Chemical Reactivity as Interpretated Using the Curtin-Hammett/Winstein-Holness Concepts

1. Reactivity differences for stereoisomers (Barton, 1950;[9] Barton, 1953[10]).
2. Relationship between product distribution, ground state equilibria of conformational isomers and their respective transition-state energies: Curtin-Hammett (C-H) Principle (Pollak and Curtin, 1950;[11] Curtin and Crew, 1955[12]).
3. Relationship between overall reaction rate of equilibrating conformational isomers and individual rate constants of each conformation: Winstein-Holness (W-H) equation (Eliel, 1953;[13] Winstein and Holness, 1955;[8] Eliel and Ro, 1956;[14] Eliel and Lukach, 1957[15]).
4. Limitations of the calculation of conformational equilibria from reaction rates (Cornubert, 1956;[16] Hückel and Hanack, 1958;[17] Kwart and Takeshita, 1965;[18] Mateos et al., 1967;[19] McKenna et al, 1976[20]).
5. Applications of conformational analysis and kinetics in photochemistry (Dauben, 1964;[21] Lewis and Johnson, 1972[22]).
6. Derivation and use of analytical expressions for complex C-H/W-H Kinetic Systems (Zefirov, 1977;[23] Seeman and Farone, 1978[24]).
7. Combined usages of C-H Principle and W-H equation for complete kinetic analyses (Katritsky et al., 1966;[25] Seeman et al., 1980[26]).

terconversion rates are significantly faster (or significantly slower) than the reaction rates.

Consider the iodomethylation of 2-isopropylpyridine (7). As the isopropyl group undoubtedly rotates during



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the course of the alkylation, one must consider the effect of all the conformations on the molecule's overall reactivity.[6,7] An additional complexity would arise if we were to consider the reaction of 2-isopropylpyridine with isopropyl iodide. In this case, conformational flexibility would be available in both reactants![3f] Unfortunately, conformational analysis has not yet reached the sophistication in which reactivity of many individual conformations can be integrated over a reaction surface. Yet, the questions (a)–(e) remain pertinent.

In summary, it is our challenge to separate two interwoven facets of conformational analysis and chemical reactivity: first, that individual conformations may have finite lifetimes[3f] and thus have both physical properties and chemical reactivities which can be determined experimentally; second, that for a molecule which exists in numerous conformations, its overall physical properties and chemical reactivities are related in some fashion to those of the individual conformations.

## *II. Brief Historical Outline of Curtin–Hammett/Winstein–Holness Kinetics*

Scheme II is the simplest system which considers the effect of conformation on chemical reactivity. In 1954, a concept which was subsequently named[5] the Curtin–Hammett (C–H) principle, was advanced which related the product ratio $[A_4]/[A_1]$ to the difference in free energies of the two reaction transition states for Scheme II.[1] Shortly thereafter, the Winstein-Holness (W–H) equation was postulated to describe the overall rate of reaction in terms of the weighted (by mole fraction) rates of reaction of the individual conformers.[8] These two concepts have served as models on which many qualitative and quantitative descriptions of conformational analysis were based.

Table I represents this author's evaluation of the major developments in the study of conformational effects on chemical reactivity as affected by C–H/W–H concepts.

## *III. The Derivation and Evaluation of the Basic Curtin–Hammett/Winstein–Holness Kinetic System*

### A. The C–H/W–H Kinetic Scheme

#### *1. Definition of the C–H/W–H Kinetic System*

The classical C–H/W–H Scheme II describes a kinetic system in which a compound exists in two interconverting isomeric forms ($A_2$ and $A_3$), each of which reacts by first-order (or pseudo-first-order) kinetics to give a different product. Scheme II applies equally for two interconverting molecules as well as two interconverting conformational isomers. Certain boundary conditions are important for Scheme II: condition I, $k_{21}$, $k_{34} >> k_{23}$, $k_{32}$ (section IIIA2); condition II, $k_{21}$, $k_{34} << k_{23}$, $k_{32}$ (sections IIIB–E, IV); condition III, $k_{21}$, $k_{34} \sim k_{23}$, $k_{32}$ (section V).

The treatments which follow are also applicable to kinetic systems in which the products are formed via bimolecular or higher order reactions but follow pseudo-first-order kinetics.

#### *2. Boundary Condition I*

When $k_{21}$, $k_{34} >> k_{23}$, $k_{32}$ a kinetic quenching situation is obtained. The product ratio at reaction completion is equal to the ratio of starting materials at reaction initiation. The two reaction rate constants $k_{21}$ and $k_{34}$ need not be equal.

There are few reactions which are faster than conformational interconversion processes. One of these is, in many cases, proton transfer. Some effort has been extended recently to uncover additional reactions which are rapid enough to act as kinetic quenchers. The fast reaction method of conformational analysis can be used when Condition I obtains.[27]

Consider the diffusion-controlled protonation of amines by strong acid. A difficult situation would arise if, during the quenching process indicated by Scheme III, incomplete mixing of the acid and amine occurred at the interface of the two media. (For a discussion on chemical selectivities and mixing, see the review by Rys.[28]) Local concentrations of amine could "momentarily" negate the desired irreversible quenching process by affording the possibility of amine–ammonium salt reactions and partial equilibration of the amine salt could result.[27] This approach is particularly important for systems whose equilibrium positions cannot be determined by alternative procedures.

There are cases in which a chemical trapping reaction occurs with a reagent other than strong acid. For example, Schlosser and Hartmann[29] and Schlosser et al.[30] report the reaction of a mixture of *cis*- and *trans*-2-hexenes with [(trimethylsilyl)methyl]potassium in tetrahydrofuran to produce a mixture of (*E*)- and (*Z*)-alkenylpotassium isomers which interconvert more slowly than they react (independently) with oxirane. The derived (*Z*)- and (*E*)-4-octen-1-ols therefore reflect the *Z*/*E* ratio of the potassium intermediates. (These reactions formally should be categorized by Scheme VII.)

We note here that Ng Ying Kin et al. regarded Condition I kinetics to be a corollary of the C–H principle.[31] For a kinetic quenching system, the ratio of products is directly and solely related to the ground state conformational distribution.

## B. Derivation of the C–H Principle

### *1. Boundary Condition II:* $k_{23}$, $k_{32} >> k_{21}$, $k_{34}$

Condition II is a commonly observed phenomena, since the rates for conformational interconversion are generally considerably greater than the rates of most organic reactions.

### *2. C–H Principle: First Derivation*[1,5,32]

With regard to Scheme II, consider the following mathematical derivation. The rates of formation of $A_1$ and $A_4$ are shown in eq 1 and 2, respectively.

$$\frac{d[A_1]}{dt} = k_{21}[A_2] \tag{1}$$

$$\frac{d[A_4]}{dt} = k_{34}[A_3] \tag{2}$$

The ratio of the rates of product formation (eq 3) is obtained by dividing eq 2 by eq 1. Equation 4 follows directly.

$$\frac{d[A_4]/dt}{d[A_1]/dt} = \frac{d[A_4]}{d[A_1]} = \frac{k_{34}}{k_{21}}\frac{[A_3]}{[A_2]} \tag{3}$$

$$\int d[A_4] = \frac{k_{34}}{k_{21}} \int \frac{[A_3]}{[A_2]} d[A_1] \tag{4}$$

Equation 4 is trivially integratable *when* $[A_3]/[A_2]$ is constant during the reaction, as it must *if* $k_{23}$, $k_{32} >> k_{21}$, $k_{34}$. Under these C–H conditions, eq 4 is thus transformed into eq 5. Integration yields eq 6 which is simplified to eq 7 when $[A_1]_0 = [A_4]_0 = 0$.[4]

$$\int d[A_4] = \frac{k_{34}}{k_{21}} K \int d[A_1] \text{ when } \left.\frac{[A_3]}{[A_2]}\right|_t = K \tag{5}$$

$$\frac{[A_4]_\infty - [A_4]_0}{[A_1]_\infty - [A_1]_0} = \frac{k_{34}}{k_{21}}\frac{k_{23}}{k_{32}} = K\frac{k_{34}}{k_{21}} \tag{6}$$

$$\frac{[A_4]}{[A_1]_\infty} = K\frac{k_{34}}{k_{21}} \text{ when } [A_4]_0 = [A_1]_0 = 0 \tag{7}$$

This derivation of the C–H principle states explicitly that product ratio $[A_4]/[A_1]$ equals the product of the equilibrium constant $K$ times the ratio of the two reaction rate constants $k_{34}$ and $k_{21}$. *The ground state conformational preference has a direct (proportional) role in the value of* $[A_4]/[A_1]$. C–H kinetics require the product ratio and the isomer distribution to be constant during the course of the reaction.

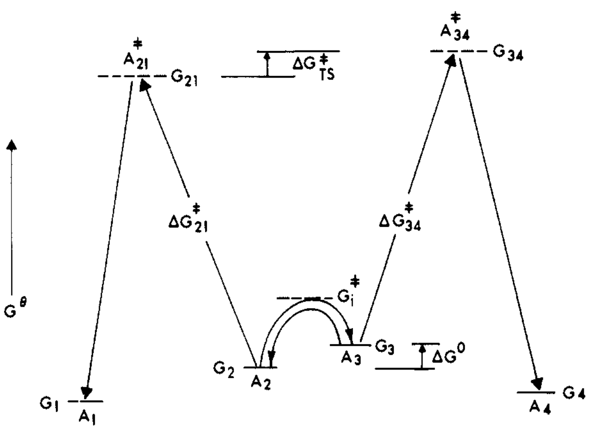


**Figure** 1. Illustration of a Scheme II system where $k_{23}$, $k_{32} >> k_{21}$, $k_{34}$. In this figure and those following, no significance is placed regarding the horizontal separation of the various states. The transition states are represented by dashed horizontal lines, to distinguish them from real chemical compounds which are represented by solid lines. All $G^{\theta}$ values refer to 1 mol of the substance. Note that the free energy $G^{\theta}$ is *not* drawn as a continuous function of the reaction coordinate.

An identical derivation of eq 1–7 was presented by Charton in 1969 to conclude that product distribution could not be used to determine which of a pair of tetrazole tautomers was present in the substrate.[33]

### *3. C–H Principle: Second Derivation*[1,5,32]

From the derivation leading to eq 7, one can incorporate the following kinetic and thermodynamic equations in relation to Figure 1,

$$K = [A_3]/[A_2] = e^{-\Delta G^\circ/RT} \tag{8}$$

$$k_{21} = \kappa_{21} k h^{-1} T^n e^{-\Delta G_{21}^{\neq}/RT} \tag{9}$$

$$k_{34} = \kappa_{34} k h^{-1} T^n e^{-\Delta G_{34}^{\neq}/RT} \tag{10}$$

$$\Delta G_{TS}^{\neq} = \Delta G_{34}^{\neq} + \Delta G^\circ - \Delta G_{21}^{\neq} \tag{11}$$

where $\Delta G_{34}^{\neq} = G_{34} - G_3$, $\Delta G_{21}^{\neq} = G_{21} - G_2$, and $\Delta G_{TS}^{\neq} = G_{34} - G_{21}$.

Substituting eq 8–10 into eq 7 and assuming equality of the transmission coefficients and grouping terms, we obtain eq 12.

$$\frac{[A_4]}{[A_1]_\infty} = e^{-\Delta G^\circ/RT} e^{-\Delta G_{34}^{\neq}/RT} e^{\Delta G_{21}^{\neq}/RT}$$

$$\frac{[A_4]}{[A_1]_\infty} = e^{-(\Delta G_{34}^{\neq} + \Delta G^\circ - \Delta G_{21}^{\neq})/RT} \tag{12}$$

Using eq 11, we obtain the important expression

$$\frac{[A_4]}{[A_1]_\infty} = e^{-\Delta G_{TS}^{\neq}/RT} \tag{13}$$

Equations 7 and 13 have one important restriction: throughout this discussion, $k_{23}$, $k_{32} >> k_{21}$, $k_{34}$ implying that $[A_3]/[A_2] = K$ at all times.[4]

## C. Definitions and Implications of the C–H Principle

### *1. Definitions of the C–H Principle*

Numerous definitions of the C–H principle have appeared over the years[5,32,34,35] all of which are substantially equivalent. In essence, they state that, for Scheme II systems, "the relative amounts of products formed from the two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion"[35] (cf. Figure 1). Inspection of eq 13 substantiates the above definition, in that the only variable to the right of the equal sign is $\Delta G_{TS}^{\neq}$.

It is incorrect, however, to conclude on the basis of the above definition or on the basis of eq 13 that the product ratio $[A_4]/[A_1]$ does not reflect in any way the relative free energies of the conformational isomers. As shown by eq 7, from which eq 13 was derived, $[A_4]/[A_1]$ is directly proportional to the ground state equilibrium distribution. This was initially pointed out by Dauben and Pitzer[32] and largely overlooked until Zefirov[23] and Seeman and Farone.[24] The population ratio does not specifically enter eq 13 since this transition-state expression treats the reaction as path independent. Examination of Figure 1 indicates that eq 13 does indeed inherently take population ratio into account, in that for a molecule $A_2$ to go to transition state $A_{34}^{\neq}$, a free energy equal to $\Delta G^\circ$ plus the free energy difference between $G_3$ to $G_{34}$ must be paid.

In general terms, eq 7 relates product distribution to experimentally measurable quantities, i.e., rate constants and equilibrium distributions. Equation 13 relates product distribution to a difference in free energy between two transition states $\Delta G_{TS}^{\neq}$; free energy is not an experimentally observable property but rather a calculatable parameter from rate constants and equilibrium distributions.

In a practical sense, eq 7 can lead to an experimental derivation of Figure 1 for any chemical system. Equation 13 cannot. On the other hand, eq 13 does lead the chemist to an interesting philosophical vantage point: the belief that the product distribution in Scheme II kinetics is independent (!!!) of the starting material composition appears so contrary to chemical intuition that the C–H Principle takes on an awesome grandeur. By accepting the posture of eq 13, one does *not* eliminate the simultaneous acceptance of opportunities afforded by its mathematical equivalent, eq 7.

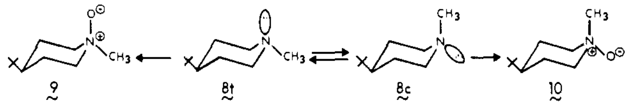
Recently, a definition of the C–H principle has been proposed[36] by the Commission on Physical Organic Chemistry, Organic Chemistry Division, of the International Union of Pure and Applied Chemistry which is a modification of one which initially appeared[35] in their provisional "Glossary of Terms in Physical Organic Chemistry". This definition satisfactorily accounts for the arguments presented above.

> Curtin–Hammett Principle: In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation, whereas the products do not interconvert), the product composition is not solely dependent on the relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states. (It is also true that the product composition is related to the relative concentrations of the conformational isomers—i.e., the conformational equilibrium constant—and the respective rate constants of their reactions: these parameters are generally—though not invariably—unknown.)[36]

### 2. Some Implications of the C–H Principle

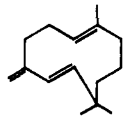
It is valuable to examine the consequences of the C–H principle. Curtin initially stated that, for a Scheme II, Condition II system, "the relative amounts of products formed from the two critical conformations are completely independent of the relative populations of the conformations..."[1] This has often led to the conclusion that it is inadvisable to infer ground state conformational populations from product distributions. Equation 7 clearly indicates that $[A_4]/[A_1] = K$ when $k_{21} = k_{34}$; without knowledge of these latter two rate constants, one cannot quantitatively determine $K$ from $[A_4]/[A_1]$.

However, a knowledge of $K$ and $[A_4]/[A_1]$ can lead to a determination of $k_{21}/k_{34}$. Hydrogen peroxide oxidation of 1-methyl-4-*tert*-butylpyrrolidine [**8t** $\rightleftarrows$ **8c**]

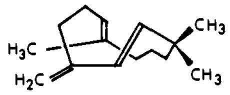


has been reported to lead to a 95:5 mixture of **9** and **10**.[37] Subsequently, it has been shown that the ratio $[\mathbf{8t}]/[\mathbf{8c}] \cong 10.5$.[38] Since this system falls into Condition II kinetics, application of eq 7 indicates that, within the experimental uncertainty of the determination of $[\mathbf{8t}]/[\mathbf{8c}]$, $k_{8c\rightarrow 10}/k_{8t\rightarrow 9} \approx 2$.

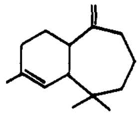
An example of a misanalysis of C–H systems was that made by Fodor[39] and later revised.[40] Initially, the quaternization product ratio of tropanes was directly equated to their ground state conformational preferences. Similarly, Yano and Nishijma proposed that the preferred conformation of γ-humulene (**11**) is **12** since



11



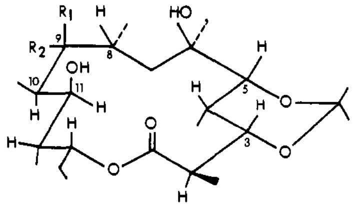
12



13

they observed the formation of a significant yield of **13** upon acid treatment of **11**.[41] While conformations such as **12** which possess the requisite transannular interactions may be necessary for ring cyclization, the product composition does *not* require to be the *preferred* conformation of γ-humulene.

It is equally unjustified to conclude that the absence of $A_1$ (or $A_4$) implies the nonexistence of $A_2$ (or $A_3$). Thus, Corey and Melvin observed that oxidation of the erythromycin analogues **14** and **15** led only to **16**.[42] The



14 $R_1 = OH, R_2 = H$

15 $R_1 = H, R_2 = OH$

16 $R_1 + R_2 = O$

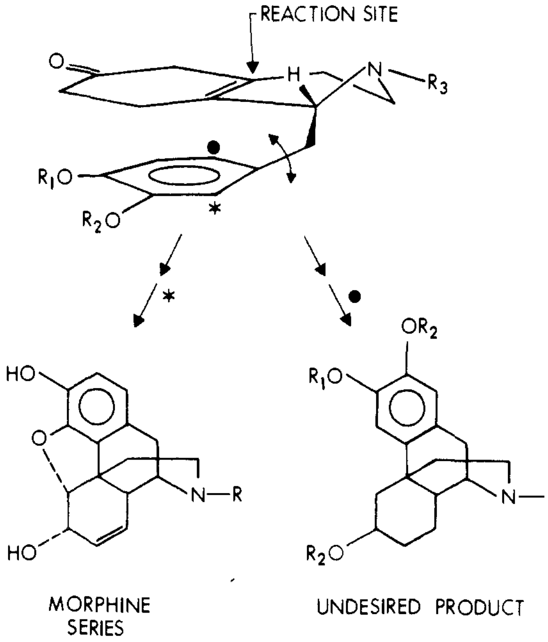


**Figure 2.** The regiochemistry of ring closure is an important feature in the synthesis of opiates. Analysis of the chemical reactivity of the various reacting conformations is crucial for success. Bonding at the "*" site can lead to morphine while ring closure at "●" site results in the incorrect substitution pattern.

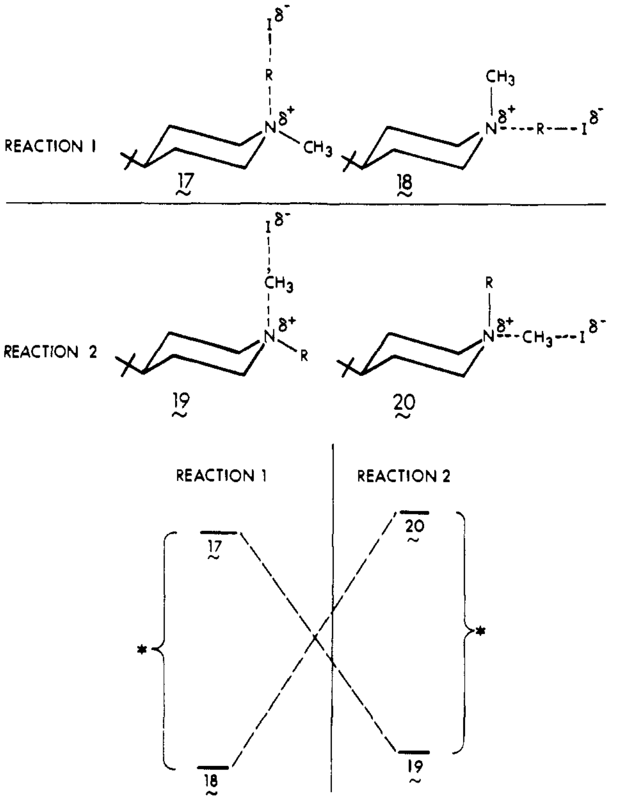


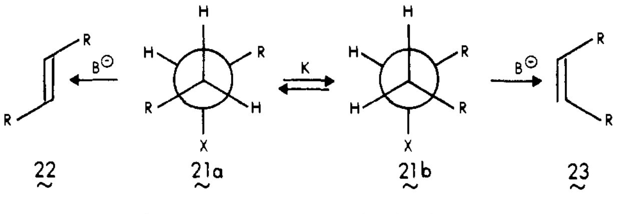
**Figure 3.** Structures **17** and **18** represent the transition states for the reaction of RI with 1-methyl-4-*tert*-butylpiperidine (reaction 1); **19** and **20** represent the transition states for the iodomethylation of 1-alkyl(R)-4-*tert*-butylpiperidine (reaction 2). The dashed lines represent qualitative stability as indicated in the inequalities listed. For cases in which there are "marked differences in stereoselectivity"[46] between reactions 1 and 2, reaction 1 should result in more equatorial alkylation than reaction 2. Note that the product ratio in each case is related to the difference in free energies of the two stereoisomeric transition states, as dictated by the C–H principle, eq 13. The "*" implies uncertainty with regard to exact placement of **18** relative to **17** and **19** relative to **20**, though the relative positions are as shown. R is not methyl.

fact that only the C-9 hydroxyl reacted to the complete inertness of the similar C-11 hydroxyl can be attributed to three possibilities: (a) that there is no equilibration between the C-11 H-inside and C-11 H-outside conformations; or (b) conformational effects in the ground state are transmitted quantitatively to the oxidation transition states; or (c) a combination of (a) and (b), as explained by use of eq 7, i.e., one conformation may well be favored, and oxidation of the C-11 hydroxyl group of that conformation is extremely slow.

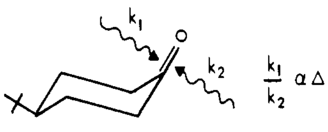
The C–H concepts can be used to design synthetic strategies. For example, a challenging problem in organic synthesis is the regiochemical preparation of morphine analogues. As indicated in Figure 2, two different coupling reactions are possible. Only one leads to the desired opiate system. To enhance the formation of the desired regiochemistry, the C–H principle would suggest two conceptual approaches: first, following eq 7, one could attempt to control both the ground-state populations and relative reaction rates; and second, following eq 13, one could control the presumed relative transition-state energies, in both cases, by appropriate substitution patterns. Rice has successfully utilized another approach: he blocked the undesired cyclization route by appropriately incorporating a halogen substituent.[43] For more recent synthetic solutions to the synthesis of morphine, see the work of Szántay.[44,45]

McKenna and his colleagues have used eq 7 indirectly to assign the regiochemistry of piperidine alkylations.[46–49] They compared the stereochemistry between an *N*-alkylpiperidine and iodomethane with the stereochemistry between the corresponding *N*-methyl substituted piperidine and the related alkyl iodide. As the former reaction was proposed to result in more axial alkylation relative to the latter reaction, McKenna et al. assigned configurations to the alkylation products, thereby deducing the stereochemistry of the alkylation reactions. The logic behind these experiments can be understood by study of Figure 3.[46–49]

Another interesting implication of the C–H principle obtains when one considers the bimolecular reactivity of a molecule which exists in two conformations as the coreactant is changed. Consider the elimination of HX from the equilibrating isomers **21a**–**21b** with a variety of bases. Under conditions in which the base does not effect the equilibrium distribution, $K$, then the product ratio [**22**]/[**23**] will vary as $k_{21a \rightarrow 22}$ and $k_{21b \rightarrow 23}$ varies.



It is important to point out one chemical feature which is *not* an implication of the C–H principle. It is not unusual to see the term "$\Delta\Delta G^{\neq}$" for a chemical system not involving the C–H principle.[50] Such an example may be found in discussions of the stereochemistry of additions to carbonyl compounds by Eliel and Senda.[51] For **25**, two directions of attack are possible, where $\Delta\Delta G^{\neq}$ relates to the difference in free energy for these two reactions. Note that both reactions presumably involve a conformationally homogeneous



25

substrate, as opposed to the C–H Scheme II.

Narula[52] recently presented an analysis of the diastereomeric transition states for the stereoselective epoxidation of acyclic allylic alcohols. His findings were "in accord with the Curtin–Hammett principle, and differs from that of others who have relied upon the preferred conformation of the allylic alcohol."[52] The C–H principle is based on an analysis of Scheme II kinetics, and for the Narula conclusions to follow directly from the C–H principle, an equilibration between reactive intermediates must obtain. Complexation–decomplexation between the olefin and the oxidant could fulfill this requirement if these reactions were indeed reversible and faster than the oxidation process itself.

## D. Derivation of the W–H Equation

### 1. W–H Equation: First Derivation[5,8,32]

The Winstein–Holness (W–H) equation (eq 14) focuses attention on the total rate of product formation for Scheme II kinetics, where we again assume that any

$$\frac{d[A_1]}{dt} + \frac{d[A_4]}{dt} = k_{21}[A_2] + k_{34}[A_3] \qquad (14)$$

non-first-order component of product formation can be treated under pseudo-first-order conditions.

At any time, $t$, during the course of the reaction, the total rate of product formation may be expressed by eq 15, where we *define* $k_{W-H}$ to be the Winstein–Holness

$$\frac{d[A_1]}{dt} + \frac{d[A_4]}{dt} = k_{W-H}\{[A_2] + [A_3]\} \qquad (15)$$

reaction rate constant.

Combining eq 14 and 15, we obtain eq 16:

$$k_{21}[A_2] + k_{34}[A_3] = k_{W-H}\{[A_2] + [A_3]\} \qquad (16)$$

Solving for $k_{W-H}$:

$$k_{W-H} = \frac{[A_2]}{[A_2] + [A_3]} k_{21} + \frac{[A_3]}{[A_2] + [A_3]} k_{34} \text{ at time } t \qquad (17)$$

At time $t = 0$ (reaction initiation), eq 18 is obtained, where $x_{20}$ and $x_{30}$ are the initial mole fractions of $A_2$ and $A_3$ respectively. (This also assumes that the initial

$$k_{W-H} = x_{20}k_{21} + x_{30}k_{34} \text{ at } t = 0 \qquad (18)$$

mole fractions are the equilibrium ones.)

As defined in eq 15, $k_{W-H}$ may well be a time-dependent *variable*. At first glance, it may seem contradictory to describe a rate constant as a variable, but note that $k_{W-H}$ is *not* a rate constant in the true sense of the term. Rather, $k_{W-H}$ is an empirical parameter[53] defined for the two coupled reactions

$$A_2 \xrightarrow{k_{21}} A_1$$

$$A_3 \xrightarrow{k_{34}} A_4$$

That $A_2$ and $A_3$ are interconverting suggests a mathematical procedure which describes total product formation by a single "empirical rate constant."

When the ratio $[A_2]/\{[A_2] + [A_3]\}$ (and consequently $[A_3]/\{[A_2] + [A_3]\}$) in eq 17 is constant throughout the reaction, $k_{W-H}$ will be constant also. This condition will obtain when $k_{23}, k_{32} >> k_{21}, k_{34}$—the same boundary Condition II under which the Curtin–Hammett principle is valid—and under these conditions, $k_{W-H}$ takes the value derived previously for $t = 0$ in eq 18. The Winstein–Holness equation can be defined by eq 17 and 19, the latter being valid under Condition II restrictions.

$$k_{W-H} = x_{20}k_{21} + x_{30}k_{34} \qquad (19)$$

$$\text{for all } t \text{ when } k_{23}, k_{32} >> k_{21}, k_{34}$$

*We now reemphasize an important distinction between the two equations describing* $k_{W-H}$. *Equation 17 is valid for all Scheme II systems, regardless of the values of* $k_{ij}$, *and is valid at all times; however,* $k_{W-H}$ *may be time dependent for some sets of* $k_{ij}$. *Equation 19 is valid for all Scheme II, Condition II systems*; i.e., *when* $k_{23}, k_{32} >> k_{21}, k_{34}$; $k_{W-H}$ *will be time independent because the fractions* $[A_2]/\{[A_2] + [A_3]\}$ *and* $[A_3]/\{[A_2] + [A_3]\}$ *are time independent.*[24]

It is interesting to note that previous derivations of the Winstein–Holness equation under Boundary Conditions II have resulted in relationships such as eq 20 which are quite similar to eq 18 and 19 in form, with one difference. The $N_E$ and $N_A$ in eq 20 were termed

$$k_{W-H} = N_Ek_E + N_Ak_A \qquad (20)$$

"mole fractions" in reviews by Winstein and Holness,[8] Dauben and Pitzer,[32] Eliel,[5,54] and Jensen and Bushweller.[55] Examination of eq 20 indicates that the corresponding terms containing the $A_i$ are mole fractions only at $t = 0$, since the product concentrations $[A_1]$ and $[A_4]$ are absent. Rather, the $N_E$ and $N_A$ in eq 20 are more appropriately termed "fractions of these [conformers] at equilibrium" as described by McKenna[27] and reflect the mole fractions considering reactant alone, with products, solvent, and catalyst not included.

### 2. W–H Equation: Second Derivation

A second Winstein–Holness representation can be derived from eq 19, as originally and independently shown by Eliel and Ro[14] and Eliel and Lukach.[15] From the definition of a mole fraction, it follows that

$$x_{20} + x_{30} = 1 \qquad (21)$$

Therefore

$$x_{20} = \frac{x_{20}}{x_{20} + x_{30}} \qquad (22)$$

Dividing the numerator and denominator of the right hand side by $x_{20}$ results in

$$x_{20} = \frac{1}{1 + \dfrac{x_{30}}{x_{20}}} = \frac{1}{1 + K} \qquad (23)$$

since $K = x_{30}/x_{20}$. It follows from eq 21 that

$$x_{30} = \frac{K}{1 + K} \qquad (24)$$

Substitution of eq 23–24 into eq 19 results in the second formulation of the Winstein–Holness equation, eq 25:

$$k_{\text{W-H}} = \frac{1}{1+K}k_{21} + \frac{K}{1+K}k_{34}$$

$$k_{\text{W-H}} = \frac{k_{21} + Kk_{34}}{K+1} \tag{25}$$

when $k_{23}, k_{32} >> k_{21}, k_{34}$.

## E. Implications of the W–H Equation

A number of additional points are worth noting.

(1) The dependency of $k_{\text{W-H}}$ on $K$ as shown by eq 25 indicates that the rate of reaction is a function of the relative populations of the ground states, just as eq 7 shows a similar type of dependency for the product ratio.

(2) Although eq 25 appears to lack symmetry (compare the $k_{21}$ term with the $Kk_{34}$ term in the numerator), the symmetrical nature of Scheme II requires eq 25 to be symmetrical as well. Resolution comes from the recognition that $K = k_{23}/k_{32}$ is defined such that $A_2 \rightarrow A_3$ is the forward reaction and $A_3 \rightarrow A_2$ is the reverse reaction of Scheme II. If Scheme II were defined in the converse, then eq 25 would imply eq 26 as follows. Let $K = 1/K'$. Then, from eq 25

$$k_{\text{W-H}} = \frac{k_{21} + k_{34}/K'}{1/K' + 1} = \frac{k_{34} + K'k_{21}}{K'+1} \tag{26}$$

(3) Equation 25 can be solved for $K$ in terms of $k_{\text{W-H}}$, $k_{21}$, and $k_{34}$, as shown by eq 27. This is the basis for

$$K = \frac{k_{21} - k_{\text{W-H}}}{k_{\text{W-H}} - k_{34}} \tag{27}$$

the kinetic method of conformational analysis, to be discussed in section IVA.

(4) Just as $k_{\text{W-H}}$ is the average of the specific rate constants of the individual conformers weighted by their mole fractions, the numerical values of certain physical properties of molecules are the weighted averages of that property for each of its conformations. Equation 28 illustrates this point, where $N_i$ is the mole fraction of the $i$th conformation. Such properties as p$K$, dipole moment, ORD/CD, Kerr constant, NMR chemical shifts and coupling constants, and enthalpy are examples of the utility of eq 28. For discussion of this

$$P = \sum_i N_i P_i \tag{28}$$

point see Jensen and Bushweller,[55] Eliel,[54,56] and Winstein and Holness.[8]

Indeed, the relationship between eq 27 and eq 28 can be noted by examination of eq 29–31, which relate the

$$K = \frac{\delta_{21} - \delta_{\text{obsd}}}{\delta_{\text{obsd}} - \delta_{34}} \tag{29}$$

$$K = \frac{J_{\text{av}} - J_1}{J_2 - J_{\text{av}}} \tag{30}$$

$$K = \frac{P_{\text{obsd}} - P_1}{P_2 - P_{\text{obsd}}} \tag{31}$$

equilibrium distribution of a molecule which exists in two interconverting forms (Scheme I) with the NMR chemical shifts ($\delta$) and coupling constants ($J$) of each of these conformers (or models of these conformers), respectively, as discussed by Eliel and Martin[57] and Jensen and Bushweller.[55] The general form of this relationship is shown in eq 31, where $P_{\text{obsd}}$ is the empirical value for the conformationally mobile compound and $P_1$ and $P_2$ are the same property for a conformationally fixed model system or for values of the property for each of the two interconverting isomers. The validity of eq 27 and 29–31 is based on the correct choice of the model systems. This point will be discussed in detail in Section IVA.

(5) For a discussion of the determination of thermodynamic parameters of interconverting conformations using an analysis of the temperature dependence of averaged intensive parameters of the conformations, see the review by Garbisch, Hawkins, and MacKay.[58]

(6) Under C–H/W–H conditions, it can readily be shown that $k_{\text{W-H}}$ is bounded by $k_{21}$ and $k_{34}$, i.e., $k_{34} < k_{\text{W-H}} < k_{21}$ or $k_{21} < k_{\text{W-H}} < k_{34}$.

(7) As has been deduced by Murr and Santiago[59] for a more complex (than Scheme II) system, the approximations made in deriving the W–H equation (Condition II) can be verified if excellent first-order kinetics for reaction are observed. This is equivalent to observing a constant ratio of $[A_4]/[A_1]$ and $[A_3]/[A_2]$ (= $K$) with regard to the identical approximations made for the C–H principle.

(8) If one knew, or could calculate, a particular property of each of two interconverting conformations and knew, or could calculate, their equilibrium distribution, then one could use eq 31 in its alternative form, eq 32, to solve for the observed gross, or weighted-averaged, property.

$$P_{\text{obsd}} = \frac{P_2 + KP_1}{K+1} \tag{32}$$

In 1951, Wood, Fickett, and Kirkwood calculated the optical rotatory power of the predominant conformations of 1,2-dichloropropane in order to assign the absolute configuration of the molecule.[60] This utilization is almost a converse of the applications discussed in (4) above, in that Kirkwood solved for the experimentally observable parameter rather than for the equilibrium constant, $K$.

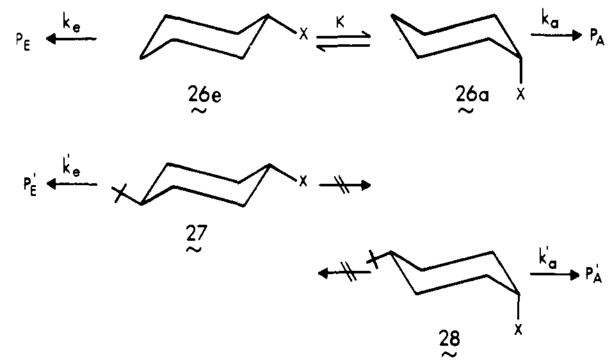
## *IV. Applications of the Curtin–Hammett/Winstein–Holness Concepts*

### A. Distinctions between the W–H Equation and the Kinetic Method of Conformational Analysis

#### *1. The Kinetic Method of Conformational Analysis: Derivation and Examples*

It is not only interesting but crucial to note that the W–H equation was originally derived[8,14,15] for the specific purpose of quantifying the ground-state distribution of conformationally mobile systems. This important development has been termed "the kinetic method of conformational analysis," in that the equilibrium constant $K$ for a Scheme I system is determined by analyzing the chemical reactivity of a related Scheme II system.

For example, the alcohols, acid phthalates, and tosylates of **26–28** were oxidized ($CrO_3$), saponified, and



solvolyzed, respectively, in three independent sets of experiments by Winstein and Holness.[8] The reactivity of the monosubstituted cyclohexyl derivatives **26a** and **26e** falls into Scheme II, Condition II in that the rates of isomer interconversion are significantly faster than the rates of product formation. It was assumed that the *tert*-butyl groups in **27** and **28** remained equatorial and that this locking substituent did not substantially alter the geometry and reactivity of the molecule. If these assumptions are valid, then $k_e'$ would serve as a model for $k_e$ (and $k_a'$ for $k_a$). Inasmuch as $k_{W-H}$, $k_e'$, and $k_a'$ were experimentally determinable for **26**, **27**, and **28**, respectively, $K$ was calculatable from eq 27. The solvolysis of cyclohexyl tosylate involves additional complexities not indicated in the equations below, including the possibility of hydride shift followed by substitution reaction. For details of these additional reactions, see Lambert and Putz.[61]

### 2. Criticisms of the Kinetic Method of Conformational Analysis

The kinetic method of conformational analysis and its instrument, the W–H equation, has received much criticism, as illustrated by the publications of Kwart and Takeshita,[18] Eliel and Biros,[62] McKenna,[27] and Jensen and Bushweller.[55] This is due to the considerable evidence accumulated by a variety of investigators that a 4-*tert*-butyl group sufficiently distorts the geometry of a cyclohexane ring, disallowing molecules such as **27** and **28** from serving as models for the monosubstituted conformers **26a** and **26e**, respectively. Two different arguments have been raised against the use of the W–H equation in the kinetic method of analysis. First, the procedure should predict the same equilibrium distribution ($K$, or $\Delta G°$, or $A$ values) for all monosubstituted cyclohexyl compounds **26a** and **26e**, independent of the choice of reaction. As shown by Kwart and Takeshita,[18] Eliel and Biros,[62] and others cited in these key references, the ground-state free energy differences between axial and equatorial conformers of the same compound appear to have different values depending on the reaction conditions chosen.

To exemplify the complexity of criteria analysis of W–H methodology, consider the work by Chapman et al. on the esterification of cyclohexanecarboxylic acids.[63] Though it was generally accepted that *cis*-4-*tert*-butylcyclohexane-1-substituted compounds usually exist primarily in the *tert*-butyl equatorial conformation, a large 1-substituent, e.g., a solvated carboxylic acid group, could compete with a *tert*-butyl group for the equatorial position. Moreover, in a comparison between acid-catalyzed esterification of a carboxylic acid group and diazodiphenylmethane esterification of the same (though much less strongly solvated and unprotonated) group, the effective size of the two carboxylic acid moieties differ significantly, leading to the determination of different $K$ values by application of the kinetic method of conformational analysis. In this case, it would be incorrect to conclude that different ground-state populations were calculated for the same cyclohexyl substrate, since differential solvation has effectively altered the substrate.[63]

The second argument is based on a consequence of the W–H equation, namely $k_{W-H}$ should be intermediate between the reference, or model rate constants, $k_{21}$ and $k_{34}$. Mateos et al., in an oft-cited reference, challenged this premise of the kinetic method by examining the solvolysis of cyclohexyl tosylates in acetic acid.[19] They reasoned that the plots of $-\log (k/T)$ vs. $1/T$ should be linear and parallel for the solvolysis of **26**, **27**, and **28**, where X = Ts. While the figure in Mateos' paper indicates that the *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates have parallel lines, the unsubstituted compound is nonparallel, thereby apparently conflicting with the theory underlying the kinetic method. Seeman[64] found it of interest to reevaluate the Mateos, et al.[19] results. Linear least-squares analysis (unfortunately there were insufficient points for nonlinear least-squares analysis) of the literature data results in three first-order equations in which the mean values of the slopes are indistinguishable, given their standard deviations.[64] Correction of a possible typographical error[65] in the table (102.5° may be replaced by 122.5°) results in smaller error limits but the three slopes remain indistinguishable based on the experimental data.

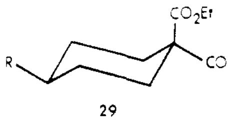
It is interesting to note, at this stage, that there has been some recent support of the kinetic method of analysis by McKenna.[20,27] They followed up a suggestion made almost a decade previously[19] by examining the *distinction* between two classes of systems: for **26**–**28**, the substituent X could represent a reactive group in which C-1 (of the cyclohexane) could either *be*, or *not be*, directly involved in the reaction. Typical examples in which the C-1 atom is involved in the reaction includes the solvolysis of cyclohexanol tosylates,[18] and the dealkylation of *N*,*N*-dibenzylpiperidinium halides,[20] *both of which fail to quantify K by the kinetic method.*

Fewer examples are available in which the reaction does not involve the ring atom. Consider the ethoxy exchange reaction of 4-substituted diethyl cyclohexane-1,1-dicarboxylate (**29**) in ethanolic sodium ethoxide.[20,27] Table II lists the relative combined rate constants for ethoxy exchange of **29**. The observation of identical combined rate constants, within experimental error, between parent compound **29a**, the 4-methyl [**29b**] and the 4-*tert*-butyl [**29c**] derivatives offers strong support for the conclusion that the 4-*tert*-butyl group does not affect the reactivity of the

TABLE II. Relative[a] Combined Rate Constants for Ester Exchange of 29 and Dealkylation of 30[b]

| R | $k_{\text{ester exchange}}$, (substrate) | $k_{\text{dealkylation}}$, (substrate) |
|---|---|---|
| H | 1[a] (29a) | 1[a] (30a) |
| $CH_3$ | 1.0 (29b) | 1.4 (30b) |
| *t*-Bu | 1.0 (29c) | 2.4 (30c) |
| Ph | 1.6 (29d) | 3.2 (30d) |

[a] Relative to R = H. [b] From ref 20 and 27.



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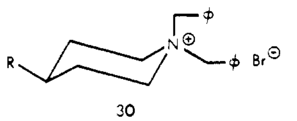

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a, R=H
b, R=CH3
c, R=t-Bu
d, R=Ph

individual ethoxycarbonyl substituents in **29c**. A less likely alternative explanation would be equal (in magnitude) but opposite (in direction) effects on the equatorial and axial ethoxycarbonyl substitutents in **29**. That the phenyl substituent in **29d** affects the combined exchange rate constant was accounted for by the polarity and polarizability of the phenyl group. For comparative purposes, Table II also lists the relative combined rate constants for sodium thiophenolate decomposition of the piperidinium bromides **30a**–**30d**. The marked effect from each of the 4-substituents in **30a**–**30d** is indicative of the involvement of the ring atom (nitrogen) in the reaction. It is interesting to contrast the results of Table II with the recent report of Abraham, Bergen, and Chadwick on the lanthanide-induced shifts of 4-phenyl- and 4-*tert*-butylcyclohexanone.[66] They concluded that a 4-phenyl group distorts the cyclohexanone ring to a lesser extent than a 4-*tert*-butyl group.

Whereas the kinetic method finds few supporters, eq 31 continues to be used, not only for NMR experimentation,[67–69] but also with such determinations as enthalpies of solution[70] and optical rotary dispersion.[71,72] This does not necessarily mean that eq 31 is less susceptible to invalid model selection than is eq 26, or that these physical measurements are less affected by substituent-induced structural changes. *However, invalidating one of the applications of the W–H equation does not necessarily invalidate all applications. Indeed, the W–H equation is always a valid kinetic description of systems which are mechanistically consistent with Scheme II.* (When the C–H/W–H assumption is not valid, i.e., when $k_{23}$, $k_{32} \sim k_{21}$, $k_{34}$, then $k_{\text{W-H}}$ is not constant during the course of the reaction but varies as the mole fractions of $A_2$ and $A_3$ vary. However, the W–H equation (eq 17) remains valid at each time $t$.) For a detailed mathematical evaluation of the W–H equation in terms of group theory, virtual rate constants, and reaction path networks, see the thorough expositions by Blaive and Metzger.[73]

## B. The Use of Free Energy Diagrams for the Evaluation of C–H/W–H Kinetics

The C–H principle and the W–H equation were derived for cases in which the rates of product formation were significantly slower than the rates of conformer interconversion (Condition II). As discussed in section IIIB (eq 7 and 13), the product ratio $[A_4]/[A_1]$ can be

$$\frac{[A_4]}{[A_1]} = K\frac{k_{34}}{k_{21}} \qquad (7)$$

$$= e^{-\Delta G_{\text{TS}}^{\ddagger}/RT} \qquad (13)$$

described by two mathematically equivalent expressions. See Figure 1.

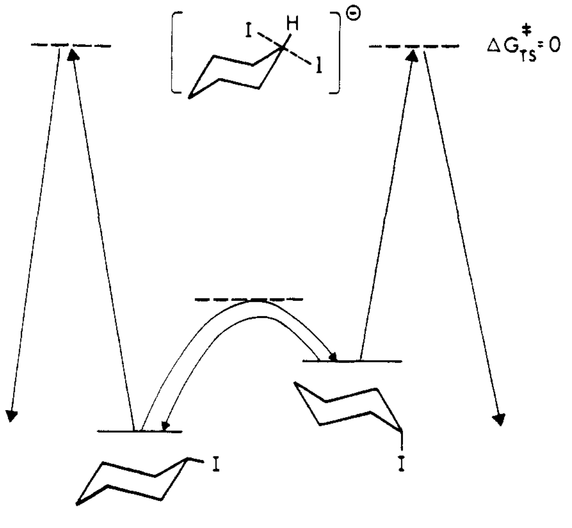


**Figure 4.** Energy diagram for a Scheme II system in which $K \neq 1$ and $\Delta G_{\text{TS}}^{\ddagger} = 0$.

An insight into the value and consequences inherent in the C–H/W–H concepts can be obtained by evaluation of eq 7 and 13 together with the appropriate free energy diagrams. A number of specific subsets of Scheme II, Condition II will be discussed below.

### *1. C–H/W–H Systems When $K \neq 1$ and $\Delta G_{TS}^{\ddagger} = 0$*

Eliel has pointed out that a symmetrical situation can arise if the same transition state obtains from both conformers, $A_2$ and $A_3$.[5] As shown in Figure 4, the ratio of products in the hypothetical reaction of radiolabeled $I^-$ with cyclohexyl iodide will be 50% axial substituted and 50% equatorial substituted—if equilibration of the products does not occur, which it does! Ignoring for the moment product conformational equilibration, we note from Figure 4 that the perfect product balance is related to the symmetry of the transition state and the principle of microscopic reversibility. The difference in reaction activation energies (which is not $\Delta G_{\text{TS}}^{\ddagger}$; see eq 13) is simply the free energy difference $\Delta G°$. Those features which make the axial iodide less stable in the ground state equally destabilize the attack of $I^-$ on the equatorial conformer, and vice versa.

### *2. C–H/W–H Systems When $k_{23}$, $k_{32} >> k_{21}$, $k_{34}$; $K \neq 1$ and $\Delta G_{TS}^{\ddagger} \neq 0$*

(a) The general Scheme II, Condition II system is illustrated by Figure 1, and mathematically described by eq 7 and 13. It is interesting to compare the relationships shown by eq 33 and 34. $\Delta G_{\text{TS}}^{\ddagger}$ is related to

$$\Delta G_{\text{TS}}^{\ddagger} = -RT \ln \frac{[A_4]}{[A_1]} \qquad (33)$$

$$\Delta G° = -RT \ln \frac{[A_3]}{[A_2]} \qquad (34)$$

the product ratio, and $\Delta G°$ is related similarly to the ground-state equilibrium distribution.

Though $\Delta G_{\text{TS}}^{\ddagger}$ reflects both $K$ and $k_{34}/k_{21}$, $\Delta G_{\text{TS}}^{\ddagger}$ is not an empirical parameter of the system. Two possibilities present themselves, as follows in (b) and (c) below.

(b) First, the energy requirements of the transition state can be *less stringent* than the energy requirements of the ground-state conformations, illustrated in Figure 5. We do not distinguish at this stage between two

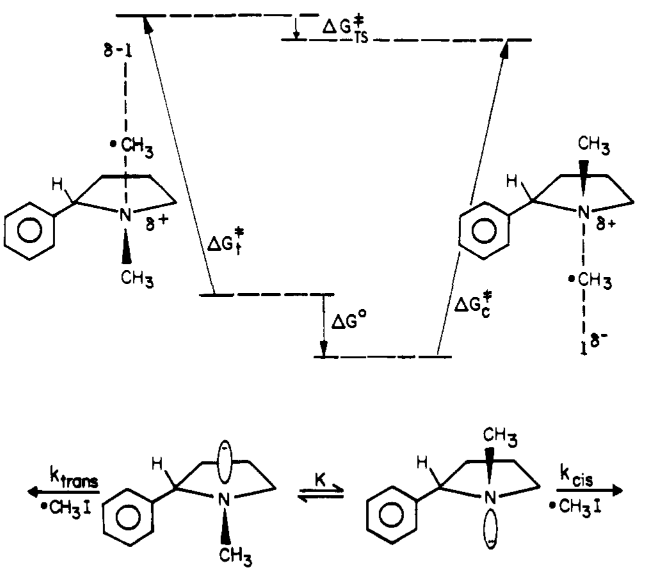
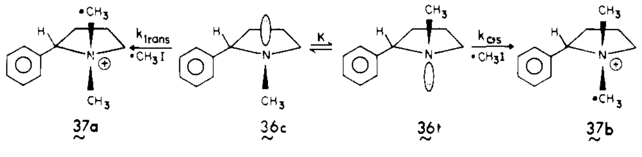


**Figure 5.** A C–H example in which the ground-state free energy difference $\Delta G^{\circ}$ is greater than $\Delta G_{TS}^{\ddagger}$. Reprinted with permission from ref 26.

subsets of this example, $\Delta G_{TS}^{\ddagger} > 0$ and $\Delta G_{TS}^{\ddagger} < 0$. With reference to the methylation of 1-methyl-2-phenylpyrrolidine (**36**), an analogue of nicotine, the



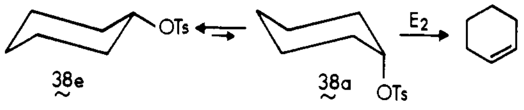
product ratio [**37b**]/[**37a**] = 1.7 while the equilibrium constant $K \geq 17$.[26,64,74]

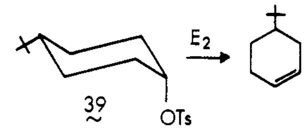
It is significantly easier for an incoming iodomethane molecule to attack **36c**, in that the reagent is trans to the large phenyl group. Conversely, reaction of iodomethane with **36t** is energetically more difficult since the reagent must approach close to the phenyl group. The energy cost reflected in $k_{36c\to 37a}/k_{36t\to 37b}$ is counterbalanced by a similar energy cost reflected in $K$. The equal and alternative explanation for this result is that (a mole of!) the two transition states have approximately the same free energy content.[75] The transition state leading to **37a** is very similar to that leading to **37b**, the major structural difference being the N-$CH_3$ distances in the bonding process, the position of the $I^-$, and the solvent orientation. Apparently, the important feature is the phenyl—N-$CH_3$ interaction vs. the phenyl—N—$CH_3$ interaction in the two transition states, and these more nearly balance than does the phenyl—N—$CH_3$ interaction vs. the phenyl—N—lone pair interaction in the ground-state pair. The products **37a** and **37b** have identical free-energy contents, ignoring isotope effects.[76]

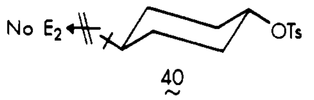
Perrin has recently observed that the above argument leads to the expression $k_{cis}/k_{trans} = K^{\alpha}$,[77] since the destabilizing factors in the ground-state conformers which dictate the magnitude of $K$ for **36c** $\rightleftarrows$ **36t** are the same factors which dictate the magnitude of $k_{cis}/k_{trans}$. The factor $\alpha$ is a measure of the degree to which the destabilization in the ground states is manifested in their respective reactions. There is a very interesting consequence of this hypothesis: for a Scheme II system, if $k_{34}/k_{21} = K^{\alpha}$, then $[A_4]/[A_1] = K\, k_{34}/k_{21} = K^{\alpha+1}$; or in other words, the product distribution is directly dependent on the ground-state conformational distribution![77,78]

Note that $\Delta G^{\circ}$ and $\Delta G_{TS}^{\ddagger}$ are generally rather small (in absolute magnitude) compared to the activation energies $G_{23}^{\ddagger}$ and $G_{32}^{\ddagger}$ (see Figures 1 and 5). This is because most organic chemical reactions are slow compared to the rates of conformational interconversion.

(c) The second possibility is that the energy discrimination of the transition states is *more stringent* than the energy discrimination of the ground-state conformations. An interesting example of this is the base-mediated bimolecular elimination of *p*-toluenesulfonic acid from cyclohexyl tosylate (**38**).[8,56] Whereas *cis*-4-







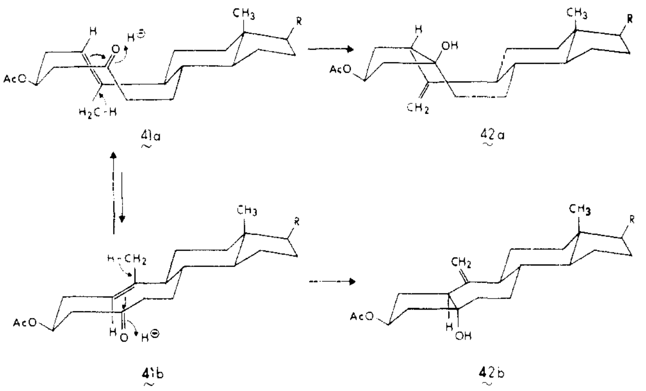
*tert*-butylcyclohexyl tosylate (**39**) readily undergoes elimination to form 4-*tert*-butylcyclohexene, *trans*-4-*tert*-butylcyclohexyl tosylate (**40**) does not undergo $E_2$ reaction. This is because the tosyl group in **39** is axial while it is equatorial in **40**, leading to the well known conclusion that $E_2$ eliminations stereoelectronically prefer a diaxial antiperiplanar orientation. This leads to the following key conclusion: although **38** is almost exclusively in an equatorial conformation **38e**, almost all reaction stems from the less populated **38a**. Given that little or no product forms from **38e**, $\Delta G_{TS}^{\ddagger}$ is very, very large; in this case, $\Delta G_{TS}^{\ddagger} >> \Delta G^{\circ}$. As emphasized by Eliel,[56] an important conclusion from the W–H kinetic method is that a compound can react exclusively in a conformation other than that which predominates in the ground-state equilibrium distribution. For an example of such a case involving a set of intramolecular aryl radical rearrangements, see the report of Köhler and Speckamp.[79]

### *3. Applications and Utilizations of Free Energy Diagrams and the C–H/W–H Kinetic System*

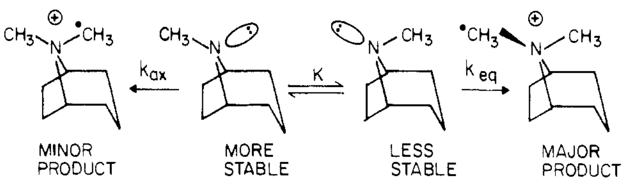
(a) Product composition can sometimes be reflected by the ground-state conformational profile. This can be seen in eq 13: when $k_{21} = k_{34}$, the product ratio is equal to $K$. For systems in which the reaction activation energies are nearly equivalent, the product composition will be nearly equal to the ground-state composition. The same result obtains when those stabilizing and destabilizing features present in the ground state are found in the respective reaction transition states.

Mihailović et al. reported that the two products of the acid-catalyzed cyclization of the seco-1,10-cholesten-5-one **41** are **42a** and **42b**.[80] They suggested that **42a** is the major product, based on the presumed ground state preference in favor of **41a** over **41b**.

(b) Jones et al. derived the values of $\Delta G_{TS}^{\neq}$ from the quaternizations of a variety of morpholines, tropanes, and piperidines with $^{13}CH_3I$ using the C–H principle.[81]



Their work neatly summarized a rather unusual result: axial alkylation predominates for the morpholines and piperidines while equatorial (relative to the six-membered ring) attack predominates for the tropanes. For the former two sets of compounds, the more stable conformer reacts predominantly; for the tropanes, the less stable conformer reacts predominantly. The similarity of the reaction sequence is underscored by the fact that in all cases, an N–$CH_3$ moiety is reacting with iodomethane.



Otzenberger et al. rationalized these results by suggesting that tropanes are less sterically hindered on the pyrrolidine ring side than the piperidine ring side, leading to a predominance of pyrrolidine ring-side attack.[82] This analysis fails to consider the consequences of the C–H principle. As discussed by Seeman et al.,[83] a decreased steric congestion on the pyrrolidine ring side favors *both* an equatorial N–$CH_3$ group in the ground state ($K < 1$) *and* equatorial attack in the transition states ($k_{eq} > k_{ax}$). A priori, one cannot intuitively quantify the relative importance of these two counterbalancing effects. In the transition state, factors such as the $N^{\delta+}$–$CH_3$–$I^{\delta-}$ geometry relative to the tropane geometry are likely to play a key role in these alkylation selectivities.

(c) The assignment of structures for products that result from stereospecific reactions can often be aided by C–H concepts. Consider the exceptionally interesting pair of alkylations studied by Gassman and Heckert.[84] As shown in Figure 6, **43** can in theory methylate to give two isomeric products, **44** and **45**; similarly, ethylation of **46** can result in the same two products. Gassman and Heckert found that **43** and **46** each gave only a single quaternary salt, and that these were different from each other.[84] Does **43** give **44** or **45**?

Of the four alkylation transition states, probably the least stable is that for the endo ethylation of **46x**, since rate constants for ethylation of various amines is considerably slower than the corresponding methylation[85-87] and since the endo position is likely to be more sterically hindered. These evaluations led Gassman and Heckert to suggest that **45** is the product from **46**, and therefore, **44** results from the methylation of **43**.[84] One interesting consequence of these product assignments is that, in the alkylation transition states of **43x** ⇌ **43n**, the net effective size of the iodomethane component is larger than that for the already bonded ethyl group. This result can be added to the unusual reactivity of tropanes discussed in section IVB3b and contrasts with the usual regiochemistry found.[83]

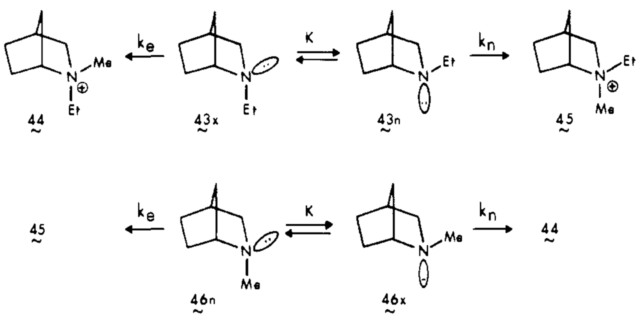


**Figure 6.** Each C–H system (**43** and **46**) represents one pair of stereospecific reactions. Only one product is formed from **43** and one from **46**, and these two products are different. From ref 84.

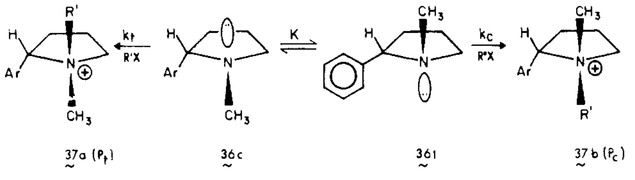
(d) Significant mechanistic information can be obtained from C–H systems when the equilibrating conformational isomers are allowed to react, in independent experiments, with a series of reagents. Such a strategy allows one to directly correlate product ratio with reaction rate ratio, since $K$ is the same for the same substrate. Eq 7 is then transferred to a series of equations:

$$\left.\frac{[A_4]}{[A_1]}\right|_{\text{reaction 1}} = K\left.\frac{k_{34}}{k_{21}}\right|_{\text{reaction 1}} \tag{35}$$

$$\left.\frac{[A_4]}{[A_1]}\right|_{\text{reaction 2}} = K\left.\frac{k_{34}}{k_{21}}\right|_{\text{reaction 2, etc.}} \tag{36}$$

where $K$ is the same ground-state equilibrium constant.

Solladié-Cavallo and Solladié examined the reaction of 1-methyl-2-phenylpyrrolidine (**36**) with a series of alkylating agents.[74] Figure 7 illustrates the chemistry involved. Whereas methylation resulted in a product ratio [**37b**]/[**37a**] = ca. 1.7,[26,74] ethylation led to an equal mixture of **37b**/**37a** and quaternization with benzyl bromide and phenacyl bromide led, in both cases, to more trans product, [**37b**]/[**37a**] = 0.58 and 0.31, respectively. $K$ has subsequently been determined: $K \geq 17$ for **36c** ⇌ **36t**.[26] Because the value of $k_{W-H}$ has been determined only for the methylation reaction, a complete energy diagram can be formulated only for the methylation of **36c** ⇌ **36t**. As shown in Figure 7, $\Delta G_{TS}^{\ddagger} < 0$ for methylation, since cis alkylation predominates. As $k_{W-H}$ has not been determined for ethylation, benzylation, or phenacylation of **36**, only a set of incomplete but nonetheless instructive energy diagrams can be formulated as shown in Figure 7. The relative placements of the free energy levels for the transition states for Figure 7(A) relative to Figure 7(B) relative to Figure 7(C) relative to Figure 7(D) are unknown. For each

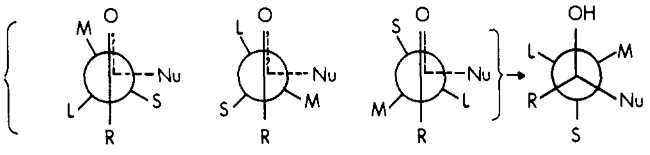


alkylation, the value of $\Delta G_{TS}^{\ddagger}$ is directly calculatable from eq 13. Should $k_{W-H}$ be determined for the last three alkylations, all eight transition-state free energy levels can be related to each other. Such information would provide answers to several questions. For example, as the reactions progress from methylation through phenacylation, $\Delta G_{TS}^{\ddagger}$ changes from negative to zero to positive to more positive. To what extent is this attributable to an increasing $k_t$ and/or a decreasing $k_c$ in this series? Barring additional experimentation, evaluation of these results using the C–H principle (eq 7 and eq 35 and 36) suggests that increasing bulk in the alkylating reagent favors alkylation of the *minor* conformation preferentially.

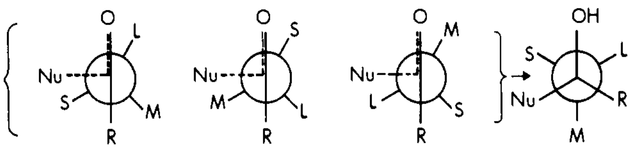
## C. Additional Uses and Applications of the C–H/W–H Concepts

(1) The prediction of product regiochemistry and stereochemistry has long interested chemists. For example, nucleophilic reagents may add to either face of the planar carbonyl group. The nucleophilic addition to carbonyls bonded to asymmetric centers has served as the archetypal reaction for evaluations of regiochemistry and stereochemistry.

Karabatsos calculated product profiles by examining the energies of diastereomeric transition states for the reaction of a nucleophile (Nu:) with a carbonyl group directly bound to an asymmetric carbon.[88] Three transition states (**47** ⇄ **48a** ⇄ **48b**) were considered which lead to one product, **49a**; three (**50** ⇄ **51a** ⇄ **51b**) to the second product, **49b**. Karabatsos concluded that two of these six transition states (**47** and **50**), were most important, since these have the smallest group of the asymmetric atom nearest to Nu. The product ratio was then calculated from the relative magnitudes of the carbonyl–substituent interactions. This is an application of the C–H principle in that the product ratio is determined as described by eq 13.



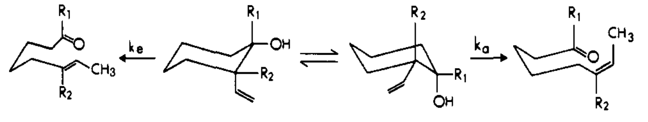
47 48a 48b 49a



50 51a 51b 49b

Other models for carbonyl additions have been presented over the years. For example, Aranda et al.[89] have recently applied the Felkin model[90,91] to the lithium aluminum hydride reduction of diterpene aldehydes. Using a force-field approach, they calculated the "energy" of various carbonyl rotomeric conformations of an otherwise rigid system and then applied semiquantitative and subjective evaluations of the reactivity of the conformations and the energetics of their respective transition states. Complete theoretical analyses must consider such factors as: (a) the relative populations of the ground state conformations;[92] (b) complete energy minimization of ground state structures; (c) development of a theoretical model for the transition state, and complete energy minimization of the model; and (d) the possibility of transition-state variation throughout the range of conformations.[93-96] For additional recent discussions of these points, see Houk,[97] Arjona,[98] and section IXC1.

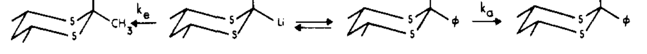
(2) For a C–H system following Scheme II, Condition II kinetics, it is not always necessary to determine experimentally $K$ in order to derive information regarding the relative reaction rates, $k_{34}/k_{21}$. In a study of the stereoselectivity of the retroene reaction, Marvell and Rusay[99] reported the product ratio (*E*)-**52**/(*Z*)-**53** formed from the interconverting **54** ⇄ **55**, and apparently (incorrectly) equated $k_e/k_a$ to the product ratio. When the C–H principle as expressed by eq 7 is used, one can calculate $k_e$ and $k_a$ *if* $K$ is known. By use of $\Delta G_R^\circ(A)$ values for substituted cyclohexanes and assuming additivity of substituent effects,[54,100,101] one can estimate $K$ for **54** ⇄ **55**, and then derive $k_e/k_a$. In this series, the minor conformation reacts faster in all cases and more of the less stable product is formed.



(E)-52 54 55 (Z)-53

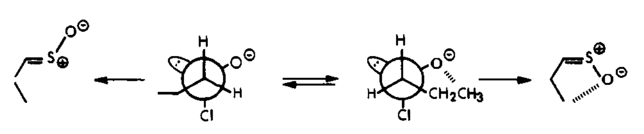
(3) The C–H principle involves the impact of three variables ($K$, $k_{34}/k_{21}$ and $[A_4]/[A_1]$) on product ratio. The calculation of any one of these three requires either the experimental observation or estimation of the other two. Can we "circumvent" these mathematical certainties?

Eliel et al. report that 2-phenyl-2-lithio-*cis*-4,6-dimethyl-1,3-dithiane **56** methylates to give >99.9% **57a**.[102] The conclude either (a) the equatorial carbanion **56e** is present to the exclusion of the axial stereoisomer **56a** or (b) that if both **56a** and **56e** are present, $k_e$ is significantly greater than $k_a$. Taking into account the results of piperidine methylation that leads to preferential axial attack (see section IVB3b), a tentative "squeezed" conclusion resulted: the steric effects necessary for conclusion (b) are not sufficient and that conclusion (a) above is more likely.

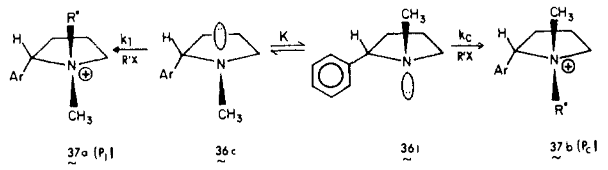


57a 56e 56a 57e

Block et al. have recently isolated, identified, and synthesized the lachrymatory factory of the onion: a 19:1 mixture of **58-Z**/**58-E**.[103] One synthetic route to the natural product involved the dehydrochlorination of the equilibrating mixture **59** ⇄ **60**, which led to a predominant formation of **58-Z**. The literature conclusion[103] that the transition state leading to **58-Z** is



58-E 59 60 58-Z



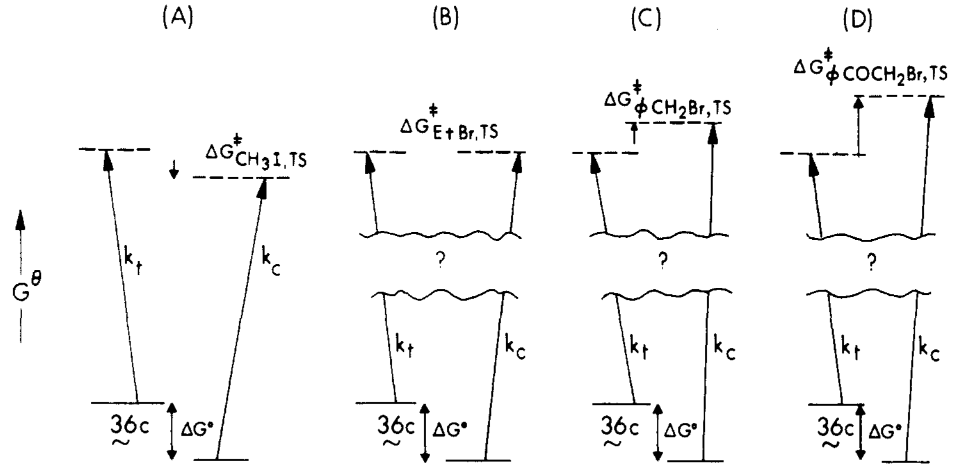
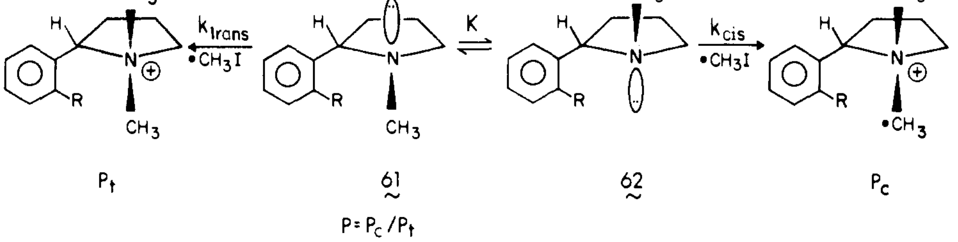


**Figure 7.** Free energy diagrams for the alkylation of **36c** $\rightleftarrows$ **36t**: (A) Methylation results are taken from Figure 5. (B) Ethylation leads to an equal mixture of $P_c$ and $P_t$; $\Delta G_{\mathrm{EtBr,TS}}{}^{\ddagger} = 0$. (C) Benzylation leads to a predominance of $P_t$. (D) Phenacylation leads to an even greater predominance of $P_t$ than found for benzylation; $\Delta G_{\mathrm{PhCOCH_2Br,TS}}{}^{\ddagger} > \Delta G_{\mathrm{PhCH_2Br,TS}}{}^{\ddagger} > 0$. Free energy levels are not drawn to scale.



favored is simply a restatement of the C–H principle. Regarding stereochemical control, two opposing factors may well be involved: a steric repulsion in the (Z) form **60** and hydrogen bonding between the oxygen and the ethyl group.

## D. The Ultimate in C–H/W–H Utility: A Combined Kinetic Treatment

### 1. General Concepts

In the original Winstein and Holness report,[8] the distinction was made between $k_{\mathrm{W-H}}$ (which is related to the conformational distribution of the ground state) and the product ratio (which is discussed as being independent of $K$). Dauben and Pitzer,[32] Eliel,[5,34,56] Hammett,[2] McKenna,[47] and Jensen and Bushweller[55] have written some of the many reviews of stereochemical concepts that deal with the C–H principle and the W–H equation *without* presenting their joint usage to determine Scheme II reaction rate constants.

The greatest utility of the C–H/W–H concepts may well be the determination of $k_{21}$ and $k_{34}$ for Scheme II systems, an application which incorporates the *combined* usage of the C–H/W–H equations. To our knowledge, such treatments can only be found in the work of the Katritzky group[85,86] and Seeman et al.[26]

TABLE III. Experimental Data and Calculated Rate Constants for 61 $\rightleftarrows$ 62[a]

| compound | $k_{\mathrm{W-H}}$ (rel) | $P^b$ | $K$ | $k_{\mathrm{cis}}$ (rel) | $k_{\mathrm{trans}}$ (rel) |
|---|---|---|---|---|---|
| R = H | 24 | 1.7 | >17 | 71 | 5.0 |
| R = $CH_3$ | 6.1 | 1.4 | >30 | 16 | 2.5 |
| R = $CH_3CH_2$ | 4.9 | 1.3 | >30 | 13 | 2.0 |
| R = $(CH_3)_2CH$ | 4.2 | 1.3 | >30 | 11 | 1.7 |
| R = $(CH_3)_3C$ | 1 | 0.28 | >40 | 1 | 1 |

[a] From ref 26. [b] $P = P_c/P_t$.

From eq 7 and eq 25, we can solve for both $k_{21}$ and $k_{34}$ in terms of the empirical rate constant $k_{\mathrm{W-H}}$, $K$, and the product ratio.

For Scheme II ($k_{21}$, $k_{34} << k_{23}$, $k_{32}$):

$$P = [A_4]/[A_1] \text{ and } K = k_{23}/k_{32} \quad (37)$$

$$k_{34} = k_{\mathrm{W-H}}\,[(K + 1)/K][P/(P + 1)] \quad (38)$$

$$k_{21} = k_{\mathrm{W-H}}\,[(K + 1)/(P + 1)] \quad (39)$$

### 2. Applications

Using eq 38 and 39, Seeman et al. calculated $k_{\mathrm{cis}}$ and $k_{\mathrm{trans}}$ for the methylation of **61** $\rightleftarrows$ **62**.[26] The product ratio $P$ was determined by $^{13}$C NMR analysis of the total reaction mixture following alkylation with $^{13}CH_3I$; the empirical rate constant $k_{W-H}$ was determined using conductometric techniques; and $K$ was determined by kinetic (diffusion controlled) quenching of **61** $\rightleftarrows$ **62** with strong acid.[26,104] Substitution of the values of $K$, $P$, and $k_{W-H}$ into eq 38–39 resulted in the calculation of the reaction rate constants for the series **61** $\rightleftarrows$ **62**. Table III lists a portion of the data available. Based on the calculated values of $k_{cis}$ and $k_{trans}$, remarkable steric effects were observed in these conformationally mobile systems.

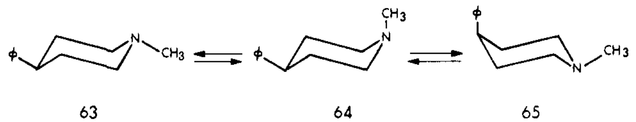
The validity of this analysis is based on the proper experimental determination of $K$, $P$, and $k_{W-H}$. For example, criticism has been leveled at the use of acid quenching experiments for the quantitation of $K$ for tertiary amines,[27,105,106] though recent work substantiates the technique if various stringent experimental conditions are met.[38,46] Thus, kinetically controlled protonation will not occur if experimental conditions allow interconversion between unprotonated amine and protonated amine. An additional complication may occur if the equilibrium distribution heavily favors one of the conformers, in which case it is difficult to determine accurately the amount of less abundant isomer. In any event, the values determined for $K$ are likely to be *minimum* values.[68,107]

We raise these issues here not to resolve questions regarding the accuracy and validity of experimental determination of $K$ for unsymmetrical amines but to suggest caution in the use of the C–H/W–H concepts for kinetic analyses. *Always to be kept in mind is that basic to the combined usage of $k_{W-H}$, $K$, and $P$ in eq 38–39 is the compatibility of their experimental determinations.* If three experiments were performed, each to obtain one of these parameters, then the experiments must be compatible with each other.

### 3. Results from the Katritzky Group

As mentioned above, Katritzky has published extensively on the combined use of C–H/W–H concepts for the analysis of piperidine quaternizations. An early study by Imbach et al., examined the reaction of *N*-alkylpiperidines by using product ratios and equilibrium constants obtained from the literature with their own determined $k_{W-H}$.[25] The major objective of this work and subsequent efforts[87] was the assignment of quaternization stereochemistry. To distinguish between preferential equatorial attack vs. axial attack, the rate constants for both possibilities were determined using eq 38–39. This was achieved by substituting $P$ and $P^{-1}$ in eq 37–39 in two separate sets of calculations using the *same* values of $k_{W-H}$ and $K$; this procedure results in two sets of $k_e$ and $k_a$, only one of which can be valid. They then subjectively decided which set of $k_e$ and $k_a$ was operative.[25,87] Subsequent publications by the Katritzky school addressed the orientation of piperidine ethylation[85] and 2-methylpiperidine methylation.[86]

The Katritzky efforts were elegant in conceptualization. For example, regarding the alkylation of 1-methyl-4-phenylpiperidine, a correction was made that allowed for the presence of ca. 1% axial phenyl conformations; i.e., three reacting conformations were considered, **63**–**65**. Thus, the equations used to calculate $k_e$ and $k_a$ were modifications of eq 38–39. When $K$ was not available, as for the methylations of 1-alkyl-2-methyl-4-phenylpyrrolidines, conclusions were advanced based on rates of product formation ($x_2k_{21}$ and $x_3k_{34}$) and not on individual rate constants ($k_{21}$ and $k_{34}$).[86]



63 64 65

## E. Error Analysis

Only two aspects of error analysis relative to C–H/W–H kinetics have appeared in the literature. One deals with the errors associated with the determination of $K$ using the kinetic method of analysis of eq 27 (sections IIIE4, IVB). This also includes use of the related eq 29–31 which deal with physical properties of either model systems or of the two interconverting isomers.

When $k_{W-H}$ is nearly identical to either $k_{21}$ or $k_{34}$, a large error may be associated with the calculation of $K$. Under these conditions, either $x_{20}$ or $x_{30}$ would be close to unity and $K$ would be very large or very small, respectively. Either the numerator or the denominator in eq 27 would involve a small difference of two large numbers and the accuracy of $K$ would be open to question.[5,54] Inspection of eq 27 indicates that these experimental difficulties would be minimized and $K$ could be optimally determined when $k_{W-H}$ falls halfway between $k_{21}$ and $k_{34}$; i.e., when $x_{20} = x_{30} = {}^1/_2$.

An important aspect of the "combined" usage of the C–H/W–H concepts is an analysis to determine the effect of experimental error in the determination of calculated values of $k_{21}$ and $k_{34}$ as a result of errors in the $k_{W-H}$, $P$, and especially $K$. Such concerns were hinted at by Baker et al.[86] and examined in detail by Seeman et al.[26] The latter authors noted a very interesting conclusion based on an error analysis of the mathematical relationships shown in eq 38–39. The experimental determination of $K$ can be fraught with difficulties, especially when $K >> 1$ or $K << 1$ (see section IVD2). The variability in the calculated values of $k_{21}$ and $k_{34}$ as a function of $K$ can be illustrated by eq 40–42,

For Scheme II ($k_{21}$, $k_{34} << k_{23}$, $k_{32}$):

$$\frac{\partial k_{34}}{\partial K} = -k_{W-H}K^{-2}\frac{P}{P+1} \text{ where } P = [A_4]/[A_1] \quad (40)$$

$$\frac{\partial k_{21}}{\partial K} = \frac{k_{W-H}}{P+1} \quad (41)$$

$$\left.\frac{\partial k_{21}}{\partial k_{34}}\right|_K = \frac{K^2}{P} \quad (42)$$

For evaluation of eq 40–42, let us define Scheme II so that $K > 1$. From eq 42, it can easily be seen that $k_{21}$ is significantly more sensitive to an error in the experimental value of $K$ than is $k_{34}$. For example, if $K = 10$ and $P = 1$, the error in $k_{21}$ will be 100 times the error in $k_{34}$.

This relationship is chemically quite reasonable. If $K$ is large, the mole fraction of $A_3$ is near unity and the mole fraction of $A_2$ is near zero. An error associated with $K$ will affect $x_{20}$ and $x_{30}$ in different fashions; the

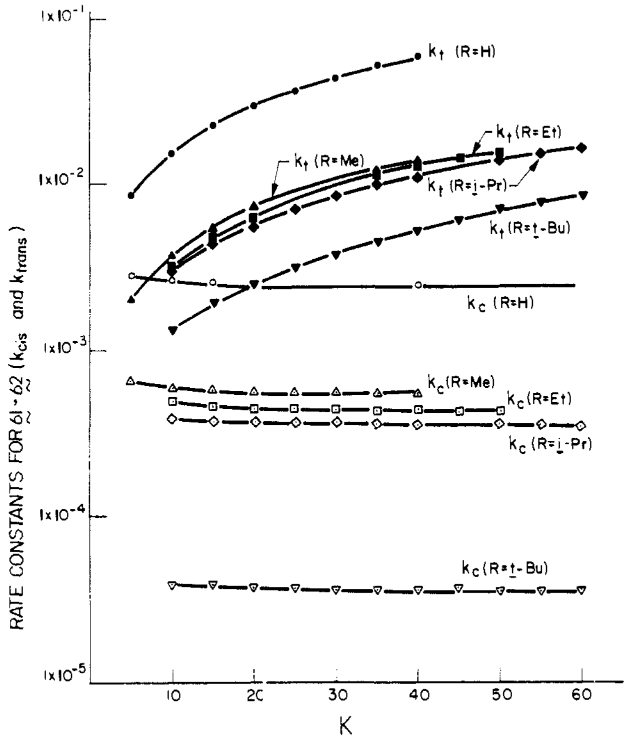


**Figure 8.** The values of $k_{cis}$ and $k_{trans}$ for **61** ⇌ **62** are shown as a function of the possible values of the equilibrium constant $K$. See Table II for additional experimental data. Reprinted with permission from ref 26.

percentage error in $x_{20}$ will be considerably greater. Since the empirical reaction rate constant $k_{W-H}$ is the weighted sum of the individual rate constants, then any deviation in the value of $x_{20}$ (and $x_{30}$) must be compensated for by a deviation in $k_{21}$ (and $k_{34}$). For the example discussed in section IVD2, Seeman et al. illustrated this point by Figure 8.[26] Note that $k_c$, which is $k_{34}$ in Scheme II terminology, is nearly independent of the value of $K$ chosen, as long as $K > 10$, while $k_{trans}$ ($k_{21}$) is markedly dependent on $K$. We emphasize that $K$ is not a variable, only that its absolute value is uncertain. Figure 8 indicates how a possible uncertainty in the experimental determination of $K$ affects $k_{cis}$ and $k_{trans}$.

## *V. Analytical Solution to the Curtin-Hammett/Winstein-Holness Kinetic System*

### A. Introduction

The analysis of Scheme II kinetic systems has played an important role in the development of conformational analysis in particular and in organic chemistry in general in the last 30 years.[34] Many chemical systems are described by Scheme II, the interpretation of which is, at the minimum, facilitated by an understanding of Scheme II implications. The analytical solution to Scheme II, coupled with an exact solution at reaction completion, provides many chemical opportunities not previously available. This is because both the C-H principle and the W-H equation were derived with a specific and somewhat limiting constraint: $[A_3]/[A_2] = K$ during the reaction. Clearly, many Scheme II chemical systems do not satisfy this constraint. The analytical solution to the generalized Scheme II system can also allow determination of the range of validity of the C-H/W-H approximations (eq 7, 13, and 25) and provides kinetic information for all Scheme II systems regardless of the values of the $k_{ij}$ and the initial concentrations of the $A_i$.

### B. Solutions at Infinite Time for Scheme II Kinetic Systems

Zefirov described an elegantly simple mathematical approach for the determination of the Scheme II product ratio at reaction completion.[23] His analysis was for the condition $[A_1]_0 = [A_4]_0 = 0$ and $[A_3]_0/[A_2]_0 = k_{23}/k_{32} = K$. These conditions are not general, and we herein present the results of applying Zefirov's methodology to the derivation of the relationship between product ratio $[A_4]/[A_1]_\infty$ and $k_{ij}$ and $A_{i0}$ for a variety of initial conditions.[64]

For all initial conditions and all $k_{ij}$,

$$[A_4]/[A_1]_\infty = [k_{23}k_{34}\{[A_2]_0 + [A_3]_0 + [A_4]_0\} + k_{21}k_{34}\{[A_3]_0 + [A_4]_0\} + k_{21}k_{32}[A_4]_0]/[k_{21}k_{32}\{[A_1]_0 + [A_2]_0 + [A_3]_0\} + k_{21}k_{34}\{[A_1]_0 + [A_2]_0\} + k_{23}k_{34}[A_1]_0] \tag{43}$$

If $[A_1]_0 = [A_4]_0 = 0$, then

$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{34}}{k_{21}}\left[\frac{k_{23}\{[A_2]_0 + [A_3]_0\} + k_{21}[A_3]_0}{k_{32}\{[A_2]_0 + [A_3]_0\} + k_{34}[A_2]_0}\right] = \frac{\dfrac{k_{23}}{k_{21}} + \dfrac{[A_3]_0}{[A_2]_0 + [A_3]_0}}{\dfrac{k_{32}}{k_{34}} + \dfrac{[A_2]_0}{[A_2]_0 + [A_3]_0}} \tag{44}$$

If $[A_1]_0 = [A_2]_0 = [A_4]_0 = 0$, then

$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{34}}{k_{21}}\,\frac{k_{21} + k_{23}}{k_{32}} \tag{45}$$

If $[A_1]_0 = [A_3]_0 = [A_4]_0 = 0$, then

$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{34}}{k_{21}}\,\frac{k_{23}}{(k_{32} + k_{34})} \tag{46}$$

If $[A_1]_0 = [A_4]_0 = 0$ and $[A_3]_0/[A_2]_0 = K$, then

$$\frac{[A_4]}{[A_1]_\infty} = K\frac{k_{34}}{k_{21}}\,\frac{(k_{21} + k_{23} + k_{32})}{(k_{23} + k_{32} + k_{34})} \tag{47}$$

It is interesting to examine the boundary conditions (section IIIA) for eq 44. When $k_{21}, k_{34} >> k_{23}, k_{32}$ (Condition I), then $[A_4]/[A_1]_\infty = [A_3]_0/[A_2]_0$ (kinetic quenching). When $k_{23}, k_{32} >> k_{21}, k_{34}$, then $[A_4]/[A_1]_\infty = K(k_{34}/k_{21})$ thereby substantiating the C-H Principle (eq 7).

Zefirov evaluated the effect of changes in free energies of activation on product distribution in Scheme II systems.[23] For example, consider the consequences of the following: $\Delta G° = 1$ kcal mol$^{-1}$; $\Delta G_{23}{}^{\ddagger} = 18$ kcal mol$^{-1}$; $\Delta G_{TS}{}^{\ddagger}$ = constant. The effect of varying $\Delta G_{21}{}^{\ddagger}$ is shown in Figure 9. As $\Delta G_{21}{}^{\ddagger}$ increases in value, $k_{21}$ decreases and $P$ (= $[A_4]/[A_1]_\infty$) eventually reaches the C-H value. At the other extreme, when $\Delta G_{21}{}^{\ddagger}$ is small, $k_{21}$ is very large requiring $k_{34}$ also to be large since $\Delta G_{TS}{}^{\ddagger}$ is fixed, $P$ reaches the kinetic quenching value.

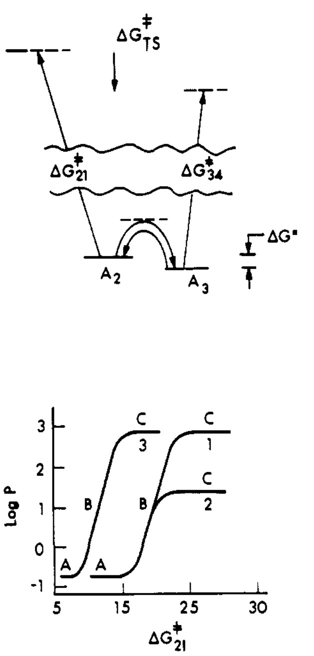


**Figure 9.** The effect of varying the activation energies for product formation when $\Delta G° = 1$ kcal mol$^{-1}$. Curve 1: $\Delta G_{23}{}^{\ddagger} = 18$ kcal mol$^{-1}$, $\Delta G_{TS}{}^{\ddagger} = 6$ kcal mol$^{-1}$; curve 2: $\Delta G_{23}{}^{\ddagger} = 18$ kcal mol$^{-1}$, $\Delta G_{TS}{}^{\ddagger} = 4$ kcal mol$^{-1}$; curve 3: $\Delta G_{23}{}^{\ddagger} = 10$ kcal mol, $\Delta G_{TS}{}^{\ddagger} = 6$ kcal mol$^{-1}$. $P = [A_4]/[A_1]_\infty$. From ref 23.

## C. The Exact Analytical Solution of Scheme II Kinetics

In order to derive information regarding the time course of events in Scheme II systems, especially for Condition III kinetics, the exact analytical solution proves to be of significant value. Equations 48–59

$$[A_1](t) = bk_{21}e^{\alpha t}/\alpha + k_{21}Ce^{\beta t}/\beta + ([A_1]_0 - bk_{21}/\alpha - k_{21}C/\beta) \tag{48}$$

$$[A_2](t) = be^{\alpha t} + Ce^{\beta t} \tag{49}$$

$$[A_3](t) = de^{\alpha t} + he^{\beta t} \tag{50}$$

$$[A_4](t) = dk_{34}e^{\alpha t}/\alpha + hk_{34}e^{\beta t}/\beta + ([A_4]_0 - dk_{34}/\alpha - k_{34}h/\beta) \tag{51}$$

$$\alpha = [-\Omega + (\Omega^2 - 4\Delta)^{1/2}]/2 \tag{52}$$

$$\beta = [-\Omega - (\Omega^2 - 4\Delta)^{1/2}]/2 \tag{53}$$

$$\Omega = k_{21} + k_{23} + k_{34} + k_{32} \tag{54}$$

$$\Delta = k_{21}k_{34} + k_{21}k_{32} + k_{23}k_{34} \tag{55}$$

$$d = bk_{23}/(\alpha + k_{34} + k_{32}) \tag{56}$$

$$h = Ck_{23}/(\beta + k_{34} + k_{32}) \tag{57}$$

$$C = \{[A_3]_0 - [A_2]_0k_{23}/(\alpha + k_{34} + k_{32})\}/k_{23}[1/(\beta + k_{34} + k_{32}) - 1/(\alpha + k_{34} + k_{32})] \tag{58}$$

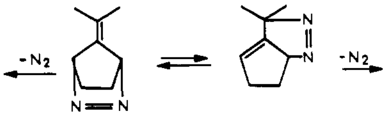
$$b = [A_2]_0 - C \tag{59}$$

$$[A_i]_0 = \text{initial concentration of } i$$

constitute the exact solution for any chemical system which is mechanistically represented by Scheme II or Scheme III under pseudo-first-order reaction conditions.[24] An alternative derivation of the exact solution, in slightly different form, was derived by Lluch at the Universidad Autónomica de Barcelona.[108]

## D. Applications of the Exact Analytical Solution

(1) Perhaps the most important utility of the exact analytical solution to Scheme II (eq 48–59) is the experimental determination of $k_{ij}$'s from time–concentration data for particular chemical systems. Though we are unaware of any examples of such a utilization to date (August 1982), computer programs have been made available to a number of investigators for such purposes.[26] The exact analytical solution is not required to achieve this kinetic analysis. For example, Cichra et al.[109] reported determining the rate constants for the pyrolysis of **66** ⇄ **67** by fitting the experimental time–concentration data to Scheme II using Runge–Kutta numerical integration procedures.[110]

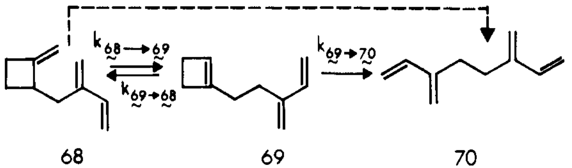


66 67

Independent of the choice of technique (numerical method or exact analytical solution), "trial" rate constants are varied by some iterative procedure (perhaps by a Simplex technique[111,112]) until a best fit to the experimental data is found. Of course, the criteria for "best fit" requires simultaneous recognition of the experimental error in the time–concentration data as well as any error in the numerical method used; an exact solution, of course, is "exact". Numerical methods are generally used when exact solutions to coupled differential equations are not available, since they are approximate solutions of the kinetic scheme and require significantly more computer time to utilize. For a brief discussion on these points and leading references, see footnote 7a in the report of Seeman et al.[113]

Cichra et al. report very small root mean square errors for the fit obtained from the numerical procedures for the independent pyrolyses of **66** and **67** for a particular set of $k_{ij}$.[109] It would be interesting to reexamine the Cichra results using the exact solution in conjunction with a sophisticated error analysis package with a goal of deriving the confidence limits for the $k_{ij}$ for the pyrolyses of **66** ⇄ **67**. Particularly valuable for such an approach is having data for the independent pyrolyses of **66** and **67**.

(2) Shea and Wise reported an investigation of the Cope rearrangement of the 1,5-hexadienes **68** ⇄ **69**.[114]



68 69 70

Two routes to the symmetrical tetraene **70** are conceivable: cyclobutene → butadiene rearrangement **69** → **70** and the less likely direct conversion of **68** → **70**. In that the latter transformation was not considered by Shea and Wise,[114] we can examine the effect of incorporating $k_{68\to70} \neq 0$ in the time course of events for the pyrolysis of **68**. Interestingly enough, setting $k_{68\to70} =$

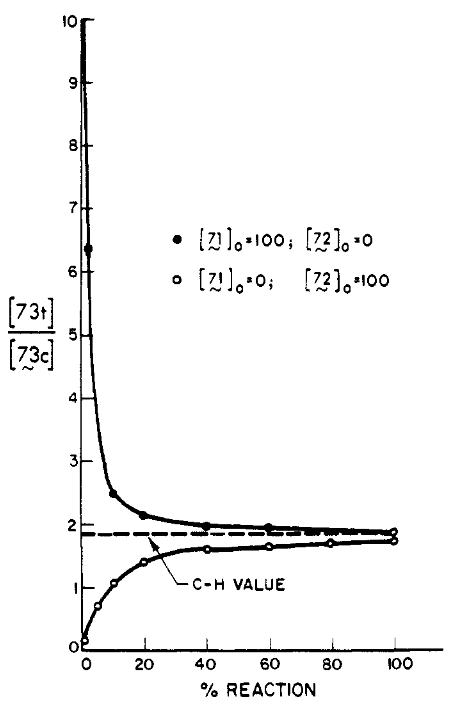
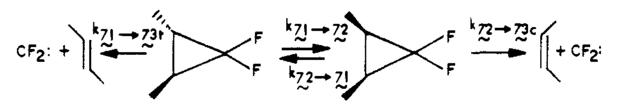


**Figure 10.** The calculated dependency of the product ratio [**73t**]/[**73c**] on the percentage of reaction in the independent pyrolyses of either **71** or **72** using rate data obtained from Dolbier and Enoch:[116] $k_{72\rightarrow71} = 3.96 \times 10^{-5}$; $k_{71\rightarrow72} = 2.07 \times 10^{-5}$; $k_{72\rightarrow73c} = 1.2 \times 10^{-6}$; $k_{71\rightarrow73t} = 1.15 \times 10^{-6}$. The dashed line in the figure represents the C–H value. Reprinted with permission from ref 24.

0.01 $k_{69\rightarrow70}$ does not affect the relative concentration of either **68** or **70** relative to the case in which $k_{68\rightarrow70} = 0$ as a function of percent reaction. The only significant difference is the time–reaction percentage relationship. It has been shown that the maximum value of $k_{68\rightarrow70}$ which would show less than 7% difference in the time profile of the reaction is $k_{68\rightarrow70} = 0.005k_{69\rightarrow70}$.[115] Under these conditions, approximately 7% of the product **70** resulted from the direct path **68** → **70**. In this example, the exact solution to Scheme II was used to determine the maximum value of a rate constant $k_{68\rightarrow70}$ which would have minimum observable effect on the reaction profile, and at the same time, quantify the relative "possible" importance of an alternative reaction pathway.

(3) The exact solution is valid for all systems correctly depicted by Scheme II, not just those in which $A_2 \rightleftarrows A_3$ involve conformational equilibria. In addition, the exact solution is valid for all initial values of $[A_2]$ and $[A_3]$. These two points are illustrated by consideration of the pyrolysis of *trans*- and *cis*-1,1-difluoro-2,3-dimethylcyclopropanes **71** and **72** reported by Dolbier and Enoch.[116] The independent pyrolysis of **71** and **72**



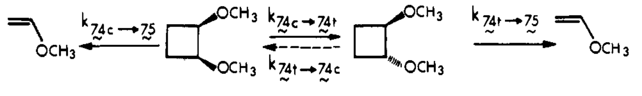
**73t** **71** **72** **73c**

followed "good reversible first-order kinetics throughout".[116] Figure 10 illustrates the use of eq 48–59 for this chemical system. When the rate constants reported by Dolbier and Enoch[116] are used, the calculated product ratio [**73c**]/[**73t**] is shown as a function of percent reaction for two different starting conditions: (a) $[71]_0 = 0$; and (b) $[72]_0 = 0$.[24]

Analysis of the system indicates that good C–H/W–H kinetics should result if the equilibrium distribution [**72**]/[**71**] = $K$ were pyrolyzed. However, results of calculations shown in Figure 10 indicate that when **71** and **72** were pyrolyzed independently, non-C–H/W–H kinetics should be obtained given the literature rate constants; i.e., the product ratio is *not* constant throughout the entire reaction. When a Scheme II system meets Condition III criteria (i.e., when $k_{21} \sim k_{23} \sim k_{32} \sim k_{34}$ and $[A_4]/[A_1]$ is not constant), $k_{W\text{-}H}$ will be time dependent and first-order kinetics should not obtain. It is to be noted, however, that if experimental observations are made *only* after ca. 25% reaction, and if there is sufficient experimental scatter in the data, C–H/W–H kinetics could appear to be time independent. Further examination of the experimental time–concentration data using the exact solution could allow a more accurate determination of the rate constants and thereby substantiate the system's presumed stereospecific mechanism.

(4) It is usually easy to propose a reaction mechanism for a chemical system, but the validation of such a hypothesis can be an enormous undertaking. Indeed, for some sets of rate constants, the distinction between two or more reaction mechanisms may require experimental data of extraordinary precision.[2]

Consider, for example, the reactivity of *cis*- and *trans*-1,2-dimethoxycyclobutanes **74c** and **74t**. Kirmse



**75** ($P_c$) **74c** (?) **74t** **75** ($P_t$)

and Murawski reported values for three rate constants.[117] They also indicated an upper limit of 1% isomerization **74t** → **74c** was observed, and we draw the unproven isomerization of **74t** → **74c** by a dashed line. To what extent can the experimental results support the reaction **74t** → **74c**? We can use the exact solution to Scheme II to determine the maximum value of $k_{74t\rightarrow74c}$ before an experimentally observable concentration of **74c** would result in the pyrolysis of **74t**. As shown in Figure 11, when $k_{74t\rightarrow74c} = 8.5 \times 10^{-7}$, the maximum concentration of **74c** < 1%. The experimental data in conjunction with the exact solution to Scheme II allow us to ascertain the maximum possible (consistent!) value of $k_{74t\rightarrow74c}$ but does *not* allow us to decide if indeed the reaction occurs at all![64]

We can examine the fraction of product which could result via the indirect path **74t** → **74c** → **75** for the rate constants shown in Figure 11.[64] Examination of the second relationship in Figure 11 indicates that at the maximum value of $k_{74t\rightarrow74c}$, approximately 12% of the product is formed by the indirect path. Figure 12 illustrates the nonlinearity of the system using for the breakpoint a value of $k_{74t\rightarrow74c}$ maximized with the three other literature rate constants. We clearly have non-C–H/W–H kinetics, in that the ratio [**74t**]/[**74c**] is not constant during the reaction.

(5) Thujopsene could exist in two conformations: the steroidal conformation **76s** and the nonsteroidal conformation **76n**. Acharya and Brown proposed the stereospecific hydroboration reaction scheme in which

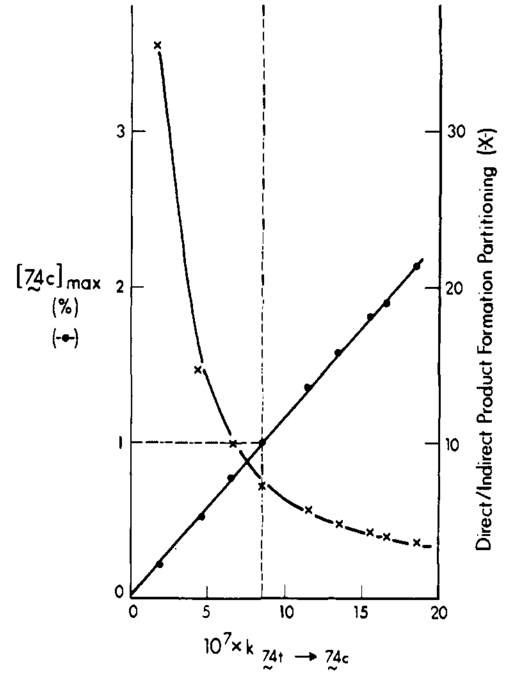


Figure 11. The maximum value of [74c] and the ratio of direct [74t → $P_t$] to indirect [74t → 74c → $P_c$] product formation are both shown as a function of potential values of $k_{74t \rightarrow 74c}$ for the pyrolysis of 74t. The experimentally suggested[117] maximum relative concentration of 74c in the pyrolysis of 74t is 1% and is represented in the figure *below* the horizontal dashed line, indicating that $k_{74t \rightarrow 74c,max} = 8.5 \times 10^{-7}$ s$^{-1}$. The product partitioning ratio lies to the left of the vertical dashed line. From ref 64.

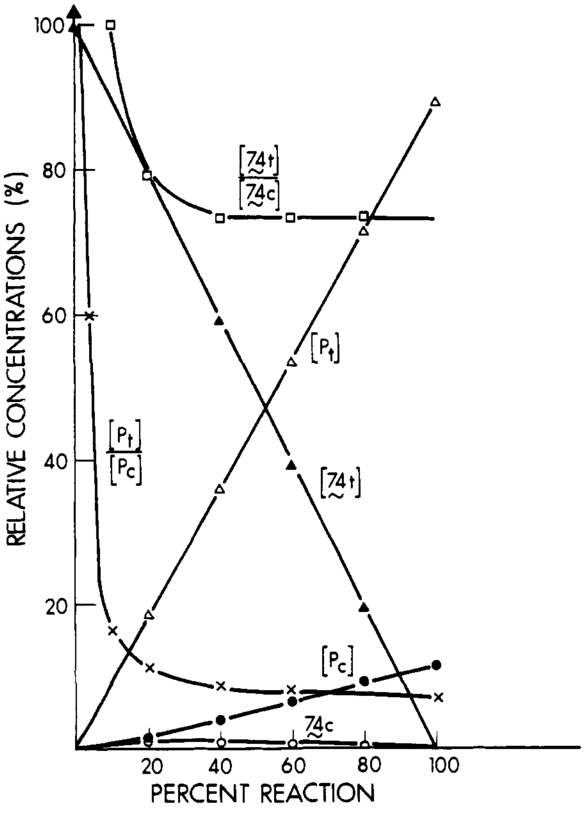
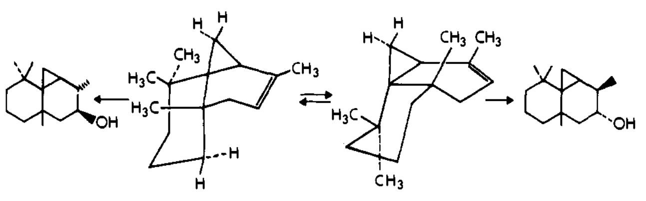


Figure 12. The maximum value of $k_{74t \rightarrow 74c}$ obtained in Figure 11 with the values for the other rate constants is used.[117] Relative concentrations of 74c, 74t, $P_c$ [the product from 74c] and $P_t$ [the product from 74t] are shown as a function of percentage reaction. Also illustrated are the ratios [$P_t$]/[$P_c$] and [74t]/[74c]. From ref 64.

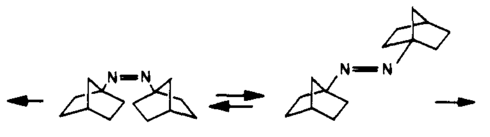


77 76s 76n 78

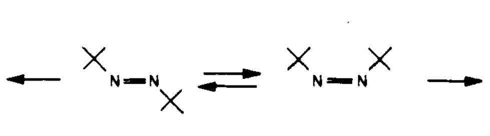
**76s** and **76n** would yield **77** and **78**, respectively.[118] Since only **77** was isolated in >96% yield, Acharya and Brown concluded that thujopsene exists preferentially in the steroidal conformation **76s**.[118]

Alternatively, **76** could exist primarily in the nonsteroidal conformation **76n** and that the hydroboration rate constant of the steroidal form ($k_{76s \rightarrow 77}$) could be considerably greater than the hydroboration rate constant of the nonsteroidal form ($k_{76n \rightarrow 78}$). The Scheme II exact solution was utilized[24] in conjunction with suggested rate constants of Acharya and Brown[118] to indicate the range of values these rate constants must have for the alternative hypothesis to obtain. Without further detailed kinetic studies, the conformational bias of thujopsene cannot be established.

(6) The exact analytical solution can be used for other Scheme II cases found in the literature to extract more information than is otherwise available. This suggests that the analysis of future work in this area will likewise be aided by the exact solution, even if complete time-concentration data are not available. For example, Seeman and Farone[24] analyzed the literature thermodynamic parameters of Engel et al.[119,120] and determined the reaction partitioning in the pyrolysis of *trans*-di-1-norbornyldiazene **79**.[120a] Thermolyses of the related



79



80t 80c

*cis*- and *trans*-*tert*-butyldiazenes, **80c** and **80t**, result in fragmentation only; in neither case was trans-cis diazene isomerization observed. The exact solution was used to determine the lower limit of the activation enthalpies for trans-cis isomerization such that these processes would not be observed. Similarly, mechanistic information regarding the kinetics of allylic rearrangements[121] can be obtained from literature results using the Scheme II exact solution.

## E. Activation Energy Considerations in Scheme II Kinetics

(1) At this stage in the development of C-H/W-H topics, we note that the rate constants $k_{ij}$ and the equilibrium constant $K$ have proven to be the essential

ingredients in the experimental evaluation of these kinetics. The division of Scheme II into three "Conditions" was made in terms of the $k_{ij}$. This contrasts with the conceptual use of activation energies ($E_{ij}$) and preexponential factors ($A_{ij}$) found in the Arrhenius equation (eq 60) and Eyring equation (eq 61) and usually cited regarding C–H/W–H matters where $k_B$ is the Boltzmann constant, $h$ is the Plank constant, and $\kappa$ is the transmission coefficient.

$$k = A \exp(-E_a/RT) \qquad (60)$$

$$k = \kappa k_B h^{-1} T^n \exp(-\Delta G^{\ddagger}/RT) \qquad (61)$$

It is not unusual to find reports in the literature in which activation parameters are reported to the exclusion of the corresponding rate constants. Philosophically, this is most remarkable since activation parameters are derived from rate constants via theoretical relationships, and not the converse. It often appears that empirical data play second fiddle to derived, theoretical parameters. There are certainly excellent reasons to deal with thermodynamic terms, not the least of which is the conceptual value of enthalpy and entropy. Nonetheless, as demonstrated by eq 7,19,43–47, and 48–59, rate constants are the fundamental descriptors of chemical kinetics.

(2) In section VD5 we discussed the attempt by Acharya and Brown[118] to assign the conformational preference of thujopsene **76**. In that only **77** was formed in the hydroboration reaction of **76**, **76s** was assigned as the predominant conformation. In ref 14 of the Acharya and Brown paper,[118a] an objection of one of the referees was reported. This referee suggested that application of the C–H principle "made it impossible to conclude" ground state preference from the hydroboration reaction. (Compare with eq 7 and eq 13 and the discussion in section IIIc.)

Acharya and Brown took exception to the referee's logic by claiming that the C–H principle was not applicable since "the activation energy for the interconversion of conformers is larger than the activation energy for the reaction the system is undergoing".[118a] They point out that the activation energy for the interconversion of cyclohexane derivatives is ca. 10–11 kcal mol$^{-1}$ [note that $\Delta G^{\ddagger}$ for *cis*-decalin is 12.6 kcal mol$^{-1}$ (cf. Dalling et al.[122])] while diborane reductions are complete in "a matter of seconds at 0 °C". It is crucial to note that the rate constant for decalin conformational inversion is $2.3 \times 10^2$ at 0 °C and $9.5 \times 10^3$ at 45 °C.[122] For the hydroboration reaction to be significantly faster than thujopsene conformational inversion, not only must its rate constant be larger than the rate constant for conformational inversion, but the concentration of borane must be large. The minor component of a mixture may well react considerably faster than a major component. We conclude that decisions regarding the applicability of the C–H approximations and the choice between Conditions I–III (section IIIA1) may be made most appropriately following comparison of the relevant rate constant data rather than by chemical intuition.

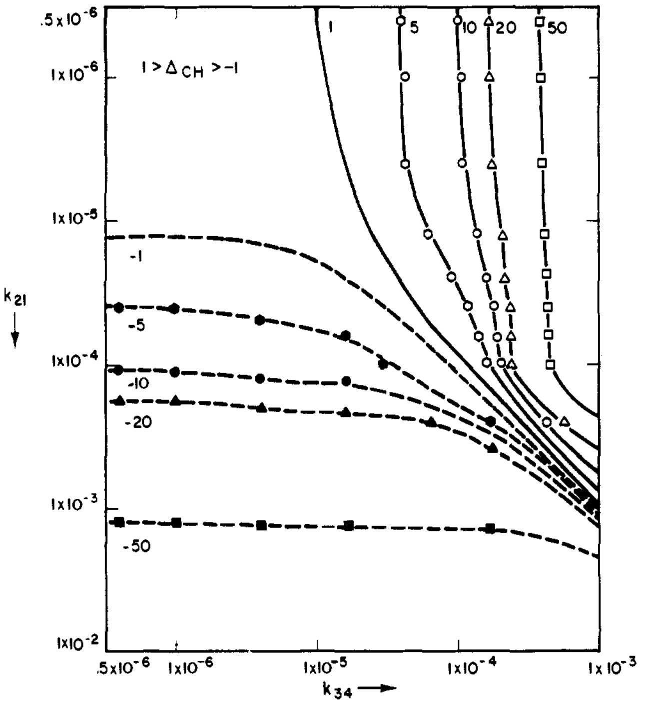


**Figure 13.** Values of $\Delta_{CH}$ contours determined at 100% reaction as a function of $k_{21}$ and $k_{34}$ when $k_{23} = k_{32} = 5.64 \times 10^{-4}$. Note that multiplication of all the $k_{ij}$ by the same constant does not change $\Delta_{CH}$. Reprinted with permission from ref 24.

## F. The Range of Validity of the C–H/W–H Approximations

The availability of the exact solution to Scheme II enabled Seeman and Farone[24] to determine for what sets of $k_{ij}$ the C–H principle was valid. They defined the terms $\Delta_{CH}$ and $\Delta_{WH}$ as indicated in eq 62–64, and arbitrarily assigned any value of $|\Delta_{CH}| <5$ and any value of $|\Delta_{WH}| <5$ as meeting the C–H/W–H approximation criteria.[123]

$$\Delta_{CH} = \frac{K(k_{34}/k_{21}) - [A_4]/[A_1]_\infty}{[A_4]/[A_1]_\infty} \times 100 \qquad (62)$$

$$\Delta_{WH} = \frac{k_{WH} - k_{obsd}}{k_{obsd}} \times 100 \qquad (63)$$

$$k_{obsd} = \frac{d([A_1] + [A_4])}{dt}([A_2] + [A_3])^{-1} \qquad (64)$$

Evaluation of $\Delta_{WH}$ is complicated because $\Delta_{WH}$ is meaningless at reaction completion since there is no product formation at infinite time; $\Delta_{WH}$ is useless at reaction initiation since it is exactly zero for all values of $k_{ij}$ at zero conversion. Since the range of validity of $\Delta_{WH}$ and $\Delta_{CH}$ are likely to be very similar, we will concentrate herein on $\Delta_{CH}$. The interested reader is referred to the original literature for full discussion regarding $\Delta_{WH}$.[24]

Figure 13 illustrates the values of $\Delta_{CH}$ for a range of $k_{21}$ and $k_{34}$ for a particular selection of values of $k_{23}$ and $k_{32}$. It is clear that for a problem requiring simultaneous consideration of four variables, one graph cannot include all combinations of the $k_{ij}$. Nonetheless Figure 13 illustrates a number of points. (a) A mathematical degeneracy occurs in the $\Delta_{CH} \simeq 0$ region of the graph. This degeneracy indicates that there will be combinations of the $k_{ij}$ for which the C–H approximation will be valid even though Condition II does *not* apply. The degeneracy will not always be along the diagonal of figures analogous to Figure 13 when $k_{23} \neq k_{32}$, i.e., when the system is not symmetrical. (b) The $\Delta_{CH}$ contours change less sharply in the upper left hand corner of

Figure 13, this being the area in which the C–H approximations are valid. (c) The values of $\Delta_{CH}$ are not always symmetrical with an interchange of variables due to the nonsymmetrical definition of $\Delta_{CH}$ in eq 62.

The range of validity of the C–H/W–H approximations can be determined by the analysis of a number of $\Delta_{CH}$ contours for a wide range of $k_{ij}$, one example of which is seen in Figure 13. Alternatively, the product ratio at reaction completion (eq 47) coupled with the definition of $\Delta_{CH}$ (eq 62) leads directly to eq 65 by

$$\Delta_{CH} = \frac{k_{34} - k_{21}}{k_{23} + k_{32} + k_{21}} \times 100 \tag{65}$$

simple mathematical manipulations.

Using the criterion that the C–H/W–H approximations will be valid when $|\Delta_{CH}| < 5$, we derive eq 66.

$$k_{23} + k_{32} > |20k_{34} - 21k_{21}| \tag{66}$$

For illustrative purposes, consider sets of $k_{ij}$ in which $k_{23} \approx k_{32}$. Then

$$k_{23}, k_{32} > |10k_{34} - 10.5k_{21}| \tag{67}$$

We can use eq 67 to derive a general conclusion regarding C–H/W–H validity. When $k_{34} >> k_{21}$ (or $k_{21} >> k_{34}$), then eq 67 will obtain if $k_{23},k_{32} > 10k_{34}$ ($k_{23},k_{32} > 10.5k_{21}$). *That is, the C–H principle and the W–H equation will appropriately approximate the reaction kinetics for balanced systems when the rate of isomer interconversion is ca. 10 times larger than the faster reaction rate constant.* This "rule of thumb" was originally deduced by Seeman and Farone[24] and depends on the relative equality of $k_{23}$ and $k_{32}$ (cf. eq 67). *Analysis of eq 66 when* $k_{23} \neq k_{32}$ *suggests that* C–H/W–H validity will obtain when the larger of the $k_{23},k_{32}$ pair is approximately 10 times larger than the larger of the $k_{21},k_{34}$ pair. For specific cases, especially those involving unbalanced systems, the validity of the C–H/W–H approximations are best determined using the exact solution at infinite time[24] directly rather than these generalizations.

We note here that eq 65–67 were derived from the exact solution at reaction completion, eq 47. With regard to the product ratio $[A_4]/[A_1]$, it is important to distinguish between the value at 100% reaction (at infinite time) and the value at a percentage reaction less than 100%. It is possible that some sets of $k_{ij}$ will result in a very time dependent $[A_4]/[A_1]$. For such cases, it could be argued that the criterion for C–H/W–H acceptability should be made at 95% reaction, or 90% reaction, etc. It may be rather pointless to place emphasis on meeting any arbitrary criterion, though it is interesting to speculate that some systems may not be closely approximated by the C–H principle at some percentage completion but meet the criterion at some other stage in the reaction.

## *VI. Curtin–Hammett/Winstein–Holness Systems Invovling Second-Order Reactions to Product (Scheme III)*[113]

### A. Definition and Boundary Conditions

Scheme III generalizes the kinetic system involving two interconverting substances, $A_2$ and $A_3$, each of which reacts with a reagent R via second-order kinetics to give products $A_1$ and $A_4$ respectively.

**SCHEME III**

$$A_1 \xleftarrow{k_{21}} A_2 + R \underset{k_{32}}{\overset{k_{23}}{\rightleftarrows}} R + A_3 \xrightarrow{k_{34}} A_4$$

Equations 68–71 are the four coupled differential equations which define Scheme III. Because of the incorporation of the second-order terms in these equations, the three conditions dealing with Scheme III also incorporate second-order terms. Clearly, the concentration of $A_i$ and R are important in comparing the overall rates of the four reactions in Scheme III.

$$\frac{d[A_1]}{dt} = k_{21}[A_2][R] \tag{68}$$

$$\frac{d[A_2]}{dt} = k_{32}[A_3] - k_{21}[A_2][R] - k_{23}[A_2] \tag{69}$$

$$\frac{d[A_3]}{dt} = k_{23}[A_2] - k_{34}[A_3][R] - k_{32}[A_3] \tag{70}$$

$$\frac{d[A_4]}{dt} = k_{34}[A_3][R] \tag{71}$$

Equation 73, which can be derived by dividing eq 71 by eq 68, is the instrument by which we can determine the product ratio $[A_4]/[A_1]$.

$$\frac{d[A_4]/dt}{d[A_1]/dt} = \frac{k_{34}[A_3][R]}{k_{21}[A_2][R]} = \frac{k_{34}[A_3]}{k_{21}[A_2]} \tag{72}$$

$$\int d[A_4] = \frac{k_{34}}{k_{21}} \int \frac{[A_3]}{[A_2]}\, d[A_1] \tag{73}$$

Equation 73 at first glance seems to indicate that the product ratio is independent of [R] since the reagent does not appear explicitly in the equation. However, as will be demonstrated subsequently in section VIB, $[A_3]/[A_2]$ is dependent on [R], thereby indicating that [R] implicitly appears in the time-dependent description of the product ratio (eq 73).[113]

We will consider the following conditions for Scheme III.[113]

Condition I: $k_{21}[R], k_{34}[R] >> k_{23}, k_{32}$

Condition II: $k_{21}[R], k_{34}[R] << k_{23},k_{32}$

Condition III: $k_{21}[R], k_{34}[R] \sim k_{23}, k_{32}$

Condition IIIA: $[R]_0 >> [A_2]_0 + [A_3]_0$

Condition IIIB: $[R]_0 \approx [A_2]_0 + [A_3]_0$

Condition I is the kinetic quenching situation and obtains when the rates of product formation are considerably faster than the rates of substrate interconversion; the product ratio is equal to the initial substrate distribution.

$$[A_4]/[A_1]_\infty = [A_3]_0/[A_2]_0 \text{ for condition I} \tag{74}$$

Condition II is equivalent to the C–H/W–H kinetic situation, in that the substrate ratio $[A_3]/[A_2] = k_{23}/k_{32} = K$ during the entire reaction. This is particularly valid toward the end of the reaction when the reagent concentration [R] becomes smaller and the overall rate of product formation drops. Under Condition II, the product ratio is described by the C–H eq 7 and 13, a direct result of integration of eq 73.

$$[A_4]/[A_1]_\infty = K\frac{k_{34}}{k_{21}} \text{ for condition II} \qquad (75)$$

Condition III is more complex, and two subsets are relevant. When the initial concentration of reagent $[R]_o$ is significantly greater than the initial substrate concentration (Condition IIIA), then pseudo-first-order kinetics are obtained and Scheme III can be approximated by Scheme II using the appropriate relationships between second-order rate constants and pseudo-first-order rate constants (eq 76–77). The exact analytical solution to Scheme II can thus be used for Scheme III, Condition IIIA kinetic systems. Because we have discussed in detail the exact solution to Scheme II and applications thereof (section V), we will not cover them in this section.

$$k_1 = k_2[R] \qquad (76)$$

or

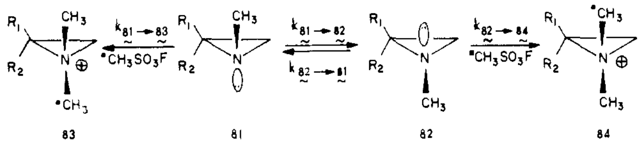
$$k_2 = [R]^{-1}k_1 \qquad (77)$$

$k_2$ is the second-order rate constant and $k_1$ is the pseudo-first-order rate constant.

Condition IIIB systems are the most complex and most difficult to treat. The substrate ratio and the product ratio are likely to be time dependent during the course of the reaction, and no simple relationship exists whereby eq 73 can be integrated. Mathematical theory and practice indicates that a power series expansion of the $k_{ij}$ can be found which describes $A_i$ as a function of time. To our knowledge, no such solution has appeared in the literature. Seeman, Sanders, and Farone examined Scheme III, Condition IIIB systems using numerical procedures and evaluated a number of consequences of these kinetics.[113]

## B. Specific Consequences of Scheme III

(1) A model system can be constructed to illustrate the properties of Scheme III, Condition IIIB.[113] Consider the methylation of the interconverting aziridines **81** ⇄ **82** which react to give **83** and **84** respectively.



Aziridine inversion rate constants[124,125] generally fall in a range of 1–100 $s^{-1}$ and alkylate[126] in a range of $1 \times 10^{-6}$–100 L $mol^{-1}$ $s^{-1}$. A set of $k_{ij}$ were chosen which incorporated a highly reactive alkylating reagent, methyl fluorosulfate.[127]

Figure 14 illustrates the product ratio [**84**]/[**83**] as a function of percent reaction for the hypothetical alkylation of **81** ⇄ **82** with rate constants listed in the figure caption. The product ratio is dependent on the relative concentration of $[R]_0/\{[81]_0 + [82]_0\}$. In all cases, the value of [**84**]/[**83**] at very low percent conversion is nearly equal to the C–H value.[113]

$$[84]/[83]|_{t\to 0} = \frac{[82]_0}{[81]_0}\frac{k_{(82)\to(84)}}{k_{(81)\to(83)}}$$

For any one particular value of $[R]_0/\{[81]_0 + [82]_0\}$, if [**84**]/[**83**] changes as a function of time, its value changes from the C–H value in the direction of the kinetic quenching value.

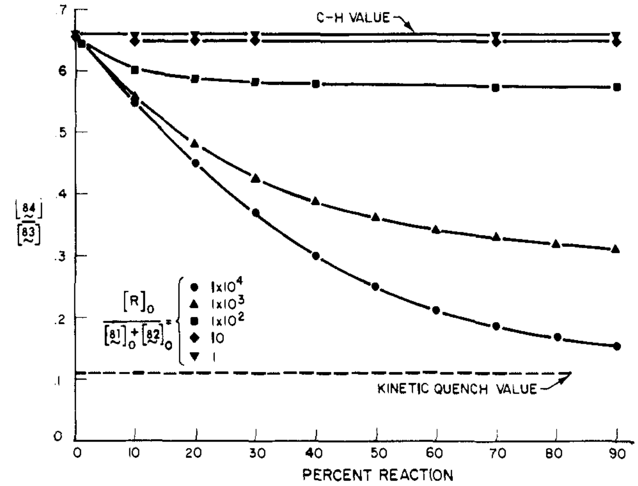


**Figure 14.** Calculated values for the product ratio [84]/[83] for Scheme III as a function of initial relative concentration of reagent R. Note that the subscript "o" denotes initial conditions. In this example, $k_{81\to83} = 16.7$ $mol^{-1}$ $s^{-1}$, $k_{81\to82} = 0.55$ $s^{-1}$, $k_{82\to81} = 5.0$ $s^{-1}$ and $k_{82\to84} = 100$ $mol^{-1}$ $s^{-1}$, $[82]_o + [83]_o = 1 \times 10^{-4}$ M. Reprinted with permission from ref 113. Copyright 1980, Pergamon (Oxford).

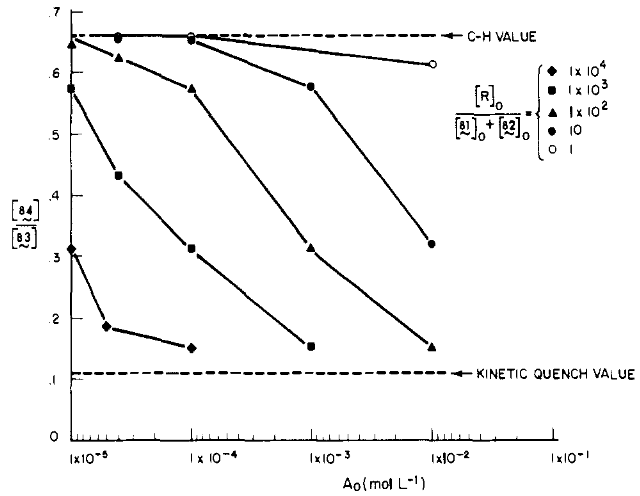


**Figure 15.** Calculated values for the product ratio [84]/[83] at 90% for the reaction of 81 ⇄ 82 as a function of initial concentration of substrate, $[81]_0 + [82]_0$. See Figure 14 caption for rate constant information. The family of curves represents constant $[R]_0/\{[81]_0 + [82]_0\}$ values. Reprinted with permission from ref 113. Copyright 1980, Pergamon (Oxford).

The time dependency of the product ratio increases as the relative concentration of R increases to the limiting value of the kinetic quenching situation (Condition I). For low relative concentrations of R, the C–H value is obtained, indicating that Condition II obtains.

While Figure 14 deals with the relative concentration of reagent to substrate, Figure 15 points out that absolute concentrations are crucial even when the initial concentration ratios are constant. Thus, for any particular relative concentration $[R]_0/\{[81]_0 + [82]_0\}$, a wide range of experimental concentrations for $[R]_0$, $[81]_0$ and $[82]_0$ may be chosen. Figure 15 illustrates the relationship between product ratio and relative and absolute reagent–substrate concentration. For any particular relative reagent–substrate concentration, as the absolute concentration of the compounds decreases, the product ratio tends toward the C–H value. This is because the overall rate of product formation is a second-order reaction, first order in substrate and first order in reagent, while the rate of invertomer interconversion 81 ⇄ 82 is first order in substrate only. As the absolute concentrations decrease, e.g., by a factor of 10, the rate of product formation decreases by a factor of 100 while the rate of invertomer interconversion decreases by only a factor of 10. The system thus behaves in a C–H fashion: fast isomer interconversion relative to product formation.[113]

At high absolute concentrations, kinetic quenching results obtain. This is due to a substantial increase in the rate of product formation relative to invertomer interconversion.

Finally, one can compare Figure 14 with Figure 15 with regard to the effect of the relative concentration of reagent–substrate; the greater the ratio $[\mathrm{R}]_0/\{[81]_0 + [82]_0\}$, the earlier (in terms of reaction percentage) the product ratio tends toward kinetic quenching conditions.

In closing this section, we note that studies by Bottini indicate that alkylations of aziridines may be complicated by competitive nucleophilic ring opening to the corresponding acyclic amines with subsequent ring closure and loss of stereochemical integrity.[126,128] Recent work by Rivoirard et al. indicates that proper choice of alkylating reagent can overcome this complexity.[129]

(2) While there are numerous examples of Scheme III kinetics in the literature, they generally fall into the Condition II category, analyzable by the C–H/W–H approximations. This is fortunate, since otherwise the mathematical treatment is complex, as indicated.

Experimentally, one can establish if Scheme III, Condition III obtains by examining the product ratio for a series of independent reactions with the relative and/or absolute concentration of reagent R varying. Indeed, it is conceivable that by manipulating reagent concentration, product specificity could be controlled in a specific desired fashion for Scheme III, Condition III systems.

(3) With regard to Scheme III, McKenna has discussed the time-dependent generation of reagent R.[27] For example, photochemical or thermal production of reagent R could occur simultaneously with the reactions of Scheme III. Even if R were highly reactive, the rate of product formation would be small since the reagent concentration would be very low. For a more detailed discussion of these topics, including experimental examples and methodology for conformational analysis, see the results of the McKenna school.[27,130]

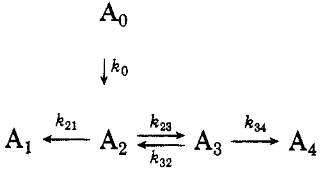
## *VII. Curtin-Hammett/Winstein-Holness Systems with "Feed-In" Mechanism*

### A. Definition and Exact Solutions

#### *1. Exact Analytical Solution*

Scheme IV defines a reaction mechanism involving an interconverting pair of compounds (or conformations), each of which reacts to give a different product. However, all material is funneled into the system via the transformation $A_0 \rightarrow A_2$. There are numerous examples in the literature which follow Scheme IV kinetics. The exact analytical solution to Scheme IV has recently become available[115] and is valid for all $k_{ij}$ and initial conditions: eq 78–92.

SCHEME IV



$$[\mathrm{A}_1](t) = [\mathrm{A}_1]_0 + k_{23}^{-1}[\delta - c_1 - c_2 + \gamma e^{-k_0 t} - \gamma + (k_{32} + k_{34})\{[c_1(e_1^{m_1 t} - 1)/m_1] + [c_2(\mathrm{e}_2^{m_2 t} - 1)/m_2] - [(\gamma e^{-k_0 t} - 1)/k_0]\}] \quad (78)$$

$$[\mathrm{A}_2](t) = \{c_1 m_1 e^{m_1 t} + c_2 m_2 e^{m_2 t} - k_0 \gamma e_0^{-k_0 t} + (k_{23} + k_{34}) \times (\delta + \gamma e^{-k_0 t})\}/k_{23} \quad (79)$$

$$[\mathrm{A}_3](t) = \delta + \gamma e^{-k_0 t} \quad (80)$$

$$[\mathrm{A}_4](t) = [\mathrm{A}_4]_0 + k_{34}\{[c_1(e^{m_1 t} - 1)/m_1] + [c_2(e^{m_2 t} - 1)/m_2] - [\gamma(e^{-k_0 t} - 1)/k_0]\} \quad (81)$$

$$c_1 = [\mathrm{A}_3]_0 - c_2 - \gamma \quad (82)$$

$$c_2 = \{[\mathrm{A}_2]_0 - \alpha[\mathrm{A}_3]_0 + \gamma\alpha + \omega^{-1}k_0^2[\mathrm{A}_0]_0 - [(k_{32} + k_{34})\gamma/k_{23}]\}/(\beta - \alpha) \quad (83)$$

$$\alpha = (m_1 + k_{32} + k_{34})/k_{23} \quad (84)$$

$$\beta = (m_2 + k_{32} + k_{34})/k_{23} \quad (85)$$

$$m_1 = [-a + (a^2 - 4c)^{1/2}]/2 \quad (86)$$

$$m_2 = [-a - (a^2 - 4c)^{1/2}]/2 \quad (87)$$

$$a = k_{21} + k_{23} + k_{32} + k_{34} \quad (88)$$

$$c = k_{32}k_{21} + k_{34}k_{21} + k_{34}k_{23} \quad (89)$$

$$\gamma = k_0 k_{23}[\mathrm{A}_0]_0/\omega \quad (90)$$

$$\delta = c_1 e^{m_1 t} + c_2 e^{m_2 t} \quad (91)$$

$$\omega = k_0^2 - a k_0 + c \quad (92)$$

$[\mathrm{A}_i]_0$ $(i = 0\text{–}4)$ = concentration of $\mathrm{A}_i$ at $t = 0$

When $k_0 >> k_{21}, k_{23}$, then Scheme IV can also be approximated by the exact solution to Scheme II.

### B. Exact Infinity Solutions

(1) Equation 93 is the exact solution at infinite time for Scheme IV kinetics for all $k_{ij}$ and $k_0$ when the concentration of all substances except for $A_0$ is zero at reaction initiation. The product ratio is independent of $k_0$ and depends solely on the rate constants of the Scheme II subset of Scheme IV! Indeed, the product ratio for Scheme IV at reaction completion is identical to that for Scheme II systems having initial concentrations $[\mathrm{A}_1]_0 = [\mathrm{A}_3]_0 = [\mathrm{A}_4]_0 = 0$ (cf. eq 46 derived in section VB). Scheme IV degenerates to Scheme II when $k_0 >> k_{21}, k_{23}$!

$$\frac{[\mathrm{A}_4]}{[\mathrm{A}_1]_\infty} = \frac{k_{34}}{k_{21}}\frac{k_{23}}{k_{32} + k_{34}} \text{ for all } k_{ij} \text{ and } k_0 \quad (93)$$

Equation 93 has two interesting boundary conditions. When $k_{23}, k_{32} >> k_{21}, k_{34}$, then the product ratio is equal to the C–H value $(k_{23}k_{34}/k_{32}k_{21})$. When $k_{21}, k_{34} >> k_{23}, k_{32}$, then the product ratio is equal to the partitioning ratio $k_{23}/k_{21}$ for $A_2$.

(2) The expression for the product ratio at reaction completion was derived some time ago (cf. the classic study of Martin and Bentrude[131]) and subsequently utilized[132,133] by applying the steady-state approximation for $A_3$ in Scheme IV. The steady-state approxi-

mation is not necessarily valid for all kinetic systems[134-136] and the validity for its use can be examined for each application.[137-139] The reaction time necessary to reach steady state can also be calculated.[140] While numerical methods are usually used to evaluate the steady-state assumption, eq 93 can be validated by evaluation of the exact solution (eq 78–92 at reaction completion; see, however, the discussion in section VF). The "area theorem" described by Benjamin and Collins[141] has also been used to derive eq 93[142,143] and is of particular value because it results in an exact solution at reaction completion.

(3) Equation 93 was used by Dervan[132,133] to derive relative rate constants for Scheme IV systems involving the thermal decomposition of nitrenes, tetrahydropyridazines, and dialkylcyclobutanes. For example, they were able to determine the *ratio* of the rate constants (Scheme V) for the diazine thermolyses. The analyses were based on product ratio distributions and not time–concentration data. Given that $k_0$ is likely to be orders of magnitude smaller than the other $k_{ij}$, the determination of the unknown constant "c" in the scheme below is improbable pending very detailed kinetic data (see section VIID3 for additional discussion on this matter).

SCHEME V

$$\begin{tikzcd}
 & \mathrm{A_0} \arrow[d, "k_0"] & & \\
\mathrm{A_1} \arrow[r, "4.89"] & \mathrm{A_2} \arrow[r, shift left, "1"] & \mathrm{A_3} \arrow[l, shift left, "c"] \arrow[r, "2.01c"] & \mathrm{A_4}
\end{tikzcd}$$

(4) Symmetrical examples of Scheme IV have been reported[142-144] in which $k_{21} = k_{34} = k_r{}^s$ and $k_{23} = k_{32} = k_i{}^s$ ($k_r{}^s$ and $k_i{}^s$ are the symmetrical reaction rate constants and the isomer interconversion rate constants respectively). For these special cases, eq 93 simplifies to eq 94 (note the inversion of the product ratio term!).

$$\frac{[\mathrm{A_1}]}{[\mathrm{A_4}]_\infty} = 1 + \frac{k_r{}^s}{k_i{}^s} \tag{94}$$

An interesting kinetic complication can arise for symmetrical Scheme IV systems. Consider the subsets of Scheme IV, namely Schemes VI and VII which described the chemical systems investigated by the Rappoport and Lee groups.[143,145,146] Note that only $\mathrm{Ar_2}$ migrates.

SCHEME VI

$$\begin{tikzcd}
 & \mathrm{Ar_1Ar_2C{=}C(X)Ar_1} \arrow[d] & & \\
\mathrm{Ar_1Ar_2C{=}C(OS)Ar_1} & \mathrm{Ar_1Ar_2C{=}C^+Ar_1} \arrow[l, "k_r{}^a"'] \arrow[r, shift left, "k_i{}^a"] & \mathrm{Ar_1C^+{=}CAr_1Ar_2} \arrow[l, shift left, "k_i{}^a"] \arrow[r, "k_r{}^a"] & \mathrm{Ar_1(SO)C{=}CAr_1Ar_2}
\end{tikzcd}$$

SCHEME VII

$$\begin{tikzcd}
 & \mathrm{Ar_2Ar_2C^*{=}C(X)Ar_2} \arrow[d] & & \\
\mathrm{Ar_2Ar_2C^*{=}C(OS)Ar_2} & \mathrm{Ar_2Ar_2C^*{=}C^+Ar_2} \arrow[l, "k_r{}^b"'] \arrow[r, shift left, "k_i{}^b"] & \mathrm{Ar_2C^{+*}{=}CAr_2Ar_2} \arrow[l, shift left, "k_i{}^b"] \arrow[r, "k_r{}^b"] & \mathrm{Ar_2(SO)C^*{=}CAr_2Ar_2}
\end{tikzcd}$$

SCHEME VIII

$$\begin{tikzcd}
 & \mathrm{A_{02}} \arrow[d, "k_{02}"] & \mathrm{A_{03}} \arrow[d, "k_{03}"] & \\
\mathrm{A_1} & \mathrm{A_2} \arrow[l, "k_{21}"'] \arrow[r, shift left, "k_{23}"] & \mathrm{A_3} \arrow[l, shift left, "k_{32}"] \arrow[r, "k_{34}"] & \mathrm{A_4}
\end{tikzcd}$$

The distinction between Schemes VI and VII involves a statistical factor which becomes critical in any attempt to compare $k_i{}^a$, the interconversion rate constant for Scheme VI, with $k_i{}^b$, the interconversion rate constant for Scheme VII. The product ratio at reaction completion is given by eq 94 for both Schemes VI and VII. However, since either one of two identical aryl groups can migrate in Scheme VII while only $\mathrm{Ar_2}$ migrates in Scheme VI, the empirical rate constants $k_i{}^a$ and $k_i{}^b$ must be corrected by a statistical factor of 2 when being compared with each other. Thus,

$$\frac{[\mathrm{A_1}]}{[\mathrm{A_4}]_\infty} = 1 + \frac{k_r{}^a}{k_i{}^a} \text{ for Scheme VI} \tag{95}$$

$$\frac{[\mathrm{A_1}]}{[\mathrm{A_4}]_\infty} = 1 + \frac{k_r{}^b}{2k_i{}^b} \text{ for Scheme VII} \tag{96}$$

where $[\mathrm{A_1}]$ and $[\mathrm{A_4}]$ refer to the products using Scheme IV nomenclature.

This distinction was not noted in the initial publications but was recently corrected by a joint paper by the Lee and Rappoport groups.[143] For an additional discussion of this type of statistical correction, see Drenth and Kwart.[147]

(5) We discussed (cf. section IIIC2) that for Scheme II systems which follow the C–H/W–H approximations ($k_{23},k_{32} >> k_{21},k_{34}$) the product ratio is directly dependent on the ground-state equilibrium distribution of conformers (eq 7). This is true for Scheme IV cases also, under the same $k_{ij}$ restrictions, as seen by examination of eq 93. However, when $k_{23},k_{32} \leq k_{21},k_{34}$, the form of eq 93 is such that the product ratio cannot be simply related to $K = k_{23}/k_{32}$.

Cabaleiro and Johnson examined the product ratios obtained from the addition of chlorine to methyl *trans*-cinnamate under a variety of experimental conditions.[148] In order to conclude, as they did, that the product "ratios are an exact measure of the proportion of the two conformations present," one must demonstrate not only that $k_{21} = k_{34}$ but also that $k_{23},k_{32} >> k_{21},k_{34}$.

(6) For an example of kinetic quench of a Scheme IV system, see section IIIA2.

### C. Implications of the "Feed-In" Mechanism

(1) With regard to Scheme VIII, let us consider the following pair of experiments: (a) $[\mathrm{A_{02}}]_0$ comprises all the starting material and $[\mathrm{A_{03}}]_0 = 0$; and (b) $[\mathrm{A_{02}}]_0 = 0$ and $[\mathrm{A_{03}}]_0$ represents the entire initial mass balance. Then, if $P_{02}$ represents the product ratio for the former experiment and $P_{03}$ for the latter experiment, one can solve for the ratio of rate constants $k_{34}/k_{21}$ in terms of $P_{02}$, $P_{03}$, and $K$ (eq 97).[64]

$$\frac{k_{34}}{k_{21}} = \frac{P_{02}(P_{03} + 1)}{K\,(P_{02} + 1)} \tag{97}$$

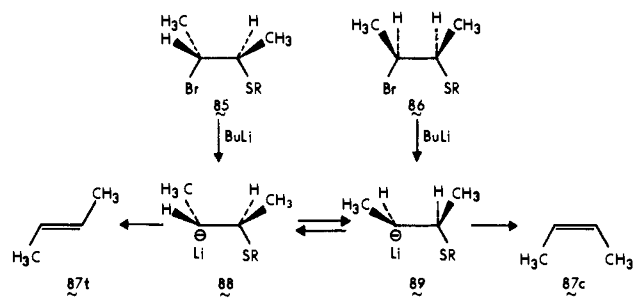


**Figure 16.** The *n*-butyllithium-induced decomposition of *threo*- and *erythro*-2-bromo-3-(ethylthio)butanes (85 and 86) are examples of Scheme IV (and VIII) kinetics. From ref 149.

where

$$P_{02} = \frac{[A_4]}{[A_1]_\infty} \text{ when } [A_{03}]_0 = 0$$

and

$$P_{03} = \frac{[A_4]}{[A_1]_\infty} \text{ when } [A_{02}]_0 = 0$$

Equation 97 has specific value in allowing the calculation of the ratio of rate constants when the product ratio of the two independent experiments (a) and (b) above are known and $K$ is either known or estimatable.

(2) For a Scheme VIII system described by eq 97, if $P_{02} > 1$, then $P_{03}$ must also be greater than one. In fact, if $P_{02} > 1$, then $P_{03} \geq P_{02} > 1$. If $P_{02} < 1$, then we cannot a priori specify anything regarding $P_{03}$.

Trost and Ziman reported the independent *n*-butyllithium-induced decompositions of *threo*- and *erythro*-2-bromo-3-(ethylthio)butanes, **85** and **86** respectively (Figure 16).[149] They state that reaction of *threo*-**85** results in ca. 1.3:1 ratio of **87c**:**87t**. According to the analysis presented directly above (section VIIC1), reaction of *erythro*-**86** should then give a predominance of **87c** also. However, the product ratio [**87c**]/[**87t**] for the latter reaction was reported to be ca. 0.25. The formation of the intermediates **88** and **89** involves a bimolecular reaction, a complexity which could affect the utility of the exact solution (eq 78–92) but does not appear to affect the derivation of the exact infinity solution (eq 93). Assuming the absence of a typographical error, this unusual result may indicate that the suggested mechanism is incorrect.

(3) For a Scheme IV system, it is interesting to determine the conditions for which a high degree of (e.g., 100:1) stereoselectivity will be obtained. Equation 93 leads to eq 98 for the reaction sequence starting with only $A_{02}$.

$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{34}}{k_{21}} \frac{k_{23}}{k_{32} + k_{34}} < 0.01 \qquad (98)$$

Therefore

$$k_{21} > \frac{100 k_{23} k_{34}}{k_{32} + k_{34}} \qquad (99)$$

If $k_{23} \sim k_{32} \sim k_{34}$, then

$$k_{21} = k_r > 50 k_i \text{ where } k_r = k_{21}, k_{34} \text{ and } k_i = k_{23}, k_{32} \qquad (100)$$

If $k_{34} = 10 k_i$, then

$$k_{21} > 9\, k_{34} = 99 k_i \qquad (101)$$

If $k_i = 10 k_{34}$, then

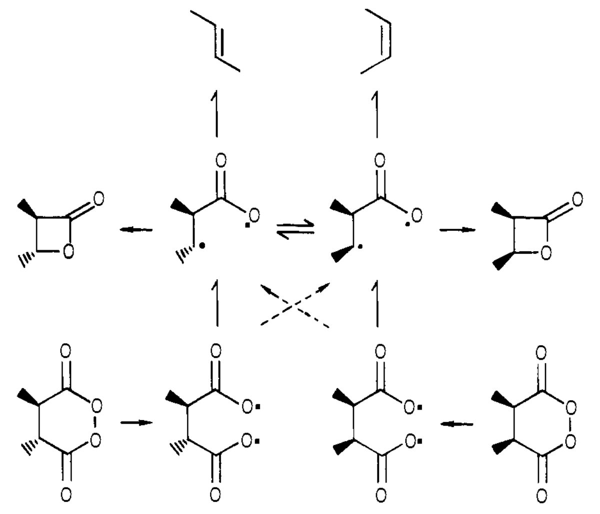
$$k_{21} > 90 k_{34} = 9 k_i \qquad (102)$$

The above calculations are presented to indicate the range of rate constants required for the observation of stereoselectivity in Scheme IV kinetics. For stereoselectivity to obtain for Scheme VIII kinetics; i.e., in the independent "feed-in" scheme, simultaneous examination of the converse of eq 100–102 indicates dual stereoselectivity when $k_{21}, k_{34} > 99 k_{23}, 99 k_{32}$.

(4) An interesting example of Scheme VIII stereospecificity was reported by White and Greene who observed stereospecific decomposition of *meso*- and *dl*-3,4-diethyl-3,4-dimethyldiazetines to *cis*- and *trans*-3,4-dimethyl-3-hexenes, respectively.[150] These elegant results lend themselves to very strong mechanistic conclusions regarding the intermediates involved in the reaction sequences.

Another example involves the solvolyses of cholest-4-en-3$\alpha$- and 3$\beta$-yl trifluoroacetates to different mixtures of 3-substituted unsaturated steroids.[151] Although the reactions involve carbocation processes, the intermediacy of conformationally distinct allylic carbocations was proposed to account for the distinctly different product mixtures obtained.

(5) When $k_{23}, k_{32} >> k_{21}, k_{34}$, the product ratio $[A_4]/[A_1]$ will be identical for Scheme VIII systems regardless of whether $A_{02}$ or $A_{03}$ is the starting material. For example, Dervan and Jones studied the thermal decomposition of *meso*- and *dl*-2,3-dimethylsuccinyl peroxides, **89** and **90**, respectively.[152] From the independent thermolyses of **89** and **90**, they observed nearly identical reaction products, 61% *trans*-butene, 28% *cis*-butene, 8% *threo*-2,3-dimethylpropiolactone, and 3% *erythro*-2,3-dimethylpropiolactone. This result not only indicates that common intermediates are involved but that the rate of interconversion between the intermediates is faster than their rate of product formation. A second, though less likely explanation, is that a single, common intermediate is formed. A third possibility suggested by Dervan and Jones is the partitioning of the possible



**90** **91** **92** **89**

intermediates **91** and **92** directly to the same set of carboxy biradicals.[152,153]

(6) Steady-state analysis applied to $A_3$ in Scheme IX leads to the overall rate constant $k_{\text{obsd}}$ indicated in eq 103 (see, for example, Castro and Freudenberg).[154]

### SCHEME IX

$$A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$

$$k_{\text{obsd}} = \frac{k_{23}\, k_{34}}{k_{32} + k_{34}} \qquad (103)$$

$$\frac{d[A_4]}{dt} = k_{\text{obsd}}[A_2]$$

Scheme IX is a subset of Scheme IV and it is interesting to compare eq 103 with the product ratio expression at infinite time (eq 93). Noting $d[A_1]/dt = k_{21}[A_2]$ for Scheme IV, the relationship between these two schemes and their kinetic descriptors follows directly.

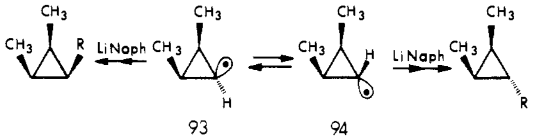
(7) Under pseudo-first-order reaction conditions (cf. section VIA), eq 78–92 also serve as the exact analytical solution to Scheme X kinetics as well. Numerical methods are required for the analysis of Scheme X systems if [R] is not in sufficient excess such that its concentration is essentially constant throughout the reaction. Also, no simple infinity solution is available for the product ratio unless pseudo-first-order conditions obtain.

### SCHEME X

$$\begin{tikzcd}
 & A_0 \arrow[d, "k_0"] & & \\
A_1 & R + A_2 \arrow[l, "k_{21}"'] \arrow[r, shift left, "k_{23}"] & A_3 + R \arrow[l, shift left, "k_{32}"] \arrow[r, "k_{34}"] & A_4
\end{tikzcd}$$

## D. Applications of the "Feed-In" Mechanism

(1) Boche and Schneider[155] and Boche et al.[156] examined the independent reactions of stereoisomeric cyclopropyl bromides with metal naphthylides (MNaph) and reported the identical reaction mixture from each isomer. Based on a literature value for the rate constant for the reaction of cyclopropyl radicals with naphthylide ion, they calculated a minimum rate constant for the inversion processes **93** ⇄ **94**. Unfortunately, the Boche reports do not contain details of their derivation of these inversion rate constants.[155,156] Comparison of these reactions with Scheme X indicates that the concentration of the naphthylide ion is a factor in the overall rate of product formation, and the reaction rate constant is a second-order parameter. The rates of product formation must be compared with the rates of isomer interconversion.



93 94

Boche et al.[156] evaluated the apparent conflict in results with Jacobus and Pensak,[157] the latter investigators reporting that 1-methyl-2,2-diphenylcyclopropyl bromides partially retain stereochemistry in their reaction with metal naphthylide. Boche et al. examined the chloro-, bromo-, and iodocyclopropanes and found: (a) that the percent net retention of configuration depended on the halogen substituent; and (b) neither inverse addition nor 25-fold dilution of alkali metal naphthylide affects the product ratio for the same halide substrate.[156] These results suggest that Scheme X molecular reactions leading to $A_1$ and $A_4$ should be affected if the partitioning mechanism operates, and the halogen dependence is not consistent with interconverting free cyclopropyl radicals. An alternative mechanism involving electron transfer to the aromatic rings was proposed by Boche et al.[156]

In another study involving the reactivity of cyclopropyl radicals, Elzinga and Hogeveen examined the homoallylic rearrangement of bicyclobutylcarbinyl radicals.[158] The intermediate bicyclobutylcarbinyl radical isomerized to a pair of inverting cyclopropyl radicals, each of which reacted by abstraction with a molecule of $CXCl_3$ (X = Br and Cl) to give the corresponding *exo*- and *endo*-bicyclo[3.1.1]pentanes. The authors suggested a mechanism in which cyclopropyl radical inversion was significantly faster than the abstraction reaction, and that the product ratio differences obtained as a function of "X" were explained by different relative rates (exo and endo) of abstraction from $CCl_4$ and $CBrCl_3$. For similar concepts in Scheme III systems in which $K$ = constant and $k_{21}, k_{34}$ vary, see section IVB5d and Figure 7.

A thorough review of the stereochemical aspects of cyclopropyl radical reactivity, including a discussion of the effects of a solid surface on the stereochemical consequences of the reactions, has been presented by Walborsky.[159] Interestingly, the kinetics are discussed in terms of a Scheme II mechanism rather than a Scheme X mechanism.

The stereochemical results of intramolecular aryl radical substitution of chiral *N*-tosylpiperidines has been explained by Kohler and Speckamp[160] on the basis of relative reactivity of two conformations (radical intermediates). One radical conformation can readily cyclize; the other does not readily cyclize due to "marked steric interaction" in the transition state(s) leading to product.

(2) The use of kinetic information for the distinction between two reaction mechanisms is perhaps the most sophisticated value of time–concentration data. Norris and Smyth-King[161] reported the $S_{RN}1$ reaction of **95** (Figure 17), which, upon ultraviolet irradiation and reaction with a nucleophilic reagent, yields the isomers **96** and **97**. In that the product ratio [**97**]/[**96**] was dependent on the concentration of sodium benzenethiolate (PhSNa), it was suggested that a competition between trapping a pyramidal benzylic radical and collapse to a planar radical obtained (Figure 17A).[161] An alternative explanation of the results is based on a pair of nonplanar, inverting cyclohexyl radicals shown in Figure 17B (see, for example, Lloyd et al.)[162] following a Scheme X mechanism. This work is an example of a system whose mechanism cannot be unambiguously determined without additional data.

(3) Perhaps the most impressive effort in chemical history aimed at distinguishing between two reaction mechanisms involves the nonclassical carbonium question (for leading references, see Brown and

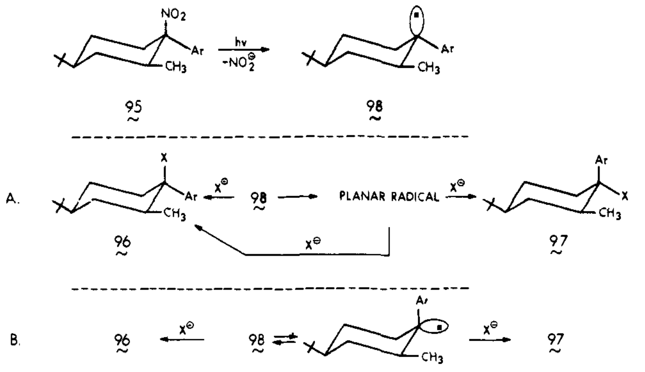


**Figure 17.** Two mechanisms [A and B] are consistent with the empirical results that varying the concentration $X^-$ can affect the product ratio. For a discussion on inverting cyclohexyl radicals, see ref 161–162.

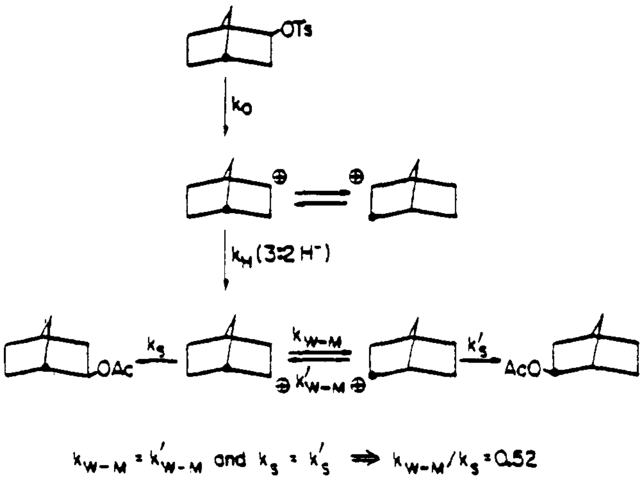


**Figure 18.** The simplest kinetic scheme which represents the classical mechanism for optically active norbornyl solvolyses is illustrated. See ref 163–164.

Schleyer[163]). The distinction to be made in this instance is between Scheme IV (classical interconverting ions) (see Figure 18) and Scheme XI (nonclassical ions). One important distinction between these two schemes is that the product ratio $[A_4]/[A_1]$ will be time dependent for Scheme IV for *some* sets of $k_{ij}$ but *must* be time independent for all Scheme XI reactions.

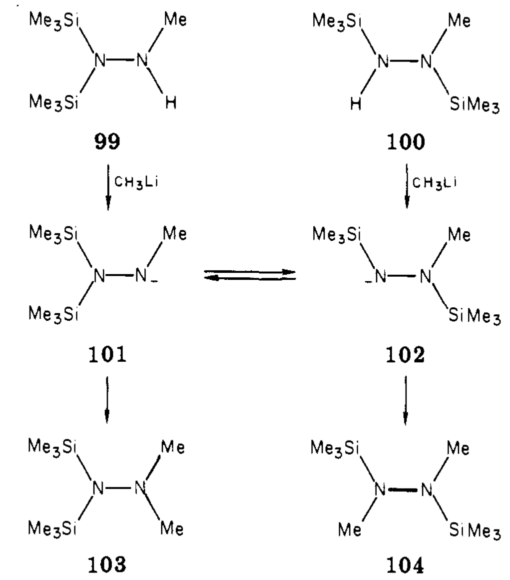
## SCHEME XI

$$\begin{tikzcd} & A_0 \arrow[d, "k_0"] & \\ A_1 & A_2 \arrow[l, "k_{21}"'] \arrow[r, "k_{24}"] & A_4 \end{tikzcd}$$

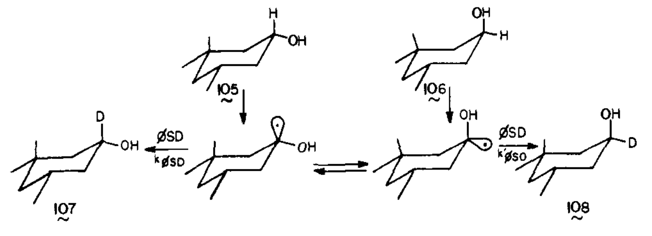
Seeman and Farone[115] faced two questions with regard to Scheme IV: (1) for what sets of $k_{ij}$ would the product ratio be time dependent? and (2) what sets (if any) of $k_{ij}$ that result in a time-dependent product ratio would be consistent with equilibrating classical ions? They examined a wide range of $k_{ij}$ sets and found that for any particular value of $k_0$, if $100k_0 > k_{21},k_{34}$, then time *independence* for $[A_4]/[A_1]$ would obtain. Given that the slow step in solvolysis reactions is the ionization step (by either the classical or nonclassical mechanism), they concluded that no sets of $k_{ij}$ consistent with norbornyl solvolyses could result in a time dependence of the product ratio. Thus, it is unlikely that any kinetic study could be designed to distinguish between Scheme IV and Scheme XI on the basis of time–concentration data. These conclusions focus on the essence of the differentiation between two reaction mechanisms.[2]

(4) Equation 93 can be used to calculate the rate constant ratio for the two key reaction types in the nonclassical–classical reaction controvery: cation–cation equilibration and solvent capture of the cation.[164] This approach is of particular value in the solvolysis of optically active norbornyl compounds for which the symmetrical Scheme IV obtained, thereby making $k_{21} = k_{34}$ and $k_{23} = k_{32}$. Equation 93 is applicable for nonsymmetrical systems and has been applied to derive the relative migration rates of aryl groups in the deamination of amines.[131]

(5) West and Bichlmeir[165] independently treated the hydrazines **99** and **100** with one equivalent of methyllithium forming the identical equilibrating mixture **101** $\rightleftarrows$ **102** in a ratio of 1:4. Reaction of this mixture "under a variety of temperatures and concentrations"[165] with methyl iodide resulted in a 55:45 mixture of **103**:**104**. The authors suggested that the isomerization rates were faster than the alkylation rates. From this data, the ratio of alkylation rate constants can be calculated using eq 93: $k_{102\rightarrow104}/k_{101\rightarrow103} = (45)/(55 \times 4) = 0.2$. The less sterically hindered nitrogen (**101**), which also bears the more localized negative charge, appears to alkylate faster.



(6) Examples exist for which the rate of product formation is competitive with (or faster than) the rate of isomer interconversion. For examples, Despax et al.[166] reported an analysis of the photoreduction of cyclohexanones and observed net retention of stereochemistry starting from either **105** or **106**. A most important observation was made that the product ratio [**108**]/[**107**] was dependent on the starting material, 11:1 from **105** and 5:1 from **106**. This allows the conclusion that the relevant reaction rates were competitive, since partitioning is observed rather than stereo-



specificity. It is likely that the abstraction rate constant is large, but the low concentration of the deuteron source (PhSD) decreases the overall rate of reaction.[113] The nonplanar character of the cyclohexyl radical center was recently confirmed by Micheau, Despax, Lattes et al.[167]

(7) Padwa et al. investigated the intramolecular cyclizations of nitrile ylides generated from the photolysis of 2*H*-azirines.[168] This is a unique C–H Scheme IV system, in that the interconverting nitrile ylides are generated in a photochemical step but react in a ground-state cyclization. The authors assumed that the rates of nitrile ylide interconversion are fast, since they require only a hybridization change akin to inversion in vinyl radicals which is known to be a low energy process; they then applied the Curtin–Hammett principle to explain their results.

(8) A very interesting example of a complex Scheme X system can be found in Mulzer and Brüntrup's analysis of the decarboxylative dehydration of 3-hydroxy carboxylic acids.[169] Space limitations cause us to refer the reader to the original report and that of related subjects.[170,171] Also, see the report of Bach for an evaluation of the stereospecificity of the alkylmercuration of allenes from which Scheme X conclusions can be obtained,[172] as well as the work of the Caserio group on the mechanisms of allylic sulfide rearrangements.[173-175]

(9) Jendralla recently reported that the deamination of *N*-(6-methyl-3-oxabicyclo[4.1.0]hept-*exo*-7-yl)-*N*-nitrosourea can be analyzed using a Scheme X mechanism.[176] In this example, the interconverting $A_2$ and $A_3$ are not conformational isomers but cationic and carbene intermediates, and the product distribution is significantly effected by the reaction conditions.

## *VIII. Photochemical Applications of the Curtin–Hammett System*

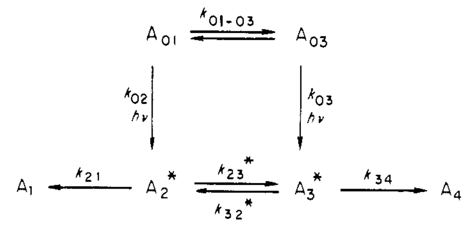
### A. General Considerations

The effect of ground-state conformation on photochemical reactivity is a natural extension of the C–H principle which was developed for ground-state chemistry. The earliest work in this field involved the effect of olefin orientation in photocyclization reactions[177] and was succeeded by studies on more subtle conformational effects on photochemical behavior.[21,71,178-182] Quantitative studies from the Lewis group[22,183,184] incorporated quantum yields, kinetic data, and Stern–Volmer plots to assess the involvement of Curtin–Hammett kinetics in photochemical reactions.

### B. Quantitative Aspects of Photochemical C–H Behavior

Scheme XII was proposed by Lewis and Johnson[22] and Lewis et al.[183] to evaluate the effect of ground-state conformation on photochemical reactivity. $A_{02}$ and $A_{03}$ represent two ground-state conformational isomers that interconvert. Upon photochemical excitation, they form excited-state conformational isomers $A_2$* and $A_3$* respectively. In addition to interconverting, $A_2$* and $A_3$* can produce different photoproducts, $A_1$ and $A_4$ respectively. Since photochemical excitation is much faster than nuclear motion (Franck–Condon Principle), the initial populations of $A_2$* and $A_3$* are related to the ground-state distribution of $A_{02} \rightleftarrows A_{03}$ as well as to the ratio of extinction coefficients $\epsilon(A_{02})/\epsilon(A_{03})$ and the wavelengths of the incident light. Two conditions can be considered for Scheme XII.

SCHEME XII

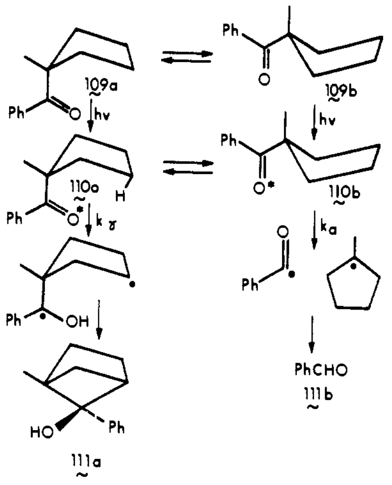


Condition I: $k_{23}^*, k_{32}^* >> k_{21}, k_{34}$

Condition II: $k_{23}^*, k_{32}^* << k_{21}, k_{34}$

Lewis and Johnson[22] argued that for Scheme XII, Condition I, the Curtin–Hammett principle would obtain, the product ratio $[A_4]/[A_1]$ would be related to eq 13, and the lifetimes of both excited state conformers $A_2$* and $A_3$* would be equal $[\tau^*(A_2^*) = \tau^*(A_3^*) = (k_{21} + k_{34})^{-1}]$. They also proposed that, for Scheme XII, Condition II systems, the product ratio $[A_4]/[A_1]$ would depend on the relative proportions of $A_3$* and $A_2$* (kinetic quenching of the excited states), and the lifetimes of the excited state conformers would be unequal $[\tau^*(A_2^*) = k_{21}^{-1}$ and $\tau^*(A_3^*) = k_{34}^{-1}]$, unless fortuitously $k_{21} = k_{34}$. For simplicity, the literature analysis neglected nonradiative decay and other excited state processes.

A number of quantitative results were obtained by the Lewis group in support of this kinetic model.[22,183] They examined the photochemistry of $\alpha$-methylcyclopentyl phenyl ketone (**109**) which was considered to exist in two conformations, **109a** and **109b**, irradiation of which leads to **110a** and **110b**, respectively. Since cyclopentane pseudorotation is quite fast, **110a** and **110b** were considered to interconvert more rapidly than either $\gamma$ abstraction (to **111a**) or $\alpha$ cleavage (to **111b**).



The Stern–Volmer plots of $\Phi_0/\Phi$ for product formation vs. quencher concentration (eq 104 for **111a** and **111b**) are shown in Figure 19. It is reasonable to assume that $k_q$, the rate constant for quenching of these

$$\Phi_0/\Phi = 1 + k_q\tau[Q] \qquad (104)$$

[Q] = quencher concentration

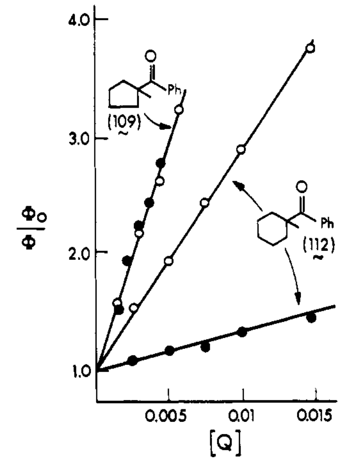
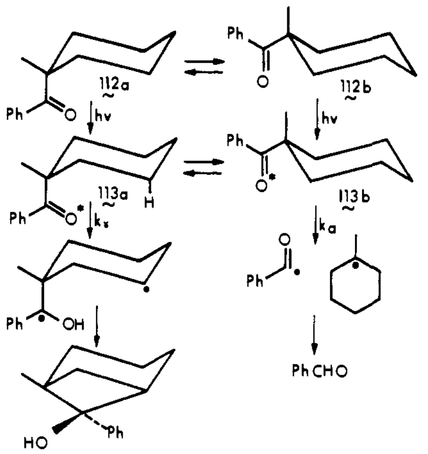


**Figure 19.** Stern–Volmer plots for naphthalene [Q] quenching of benzaldehyde (○) and bicyclobutanol (●) formation from the photochemistry of **109a** ⇄ **109b**. The identical slopes and intercepts found for quenching of both product pathways for **109a** and **109b** indicate that the resultant excited-state conformations for these two reactions have the same lifetimes; the different slopes found for **112a** ⇄ **112b** indicate that the resultant excited states have different lifetimes. Reprinted with permission from ref 22 and 183.

ketones, is independent of conformation and structure. One can see that if the lifetimes of the two excited-state conformations are identical, the Stern–Volmer plot for each product should have the same slope and intercept. Figure 19 supports the contention that the photochemistry of **109a** ⇄ **109b** follows Scheme XII, Condition I kinetics.

Lewis et al. also examined the photochemistry of the related cyclohexane **112a** ⇄ **112b**.[22,183] Since the rate of cyclohexane ring inversion is significantly slower than the rate of cyclopentane pseudorotation, these workers suggested that Scheme XII, Condition II kinetics might obtain for **112a** ⇄ **112b**. Similar photochemical reactions were observed for 112 as were seen for 109. Figure 19 shows that the α cleavage reaction leading to benzaldehyde has a significantly different Stern–Volmer slope than does the γ abstraction reaction leading to bicyclobutanol formation. Therefore, Lewis and Johnson concluded that the excited state conformers **113a** and **113b** have *different* lifetimes, and that the rates of reaction of these excited states were faster than the rates of excited-state conformational interconversion.[22]



Lewis et al. also studied the photochemistry of cyclohexyl phenyl ketone itself.[183] They observed a Stern–Volmer quenching plot that had two linear portions, one at high quencher concentration and one at low quencher concentration. They concluded that two different excited states were involved with different lifetimes, and that these were the two excited-state conformers having an axial (in one) and an equatorial (in the other) substituent which interconvert more slowly than they react.

In a related study, Wagner and Scheve[184a] reported that irradiation of 1,4-dimethyl-4-benzoylpiperidine forms two kinetically distinct triplets, in a manner similar to the photochemistry of 1-methyl-1-benzoylcyclohexane studied by Lewis.[22] Wagner and Scheve concluded on the basis of sensitization studies and quantum efficiencies that these triplets correspond to the two chair conformations of the piperidine which do not interconvert.

Wagner and Stratton more recently suggested a "speculative" explanation for the photo rearrangement of 2-phenylcyclohexanone[184b] to *trans*- and *cis*-6-phenyl-5-hexenal. In this case, two distinct triplets are also formed, and these were demonstrated *not* to be simply the equatorial and axial phenyl conformations. The explanation involved two different motions of the α-carbon during cleavage, one forming a biradical in a geometry disposed to produce a *trans*-enal while the other would require additional motion and could form either the *cis*- or *trans*-enal. Other studies have been reported over the years which incorporate conformational mobility (or the lack thereof) of photochemically generated biradicals to explain observed product distributions.[185]

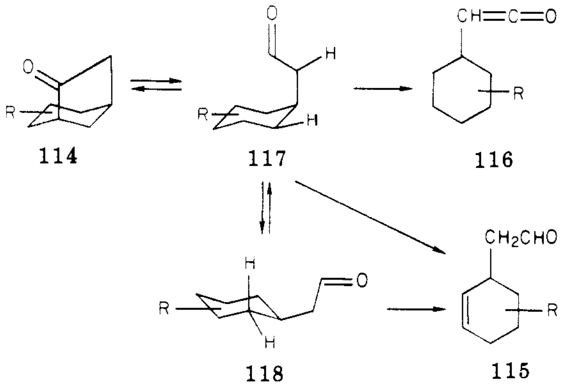
Wagner and Chen reported that excited-state conformational processes appeared to be rate limiting in their study of the photoenolization of *o*-alkylphenyl ketones.[181a] This conclusion was required by their model of discrete syn and anti triplet conformations in which hydrogen abstraction was faster than conformational interchange of the anti to the syn form.

Havinga and co-workers have proposed the NEER principle, namely that different, interconverting ground-state conformations may have different absorption spectra and that these may result in nonequilibrating excited-state conformations.[181b] They recently used this principle to explain some of their photochemical wavelength dependencies observed in the vitamin D series. The NEER principle may well have its roots in the previous studies of "accordancy" of Baldwin and Krueger[71] as exemplified by the results of the Dauben school.[178]

## C. Additional Examples of Photochemical C–H Systems

(1) The effect of substituents in C–H photochemical systems was studied by Agosta and Wolff.[186] Irradiation of bicyclo[3.2.1]octan-6-ones 114 led to ketene 116 and the aldehyde 115. The product ratio depended on the degree and position of substitution, and the results were explicable based on conformational evaluation of the two biradical conformers 117 ⇄ 118. Agosta and Wolff[186] also examined the effect of temperature on product ratio, and interpreted their results in terms of increasing the rates of interconversion 117 ⇄ 118.

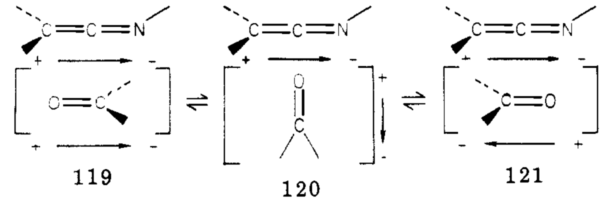
(2) Scheffer et al. examined the effect of substituents in introducing barriers to conformational change in


114 117 116 118 115

biradicals formed in the photochemical reactions of tetrahydro-1,4-naphthoquinones.[187] They observed three different reaction products which result from three different bridging pathways for the diradical species initially formed. Based on an evaluation of the substituent effect on product composition, Scheffer et al. suggested that the originally formed diradical can convert to two other conformations, and that each of these three conformations is the direct precursor of one of the three bridged products. They further contended that the bulky substituents restricted the conformational isomerism of the diradical species, thereby controlling the product distribution.[187] If these postulates are correct, this is an interesting example of conformational control in photochemical reactions.

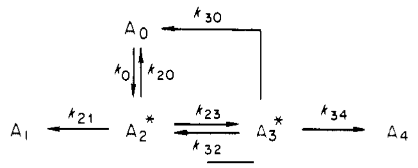
(3) With regard to the photochemistry of aryl cyclobutyl ketones, Alexander and Uliana[188] proposed that the quantum efficiency of the reaction(s) was related to the conformational equilibrium between one reactive conformer and two unreactive conformers. They ruled out two other mechanisms, one in which the quantum yields were controlled by ground-state conformational equilibria and the second in which the photochemical efficiencies were determined by excited-state ring inversion. The distinction between these three mechanisms was made by evaluation of the experimental quantum yields as a function of triplet lifetimes: three different relationships were derived, one for each of the three possible mechanisms. Only one fit the experimental results.

(4) In an early study that predated the wide-spread recognition of the exiplex concept, Singer and Davis[189] suggested that the regiochemistry of ketenimine–fluorenone cycloaddition was controlled by the relative population of three ground state species, **119** ⇄ **120** ⇄ **121**. The ground-state distributions were approximated by a crude calculation of potential energy based on dipole moments.


119 120 121

(5) Cooke and Lyon examined the stereochemical outcome of the photochemistry of substituted thujones having the bicyclo[3.1.0]hexan-3-one system.[190] Depending on the number of methyl substituents, configurational isomers gave either identical *or* nonidentical 1,5-hexadiene products following decarbonylation–ring cleavage photolyses. The results were explained in terms of a photochemical C–H principle in which the identical product mixture resulted from rapid carbon–carbon bond rotation of the intermediate compared to product formation. However, addition of a second methyl group resulted in nonidentical product mixtures, indicating that stereochemical integrity at different sites of the intermediate(s) is not equally maintained.

SCHEME XIII



(6) Solomon et al.[191] recently studied the copper(I) catalyzed photocyclization of alkenylallyl alcohols and noted that in most cases, the less stable bicyclo[3.2.0]heptan-2-ol was formed stereoselectivity. They rationalized their results on the basis of preferential formation of a tridentate ligand (involving both olefins and the hydroxide group) rather than a bidentate ligand (involving only the olefins). Even though these two ligands were presumed to be in equilibria, the more stable ligand was the precursor to the major product. In one case, additional methyl substituents on the diene apparently reversed the stability of the two ligands due to steric effects, and nonstereoselective product formation was observed. These results were illustrated by a C–H kinetic scheme.

(7) As a final commentary in this discussion of photochemical C–H systems, consider the consequences of Scheme XIII that takes into account radiative and nonradiative decay of the excited-state species to starting material. Equation 105 can be derived from

$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{34}}{k_{21}} \frac{k_{32}}{k_{21} + k_{32} + k_{30}} \tag{105}$$

Scheme XIII by use of the "area theorm" of Benjamin and Collins.[141] It is particularly interesting to note that the product ratio is independent of $k_{20}$, just as it is independent of $k_0$.

## *IX. Extensions of Curtin–Hammett/Winstein–Holness Kinetic Systems*

### A. Three-Component Kinetics

(1) Scheme XIV is a simple three molecule subset of the C–H system, and its exact solution and that for the related Schemes XV and XVI are well-known and quite straightforward.[138,192]

SCHEME XIV

$$A_2 \xrightarrow{k_{23}} A_3 \xrightarrow{k_{34}} A_4$$

SCHEME XV

$$A_2 \xrightarrow{k_{23}} A_3 \xleftarrow{k_{43}} A_4$$

SCHEME XVI

$$A_2 \xleftarrow{k_{32}} A_3 \xrightarrow{k_{34}} A_4$$

(2) Scheme IX, often referred to as the Lindemann scheme, is the classic sequence involving a reversible

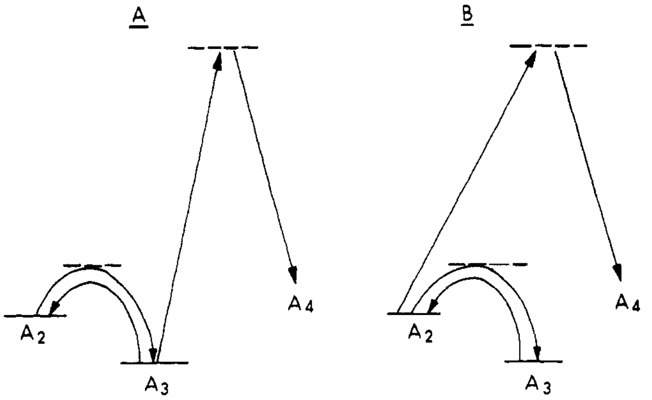


**Figure 20.** Two examples of Scheme IX are illustrated. Product formation occurs from the more stable component in (A) and from the less stable component in (B). Note that the energy levels in (A) and (B) are identical. From ref 195.

reaction whose solution is well known.[2,138,192,193] General approximations and steady-state treatments for Scheme IX are also well-known.[138,194] In section VIIC6, we discussed the steady-state treatment for the empirical rate constant and compare the result to the consequences of Scheme IV solutions at reaction completion. Scheme IX describes the situation in which a compound reacts from only one of two conformations (see section IVC4).

Best et al. examined the kinetic consequences of a pair of Scheme IX systems shown in Figure 20.[195] In Figure 20A, reaction takes place from the more stable substrate while in Figure 20B, reaction proceeds from the less stable substrate. In the latter case, $A_3$ must interconvert to the less stable $A_2$ before reaction whereas in the former case (Figure 20A), reaction occurs directly from the more stable conformer.

Best et al. indicated that the rates of reaction in these two cases will be identical as long as the rates of interconversion between $A_2$ and $A_3$ are significantly faster than the rate of product formation (C–H/W–H assumption).[195] This conclusion was derived by application of rate and equilibrium laws and can be verified by use of the exact solution to Scheme IX (subset of Scheme II). These authors utilized this kinetic result as the basis for the frequently observed correlation between high preference in the ground state and fast reaction rate constants.

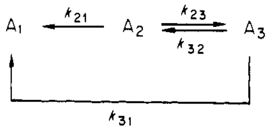
Note also that the related Scheme XVII has also been solved in closed form.[192]

SCHEME XVII

$$A_1 \xrightarrow{k_{12}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3$$

(3) Scheme XVIII is a special case of the C–H/W–H Scheme II in which only one product is formed from two interconverting substrates. The integrated rate equations have been reported by Evans,[196] Alberty and Miller,[192] and Lewis and Johnson[197] and can be derived by making the appropriate changes in the exact solution to Scheme II. We have discussed in section VD a number of applications of Scheme XVIII, including the calculation of the precursor–product ratio, i.e., the percentage of $A_1$ which derives from $A_2$ (and $A_3$).

SCHEME XVIII



Zimmerman et al. have utilized a very detailed mathematical evaluation of Scheme XVIII to analyze donor–acceptor systems in excited-state energy transfer.[198]

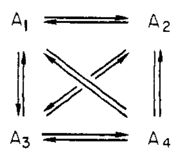
(4) We illustrate the standard kinetic scheme for micellar catalysis in Scheme XIX, where M refers to the micelle and S the substrate;[199,200] $k_m$ and $k_o$ refer to the rate constants for product formation within the micelle and outside the micelle, respectively. The similarity of Scheme XIX to C–H kinetics (Schemes II and IV) is readily apparent, though it combines first-order and second-order reactions to product.

SCHEME XIX

$$\text{products} \xleftarrow{k_o} M + S \overset{K}{\rightleftharpoons} MS \xrightarrow{k_m} \text{products}$$

In an application of Scheme XIX, Kurz studied the transition-state characteristics for certain catalyzed reactions.[201] In these cases, it was assumed that an equilibrium distribution between the uncomplexed and complexed substrate was maintained during the reaction.

SCHEME XX



## B. Four-Component Kinetics

(1) McLaughlin and Rozett used Laplace transform methodology to derive exact solutions to the general four-component Scheme XX.[202] The set of equations presented can, by insertion of the appropriate initial conditions, allow the solution for all combinations of consecutive or reversible first-order, or pseudo-first-order, reactions between four components. As of 1972, a listing of a Fortran IV program was offered by McLaughlin and Rozett.[202] For an earlier treatment, see Matsen and Franklin.[203] We do not reproduce the solution here, but inspection of the exact solution to Scheme II (which is a subset of Scheme XX) in section VC correctly suggests that it is complicated indeed.

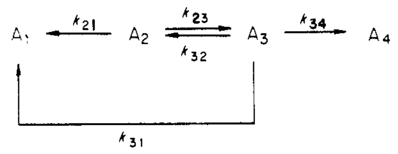
(2) Scheme XXI represents a simple subset of the C–H kinetic scheme and is exemplified by a recent report of Mulzer and Zippel[171] on the epimerization and decomposition of the β-lactones, *cis*- and *trans*-4-*tert*-butyl-3-phenyloxetanones. While the cis lactone epimerized to the trans lactone, it was shown that the trans lactone did not epimerize to the cis lactone. The lactones stereospecifically decarboxylated to the *cis*- and *trans*-1-phenyl-2-*tert*-butylethylenes.

SCHEME XXI

$$A_1 \xleftarrow{k_{21}} A_2 \xrightarrow{k_{23}} A_3 \xrightarrow{k_{34}} A_4$$

(3) Scheme XXII represents the C–H kinetic scheme in which one of the two interconverting substrates reacts to give both products while the second substrate only produces one of the two products. Application of

SCHEME XXII



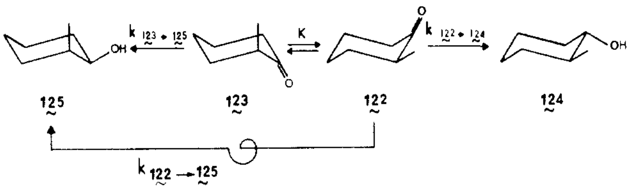


**Figure 21.** The sodium borohydride reduction of the conformationally mobile 2-methylcyclohexanone involves the formation of *cis*-2-methylcyclohexanol (**125**) from both **123** ⇄ **122** while **124** is obtained from reduction only of the equatorial conformer. Wigfield et al. indicate that the total product ratio [**124**]/[**125**] = 0.69/0.31 and that ca. 51% of **125** arises from **123** while 49% stems from reduction of **122**, i.e., $c = 0.49/0.51$.[172] Application of eq 107 leads to the ratio of the rate constants for axial reduction pathways, $k_{122\to124}/k_{123\to125} = 4.5K^{-1}$. Note that reduction of **122** to **125** initially forms the stereoisomer of **125** in which the methyl group is equatorial and the hydroxyl group is axial; ring inversion then is possible. Only one stereoisomer of **125** is shown for simplicity. From ref 204a.

the ideal law of mass action[2] to Scheme XXII cases for which $[A_3]/[A_2] = K$ during the course of the reaction leads to eq 106. It is interesting to compare eq 106 for

$$\frac{[A_4]}{[A_1]_\infty} = K\frac{k_{34}}{k_{21} + Kk_{31}} \tag{106}$$

Scheme XXII with eq 7 for Scheme II. The term $Kk_{31}$ in the denominator of eq 106 takes into account the portion of the substrate mixture $A_2 \rightleftarrows A_3$ which funnels into product via $A_3 \to A_1$.

Equation 106 can be readily transformed into eq 107 where $c$ is defined as the ratio of the rate of formation of $A_1$ from $A_3$ vs. $A_2$. Note that for some sets of $k_{ij}$, $c$

$$\frac{k_{34}}{k_{21}} = \frac{c+1}{K}\frac{[A_4]}{[A_1]_\infty} \tag{107}$$

$$c = \frac{k_{31}[A_3]}{k_{21}[A_2]}$$

could be time dependent; i.e., when $[A_3]/[A_2] \neq K$.

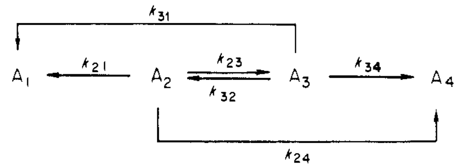
Equation 107 can be quite valuable. Consider the stereochemical outcome of the reduction of 2-methylcyclohexanone.[204] Figure 21 summarizes the relevant stereochemical information. Note that no *trans*-2-methylcyclohexanol is formed from the axial conformer **113**. The product distribution is listed in the caption of Figure 21; from this information, $c = 0.49/0.51$ and [**124**]/[**125**] = 0.69/0.31. Substitution of these values into eq 107 results in an expression (eq 108) that relates

$$\frac{k_{122\to124}}{k_{123\to125}} = 4.5K^{-1} \tag{108}$$

the ratio of axial reduction rate constants to the equilibrium distribution constant, $K$.[64]

(4) Scheme XXIII represents the symmetrical C-H/W-H system in which both products are formed from each interconverting substrate. The exact solution to Scheme XXIII is contained in the solution of the more general Scheme XX. Guthrie et al.,[205a] Jaeger and Cram,[205b] and Jaeger et al.[206] utilized methodology previously developed by Almy[207] for the analysis of Scheme XXIII systems using an exact solution. Zefirov and Palyulin reported an analytical solution and a solution at reaction completion to Scheme XXIII when $[A_3]_0/[A_2]_0 = K$ (eq 109).[208]

SCHEME XXIII



$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{24}c_1 + Kk_{34}c_2}{k_{21}c_1 + Kk_{31}c_2} \tag{109}$$

$$c_1 = k_{23} + k_{32} + k_{34} + k_{31}$$

$$c_2 = k_{23} + k_{32} + k_{21} + k_{24}$$

Equation 109 can readily be seen to degrade to lesser included cases, e.g., to eq 7 when $k_{23}, k_{32} >> k_{21}, k_{34}$ and $k_{24} = k_{31} = 0$. When the rate constants for the interconversions $A_2 \rightleftarrows A_3$ are much greater than the rate constants for all of the product formations, then eq 110

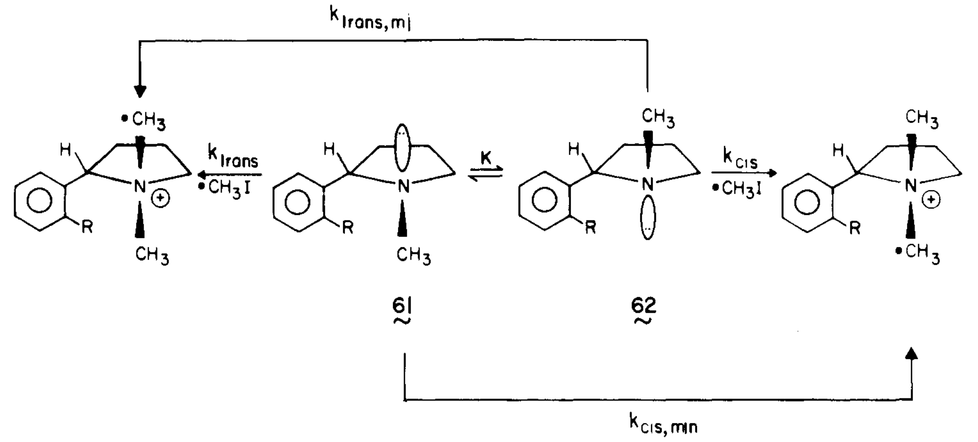
$$\frac{[A_4]}{[A_1]_\infty} = \frac{k_{24} + k_{34}K}{k_{21} + k_{31}K} \text{ when } k_{23}, k_{32} >> \text{other } k_{ij} \tag{110}$$

can be derived either from eq 109 or by procedures illustrated in section IIIB, previously achieved by Hutchins[209] and Monnier and Aycard.[210]

Equation 110 has been applied by Hutchins to derive the reduction stereochemistry of substituted cyclohexanones with a variety of hydride reagents[209] and by Monnier and Aycard to explain the stereoselectivity of the chlorodecarboxylation of cyclohexane and cyclohexenecarboxylic acids.[210] The exact solution to Scheme XXIII was used by Jaeger et al. to examine the isomerizations of imines of $\alpha$-(4-pyridyl)ethylamine which served as models for the proton-transfer steps of biological transaminations.[206] Previous studies by Cram had utilized this exact solution in the examination of stereospecific transaminations of other imine derivatives.[205]

Scheme XXIII takes on a special philosophical importance relative to some Scheme II kinetic systems. In their very detailed and often cited critical analysis of the use of the W-H equation for the determination of ground-state equilibrium distributions (cf. section IVB), Kwart and Takeshita[18] observed that the original kinetic analysis due to Winstein and Holness[8] and Eliel and Ro[14] did not include crossover reaction to products. For Scheme II systems, the formation of $A_2$ (and $A_4$) derives only from $A_1$ (and $A_3$). Alternatively, both products could result simultaneously from both starting materials as indicated by Scheme XXIII.

By application of transition-state theory, Kwart and Takeshita proved that the total rate of product formation for a chemical system is identical regardless of whether it is analyzed by Scheme XXIII kinetics or by Scheme II kinetics when $k_{23}, k_{32} >> k_{21}, k_{34}$.[18] Of course, this analysis implies that the $k_{21}$ derived for a Scheme II mechanism is *not* identical to the $k_{21}$ derived for a Scheme XXIII mechanism for the same chemical system. The derivation of this conclusion is identical to



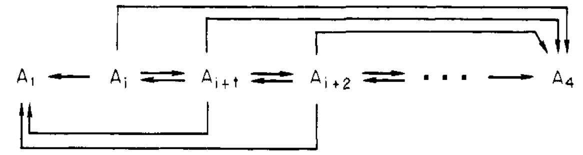
that proposed by Best et al.[195] for Figure 20 kinetics, discussed previously in section IXA.

Cross products were subsequently discussed in detail by McKenna with regard to the quaternization of *N*-alkylpiperidines.[27,46,47] "Normal" reaction was defined by McKenna to mean axial (equatorial) attack on an N-equatorially (axially) substituted piperidine; cross reaction involves the converse, e.g., axial attack on an N-axially substituted piperidine.

Seeman et al.[26] summarized these concepts with regard to the alkylation of nicotine analogues **36** and **61**⇄**62** discussed previously in sections IVE2 and IVF. The combined C-H/W-H treatment for the analysis of Scheme II, Condition II systems (section IVE) involves the solution of two equations (the C-H equation 7 and the W-H eq 25). Five independent parameters are present in these two equations: $[A_4]/[A_1]$, $K$, $k_{W\text{-}H}$, $k_{21}$, and $k_{34}$. It was shown[26] (section IVD) that the experimental determination of the first three allowed the solution to the last two, $k_{21}$ and $k_{34}$. If these types of reaction were to be evaluated using a Scheme XXIII mechanism rather than a Scheme II mechanism, two additional reaction rate constants must be included ($k_{24}$ and $k_{31}$) and one would be left with two equations and four unknowns. Without additional information, one could not proceed further.

Clearly, Schemes II and XXIII are not identical. Nonetheless, in a similar fashion to Kwart and Takeshita,[18] McKenna[46] concluded that, in terms of reaction rate, the system can be analyzed as if all product $A_1$ were obtained from $A_2$ via $A_{21}$ (see Figure 1). McKenna also concluded that the cross products would not affect the kinetic analysis. With regard to nitrogen quaternization, a significant amount of literature has analyzed the reaction by a Scheme II mechanism. Many additional reactions are treated as Scheme II mechanisms although they could have been alternatively described by Scheme XXIII as well. At present, there has been neither experimental nor theoretical evidence to support Scheme XXIII over Scheme II for any chemical system. Further, Scheme II has served as the basis for numerous major quantitative and systematic relationships in a variety of chemical fields (see the previous pages for numerous examples). Since the current distinction "is irrelevant to any presently observable phenomena"[2] it is of value to consider whether Scheme II and XXIII can be considered mechanistic alternatives of each other. For additional philosophical implications of this question, the reader is referred to Hammett,[2] Maurer et al.,[211] Wieland,[212] and the classic work of Popper.[213]

SCHEME XXIV



## C. Multicomponent Kinetics

There are clearly an infinite number of possible multicomponent kinetic systems, most of which are outside the scope of this review. We will focus on a few mechanisms which bear directly on the basic C-H/W-H kinetic Scheme II.

(1) Scheme XXIV represents a series of interconverting substrates, $A_i$, each of which reacts to give two different products, $A_1$ and $A_4$, with rate constants $k_{i1}$ and $k_{i4}$, respectively. Scheme XXIV is a generalization of the C-H/W-H Scheme XXIII in that the reacting substrate can be considered to consist of a large number of interconverting conformations. Fernândez-Gonzles and Pêrez-Ossorio[214] presented the "generalized" Curtin-Hammett principle (eq 111) for Scheme XXIV

$$\frac{[A_4]}{[A_1]_\infty} = \frac{\sum_i \exp(-\Delta G_{i4}^{\ddagger}/RT)}{\sum_i \exp(-\Delta G_{i1}^{\ddagger}/RT)} \qquad (111)$$

cases when the rates of isomer interconversion are significantly greater than the rates of product formation. $\Delta G_{i4}^{\ddagger}$ and $\Delta G_{i1}^{\ddagger}$ represent the free energy levels of the transition states from $A_i$ leading to $A_4$ and $A_1$, respectively.

Alvarez-Ibarra et al. utilized the "generalized" C-H eq 111 to calculate the stereoselectivity of lithium aluminum hydride reductions of alkyl aryl ketones.[215] More recently, Arjona et al. extended this procedure to predict the stereochemistry of methyl- and phenylmagnesium bromide additions to a series of chiral carbonyl compounds.[216] In these studies, relative energies of the competitive transition states are empirically quantified in a manner similar to that advanced by Karabatsos[88] and discussed in section IVC1. The similarity between the experimental product ratios and the theoretical predictions using the Perez-Ossorio method[214] is impressive considering the simplicity of the treatment.

SCHEME XXV

$$\begin{tikzcd}
 & A_0 \arrow[dl, "k_{02}"'] \arrow[dr, "k_{03}"] & & \\
A_1 & A_2 \arrow[l, "k_{21}"'] \arrow[r, shift left, "k_{23}"] & A_3 \arrow[l, shift left, "k_{32}"] \arrow[r, "k_{34}"] & A_4
\end{tikzcd}$$

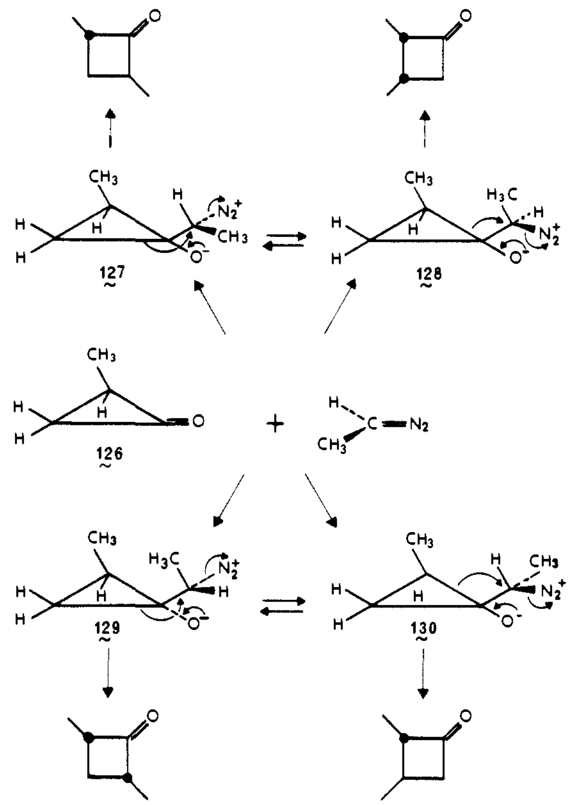


Figure 22. The products resulting from the reaction of diazoethane and methylcyclopropanone depend on the regiochemistry of attack, two modes of which are indicated. Only the cis mode of addition is illustrated. From ref 217.

(2) Scheme XXV represents an extension of the "feed-in" mechanism represented by Scheme IV. Scheme XXV can also be extended to second-order reactions to product. The "area theorem" method of Benjamin and Collins[141] (see section VIIB2b) cannot be applied to Scheme XXV because of the "extra" terms involving the formation of both $A_2$ and $A_3$ directly from $A_0$. While we suspect that the product ratio for Scheme XXV is independent of $k_{02}$ and $k_{03}$, an exact analytical solution is not presently available to Scheme XXV for confirmation.

(a) An interesting example of a Scheme XXV system was reported by Turro and Gagosian[217] and involves the mechanism of diazoalkane addition to cyclopropanones. As illustrated in Figure 22, diazoethane could add cis or trans to the methyl substituent of methylcyclopropanone (**126**); because one chiral center exists in the starting material **126**, two additional chiral centers are formed in the initial adducts **127** ⇄ **128** and **129** ⇄ **130**. (Trans addition is also possible but is not illustrated in Figure 22.) According to Turro and Gagosian, each of these intermediates **127**–**130** forms a unique product. They calculated the "interaction energies" for **127**–**130** by simply summing the 1,3 interactions in each zwitterionic rotamer. An excellent correlation between the cyclobutanone product ratios and the interaction energies, which essentially are the relative transition-state energies, was found. While Turro and Gagosian's application of the C–H principle is somewhat vague, one interpretation of their results is that the rates of interconversion between **127** ⇄ **128** and **129** ⇄ **130** are significantly faster than their respective rates of product formation (the C–H approximation!).

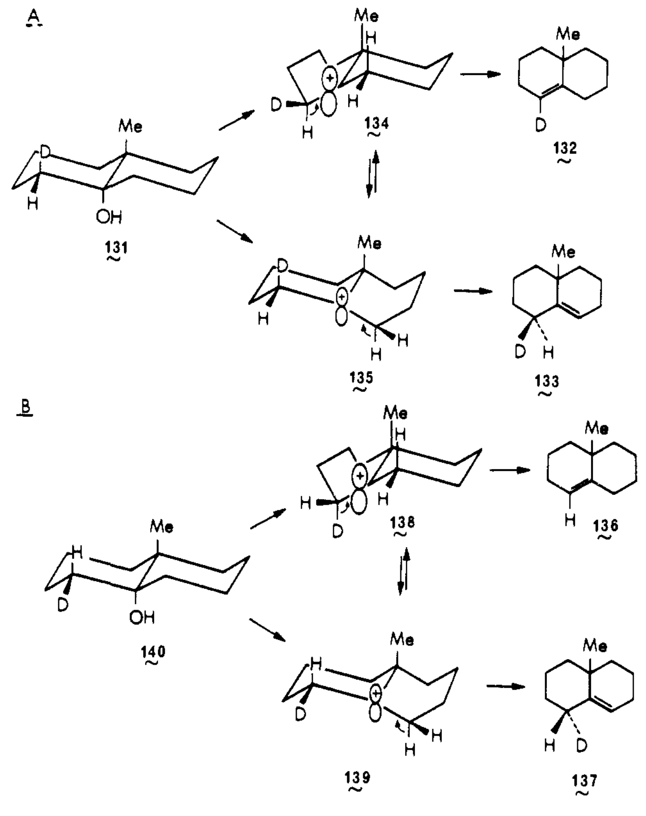


Figure 23. The dehydration of 131 and 140 are examples of a Scheme XXV mechanism. (A) Dehydration of 131 results in the formation of 132 and 133 via syn elimination. (B) Dehydration of 140 can occur with loss of either a proton (from 139) or a deuteron (from 138). From ref 218.

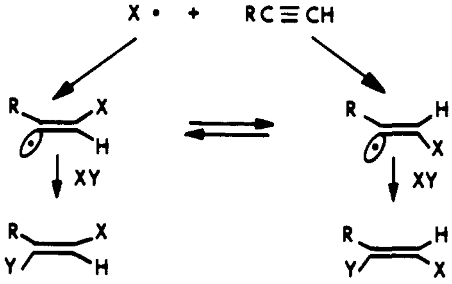
(b) Coxon and Lindley examined the regiospecific dehydrations of 9-hydroxy-10-methyldecahydronaphthalenes.[218] In a very elegant use of isotopic labeling, they uncovered an interesting Scheme XXV system as shown in Figure 23. Treatment of alcohol **131** with acid gave the monodeuterated olefins **132** and **133** from **134** ⇄ **135**; neither **136** or **137** was observed. This result establishes that the hydrogen lost was originally syn to the departing C(9)-hydroxyl moiety. Similar reaction of alcohol **140** therefore must lead to a mixture of **136** and **137**; the experimental result was a ratio [**137**]/[**136**] = 2.2 ± 0.4. Coxon and Lindley concluded the rates of interconversion between the intermediate cations must be at least comparable with the rate of proton loss from these intermediates. Had the rates of conformational interconversion between these cations been significantly slower, Coxon and Lindley reasoned that the products **136** and **137** would have been formed in equal amounts.[218] An additional factor not mentioned by Coxon and Lindley involves the unequal rates of product formation due to a primary isotope effect[219] in the loss of the proton (deuteron), and it is possible that such an effect could be responsible for a product ratio of 2.2 ± 0.4.[219a]

(c) Two examples of a Scheme XXV mechanism involving second-order reaction to product have been reported by Wedegaertner et al.[220] and Kampmeier and

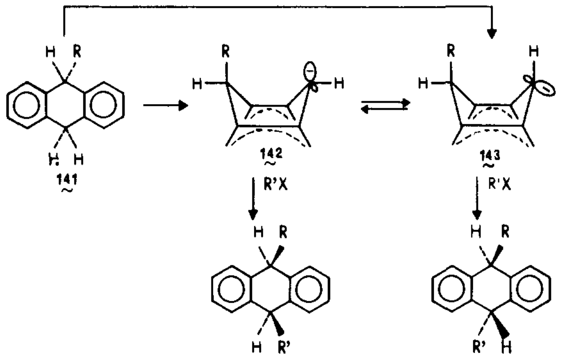
SCHEME XXVI

$$\begin{tikzcd}
 & A_{02} \arrow[d, shift left] & A_{03} \arrow[d, shift left] & \\
A_1 & A_2 \arrow[l] \arrow[u, shift left] \arrow[r, shift left] & A_3 \arrow[l, shift left] \arrow[u, shift left] \arrow[r] & A_4
\end{tikzcd}$$

Chen[221] and involve vinyl radicals formed in the addition of radicals to alkynes. In the former reference, a C–H analysis is presented along with a discussion of the possible boundary conditions. These studies report the effect of reagent concentration on product stereochemistry as well as a discussion on the rate constants involved in these reactions.



(d) Fu et al.[222] examined the stereochemistry of alkylation and protonation of a wide series of 9-alkyl-10-lithio-9,10-dihydroanthracenes **141**. The intermediate anion can exist in axial **142** and equatorial **143** conformations, and the alkylation of each of these results in *cis*- and *trans*-9,10-dialkyl-9,10-dihydroanthracenes, respectively, assuming that the originally bonded 9-substituent is entirely in the preferred 9-axial orientation.



The cis product is formed preferentially when 141 (R = isopropyl) is reacted with iodomethane, bromomethane, iodoethane, and bromoethane while the trans product is formed with isopropyl bromide. Evidently, steric hindrance due to the presence of R becomes dominating in the reaction of **142** as the alkylating reagent increases in size and decreases in reactivity; perhaps a later transition state and increased solvation requirements play a major factor in these reactions as R′ progresses from methyl to ethyl to isopropyl.

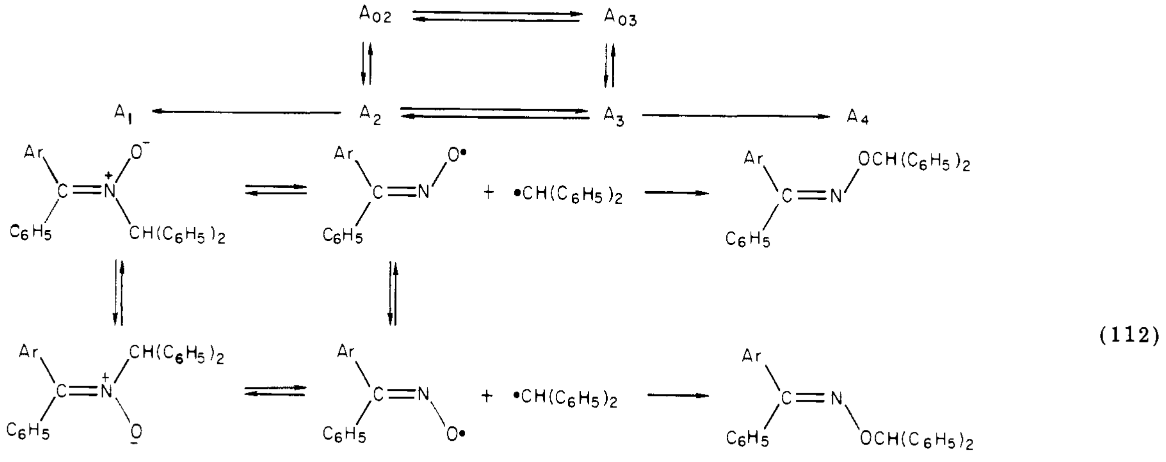
(3) Huisgen and Graf[223] reported an example of Scheme XXVI kinetics involving the stereochemistry of tetracyanoethylene cycloadditions to thioenol ethers. Increasing the solvent polarity increased the observed nonstereoselectivity, thereby suggesting the importance of a zwitterionic intermediate. Evidence was also presented for the reversibility of the formation of the initial intermediate to starting material. Note the relationship between Scheme XXVI and the two "feed-in" mechanisms Schemes IV and VIII.

(4) Dobashi et al.[224] examined the rearrangement of nitrones to *O*-alkyloximes (eq 112) using the mechanism generalized by Scheme XXVII. They were able to measure the rate constants of starting material interconversion and also estimate the rate constants of interconversion of the intermediates $A_2$ and $A_3$. This particular example is noteworthy in that the final reactions to product are second order, incorporating the concentration of two radical species, both formed in the intitial fragmentation step.

(5) Samuelson and Carpenter utilized Scheme XXVIII in conjunction with a sophisticated kinetic isotope effect argument as a tool for mechanistic discrimination between different reaction mechanisms.[225] Scheme XXVIII is related to the C–H/W–H concept as noted by the kinetic implications of the portion of the Scheme inside the dashed rectangle. An additional example of Scheme XXVIII kinetics involves the mechanism of electrocyclic aromatic substitution by the diazo group in $\beta$-aryl-$\alpha,\beta$-unsaturated diazoalkanes reported by Miller et al.[226]

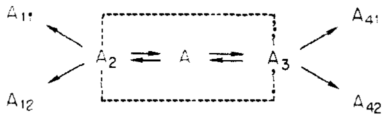
(6) Over the past years, the remarkable efforts of the Gajewski group have resulted in the successful analysis of a number of very complicated multistep mechanisms.[227] Numerical integration of the appropriate differential rate equations for the mechanism was usually performed. Gajewski reanalyzed literature results for a Scheme XX system using a Runga–Kutta numerical procedure and obtained a new set of rate constants.[227a] Gajewski pointed out that the new values

SCHEME XXVII

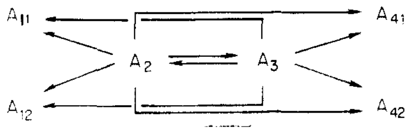


(112)

SCHEME XXVIII



SCHEME XXIX



are not unique but rather indicate the range of values which produce the same (within experimental error) time–concentration data. The Gajewski values lend themselves to alternative interpretations of the reaction. von E. Doering and Mastrocola[228] studied the thermal rearrangements of 1-cyano-2-vinylcyclobutanes which were described by Scheme XX kinetics as well as by more complex mechanisms.

A number of related examples which are related to both Scheme XXIX and Scheme II was reported by Gajewski and Salazar[227b,c] for the thermal rearrangement of 1,3-dimethylenecyclopentane, and *cis*- and *trans*-4,5-dimethyl-1,3-dimethylenecyclocyclopentane. These are represented by Scheme XXIX. Again, numerical integration of the differential rate expressions were compared with the experimental time–concentration data in order to derive the rate constants.

## *X. Additional Considerations and Commentary*

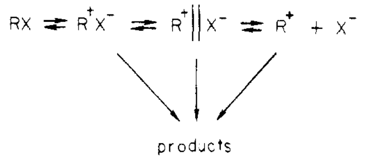
### A. Reactive Conformations and Rapid Equilibria

(1) The adoption of any mechanistic scheme for a chemical system implies the existence of the discrete species detailed in that scheme. When we deal with substances capable of fast reversible interconversions, e.g., conformational isomers, we must keep in mind that any one subset of A, e.g., $A_i$, may itself be a composite of many conformers. We generally tend to categorize the conformations of a substance into those subsets which, all together, react to give a specific product. Thus, our first example in section I indicated two conformations for 1,2-dimethylpyrrolidine (**1**), in which the methyl groups are either cis or trans. This is a particularly convenient categorization, considering that the example dealt with nitrogen alkylation either trans or cis to the 2-methyl group. Different pyrrolidine ring conformations (e.g., pyrrolidine pseudorotation[229]) were not considered. It would be an incorrect generalization to suggest that the pairs of pyrrolidine ring conformers, differing only by nitrogen substituent orientation, would react comparably with each other.

Consider a molecule which exists in a number of conformations, some of which react along one (or more) minimum energy path(s) to the transition state(s) leading to product. We can speculate regarding two matters of "timing": first, to what extent is molecular motion of the ground-state species related to the initiation of product formation? Second, are the routes to the different transition states related?

Leffler and Grunwald[230] have emphasized that it is formally correct to discuss the conformer reaction rate constants *independent* of the conformer interconversions. They point out that this analysis is independent of the mechanism of activation. Although there may be numerous minimum energy paths to the respective transition states for product formation, Leffler and Grunwald conceptualize "detailed balancing at all levels under C–H/W–H conditions."[230] This implies that the molecules can traverse from one path to another along the potential energy surface leading to all the transition states when isomer interconversion is rapid relative to product formation.

SCHEME XXX

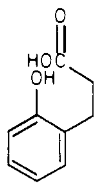


This issue can rapidly become unmanageable if one considers additional mechanistic complexities. For example, if we are dealing with a solvolysis reaction as discussed in section IVB1 for **26–28**, we may wish to consider the implications of the classical Winstein scheme of "intimate", "solvent-separated", and "completely separated" ion-pair intermediates for *each* conformation, shown by Scheme XXX.[135] Alternatively, for C–H/W–H systems, theoretical calculation of the relevant transition-state energies may avoid the task of considering ground-state isomer interconversion and populations entirely.[231]

(2) Sekhar and Tschuikow-Roux[232] reported the stereochemical consequences of dehydrofluorination of 1,1,2-trifluoroethane (**144**). On the basis of microwave spectroscopy, they indicate that **144** exists in three stable, staggered forms. However, the planar four-center cyclic transition states required for elimination of HF correspond to the maximum in the ground-state potential energy surface of **144**. While maxima and minima certainly exist on this potential energy surface, the barriers are likely to be low compared to the barriers for dehydrofluorination. What is the relationship between rotation and elimination in this reaction? One of the challenges in physical organic chemistry is the derivation of the consequences of conformational motion on chemical reactivity.

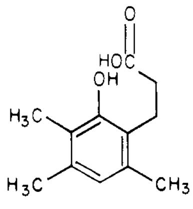
(3) Stereopopulation control of organic chemical reactions was advanced by Milstein and Cohen[233] to explain the remarkable rate differences noted in the lactonizations of **145–148**. This concept emphasizes the increase in the population of the more productive conformers in a substrate, thereby presumably leading to a faster product formation. These observations were soon followed by similar results for additional alkyl-substituted *o*-hydroxyhydrocinnamic acids and related compounds.[234–236] For stereopopulation control to operate, restriction of rotational (or conformational) freedom of a substrate leads to a narrow distribution of reactive conformational isomers while removing nonreactive conformational isomers from the substrate distribution. Danforth et al.[237] and Winnans and Wilcox[238] subsequently established that a considerable percentage of the rate enhancement of **147** and **148** was due to relief of steric congestion in the ground state.

(4) When the rate constants for isomer interconversion ($k_i$) are greater than the rate constants for reaction to product ($k_r$), then the observed rate of product for-



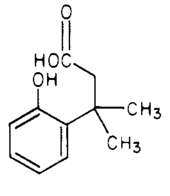
145

$k_{rel}$ 1



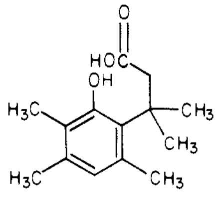
146

1.05



147

$k_{rel}$ 400



148

ca. $10^{11}$

mation involves an averaging of effects over all the reacting isomers. The expression "rapid equilibrium" is often found in the literature. When $k_i >> k_r$, the equilibria are maintained, since the isomer interconversions are more "rapid" than the reaction to product. At the other extreme, when $k_r >> k_i$, then each isomer reacts *as if it were not capable* of reversible interconversion.

(5) van Gerresheim, Kruk, and Verhoeven[239] recently discussed two methods to extract the rate constant of an intramolecular redox system ($k_n$) using, in both cases, $^1$H-spin transfer experimentation of a Scheme II system. They were able to extract the value of $k_n$ from the time-resolved spin saturation data. This type of experimentation has recently been used to derive information regarding conformational processes as well.

### B. Solutions to and Differentiation between Complex Chemical Systems

The mathematical solution of any kinetic system is often the initial step in the application of mathematical models to the solution of chemical problems. A number of exact solutions are already available for a wide variety of complex mechanisms (see, for example, the excellent resource presented by Rodiguin and Rodiguina[240]). Integration of a set of first-order differential equations is always possible[2,193] and generalized matrix methods for the exact solution of multicomponent kinetic systems have been used.[241,242] Numerical methods have been applied to completely first-order systems[227] and to the more complex cases involving second-, or higher, order reactions.[243,244]

Guthrie has recently published two methods for deriving rate constants when analytical solutions are not obtainable, and he has illustrated these using data from the reaction of steroidal imidazoles with aryl esters.[245] The simulation of the behavior of very complex, multistep, chemical reactions containing "an almost unlimited number of elementary reactions" are being achieved using computer procedures.[246] Very interesting methods continue to be advanced for solving kinetic problems. For example, Ahlberg and Ek[247] have described the mathematical treatment of *reversible* reactions as a series of *irreversible* reactions which leads to time–concentration information.

Essential to any mechanistic study is the validation of the mechanism itself. The differentiation between various kinetic schemes is a difficult task at best[211] and impossible at worst.[2] Kafarov and Pisarenko have recently reviewed the current state of the art regarding the identification and validation of kinetic models.[248] Koda et al. have published an algorithm for determining the sensitivity of various parameters, such as rate constants, on kinetic mechanisms.[249] They point out that three routines are needed for the "sensitivity" analysis of reaction mechanisms, and that a complete code for achieving that goal is now available. It incorporates: (a) the formation of the rate equations; (b) integration of the ordinary differential equations; and (c) performing sensitivity analysis on the substrate concentrations.

## XI. The Development of the Curtin–Hammett/Winstein–Holness Concepts: A Historical Perspective

> The way in which a scientist remembers and publishes his arguments is not necessarily the order in which the idea originally occurred to him... Scientists are notoriously forgetful about the origin of their most interesting conjectures...[250]

In their authoritative treatise "Conformational Analysis", Eliel, Allinger, Angyal, and Morrison conclude that, "Conformational effects on reactivity may be understood in terms of two now well-recognized relationships,"[251] the Curtin–Hammett principle and the Winstein–Holness equation. These two relationships form the mathematical basis from which the consequences of a wide range of organic reactions may be determined, as described in previous sections. To perceive the origin of these concepts, it is valuable to place the concepts of stereochemistry and conformational analysis in the perspective of the early 1950s when the Curtin–Hammett and Winstein–Holness concepts were first advanced.

We shall first briefly enumerate some of the important milestones in the development of conformational analysis. For additional historical details, the reader is referred to the works of Ramsay,[252] Eliel,[5,34,54,56,67] Riddell,[253] and references cited therein.

The original suggestions that cyclohexane is puckered were made by Sachse[254] in 1890 and Mohr[255] in 1918. Experimental results supporting this hypothesis became available starting from the early 1920s in the form of X-ray analyses by Bilicke;[256] isolation of *cis*- and *trans*-decalin by Hückel;[257] Raman and other spectroscopic studies of acyclic and cyclic compounds by Kohlrausch[258] and Mizushima;[259] and electron diffraction, dipole moment, and X-ray analyses by Hassel.[260] In addition, theoretical calculations of total energy barriers were developed by Eyring[261] and Pitzer.[262] In total, these studies and others presented evidence for preferred "chair" conformations of cyclohexanes, for two types of cyclohexane bonds, and for hindered rotation in organic molecules.

Derek Barton, whose contributions in the early 1950s to conformational analysis led to a joint Nobel Prize in 1969 with Hassel, recently commented:

> The calculations of Eyring showed that boat conformations were more stable than chair and that eclipsed conformations were more stable than staggered! In addition Langseth and Bak (*J. Chem. Phys.*, **1940**, *8*, 403) found that cyclohexane was planar (as determined by Raman spectrosco-

> py). Most more senior organic chemists of the epoque did not believe any of the evidence.[263]

Considering the wide variety of information available in the chemical literature, it may be somewhat surprising to the post-1950 chemist that "most chemists, especially organic chemists, depicted the molecule (cyclohexane) as a planar hexagon even as late as 1948".[56] Why was there such a delay in the development of conformational analysis? The answer lies in the complex matrix of chemists and their intellectual environment: the chemical literature, including obscure journals; old and presumably tested ideas and theories; the difficulties that oceans and continents rendered to scientific communication in the first half of the 20th century; global conflicts; and the failure of different chemical disciplines to "communicate" with each other.

Many of the fundamental contributions on which conformational analysis soundly rests were initially published by physical and theoretical chemists, often in rather obscure journals. Hassel's most significant work appeared in Norwegian[260] in the midst of the Second World War, a circumstance which understandably caused a delay in the results being well disseminated. In addition Eliel has suggested that "the failure of conformational analysis to take hold prior to 1950 was probably due to a lack of simultaneous comprehension and appreciation of physicochemical principles on one hand and organic reactivity on the other".[56]

It is interesting to contrast the original goals which spurred physical chemists to explore properties of molecules, such as their conformations, with the use of these results by organic chemists. For example, Mizushima, who with his students was responsible for major experimental results on internal rotation, stated that,

> one of the incentives for starting these researches was provided by the study on the anomalous dispersion and absorption of undamped short electric waves made by the author [Mizushima] in the 1920s. We became interested in studying the rotation of two halves of a molecule relative to each other, a rotation which organic chemists supposed for some time to be completely free.[259b]

A chronology of the titles of some of Mizushima's publications depicts a profile of progress in this area:

"Intramolecular Potential of Ethane Derivatives" (1936)[264]

"Rotation About S–S Bond" (1937)[265]

"Raman Spectra of Deuterio-1,2-Dibromoethanes" (1939)[266]

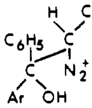
"Dielectric Constant of Liquid 1,2-Dichloroethane and the Equilibrium Ratio of Rotational Isomers" (1943)[267]

"The Entropy Difference Between the Rotational Isomers" (1952)[268]

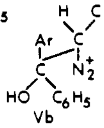
To illustrate how easy it was to miss some of this early work, consider the pioneering but overlooked contributions of P. H. Hermans in the 1920s.[269] Hermans was probably the first to appreciate the importance of conformational analysis in both acyclic and cyclic systems. His work was largely unrecognized, not only *preceeding* the development of conformational analysis in the mid-1950s but also for many years *after* the impact of stereochemistry and conformations were well-recognized by practicing chemists. Eliel rediscovered Herman's work shortly before the Le Bel–van't Hoff Centennial at Atlantic City in 1974 and "he attended the Centennial celebrations as our guest".[270]

There is much evidence that many results, which could have led to an earlier development of conformational analysis, were not recognized until many years after their original publication. For an interesting example which bears directly on the topic of this review, refer to a paper submitted for publication in early August, 1949. At least six months prior to the classic 1950 Barton paper[9] (see below), Pollak and Curtin stated,[11] without mathematical derivation, the fundamental concept of what was years later to be referred to as the Curtin–Hammett principle. In discussing the mechanism of the nitrous acid-mediated rearrangement of 1,2-diphenyl-1-aryl-2-aminoethanols, they said:

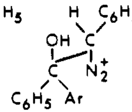
> The geometry of the reacting molecule can influence the reaction in one or more of several possible ways. Molecules with the general formula V have three staggered configurations which are presumed initially to be in equilibrium with one another. Should Va have a sufficiently lower free energy to be present in appreciably greater concentration than Vb, a larger fraction of rearranging molecules would have the correct configuration for the replacement of nitrogen by phenyl rather than by aryl.



Va

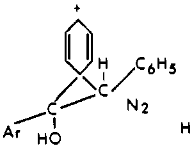


Vb

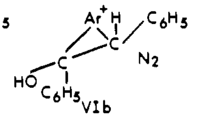


Vc

> Furthermore, if the diazonium ion V loses nitrogen with simultaneous migration of phenyl, the transition state has the configuration VIa while migration of aryl leads to transition state VIb. It seems possible that VIa may be of sufficiently lower energy than VIb to influence the relative rates of the two migrations.[11]



VIa



VIb

There must have been considerable resistance to these new concepts, and "the impact of the articles was not immediately felt in all areas of chemistry".[271] Further elucidation of these concepts by Curtin proved difficult, and Curtin rather willingly though temporarily held back on their publication. Curtin recalls:

> Pete and I had a couple of typewritten pages discussing the principle in our manuscript of the second paper on the reaction of amino alcohols with nitrous acid (*J. Am. Chem. Soc.*, **73**, 992 (1951)). The discussion wasn't very clear, and when a referee objected to it, the editor suggested that we take it out—which we did. It next surfaced in my talk at Wayne State in 1954.[272]

The first half of the twentieth century witnessed important yet sporadic and not generalized contributions to stereochemical thinking and conformational analysis. Remarkably, even in the late 1940s, "the tendency on the part of most organic chemists was still to talk rather generally of the importance of steric effects rather than to look more carefully at the actual conformation of the molecule".[273] The years 1950–1955 were to see a rather dramatic series of major breakthroughs which would culminate in a set of fundamental concepts and principles. These ideas were to erupt almost simultaneously from laboratories on both sides of the Atlantic. D. H. R. Barton has been credited by many of his peers with having "broken the ice" in his 1950 pioneering publication in *Experientia*.[9] Barton explained his approach to science:

> In my scientific life whenever I have undertaken some experiments it has been with a theoretical principle in mind: I have never done experiments at random. The things that I have discovered have often been the responses to a particular challenge, and often the response has been made very quickly. A question is posed—sometimes by an experiment, sometimes by a lecture, sometimes in the course of conversation, and one just sees the solution.
>
> The paper on conformational analysis arose exactly like that. I was listening to Professor Louis Fieser, an expert on steroid chemistry, describing in a seminar at Harvard how he was unable to understand certain relationships between the ease of hydrolysis of esters in the steroid field. I knew at once, from having the shape of the molecule in my mind, how this phenomenon could be explained. I thought a little bit more about it, and then wrote the paper on conformational analysis. But I certainly did not plan to write a paper on conformational analysis. It came about in a series of steps—the concern with molecular shape and stereochemistry; a brief study to determine molecular dimensions by the measurement of dissociation constants of acids; my scientific past leading me to thinking about shapes of molecules. When finally Fieser posed his problem in his seminar, I could immediately see the answer. But it was not planned.[274]

Sir Derek Harold Richard Barton (1918–). Dupont Jackson Laboratory, Wilmington, Delaware. "This picture was taken within a month or so of writing the 1950 paper on Conformational Analysis."

Barton's classic 1950 paper[9] induced rapid changes in the way organic chemists as a whole described and evaluated their work. Barton stimulated chemists to examine and to understand the effects of conformation and stereochemistry on chemical reactivity. A key example of his was the demonstration that axial and equatorial substituents on cyclohexanes displayed significantly different chemical reactivities. Barton conceptualized:

> that although one conformation of a molecule is more stable than other possible conformations, this does *not* mean that the molecule is *compelled* to react as if it were in this conformation or that it is rigidly fixed in any way. So long as the energy *barriers* between conformations are small, separate conformations cannot be distinguished by the classical methods of stereochemistry.[9]

Barton's contemporaries immediately recognized and seized upon these now formalized ideas that proved to be of "incalculable benefit to subsequent workers".[15] Chemists now focused their attention on such topics as:

(a) the demonstration of the existence and physical properties of preferred conformations;

(b) the reasons for the existence of preferred conformations;

(c) the chair and alternate shapes of six-membered rings;

(d) the relative stability of conformational isomers, especially the energy differences between the chair and boat forms of cyclohexane;

(e) the nature of the two different monosubstituted cyclohexanes;

(f) the stereochemistry of fused systems, e.g., decalins and hydrindans;

(g) the physical separation of pure conformational isomers;

(h) early theoretical models, e.g., Westheimer's force-field approach;[275]

(i) methods to lock particular conformations; and

(j) techniques to illustrate nonplanar stereochemical and conformational concepts.

These concepts formed the stepping stone from which stereochemical thinking blossomed. For these contributions, Barton shared with Hassel the 1969 Nobel Prize in Chemistry.

A testament to the state of the art of the 1950s may also be obtained from the development of the required vocabulary. In late 1953 and early 1954, Barton, Hassel, Pitzer, and Prelog jointly published the *identical* manuscript in two prestigeous journals, *Nature*[276a] and *Science*.[276b] "Nomenclature of Cyclohexane Bonds" provided an international recommendation for the now well-accepted terms "axial" and "equatorial", the former "suggested to us by Professor C. K. Ingold".[276]

Barton intentionally chose chemical examples which were "mostly rigid"[15] and "homoconformational",[67] usually taken from the steroid and triterpene literature. "It has, however, always been the contention of the author [Barton] that the principles of conformational analysis are best illustrated by reference to molecules built up of an array of fused cyclohexane rings, where the stereochemical configurations often render a choice of preferred conformation unambiguous."[277] Nonetheless, the full implications of conformational effects on chemical reactivity required the analysis of systems which exist in more than one reactive conformation.

To fully appreciate the implications of conformations on chemical reactivity, it became necessary to generalize the kinetic and thermodynamic consequences of conformationally mobile, chemically reactive systems. The simplest chemical kinetic scheme which, in theory, incorporates the required elements is one described by Scheme II. Here, a molecule exists in two interconverting conformations, each of which reacts to give a different product. This is the system "formally" addressed by Curtin (and Hammett) in 1954,[1] Winstein and Holness in 1955,[8] and Eliel and Ro in 1956[14] and "informally" treated by Pollak and Curtin in 1950,[11] Kirkwood in 1953,[60] and Eliel in 1953.[13]

SCHEME II

$$A_1 \xleftarrow{k_{21}} A_2 + R \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} R + A_3 \xrightarrow{k_{34}} A_4$$

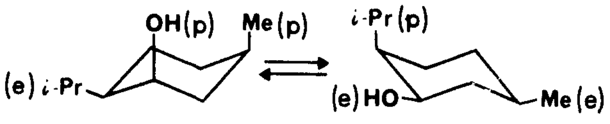
In a rather unrecognized contribution to conformational analysis, Wood, Fickett, and Kirkwood utilized the Kirkwood theory of optical rotatory power to determine the absolute configuration of the conformationally mobile 1,-dichloropropane.[60] They proposed eq 113 which related four properties of 1,2-dichloropropane: (a) ground-state equilibrium distribution of the "only two [conformations which] are considered to have sufficiently low energies to make appreciable contributions",[60] which they estimated from electron diffraction and dipole moment data; (b) the calculated (Kirkwood theory) optical rotatory power of these two conformations; and (c) the "gross" optical rotatory power of the molecule itself.

$$\alpha_{\text{calcd}} = [\alpha_t + \alpha_s \exp(-\Delta F/RT)]/[1 + \exp(-\Delta F/RT)] \quad (113)$$

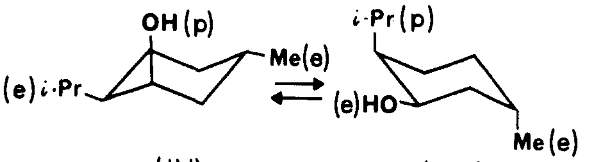
Kirkwood's study was indirectly a precursor to the Winstein-Holness equation[8] (see section IIID), as can be seen by a comparison of eq 113 with eq 25 in section IIID2. In Kirkwood's work, however, the objective was a comparison of $\alpha_{\text{calcd}}$ with $\alpha_{\text{obsd}}$ in order to assign the absolute configuration of the molecule. In the W–H application, the goal was the experimental determination of the equilibrium distribution of the conformational isomers. While the Kirkwood publication received acclaim for its contribution toward the calculation of optical rotatory properties, it failed to receive attention in the field of conformational analysis. This is yet another example of the failure of concepts to pass the multidisciplinary barrier in the early 1950s.

In his 1953 *Experientia* publication entitled "The Origin of Steric Hindrance in Cyclohexane Derivatives",[13] Eliel presented perhaps the best early example of the application of conformational analysis to chemical reactivity problems. Eliel was able to explain Read and Grubb's results of 20 years previous on the relative rates of esterification of the four menthol isomers. In doing so, Eliel very cleverly illustrated the complexities caused by conformationally mobile systems. He explained that:

> if neoisomenthol and neomenthol reacted in their stable conformations—III and IV—one would expect IV to be esterified more rapidly than III. In III there is severe crowding of the polar hydroxyl group by the nonadjacent polar [axial] methyl group while in IV the crowding is much less severe. Yet neomenthol (IV) is esterified only at one-third the rate of neoisomenthol (III). This is reasonable only if the molecules are converted to the less stable conformations—IIIa and IVa—prior to esterification. In these conformations—IIIA and IVa—the hydroxyl group is in the less crowded equatorial position and therefore more easily accessible to the esterifying reagent. The change from IV to IVa will be less facile than from III to IIIA, since in the former *two* alkyl groups (methyl and isopropyl) have to be forced into the crowded polar positions, in the latter only *one* (isopropyl). Therefore, making the reasonable assumption that IIIa and IVa are of the same order of reactivity, III should be esterified more readily than IV, which is in accordance with the experimental facts.[13,278]



(III) (IIIa)



(IV) (IVa)

Perhaps the C–H principle had such an impact because it initially focused, not on the ground-state conformations, but rather on the respective transition states. The C–H principle was most timely, since Barton[277] and many others[279] appeared to accept the incorrect literature conclusion[39,40] that ground-state conformational preferences of mobile systems could be uniquely determined by correlation with reaction product ratio composition. The *N*-methyl group in a number of tropane alkaloids had been incorrectly assigned as axial based on predominant equatorial alkylation.[39]

The origin of the C–H principle and the W–H equation simultaneously combined noteworthy aspects of both competitiveness and collaboration; of both selflessness and perceptions which, in a few cases, led to rather cool feelings.

Curtin had joined Columbia University in 1946 as an instructor following graduate work at Illinois, to which he returned in 1951 as an assistant professor. The critical interchange with Hammett occurred shortly before Curtin left Columbia.

Curtin has emphasized that the underlying C–H concepts were "pointed out by Professor L. P. Hammett in 1950",[1] first in Curtin's often cited 1954 review of "Stereochemical Control of Organic Reactions" in the *Record of Chemical Progress*,[1] and later in Curtin's 1955 article with Crew which discussed the nitrous acid rearrangements of α-hydroxy amines.[12] Hammett, on his part, has rendered complete credit to Curtin: "Because Curtin is very generous in attributing credit, this is sometimes referred to as the Curtin–Hammett principle [rather than] the Curtin principle."[280] Hammett recalls:

> At that time ("over 25 years ago") the idea was prevalent among chemists that one could determine the configuration of a reactant from the structure of a reaction product. At that time Curtin was on the staff at Columbia, and was puzzled about this idea. In a rather casual con-

Louis Plack Hammett (1894–). October, 1954.

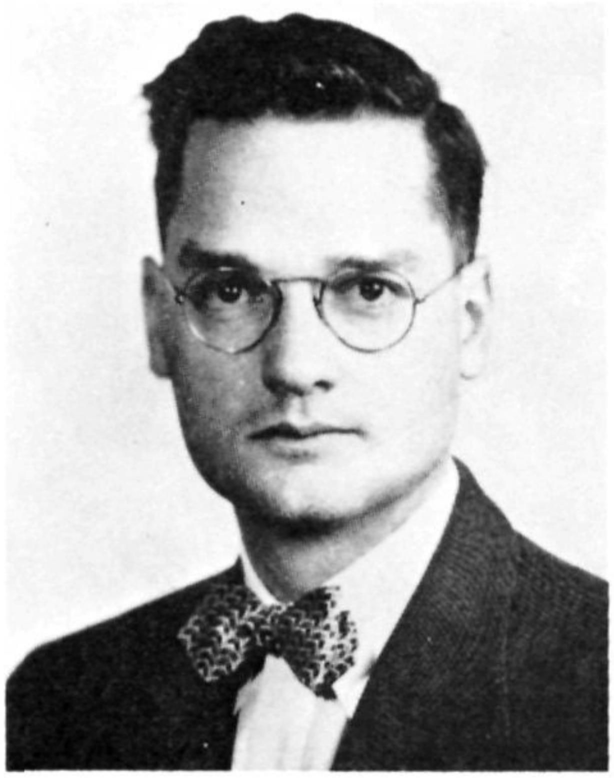
> versation I pointed out that, in terms of transition-state theory, the idea was fallacious and that the structure of the product from a rapidly interconverting set of conformers was determined solely by the structure of the transition state.[281]

In contrast, Curtin,

> can't, in all honesty, recall any details of our conversation (with Hammett)—and, in fact, it may have been Pete Pollak who first presented Louis [Hammett] with the problem... When Peter Pollak (one of my earliest graduate students) was carrying out his work on the effect of configuration on the course of reaction of diastereoisomeric amino alcohols with nitrous acid, we had attempted at length and unsuccessfully to find some basic relationship between the relative rates of formation of the two rearrangement products on the one hand and the conformational equilibria on the other. Thinking that there might be a complex underlying theory, we talked at some length to Ralph Halford about the possibility of some statistical mechanical approach which might be fruitful but were still not happy with anything that any of us had thought of. Previously Louis Hammett had struggled unsuccessfully with the problem of explaining the effect of substituents such as methyl groups in accelerating ring closure reactions as in the formation of tetramethylsuccinnic anhydride from the acid. When he heard our problem, Louis had the inspiration leading to the solution of both problems simultaneously.[272]

There was yet at least one other literature precedent for the C–H principle. In his 1952 publication in the *Record of Chemical Progress*,[282] later *identically* republished in 1955 in the *Journal of Chemical Education*,[283] Melvin Newman postulated his "best method of predicting relative rates"[282,283] of conformationally mobile systems. "That isomer which forms the most strained activated state will be the one which reacts at the slower rate."[282,283]

Barton wrote in 1955 that "the quantitative aspects of this subject have, however, scarcely been touched and it is clear that much useful work can be done by physical organic chemists in this direction. A valuable introductory paper has been provided by Winstein and Holness."[277] Published some two years after the C–H principle, the W–H equation represented the first example of "Quantitative Conformational Analysis".[8] The W–H equation was developed to determine the ground-state equilibrium distribution of a pair of interconverting conformations by using as models analogues fixed or "locked" in specific conformations, e.g., *cis*- and *trans*-4-*tert*-butylcyclohexanol served as models for the axial and equatorial hydroxyl-substituted conformations of cyclohexanol.



David Yarrow Curtin (1920–). This picture accompanied the first publication in which the Curtin–Hammett principle was presented.[1] 1954.

Saul Winstein (1912–1969). California, mid-1950s.

Winstein and Holness pointed out the relationship between their work and that of Curtin—they analyzed the same kinetic Scheme II—but W–H were interested in developing a procedure to quantify ground-state equilibria while C–H focused attention on product

Norris J. Holness (1927–). Mid-1950s.

distribution. Simultaneous with Winstein and Holness' investigations,[8] Eliel and Ro[14] and Eliel and Lukach[15] were deriving the same quantitative relationships, though in a slightly different though equivalent mathematical form. While the W–H equation's initial utilization was later found by Kwart,[18,19] Eliel,[62] and others[27] to have specific limitations (see section IVA and discussion below), it remains a valid description of the kinetic consequences of all Scheme II chemical examples with additional utilities not discussed on the original publications.

Winstein's primary research interests are evident from such phrases of his as "neighboring-group participation", "solvent participation", "internal return", "anchimeric assistance", "intimate ion pair", "ion-pair return", "bridged ions", "nonclassical ions", and "homoaromaticity."[284] He nonetheless had impact on many other areas of chemistry which were peripheral to his mainstream investigations. Winstein's goal was to "understand everything thoroughly".[284] As his associates Young and Cram wrote of him, "From a program of research whose experiments were conceived on the basis of a superb central idea flowed a wealth of new molecular rearrangements, new stereochemical concepts, and new mechanistic insights."[284] The Winstein–Holness equation was one of these. Commentary from Eliel is relevant:

> In the summer of 1953 Saul Winstein visited Notre Dame for an extended period as Reilly lecturer and I asked him about the extent of his own interest in doing quantitative work in conformational analysis. At that time Winstein indicated that he was only interested in assessing conformational effects on solvolysis, explaining that this was essential so that he would be able to apportion rate differences between stereoisomers as to their origin from either conformational or neighboring-group effects. [The W–H equation appeared in Winstein's nineteenth paper on "Neighboring Carbon and Hydrogen."] (As it later turned out, conformational effects in solvolysis reactions are small and Winstein's theory of neighboring-group effects was never jeopardized.) In 1954 I did a good bit of thinking about conformational analysis in mobile systems; I remember some interesting conversations on this topic with Nathan Kornblum, Richard Noyes, and Ronald Bell during a car trip to the Reaction Mechanisms Conference in New Hampshire in the summer of 1954. At that time, I had already initiated experimental work with Carl Lukach and with Roland Ro following submission of a proposal to the Office of Ordinance Research of the U.S. Army. The clarification of the situation came to me in the late fall of 1954 and I wrote to both William Dauben [dated Dec 20, 1954] and David Curtin [dated Dec 22, 1954] about it. (David Curtin responded with some helpful suggestions.) I was thus quite taken aback when in January 1955 I received a preprint of the famous Winstein/Holness paper [received by *J. Am. Chem. Soc.* on Jan 22, 1955]. Winstein obviously had changed his mind about strictly working on solvolysis.[285]

Ernest Ludwig Eliel (1921–). "At the Notre Dame Post Office, 1960. It could be claimed (probably falsely) that what I am carrying is part of the *Stereochemistry* manuscript."

Because of the significant cross-fertilization of ideas involving conformational analysis in the 1950s, it is almost fruitless to attempt to define unique attributions. Eliel had hosted Winstein at Notre Dame, and Eliel had discussed many of his ideas with others, including Barton, Mizushima, Brown, Curtin, and Dauben, the latter having worked closely with Pitzer and having the distinction in 1955 of writing the first review[32] which treated both the C–H principle and the W–H equation. Barton had spent considerable time at both Harvard and at UCLA during those years, and had sent Holness as a postdoctoral student to Winstein. Barton recalls:

> The facts are that I spent 9 months at Harvard (1949–1950) as a replacement for R. B. Woodward who was on sabbatical leave (in his own office!). My visit to U.C.L.A. was in 1953 for 3–4 days and

> I gave two lectures on caryophyllene chemistry and on the stereochemistry of triterpenoids. I remember the first lecture because I managed to rout Winstein by replying to his question with another question—to which he did not know the answer! The second lecture was very peaceful.[263]

Eliel further stated: "It is my impression that the person who pushed towards generalization of the subject was Holness who, of course, had got his Ph.D. with Barton and was well-versed in the principles of conformational analysis. However I have never been able to confirm this."[285]

John Holness confirms this suspicion:

> D. H. R. Barton was my supervisor for my Ph.D. When I joined him we were interested at first in the effects of conformation on optical activity in sterols and later in the triterpenoids where we wrestled with such simple matters as the cis or trans arrangement or fused cyclohexane rings. At that time—the later 1940s—while we were waiting for new University buildings we worked under almost primitive conditions. Our most complicated piece of apparatus was a simple polarimeter, now probably a museum piece.
>
> DHRB spent several months at Harvard with Woodward during this time when he was developing his concepts of polar and equatorial bonds in these fused ring compounds. He was a visiting lecturer at UCLA in 1953 or 1954.
>
> As a result of my work in this field I went out to UCLA at the beginning of 1952 and worked on the rates of acetolysis of *p*-toluenesulphonates and *p*-bromobenzenesulfphonates of compounds where the stereochemistry of the leaving group was well defined. I shared a small lab in the old chemistry building with Arnold Fainberg. Saul had a small office in one corner of the lab...
>
> My work with DHRB on steroids and triterpenoids must certainly have influenced the direction of the research at UCLA. We tried to make suitable derivatives of some steroid molecules for solvolysis studies but several experimental difficulties appeared. The derivatives seemed too unstable. We looked for simpler analogues and *t*-butylcyclohexanol presented itself—I forget where the idea arose. I believe this work was done in late 1953. I went out to California at the beginning of 1952 and stayed there until mid-1954.
>
> As I recall the solvolysis work was completed largely before the theory became very far advanced. At the start we were interested mainly in the relative reactivity of the two isomers compared with that of cyclohexanol. We were, of course, well aware of Hammett's work but I cannot remember any details of correlations which we might have looked into...[286]

Eliel's surmises can thus be supported. Eliel developed his quantitative expression of the W–H equation late in 1954, probably after Holness had completed his postdoctoral research in California. Further, Holness' experimental work was finished, as best as Holness himself can recall, prior to the completion of the conformational analysis deductions, implying that Holness and Winstein developed their ideas after the latter's visit to Notre Dame. How much Eliel influenced Winstein, and vice versa, is an open question.

Eliel, of course, has continued his studies in the areas of conformational analysis and stereochemistry, and in addition to his many research publications, he has significantly contributed to the field in terms of his classic textbooks,[3e,5] review articles,[287] and editorship of "Topics in Stereochemistry".[289] On the other hand, the W–H contribution was more of a foray for Winstein, a venture outside his usual sphere. It is somewhat incongruous that Winstein's name would be attached to an important concept out of his mainstream research while Eliel's contributions would be recognized without the honor of his name attached to a specific concept. This might be, in part, Eliel's own doing: Curtin has pointed out that "Eliel was the first to call the principle the "Curtin–Hammett principle""[272] in Eliel's *Stereochemistry* text.

Scientists are sensitive to inaccurate or incomplete attributions. On the one hand, Eliel's name was not attached to the Winstein–Holness equation. On the other, Eliel has requested this author in the current review to:

> Please make sure that the original authors receive the principal credit rather than my book. It is true that I may have clarified some concepts, but the concepts were already there. (Some of my scientific friends have complained over the years that *my* book is cited for *their* original work rather than their papers; of course there is not much I can do about that!)...[290]

With Barton's reviews in 1953,[10] 1955,[277] and 1956,[291] Newman's "Steric Effects in Organic Chemistry" in 1956 which led off with a review by Dauben and Pitzer on "Conformational Analysis",[32] and Orloff's detailed "Stereoisomerism of Cyclohexane Derivatives"[292] in 1954, the fundamental qualitative and quantitative tenents and applications of conformational analysis were well established. Eliel's series on "Conformational Analysis" was formally initiated with Conrad Pillar in 1955 with a study on "The Conformation of a Six-membered Ring *cis*-1,2-Fused to a Five-membered Ring",[293] referring back to the classic work of Hückel.[257] Curiously, neither Eliel's 1953 paper on menthol isomer esterifications[13] discussed above nor his 1956 report with Ro[14] which reported their independent derivation of the W–H equation were included in Eliel's "Conformational Analysis" series!

The distinction was now being made in the literature[291] between conformational analysis and configurational analysis, the latter usually dealing with the reactivity of diastereomers (e.g., Cram's and Prelog's rules). The reactivity of conformationally mobile systems was being actively examined, along with the reactivity of more rigid substrates.

The frequent use of the W–H equation in the determination of the equilibrium distribution of reacting substrates[67,294] was questioned and subsequently curtailed as a result of Kwart and Takashita's 1964 paper entitled "Evaluation of the Relative Importance of Charge–Dipole Interactions and Steric Strain Acceleration in Conformationally Mobile Systems".[18] Kwart writes:

> ...The evident success of the Winstein–Holness, Eliel–Ro treatment in relating reactivity and

> conformational orientation of functional groups was impressed upon me by Eliel's article in the *Journal of Chemical Education.* At that juncture our principal effort was directed toward correlating the effects of polar groups on reactivity at remote reaction sites separated by low dielectric space... We therefore were drawn to explore the limits of applicability of the kinetic method of conformational analysis.
>
> Our studies involved extensive rate measurements principally in solvolysis and in addition reactions at centers attached directly to a ring carbon. It became very clear, almost from the start, that a 4-*t*-butyl group as well as other substituents, bulky or polar, alter the conformational structure of the cyclohexane ring in ways that could not be truly called "subtle". Thus the determination of *A* values according to the W–H method could be perceived to be not really independent of the nature of the transition state for reactions in which (say) cyclohexyl and 4-*t*-butylcyclohexyl tosylates were to be compared. Such a conclusion tended to dispute the basic assumption of the Winstein–Holness, Eliel–Ro treatments.[295]

Harold Kwart (1916–1983). France, 1980.

Possibly encouraged by Kwart's conclusions, Eliel and Biros subsequently concluded, on the basis of "Acetylation Rates of Substituted Cyclohexanols", that

> the lack of constancy of (the calculated rate constants, $k_a$ and $k_e$) in conformationally rigid models makes it impossible to assert which of the various values, if any, apply to the monosubstituted, conformationally heterogeneous system... It is quite surprising that the kinetic method has given as good results as it has.[62]

Kwart provided additional "Direct Evidence of Limitations in the Applicability of the Kinetic Method of Conformational Analysis", though later evaluation (cf. section IVA2 of this review) of this study indicated that Kwart's data were insufficient to substantiate his correct and oft cited conclusions:

> It is our opinion, that the kinetic method cannot be justified merely because it seems to work sometimes. Its use can only be tentatively subscribed where the reaction center is not on the carbocyclic ring...and where the transition state may not involve a change in the hybridization of any ring atom.[19]

These criticisms spurred considerable emotion and additional research, as evidenced by Kwart:

> When I questioned Winstein as to the limitations on the assumptions of the W–H equations he waxed very indignant. It took several exchanges...before I could convince him that I really understood the origins and significance of his treatment. With passage of time, however, he got bored with the subject and our controversy, which never really surfaced into public argument (like the Winstein–Brown feud), subsided completely. Subsequent to that, we had only cordial relations and at least one fruitful discussion on topics of contemporary interest. In any case, our research interests drifted apart after our encounter on the W–H "principle" and, thus, no other occasions for controvery occurred thereafter.[296]

There was some defense for the use of "*t*-Butyl Derivatives as Reactivity Models in the Kinetic Method of Conformational Analysis",[297] as communicated by McKenna in 1974. McKenna cleverly examined the rates of reaction in 4-substituted-1,1-disubstituted cyclohexanes and concluded, "that this work provides the most direct experimental evidence available to date on the lack of interference of a conformation-holding 4-*t*-butyl group on the rate constants of cyclohexane derivatives not involving the ring atom."[27] For reactions which involve the ring atom (e.g., piperidine quaternization and solvolyses of cyclohexyl tosylates), the kinetic method does fail.[20,27,297] Eliel had also concluded that "the 4-*t*-butyl compounds are more free of polar and steric difficulties and simulate whatever distortions occur in the ground and transition states of the monosubstituted compounds better than do other conformationally homogeneous compounds."[62]

McKenna has further commented:

James McKenna (1922–). Derbyshire Peak District near Sheffield, England, 1960.

> Surely what had to be done, if rather late in the day, was to demonstrate as well as one could that the 4-*t*-butyl derivatives were indeed good reactivity models for the unsubstituted parents...[298]

McKenna's demonstration that the W–H equation would, in some cases, accurately determine ground-state equilibrium distributions vindicates Winstein, a man who was "devot[ed] to the idea of being correct."[284] Kwart concluded:

> I know that Eliel concurs with McKenna in the notion that when the reaction center is at least one atom removed from a ring atom, the 4-*t*-butyl blocking group is acceptable for kinetic conformational analysis. I was inclined to go along with this as an approximation which would very often be a good one, although I still hold the reservation that this cannot be the case invariably...[296]

Validation studies have long since ceased. The W–H concept is currently used with physical measurements other than rate constants, e.g., heats of reaction and NMR parameters, to achieve the original goals.[67–72] The W–H equation has had additional impact in ways not suggested in the 1950s. Nicolai Zefirov concluded:

> that the determination of *A* values by kinetic methods is not very important, though it may be applied in some particular cases. However, the problem of reactivity is very important but the whole literature is overfilled with just "brutto" rate constants without dividing them into the rate constants for individual conformers. Hence, my pessimistic view is as follows: we are in the embryonic stage of the whole problem, concerning the understanding of reactivity, in spite of the mountains of related papers.[299]

The quantitative nature of the W–H equation and the controversy which surrounded its use with model systems and the kinetic method of conformational analysis spurred research in this area for some time. The use of locking groups became a standard technique in alicyclic chemistry. The search for substituent-induced distortions in ring systems rapidly extended to the investigation of additional conformational effects, such as anomeric orbital and special hydrogen-bonding interactions in saturated heterocycles which alter ring conformations.[3a]

The Curtin–Hammett principle drew the attention of McKenna,[47] Katritzky,[85] and their colleagues as a means to determine the stereochemistry of piperidine and pyrrolidine quaternization. These novel applications were not geared toward determination of conformer reaction rate constants but more simply toward the deduction of reaction stereoselectivity and product structure (i.e., determination of configuration of diastereomeric nitrogen quaternary salts). In the meantime, the C–H principle was cited numerous times in the literature to reference the controlling feature of relative transition-state energies for Scheme II systems.

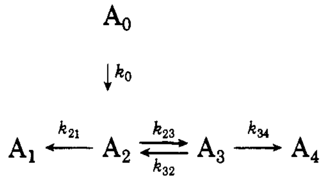
Conformational analysis soon found application in the field of photochemistry. Dauben,[21,178] Baldwin,[71] and Hammond[177] among others recognized that ground-state conformational effects could control organic photochemical reactivities. In the early 1970s, Lewis and his co-workers elegantly demonstrated in a quantitative fashion the value of the C–H principle to the understanding of reactivity of excited-state species.[22,183]

At this stage, one can divide the advancements of conformational analysis into two basic components: first, the recognition that for a molecule which exists in different conformations, each has its own unique physical and chemical properties; and second, the laws of chemical kinetics and mass balance, which had found so much utility in the analysis of the reactivity of molecules, could also be incorporated in the analysis of the various conformations of molecules. This logically leads into the next stage of development of C–H/W–H kinetics and quantitative conformational analysis: the application of these concepts to more complex chemical mechanisms.

For example, the chemical reactions which appeared in Curtin's earliest works[1,11,12] which incorporate the C–H principle do *not* fit into Scheme II kinetics, the reaction sequence for which the C–H principle was derived. The "feed-in" mechanism (Scheme IV) discussed in section VII more accurately matches the chemistry of Curtin's early studies. Martin and Bentrude subsequently analyzed the mechanism of the deamination of $\beta$-amino alcohols in terms of Scheme IV kinetics and concluded that the rates of interconversion between reactive conformations was competitive with their rates of reaction.[131] Reviewing this work, Eliel concluded that

> deamination of amino alcohols of the type $ArAr'COHCH(NH_2)R$ [is] neither...one in which the activation energy is high compared with the rotational barrier (and to which the Curtin-Hammett principle applies) and the other in which the activation energy is much lower than the barrier (where product composition reflects on population of the ground-state conformations). Rather, this particular reaction occupies an intermediate position where the reaction studied and rotation are about equally fast.[5]

**SCHEME IV**



$$\begin{tikzcd} & A_0 \arrow[d, "k_0"] & & \\ A_1 & A_2 \arrow[l, "k_{21}"'] \arrow[r, shift left, "k_{23}"] & A_3 \arrow[l, shift left, "k_{32}"] \arrow[r, "k_{34}"] & A_4 \end{tikzcd}$$

Some of the important consequences of the C–H principle and the W–H equation were retarded by the compartmentalization of these concepts which resulted from the very fashion that they were introduced and initially put to use. Consider that the C–H principle was intended to demonstrate that ground-state distribution in rapidly interconverting conformations was unrelated to product composition. The net consequence of this well-accepted and valid interpretation, described by eq 13, led to resistance of the equally valid use of eq 7. Consider that the W–H equation was developed

$$\frac{[A_4]}{[A_1]} = K\,\frac{k_{34}}{k_{21}} \tag{7}$$

$$\frac{[A_4]}{[A_1]} = e^{-\Delta G_{TS}^{\ddagger}/RT} \tag{13}$$

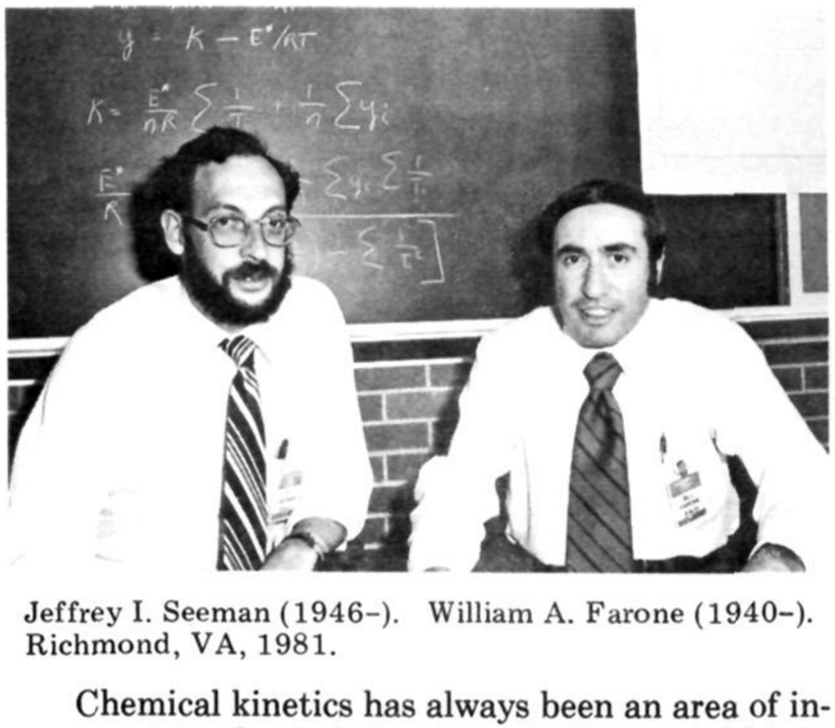
for Scheme II when $k_{21}, k_{34} << k_{23}, k_{32}$ and $[A_4]_0 = [A_1]_0 = 0$

as a kinetic method of conformational analysis. When distinct limitations to this use became apparent, the W–H equation was set aside—even though it remained valid for all Scheme II systems (only the use of models for $k_{21}$ and $k_{34}$, $k_{ax}$ and $k_{eq}$, were sometimes invalid).

In 1966, Katritzky and his colleagues mathematically combined the C–H/W–H equations so that they could solve for the values of the individual conformation's reaction rate constants.[25] This fundamental step forward was later characterized by McKenna as an "extremely difficult task",[300] not because of any complexity in the mathematical analysis but because an alternative procedure was necessary "to determine satisfactorily...the appropriate base–conformer equilibrium constant in tertiary piperidines."[300] Further studies along these lines including an error analysis discussion were later reported by Seeman et al.[26] who were also beset with the difficulty of determining the invertomer ratio of cyclic tertiary amines.

The Martin–Bentrude analysis[131] referred to above was accomplished by use of the steady-state analysis for the requisite mechanism. While such an application is usually an approximation, in this case it resulted, unbeknown to the authors, in an exact solution at reaction completion, as demonstrated when the exact analytical solution to Scheme IV kinetics became available. In 1960, Lewis and Johnson analyzed "The Reactions of *p*-Phenylene-bis-diazonium Ion with Water" using the exact analytical solution to a symmetrical C–H/W–H Scheme ($A_1 \leftarrow A_2 \rightleftarrows A_3 \rightarrow A_1$).[197] It rapidly became evident that many organic chemical reactions had to be characterized by mechanisms more complicated than the C–H/W–H Scheme II. This led to the evident conclusion that while the C–H/W–H concepts could often reveal qualitative features regarding these more complex systems, they were insufficient for quantitative analyses.

Mathematical knowledge has long been available to produce exact analytical solutions for any set of first-order reactions, or second-order reactions that can be treated as pseudofirst order.[193,240] Unfortunately, knowing that a solution is theoretically available and obtaining it in closed form can often be a chore, especially for those who are steeped in mechanistic organic chemistry rather than mathematical analysis. Farone, who together with Seeman has analyzed a number of C–H/W–H systems, commented:



Jeffrey I. Seeman (1946–). William A. Farone (1940–). Richmond, VA, 1981.

> Chemical kinetics has always been an area of interest to physical chemists who like to dabble in applied mathematics. Since I fall into this category, it should be no surprise that I developed an interest in the Curtin–Hammett/Winstein–Holness problem. The problem is a clear example of the application of standard mathematical techniques to help provide insight into, what can be, some rather nonstandard chemistry. The general philosophy of using mathematical models to explore chemistry requires much further work. The objective is to be able to think about reactions in quantifiable terms with defined assumptions and conditions. The discipline of thought required to do this represents an important joint effort between chemist and applied mathematician.[301]

Computer technology certainly encouraged chemists to apply complex mathematical solutions to chemical problems. Nonetheless, there remained barriers for organic chemists to obtain exact analytical solutions for their kinetic schemes. Rather, numerical methods were often applied; this approach had the advantage that standard computer programs were available which could readily be modified for the mechanisms of interest. The major difficulty in numerical methods is of course their approximate nature, though by judicious and meticulous computer techniques, roundoff errors can be minimized and often even estimated.

There are numerous examples in the literature of the use of numerical methods to derive time–concentration data for complex reaction mechanisms. Perhaps the most notable is the series of publications of Gajewski involving the thermochemistry of interconverting isomeric species.[227] Others involved in similar applications include von E. Doering,[228] Berson,[302] and Saunders,[303] the latter often being cited for supplying the computer programs to other investigators.[109,228]

The application of these mathematical procedures to the parent C–H/W–H Scheme II lagged far behind. This situation parallels the development of conformational analysis itself: a void is apparent, results are considerably late in developing, but all at once, a flow of important contributions appear. Within a few months in 1977, three independent groups, Zefirov in Moscow,[23] Lluch in Barcelona,[108] and Seeman and Farone in the United States,[24] had simultaneously examined the limitations of the C–H/W–H concepts proposed 25 years earlier.

There was no technological reason for this delay, as all three groups used rather well-established mathematical procedures. Zefirov published the exact solution at reaction completion to the C–H/W–H Scheme II.[23] This was followed shortly thereafter by Seeman and Farone's publication and detailed utilization of the exact analytical solution to Scheme II.[24] In these two publications, one goal was the determination of the conditions under which the C–H principle applied; i.e., the C–H principle is valid only when the rates of isomer interconversion *are greater than* the rates of isomer reaction. Having in hand the exact analytical solution, Zefirov, Seeman, and Farone were able to quantify precisely the "are greater than" in the C–H definition.

Seeman and Farone had become interested in the C–H principle because of its application to the chemistry of nicotine and related tobacco alkaloids they were investigating.[26,83,304] Zefirov, on the other hand, had noticed that of the many publications dealing with conformational analysis, most seem to be concerned with the determination of ground-state equilibrium distributions rather than conformer reactivity. Zefirov has summarized his involvement:

> I have published the general paper entitled "Conformational Analysis" in *Zh. Vses. Khim. Ova.* where I tried to present my general view on

Nikolai S. Zeferov (1935–). "At last I have made a picture of my face in my lab. In "equation" time I have been younger and hence better. Hope not so much." Moscow, April 1981.

> the status of conformational analysis. The focus had been on the dynamics of nonreacting molecules and later I transformed these ideas into a review. However, thinking during the writing of the first paper I recognized that the problem of dynamics of molecules and its relation with reactivity is spectacularly badly solved. Hence, of 12 full pages of review only one page concerned reactivity problems (C–H, etc). Fortunately enough, I was invited by Dr. O. Achmatowicz to give a lecture in Poland at our stereochemical school; there I received free time to think and to discuss this problem. The result was evident: the problem was solved (in the form of the first *Tetrahedron* paper) in 3 days. Another good luck; my co-worker Dr. Palulin had been free enough to help me in analytical solving this problem... My plans have been and are directed mainly toward bimolecular problems. I feel that it is of importance not only in conformational analysis but in general mechanistic organic chemistry, say in ion-pairing phenomenon, etc.[305]

Some investigators with a particular penchant toward the use of mathematical models for the solution of chemical problems have continued to extend the original C–H/W–H schemes. Included in this area are Farone, Seeman, and Zefirov. "Now Dr. Palylin and I are writing some sort of (review?) article", writes Zefirov, "where we should like to present the full "cross" equation [section IXB4 and Scheme XXIII] without restrictions, and than to trace all particular cases. In our intent it must be "logical" but not "historical". One of the goals is the acquaintance of the chemical community in my country with that interesting problem."[299]

Perhaps the most important interdisciplinary aspect of Curtin–Hammett kinetics involves the impact of conformational analysis in biological systems. Many studies have been published in recent years which attempt to determine the role of conformations on the pharmacological properties of important biologically active molecules. The most conclusive results from these investigations often come from studies of molecules that are conformationally restricted to particular geometries. Yet, such studies do not clarify the impact of conformational freedom on pharmacological activity more than the original studies of Barton in the 1950s on the chemistry of conformationally fixed systems clarified the chemistry of conformationally mobile systems.

Unfortunately, the complexities of the kinetics relevant to biologic systems have left the challenge of conformational effects rather open at this time. As McKenna has observed:

> For years, I have been criticising authors whose papers I have been sent to referee, when it seemed to me that they have been overly concerned about the detailed reactant state conformations of biologically active organic compounds. The question I always posed, as referee, was: what about the conformations of *competitive transition states* in the reactions of biological interest? I never got any satisfactory feedback, but I notice that programmes are beginning to come on the market now permitting displays on graphics terminals of the energetics (potential energy only, however!) of the interaction of mobile systems with putative receptor sites.[306]

Compared to the 1950s, chemists 30 years later are successfully and frequently dealing with more complex molecules, reactions, and mechanisms. These require spectroscopic and other techniques more sophisticated and more sensitive than ever before in addition to mathematical manipulations automated by extraordinarily powerful computers. The molecular mechanics approach of Westheimer[274] of the 1950s has been augmented, enhanced, and supported by a variety of semiempirical algorithms, modern force fields, and ab initio programs. These advancements not only have allowed chemists to solve the challenges of the 1980s, but they have also created the challenges of the 1980s. Chemistry, and science in general, has benefited and will continue to benefit from the multidisciplinary approach to problem definition and problem solving.

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Eliel *began* his *1960* review of "Conformational Analysis in Mobile Systems" with a definition of the term "conformation".[67] In a footnote, Eliel stated:

> If the reader is not familiar with the basis of conformational analysis, it is strongly suggested to him that, rather than continue reading the present article, he turn to one of the reviews for background information... Even if the reader, after reading the above reviews, does not find the time to return to the present article, the author feels that he has performed a worthwhile service by attracting the reader to this important field.[67]

Eliel *concluded* his *1975* review of "Conformational Analysis—The Last 25 Years" with the observation that "we have never defined the term "conformation"...for there is still no generally accepted definition of what conformation is".[56]

This juxtaposition of quotes from two review articles written some 15 years apart by the same author highlights the needs of a developing field to a body of researchers. In the early 1960s, conformational analysis was a relatively new field, especially to those chemists educated 10 years earlier who carried with them little intuition regarding the three dimensional characteristics of organic molecules. A definition of the term "conformation" was needed as the basis for progress. By the mid-1970s, a significant framework of knowledge in the field of conformational analysis was in hand. The thoughtful scholar was then in a position to place emphasis on the subtleties of the field. For example, if conformational isomers are distinguished from configurational isomers based on a criterion of "rotation about single bonds", how does one treat hindered rotation: what energy barrier and/or bond order does one (arbitrarily?) choose to categorize one set of species as conformational isomers and another as configurational isomers?

Recently, some controversy has occurred regarding another definition, that of the Curtin–Hammett principle itself. In 1979, a provisional definition of the C–H principle was advanced by the IUPAC Commission on Physical Organic Chemistry as part of a "Glossary of Terms Used in Physical Organic Chemistry".[35] This definition included the potentially misleading phrase "the product composition does not depend on the relative proportions of the conformational isomers in the substrate..."[35] which is typical of the C–H definition found in texts and in the literature. It failed to consider the alternative and equivalent expression illustrated by eq 7 in which product composition is shown to be directly dependent on both the ground-state equilibrium distribution of conformational isomers *and* their respective reaction rate constants.

The question concerning the most complete and usable definition of the C–H principle was subsequently the subject of a number of communications over a 2 year period between Seeman and Professor V. Gold, editor and compiler of the IUPAC commission preparing the "Glossary". In May, 1982, Gold wrote:

> I think that I am in complete agreement with your [Seeman's] scientific interpretation of the Curtin–Hammett principle. The problem that faces us is the more trivial (though more human) one of correct attribution. I believe that the version accepted by IUPAC (as yet still unpublished but approved for publication) correctly states the principle which Curtin and Hammett recognized (though it makes the underlying provisos more explicit). You correctly point out that the statement can be misinterpreted, and—speaking for myself—I would be inclined to recommend the introduction in the Glossary of a cautionary note to that effect. However, it would seem to be wrong to attribute those reservations to Curtin and Hammett.[307]

In August 1982, Gold indicated that "my colleagues on Commission III.2 of IUPAC agreed"[36] to a new definition of the C–H principle which is included in Section III.C.1 of this review. Receipt of this revision is quite timely, given that this review was in its final draft nearly 30 years after the initial presentation of the C–H principle.

It has been many years since the revolution in chemical thinking which led to the application of conformational analysis to almost all areas of organic chemistry. In spite of the possible absence of a commonly accepted definition of "conformation" and ambiguities regarding the definition of the earliest principle dealing with the reactivity of conformations, it is clear that chemistry is now better understood and better defined because of conformational analysis.

In 1954, Barton said: "It pays to speculate as widely and wildly as possible; people only remember when you are right!"[308] Given today's knowledge of chemistry, one might question if Barton in 1950 was indeed speculating when he ushered in the field of conformational analysis.

## XII. Acknowledgments

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(4) Throughout this paper, $[A_i]$ represents the concentration of $A_i$, the *i*th chemical entity which reacts with rate constant $k_{ij}$ in the reaction $A_i \rightarrow A_j$. $[A_i]_0$ and $[A_i]_\infty$ represent the initial and final concentrations of $A_i$, respectively. $\Delta G_{ij}^*$ represents the free energy of activation for the $A_i \rightarrow A_j$ transformation. $[A_i]/[A_j]_\infty$ represents the ratio of the concentrations of $A_i$ and $A_j$ at infinite reaction time, i.e., at reaction completion.

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(278) (a) The situation is actually more complex than Eliel indicates. The conformational distribution of neomenthol is very much biased toward IV. The low reactivity of neomenthol (IV $\rightleftarrows$ IVa) is due to two factors: (i) the predominant isomer IV is esterified extremely slowly, because the hydroxy group is axial; and (ii) the equatorial hydroxy group of IVa has a large esterification rate constant *but* its mole fraction is very small, leading to a low *rate* of esterification. Neoisomenthol is esterified more rapidly than neomenthol because IIIa is highly populated *and* has a large esterification rate constant. Eliel suggested that neomenthol was esterified only in its equatorial hydroxy conformation IVa. Winstein and Holness, in footnote 56 of their classic 1955 paper,[8] contradict Eliel's conclusion and suggest that neomenthol "reacts negligibly in the equatorial modification".[8] It is likely that neomenthol reacts competitively from *both* IV and IVa.[278b] (b) Conclusion reached by E. L. Eliel and this author, Aug 31, 1982.

(279) (a) Indeed, in Hanack's 1965 authoritative text,[39e] he apparently accepted Fodor's mid-1950s conclusion[39e,279b,c] regarding the orientation of the *N*-methyl group in tropanes. Hanack wrote: "It could be shown that in the formation of a quaternary salt from a tropane derivative, the substituent added to the nitrogen last was situated over the pyrrolidine ring. From the steric course of the quaternization, it may be concluded that the methyl group in tropane exists preferably in the position axial, relative to the piperidine ring."[3d] (b) Fodor, G. *Acta Chim. Acad. Sci. Hung.* **1955**, *5*, 379–442. *Chem. Abstr.* **1955**, *49*, 11673b. (c) Fodor, G. *Bull. Soc. Chim. Fr.* **1956**, 1032–1039.

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