The Curtin-Hammett Principle and the Winstein-Holness Equation

New Definition and Recent Extensions to Classical Concepts

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One measure of value of a scientific principle is its frequency and scope of usage. Concepts are frequently developed for specific applications. It will be argued for the cases discussed herein, and perhaps more generally, that the original applications of a particular theory can serve unwittingly as an unfortunate limitation: the full development of the theory may be impeded if the theory is "locked into" its original application by a unidirectional mindset of potential users.

The simplest kinetic system which exemplifies the effect of conformation on chemical reactivity is shown in eqn. (1). Here, two different conformations A_2 and A_3 of the same molecule react with rate constants k_{21} and k_{34}, respectively, to give two different products, A_1 and A_4. One can easily envision extensions of eqn. (1) to more complex situations involving conformations, some (or all) of which react to form one or more products. A significant variable is the magnitude of the rate constants for conformational interconversion k_c (k_{23} and k_{32} in eqn. (1) relative to the rate constants for reactivity k_r (k_{21} and k_{34}). Because the rates of conformational interconversion are generally, though not invariably, larger than their rates of chemical reactivity, (*1*), we shall limit ourselves in this and the next four sections below to the Curtin-Hammett/Winstein-Holness conditions, namely $k_c \gg k_r$ ($k_{23}, k_{32} \gg k_{21}, k_{34}$ in eqn. (1).

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftarrows}} A_3 \xrightarrow{k_{34}} A_4 \qquad (1)$$

$$K = \frac{k_{23}}{k_{32}}$$

For C-H/W-H applications $k_{23}, k_{32} \gg k_{21}, k_{34}$.

Equation (1) has three experimentally measurable parameters associated with it: the equilibrium distribution of A_2 and A_3, i.e., $[A_3]/[A_2] = K$; the product ratio, $[A_4]/[A_1]$; and the total, empirical reaction rate constants, $k_{W\text{-}H}$. Under the C-H/W-H conditions, $[A_3]/[A_2]$ is time invariant. Hence, K may be determined in the absence of chemical reactivity, i.e., under conditions where A_1 and A_4 are not being produced. The product ratio can be determined at reaction completion *or* at any time during product formation, since the product distribution is time invariant for any system in which the rates of conformer interconversion are much faster than the rates of product formation. The empirical reaction rate constant $k_{W\text{-}H}$ is experimentally determined *as if* the kinetic system were simply one compound reacting to form a second compound with rate constant $k_{W\text{-}H}$. This last point will be discussed in more deatil in the section on the Winstein-Holness equation below.

A thorough knowledge of the properties of eqn. (1) kinetics should then serve two important purposes: (1) we will be able to analyze the many chemical mechanisms which are described by eqn. (1); and (2) we can use eqn. (1) interpretations as the basis for the evaluation of more complex kinetics systems alluded to above.

Barton's classic 1950 paper (*2*) on stereochemistry and conformational analysis led the way to the formulation of two concepts (*3–5*) that provided the first quantitative relationships between conformations and their chemical reactivity. These are the Curtin-Hammett principle and the Winstein-Holness equation. Importantly, these two principles treated the same kinetic system, namely eqn. (1).

The Curtin-Hammett Principle

The Curtin-Hammet (C-H) principle (*1*, *3*, *6*) was proposed in the early 1950's to alert chemists to the error of directly equating the ground state equilibrium distribution of a mobile system ($K = k_{23}/k_{32} = \exp(-\Delta G°/RT)$ in eqn (1) to the product distribution $[A_4]/[A_1]$ (eqn. 2). In fact, the

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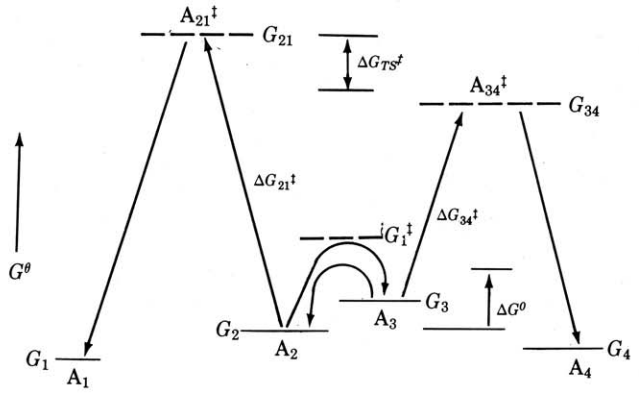


Figure 1. Illustration of an eqn. (1) system where k_{23}, $k_{32} \gg k_{21}$, k_{34} and where the less stable conformation (A_3) reacts via the more stable ($G_{34} < G_{21}$) transition state. In this figure, no significance is placed regarding the horizontal separation of the various states. The transition states are represented by dashed horizontal lines, to distinguish them from real chemical compounds which are represented by solid lines. Note that the free energy G° is not drawn as a continuous function of the reaction coordinate.

original statement of the principle was essentially repeated in numerous definitive texts and reviews (*7, 11*) as well as in the provisional version of the "Glossary of Terms in Physical Organic Chemistry" (*12*) and by the I.U.P.A.C. Commission on Physical Organic Chemistry in 1979:

> the relative amounts of product 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. (*12*)

In terms of Figure 1, the product ratio is given by eqn. (3), in which K, the ground state equilibrium distribution, does *not* appear explicitly. $\Delta G_{TS}^{\ddagger}$ is simply the difference in Gibbs free energy of the two transition states leading to products A_4 and A_1.

$$\frac{[A_4]}{[A_1]} \neq K \tag{2}$$

$$\frac{[A_4]}{[A_1]} = e^{-\Delta G_{TS}^{\ddagger}/RT} \tag{3}$$

It is worthwhile to consider a condensed derivation of eqn. (3) (*1, 3, 7, 8, 11,*). For eqn. (1),

$$\frac{d[A_1]}{dt} = k_{21}[A_2 \tag{4}$$

$$\frac{d[A_4]}{dt} = k_{34}[A_3 \tag{5}$$

Therefore, dividing eqn. (5) by eqn. (4) and integrating, we obtain

$$\frac{[A_4]}{[A_1]} = \frac{[A_3]}{[A_2]}\frac{k_{34}}{k_{21}} = K\frac{k_{34}}{k_{21}} \tag{6}$$

when $k_{23}, k_{32} \gg k_{21}, k_{34}$.

Substituting the well-known relationships eqns. (7–9) into eqn. (6),

$$K = e^{-\Delta G^{\circ}/RT} \tag{7}$$

$$k_{21} = ATe^{-\Delta G_{21}^{\ddagger}/RT} \tag{8}$$

$$k_{34} = ATe^{-\Delta G_{34}^{\ddagger}/RT} \tag{9}$$

we obtain the classical C-H expression, eqn. (3), where

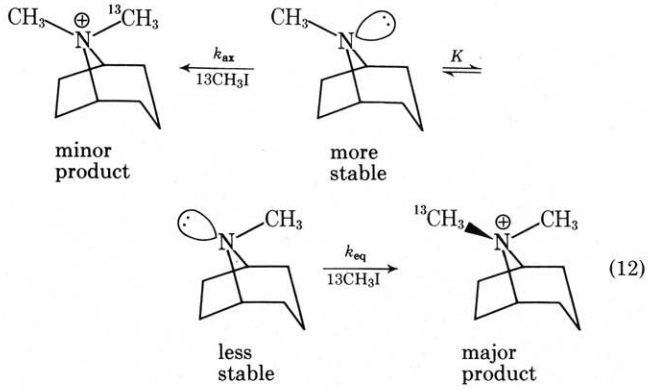
$$\Delta G_{TS}^{\ddagger} = \Delta G_{34}^{\ddagger} + \Delta G^{\circ} - \Delta G_{21}^{\ddagger} \tag{10}$$

(see Fig. 1).

At this stage, it is important to emphasize an important consequence of this derivation: the classical C-H expression embodied in eqn. (3) is based on the previous derivation of eqn. (4).

$$\frac{[A_4]}{[A_1]} = K\frac{k_{34}}{k_{21}} \Rightarrow e^{-\Delta G_{TS}^{\ddagger}/RT} \tag{11}$$

The C-H principle has been frequently used over the last 30 years as an aid to understanding the chemistry of eqn. (1) and eqn. (1)-like systems. The C-H principle succeeded in limiting the incorrect equating of product ratios with ground state equilibrium distributions. Further, it provided the basis for understanding why a major product can arise from a less stable minor conformation, the chemistry of tropane alkylations being the classic example (*13*) (eqn. (12)). Here, the transition state (TS) leading to equatorial alkylation (relative to the six-membered ring, k_{eq}) is more stable than the TS leading to axial alkylation (k_{ax}). This interesting and certainly not unique combination of rate constants is illustrated in Figure 1, where the *less* stable conformation reacts faster via the *more* stable transition state. Equation (12) provides an important example of the failure of ground state conformational distribution (K) to be equal to reaction product distribution ($[A_4]/[A_1]$) (c.f., eqn. (2)). The reader is referred to the recent comprehensive review (*1*) of the Curtin-Hammett principle or to *Science Citations Index* for additional uses and applications of the C-H concepts.

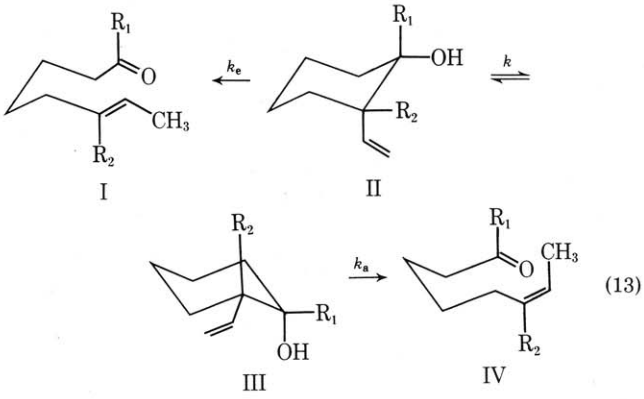


(12)

We now focus attention on chemical systems which have *not* been generally analyzed by the C-H principle. Perhaps because the C-H principle has classically been formulated in terms of an independence of product distribution from ground state conformational distribution (eqn. (3)), it has been little used with regard to its alternative, in fact, precursive form (eqn. (6)). While eqn. (3) has significant conceptual value and can be used for qualitative information and intuitive judgements, it does not provide much quantitative information, because the parameter $\Delta G_{TS}^{\ddagger}$ is a rather peculiar parameter. Free energy is not a measurable quantity as is for example, an equilibrium constant, and the difference in free energy of two transition state levels is even more vague as an experimental parameter. However, eqn. (6) precisely describes the relationship between product distribution and rate constants and an equilibrium constant, thereby offering a number of uses not available from eqn. (3).

Consider, for example, the product ratio for eqn. (13) chemistry (*14*). The literature report equates the ratio of rate constants k_a/k_e to the product ratio (*14*) while application of eqn. (6) indicates the correct relationship to be as shown in eqn. (14). Experimental determination of K or estimation of K by application of additivity of substituent

effects for substituted cyclohexanes (*15*) would then lead to the correct value for k_a/k_e.



(13)

$$\frac{[IV]}{[I]} = K\frac{k_a}{k_e} \Rightarrow \frac{k_a}{k_e} = K^{-1}\frac{[IV]}{[I]} \qquad (14)$$

For another utility, consider the consequences of Figure 2 chemistry which result from the use of different alkylating agents on the nicotine analog, 1-methyl-2-phenylpyrrolidine (V) (*16*). If we limited ourselves to the original C-H eqn. (3), then we would focus our attention solely on the portion of Figures 2A–D in which the transition state free energy levels are depicted. However, use of eqn. (6) brings together the complete free energy diagram, and we can now see the relationships between $\Delta G°$ for Vc ⇄ Vt and $\Delta G_{TS}^{\ddagger}$ for the four coupled reactions. A knowledge of the empirical reaction rate constants $k_{W\text{-}H}$ would allow the derivation of k_t and k_c in each case. This application is discussed in the section on the combined kinetic treatment below. The product ratios are experimentally measurable, and the conformational equilibrium constant is the same for each alkylation since the substrate V is constant. Thus, one could make the interesting comparison of the ratio of reaction rate constants as a function of alkylating agent.

In summary, the C-H principle can be appropriately used for a variety of chemical applications, some of which use the eqn. (3) formalism while others use the eqn. (6) formalism.

It is important to note that eqn. (6) conflicts with the original (*3, 7–11*) C-H definition, in that the product ratio *is directly dependent* on the relative populations of conformations. This seeming contradiction between eqn. (1) and eqn. (6) disappears when it is realized that $[A_4]/[A_1]$ is explicitly dependent on $\Delta G_{TS}^{\ddagger}$ which is itself implicitly dependent on K.[2] A definition which satisfactorily accounts for these arguments has more recently been proposed by the I.U.P.A.C. Commission on Physical Organic Chemistry (*19*).

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 formally related to the relative concentrations of the conformational isomers (i.e., the conformational equilibrium constant) and the

[2] This point was clearly stated almost simultaneously by Zefirov (*17*) and Seeman and Farone (*18*).

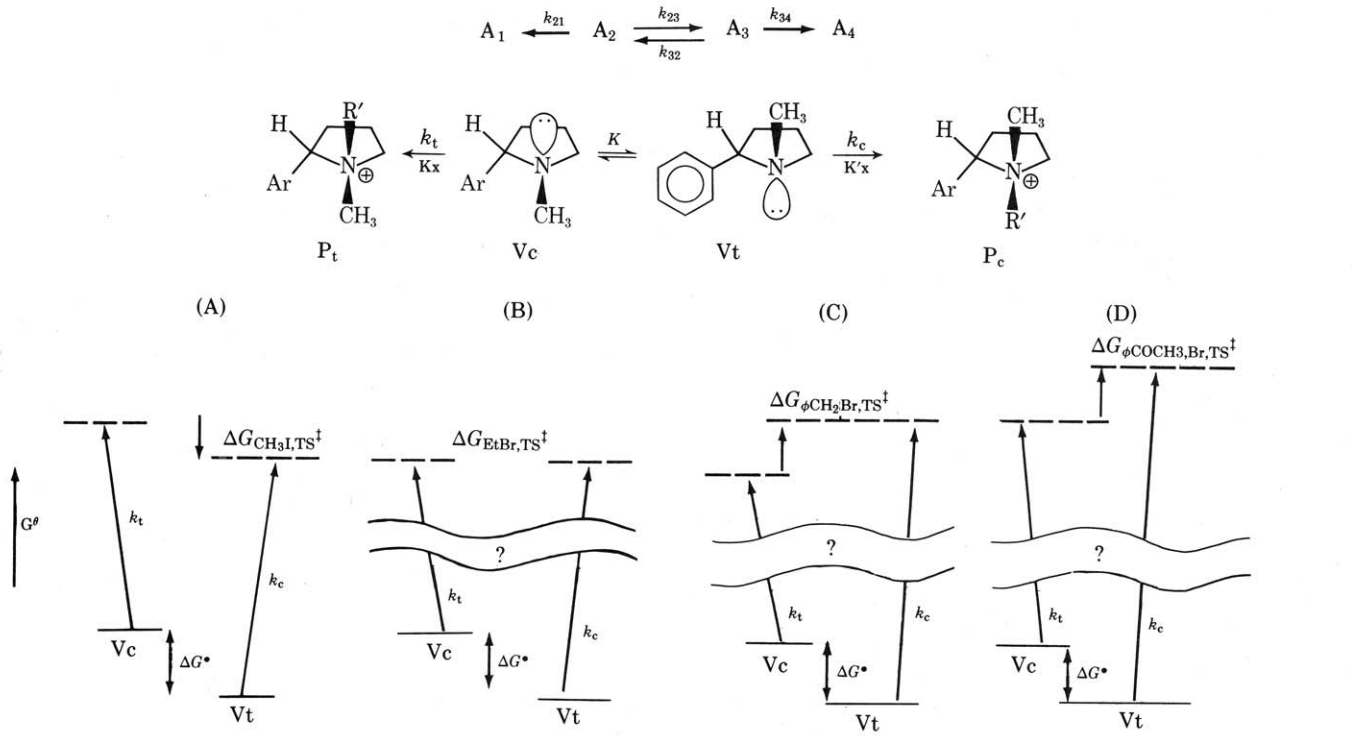


Figure 2. Free energy diagrams for the alkylation of Vc ⇄ Vt. (A) Methylation leads to a predominance of P_c. (B) Ethylation leads to an equal mixture of P_c and P_t; $\Delta_{EtBr,TS}^{\ddagger} = 0$. (C) Benzylation leads to a predominance of P_t. (D) Phenacylation leads to an even greater predominance of P_t than found for benzylation; $\Delta G^{\ddagger}_{PhCOCH_2Br,TS} > \Delta G^{\ddagger}_{PhCH_2Br,TS} > 0$. Free energy levels are not drawn to scale. For the purposes of comparing this figure with Figure 1, examine the two equations at the top ot this figure. It is useful to note that:

$$A_1 = P_T \quad A_3 = Vt \quad k_{21} = k_t$$
$$A_2 = Vc \quad A_4 = P_c \quad k_{34} = k_c$$

respective rate constants of their reactions: these parameters are generally—though not invariably—unknown (*19*).

A Direct Relationship Between Product Ratio and Conformer Distribution

The original definition (*3*, *7–11*) of the C-H principle (eqn. (1)) cited the *independence* of the product ratio from the conformer distribution (eqn. (3)). The more recent definition (*19*) claims that the product ratio is *related to both* the conformer distribution and the ratio of reaction rate constants (eqn. (6)). It has recently been claimed by Perrin and this author (*20*) that under conditions where linear free energy relationships obtain, i.e., where additivity of substituent effects occurs, the product ratio is *solely dependent* on the ground state equilibrium distribution (eqn. (15)). However, the product ratio dependence on the reaction rate constants is now transformed into a dependence on the parameter α. This alternative mathematical C-H relationship brings into focus additional aspects of eqn. (1) chemistry.

$$\frac{[A_4]}{[A_1]} = K^{1-\alpha} \tag{15}$$

Equation (15) makes intuitive sense from a chemical perspective. Consider Figure 2A. The conformational equilibrium distribution K is large (>1) because of a sizeable steric destabilization in Vc between the *cis*-N-methyl group and the aromatic ring, not present in Vt. Similarly, the ratio $k_{V\rightarrow P_c}/k_{Vc\rightarrow P_t}$ is small (<1) because the methyl iodide must approach trans to the aromatic ring in the Vc → P_t reaction but cis to the aromatic ring in the Vt → P_c reaction. There is thus a counterbalancing of steric effects, the factors which influence K to be large similarly cause $k_{V\rightarrow P_c}/k_{Vc\rightarrow P_t}$ to be small (*21*, *22*). This balancing of effects is indicated by eqn. (16), where α is a reaction-dependent parameter. In essence, α quantifies the net effect of substituents on $\Delta G°$ and $\Delta G_{TS}^{\ddagger}$. As illustrated in eqn. (17), eqn. (15) is derived from eqn. (16) and the Curtin-Hammett principle (eqn. (6)).[3]

$$\frac{k_{34}}{k_{21}} = K^{-\alpha} \tag{16}$$

$$\frac{[A_4]}{[A_1]} = K\frac{k_{34}}{k_{21}} \tag{17}$$

Under conditions where LFER are valid, eqn. (17) can be further reduced to

$$KK^{-\alpha} = K^{1-\alpha}$$

Inspection of Figure 2A indicates that for methylation $P_c/P_t = [A_4]/[A_1]>1$ which implies that α <1 (eqn. (15)). However, for the same conformationally mobile substrate Vc ⇄ Vt, Figures 2C and 2D indicate that for benzylation and phenacylation, $P_c/P_t = [A_4]/[A_1]<1$; in these latter cases, α >1. This change over in product ratio is a direct consequence of an increasing bulk of the alkylating reagent and of overall slower reactions to product (later transition state). In the former case, the iodomethane acts as if it were *smaller* than the methyl group already attached to the N-methylpyrrolidinyl moiety. For benzylation and phenacylation, the incoming group acts as a substantially *larger* moiety compared with the already bonded N-methyl group. This product ratio profile also serves as the theoretical underpinning of the methodology suggested by McKenna (*24*) for making stereochemical assignments of the diastereomeric products formed in quaternization of piperidines and other pyrrolidines.

The concepts embodied in eqn. (15) thus permit both the stereochemical assignments of the products formed in eqn. (1) reactions systems (e.g., Fig. 2) and also the estimation of equilibrium constants K from experimental product ratios (*20*). It is in this latter sense that the original intent of the Curtin-Hammett principle is seemingly contravened, though in fact the C-H principle is neither violated nor infringed.

The Winstein-Holness Equation

Developed simultaneously by Winstein and Holness (*4*) and Eliel and Ro (*5*), the Winstein-Holness (W-H) equation also deals with eqn. (1) chemistry. The total rate of product formation (eqn. (18)) follows directly for eqns. (4) and (5).

$$\frac{d[\text{Products}]}{dt} = \frac{d[A_1]}{dt} + \frac{d[A_4]}{dt} = k_{21}[A_2] + k_{34}[A_3 \tag{18}$$

We now *define* $k_{W\text{-}H}$ to be a total, empirical reaction rate constant (eqn. (19)). Note that $k_{W\text{-}H}$ is *not* a rate constant in the usual sense but is an empirical parameter defined for the two coupled reactions in eqn. (1) which lead to product.

$$\frac{d[\text{Products}]}{dt} = \frac{d[A_1]}{dt} + \frac{d[A_4]}{dt} \equiv k_{W\text{-}H}\{[A_2] + [A_3]\} \tag{19}$$

Combining eqns. (18) and (19),

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

and solving for $k_{W\text{-}H}$, we obtain eqn. (20)

$$k_{W\text{-}H} = k_{21}[A_2]/\{[A_2] + [A_3]\} + k_{34}[A_3]/\{[A_2] + [A_3]\} \tag{20}$$

Ultimately, we solve for $k_{W\text{-}H}$ (eqn. (21)).

$$k_{W\text{-}H} = \chi_2 k_{21} + \chi_3 k_{34} \tag{21}$$

where χ_i = mole fraction of the ith reactive conformation in eqn. (1).

A number of important consequences result from the C-H/W-H assumption, which states that the rate constants for conformational interconversion are much larger than for

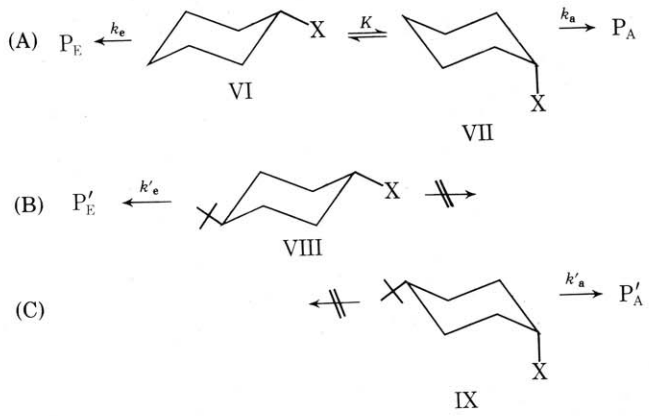


Figure 3. The use of conformationally fixed analog of conformationally mobile systems for the determination of ground state equilibrium distributions, known as the kinetic method of conformational analysis.

[3] It is interesting to note that we can easily derive from eqns. (7), (11), and (15)

$$\Delta G_{TS}^{\ddagger} = (1-\alpha)\,\Delta G°$$

This is a mathematical formulation of the intuitive "counterrelationship" embodied in eqn. (16). Furthermore, it is related to the familiar rate: equilibrium relationship (*23*)

$$\Delta\Delta G \sim \Delta\Delta G°$$

reaction, i.e., k_{23}, $k_{32} \gg k_{21}$, k_{34} (*16–18*). First, $[A_3]/[A_2]$ is constant during the course of an eqn. (1) reaction. This implies that both χ_2 and χ_3 are also constant during the reaction, which indicates that $k_{W\text{-}H}$ is also constant (see eqn. (21)). *Thus, while* $k_{W\text{-}H}$ *is not a reaction rate constant but an empirical rate constant, it nonetheless maintains a constant value and does not vary with time during the course of the reaction.* (This same conclusion can also be obtained by consideration of eqn. (22). Since K, k_{21}, and k_{34} are all constant when k_{23}, $k_{32} \gg k_{21}$, k_{34}, $k_{W\text{-}H}$ must also be time independent.)

The W-H equation was developed in the mid-1950's for one specific purpose, namely as a kinetic method of conformational analysis. At that time, there were few other methods by which one could experimentally determine the equilibrium distribution of a conformationally mobile system, quite in contrast to the current state of the art in which high field, low temperature and multinuclear magnetic resonance readily affords such determinations (*25*).

One of the major goals of conformational analysis is the quantitative determination of equilibrium distributions in conformationally mobile systems, e.g., eqn. (1). For an eqn. (1) system, one can solve for K in terms of k_{21}, k_{34}, and $k_{W\text{-}H}$ from eqn. (21), as shown in eqn. (22), keeping in mind the C-H/W-H requirement that k_{23}, $k_{32} \gg k_{21}$, k_{34}.

$$K = \frac{k_{21} - k_{W\text{-}H}}{k_{W\text{-}H} - k_{34}} \tag{22}$$

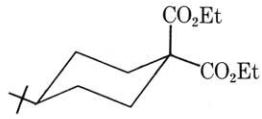
The basic idea behind the kinetic method of conformational analysis is illustrated in Figure 3. The goal is the determination of K for the monosubstituted cyclohexane VI $\rightleftarrows$ VII. We know from the above discussion that eqn. (22) is a valid mathematical formulation for K as long as k_{21}, $k_{34} \ll k_{23}$, k_{32}. Unfortunately, it is not possible to determine experimentally k_e and k_a, the reaction rate constants of VI and VII, directly from the reaction shown in Figure 3; only the empirical $k_{W\text{-}H}$ is experimentally obtainable. Thus, one cannot directly use eqn. (23). To circumvent this impediment required the following ingenious insight made in the early 1950's by Winstein and Holness (*4*) and Eliel and Ro (*5*).

$$K = \frac{k_e - k_{W\text{-}H}}{k_{W\text{-}H} - k_a} \tag{23}$$

The *tert*-butyl derivatives VIII and IX were prepared as conformationally rigid analogues of VI and VII, respectively. Because VIII and IX are fixed into the conformations shown, Winstein and Holness (*4*), Eliel and Ro (*5*), and other investigators (*1*) measured the rates of reaction of VIII and IX (k'_e and k'_a, respectively) and assumed that $k_e = k'_e$ and $k_a = k'_a$. By application of eqn. (24) which is analogous to eqn. (23), they then calculated K for Figure 3 systems.

$$K = \frac{k'_e - k_{W\text{-}H}}{k_{W\text{-}H} - k'_a} \tag{24}$$

The assumption that $k_e = k'_e$ and $k_a = k'_a$ is equivalent to assuming that VIII and IX are valid reactivity models for VI and VII, respectively. By the mid-1960's, it became clear from the work of a number of laboratories (*26, 27*) that this assumption is not always valid since the *tert*-butyl group, or other locking groups, could affect the geometry of the cyclohexane moiety and thereby render the ring-locked models invalid. McKenna subsequently provided strong evidence that when the reaction indicated in Figure 3 does *not* involve the ring atom (e.g., ester exchange in 4-*tert*-butyl diethyl cyclohexane dicarboxylate (X), there is no significant interference of the *tert*-butyl group on the rate constants of substituted cyclohexanes and the kinetic method of conformational analysis is accurate (*28, 29*).



X

Thus, the breakdown in the kinetic method of conformational analysis was not in the derivations of eqns. (22) and (23). Indeed, eqn. (22) is a valid mathematical expression for eqn. (1), just as eqn. (23) is valid for the reactions of unsubstituted cyclohexyl derivatives. Rather, for some model systems (e.g., Figure 3), eqn. (23) and eqn. (24) are *not* equivalent (eqn. (25)), since $k_e \nsim k'_e$ and $k_a \nsim k'_a$.

$$K = \frac{k_e - k_{W\text{-}H}}{k_{W\text{-}H} - k_a} \nsim \frac{k'_e - k_{W\text{-}H}}{k_{W\text{-}H} - k'_a} \tag{25}$$

Hence, the kinetic method of conformational analysis, the *raison d'être* for the W-H equation, became of minor utility for two reasons: first, lingering suspicions always remain concerning the limitations of the model systems; and second, modern methods of spectroscopic analysis are available which more simply and more directly allow for the experimental determination of conformational equilibrium constants.

Since the W-H equation had been used for only one purpose, and since that utility had become historically interesting but chemically obsolete, the W-H equation itself became little used. What is striking is that the W-H equation itself has been (incorrectly) assumed to be invalid by many workers for *any* application, rather than just the kinetic method application. In fact, *the W-H equation is a valid kinetic descriptor for eqn. (1) kinetics when* k_{23}, $k_{32} \gg k_{21}$, k_{34}. It is incorrect to conclude that the W-H equation is invalid because one of its applications is faulty (*1, 16, 17, 18*).

In contrast to a decline in utilization of the kinetic method of conformational analysis, analogous W-H relationships continue to be used for relating conformational equilibria with molecular properties *other than* chemical reactivity. In all cases, the property is described as the mole fraction-weighted sum of that property (P) for each of the conformations (eqn. (26)). Since eqn. (26) is analogous to the Winstein-Holness eqn. (21), and since $K = \chi_3/\chi_2$, one can solve for K and derive eqn. (27) which is analogous to eqn. (22). Such properties as NMR chemical shifts (eqn. (28)) and coupling constants (eqn. (29)), pK, dipole moment, ORD/CD, Kerr constant, and enthalpy are examples (*1*) of the utility of eqns. (26) and (27). We note that the continuing application of eqns. (26)–(29) can frequently suffer the same criticism as that levied on the kinetic method of conformational analyses, namely the reliance on conformationally fixed models for approximated values of P_1 and P_2.

$$P = \sum \chi_i P_I \tag{26}$$

where χ_i = mole fraction of the ith conformation.

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

where

$$P_{obsd} = \chi_1 P_1 + \chi_2 P_2 \tag{27}$$

$$K = \frac{\delta_1 - \delta_{obsd}}{\delta_{obsd} - \delta_2}$$

where

$$\delta_{obsd} = \chi_1 \delta_1 + \chi_2 \delta_2 \tag{28}$$

$$K = \frac{J_1 - J_{obsd}}{J_{obsd} - J_2}$$

where $$J_{obsd} = \chi_1 J_1 + \chi_2 J_2 \quad (29)$$

One might conclude from examination of the literature that "the Winstein-Holness equation is wrong or at best grossly approximate." This conclusion is false. Perhaps the strongest counter is to establish a single valid utilization of the W-H expression. We cite three. 1) The studies of McKenna (*28*, *29*) illustrate (some of the few) examples of the valid application of the kinetic method of conformational analysis. 2) Application of eqns. (26)–(29) and similar expressions for conformational analysis are widespread. 3) The combined C-H/W-H kinetic treatment has been used for the derivation of k_{21} and k_{34} (eqn. (1)), using a value of K determined in an alternative fashion (see next section) (*16*, *31*, *32*). We conclude, therefore, that the W-H equation has a number of growing, valid applications.

The Ultimate in C-H/W-H Utility: A Combined Kinetic Treatment

Perhaps the ultimate experimental challenge relating to eqn. (1) is the determination of the individual reaction rate constants, k_{21} and k_{34}. As the C-H principle (eqn. (5)) and the W-H equation (eqn. (21)) both relate to eqn. (1) kinetics, the former to product ratio and the latter to rate of total product formation, it is a rather simple matter (in theory) to combine the two and solve for k_{21} and k_{34}. The results of this mathematical synthesis and minor algebraic modifications are shown in eqns. (24) and (25).

For eqn. (1) $k_{23}, k_{32} \gg k_{21}, k_{34}$):

$$k_{21} = k_{W\text{-}H}\,((K+1)/(P+1)) \quad (30)$$

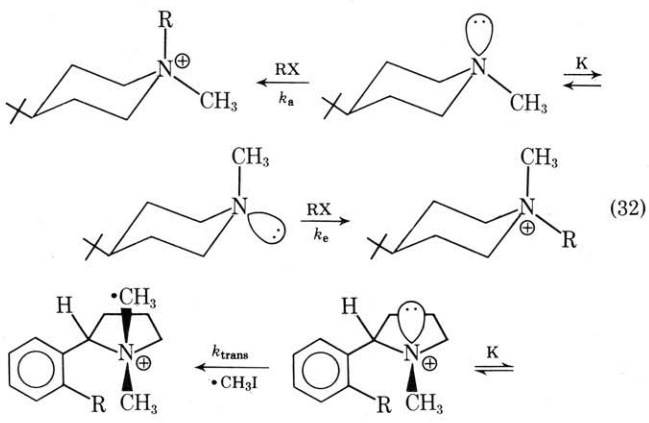
$$k_{34} = k_{W\text{-}H}\,((K+1)/K][P/(P+1)) \quad (31)$$

where

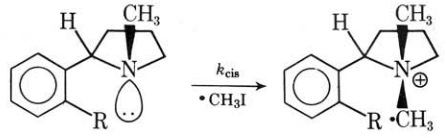
$$P \equiv [A_4]/[A_1]$$

Note that k_{21} and k_{34} are solved in terms of the empirical W-H rate constant $k_{W\text{-}H}$, the conformer equilibrium distribution K, and the product ratio $[A_4]/[A_1]$. As these three parameters are, at least in principle, capable of being determined experimentally, the combined usage of the C-H principle and the W-H equation leads to the solution of the most informative chemical goal of conformational analysis: the reaction rate constants of each conformation.

This fundamental step forward in C-H/W-H thinking, characterized by McKenna as an "extremely difficult [experimental] task"(*30*), was first achieved by Katritzky and his group (*31*, *32*) and later studied in more detail by the present author and his collaborators (*16*). Katritzky et al. were interested in establishing stereochemistry of piperidine alkylations (*31*, *32*) (eqn. (32)) while we (*16*) evaluated the effect of various conformational processes on chemical reactivity (eqn. (33)). In both cases, the ultimate goal of calculating the reaction rate constants of the predominant conformations (k_a and k_e in eqn. (32) and k_{trans} and k_{cis} in eqn. (33) was achieved (*16*, *31*, *32*).[4]



(32)



(33)

Extensions of the C-H/W-H Concepts

Thus far, we have specifically limited ourselves to chemical examples in which the rates of conformational interconversion are much faster than the rates of chemical reaction, i.e., $k_{23}, k_{32} \gg k_{21}, k_{34}$. This is a very reasonable condition, since most conformational processes are faster than chemical reactions (*1*, *7*, *8*, *10*, *11*). Of course, the restrictions on the basis of which eqns. (3), (6), (11), (15), (21), and (22) were derived are not always experimentally valid. What happens when $k_{23}, k_{32}, \sim k_{21}, k_{34}$ or when $k_{23}, k_{32} \ll k_{34}, k_{21}$?

As both the C-H principle and the W-H equation were derived under the assumption of fast conformational interconversions/slow chemical reactions, the C-H/W-H principles are clearly valid *only* when this assumption is valid. Zefirov (*17*) in 1977 advanced an exact solution for the product ratio $[A_4]/[A_1]_\infty$ for eqn. (1) at reaction completion for any set of rate constants k_{ij} (i,j = 1–4). Seeman and Farone (*18*) shortly thereafter published the exact, analytical solution to eqn. (1) for any set of k_{ij}. These mathematical treatments not only verified the C-H/W-H expressions (eqns. (3), (6), (11), (15), (21), and (22)) but also 1) showed that the C-H/W-H equations were valid as long as $k_{23}, k_{32} \gtrsim 10k_{21}, 10k_{34}$; and 2) allowed the analysis of chemical systems in which the C-H/W-H assumption was not operative. As this extension is outside the scope of the present article, the reader is referred to the original literature (*17*, *18*) and the detailed review (*1*) of the subject.

In the last few years, important insight into the reactivity of conformational isomers has been obtained under conditions in which the rates of chemical reaction were significantly faster than the rates of conformational interconversion. In some cases, one of two conformations of a particular molecule reacts much faster than the other conformation; under this set of constraints, at "reaction completion," the material isolated contains 1) the product from the more reactive conformation, and 2) the unreacted, less reactive conformational isomer. For an excellent and very recent discussion of eqn. (1) (and eqn. (34)) chemistry when k_{21} (k_{34}) > k_{23}, k_{32}, see the review by Oki (*35*).

Equations (34) and (35) illustrate the nature of more complex extensions to the basic C-H/W-H eqn. (1). Equation (34) refers to a system in which the reactions to product are bimolecular, involving a reagent, R. Of course, under pseudo-first-order conditions (i.e., when $[R]_0 \gg \{[A_2]_0 + [A_3]_0\}$, where the subscript 0 refers to the initial t = 0 concentrations), eqns. (1) and (34) are "in practice" identical. However, pseudo-first-order conditions are not always operative. A full discussion of eqn. (34) chemistry is now available (*1*, *33*).

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

$$\begin{array}{c} A_o \\ \downarrow k_o \end{array}$$

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftarrows}} A_3 \xrightarrow{k_{34}} A_4 \quad (35)$$

[4] The determination of k_{21} and k_{34} requires the experimental determination of $k_{W\text{-}H}$, K, and P (eqns. (30) and (31)). As these three parameters are generally not determined under the same experimental conditions, their combined usage is a verifiable assumption of the technique.

Equation (35) illustrates a C-H system in which all material is funneled into the equilibrating system $A_2 \rightleftarrows A_3$ via A_0 (*1*). There are many examples of eqn. (35) chemistry, including some of the systems first treated in the early 1950's by Curtin (*3, 6*) and used in his initial pronouncements of what was later to be called the C-H principle.

One can readily see that many extensions to the basic eqn. (1) system can be formulated. A basic understanding of eqns. (1), (34), and (35) will provide the fundamental insight to many of these more complex mechanisms.

Conclusions

In their authoritative treatise "Conformational Analysis," Eliel, Allinger, Angyal, and Morrison (*34*) conclude that , "Conformational effects on reactivity may be understood in terms of two now well-recognized relationships," the Curtin-Hammett principle and the Winstein-Holness equation. The C-H principle was designed to place a conceptual barrier between ground state conformational populations and product compositions. It was formulated in terms of eqn. (3). That initial concept, as important as it was in the 1950's and as important as it continues to be in the 1980's, impeded other useful and equally valid consequences of the C-H principle that are now being advanced. The W-H equation was designed to calculate conformer equilibrium distributions by use of the kinetic method of conformational analysis. It was abandoned largely because of the development of modern spectroscopic methods which could more easily and more reliably serve that initial application. Nonetheless, because the W-H equation is a valid kinetic description for the reactivity of conformationally mobile systems, it has valuable utilities far exceeding its initial application.

With regard to the development of conformational analysis, we note that some of the reviews of conformational analysis discuss one but not both of these two fundamental principles. Further, of those texts or reviews which discuss both the C-H principle and the W-H equation, always within the same section, not one has melded them together as achieved in the derivation of eqns. (30) and (31). These are further manifestations of the hypothesis mentioned at the outset of this article, namely that the original specific applications of both the C—H principle and the W-H equation placed an inherent barrier to their extensions and to their combination into more powerful formalisms.

We have briefly demonstrated herein that the C-H principle and the W-H equation have values far exceeding those originally intended. Worthy of note are the small but hopefully influential number of cases in the literature (*1*) which have taken advantage of the extended capabilities of both the C—H principle and the W-H equation. We look forward to additional applications and extensions of both of these concepts. Further, we urge future authors of reviews[5] and textbooks to follow the lead of the I.U.P.A.C. Commission on Physical Organic Chemistry (*19*) and incorporate the more modern definition of these concepts.

[5] For a very recent example of the acceptance of the herein recommedned definition of the C-H principle, see ref. (*35*).

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Literature Cited

(1) See the comprehensive review on Curtin-Hammett/Winstein-Holness kinetics: Seeman, J. I., *Chem. Rev.*, **83,** 83 (1983).
(2) Barton, D. H. R., *Experientia*, **6,** 316 (1950).
(3) Curtin, D. Y., *Rec. Chem. Prog.*, **15,** 111 (1954).
(4) Winstein, S., and Holness, N. J., *J Amer. Chem. Soc.*, **77,** 5562 (1955).
(5) Eliel, E. L., and Ro, R. S., *Chem. Ind.*, 251 (1956).
(6) Pollak, P. I., and Curtin, D. Y., *J. Amer. Chem. Soc.*, **72,** 961 (1950).
(7) Eliel, E. L., "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, **1962,** pp. 149–156, 234–239.
(8) Hammett, L. P., "Physical Organic Chemistry," McGraw-Hill, New York, **1970,** Chap. 5.
(9) Eliel, E. L., Allinger, N., Angyal, S. J. and Morrison, G. A., "Conformational Analysis," Wiley, New York, **1965.**
(10) Leffler, J. E. and Grunwald, E., "Rates and Equilibria of Organic Reactions as Treated by Statistical, Thermodynamic, and Extra-thermodynamic Methods," Wiley, New York, **1963,** pp. 119–120.
(11) Dauben, W. G., and Pitzer, K. S., *in* "Steric Effects in Organic Chemistry," (*Editor:* Newman, M. S.), Wiley, New York, **1956,** Chap. 1.
(12) Gold, V., *Pure Appl. Chem.*, **51,** 1725 (1979).
(13) For reviews of this subject and pertinent references, see: Fodor, G., Frehel, D., Cooper, M. J., and Mandava, N., *in* "Conformational Analysis," (*Editor:* Chiurdoglu, G.), Academic Press, New York, **1971,** pp. 73–91; Coffey, S., (*Editor*), "Rodd's Chemistry of Carbon Compounds," Elsevier, Amsterdam, **1977,** pp. 205–209; Fodor, G., *Experientia*, **11,** 129 (1955); Weisz, I., Agócs, P., Szabó, A., and Kovács, K., *Acta Chim. Acad. Sci. Hung.*, **64,** 257 (1970); Fodor, G., Chastain, R. V., Jr., Frehel, D., Cooper, M. J., Mandava, N., and Gooden, E. L., *J. Amer. Chem. Soc.*, **93,** 403 (1971).
(14) Marvell, E. N., and Rusay, R., *J. Org. Chem.*, **42,** 3336 (1977).
(15) Eliel, E. L., and Manoharan, M., *J. Org. Chem.*, **46,** 1959 (1981).
(16) Seeman, J. I., Secor, H. V., Hartung, H., and Galzerano, R., *J. Amer. Chem. Soc.*, **102,** 7741 (1980).
(17) Zefirov, N. S., *Tetrahedron*, **33,** 2719 (1977).
(18) Seeman, J. I., and Farone, W. A., *J. Org. Chem.*, **43,** 1854 (1978).
(19) Gold, V., *Pure Appl. Chem.*, **55,** 1281 (1983).
(20) Perrin, C. L., and Seeman, J. I., *J. Org. Chem.*, **49,** 2887 (1984).
(21) Seeman, J. I., Secor, H. V., Whidby, J. F., and Bassfield, R. L., *Tetrahedron Lett.*, 1901 (1978).
(22) Seeman, J. I., Secor, H. V., Chavdarian, C. G., Sanders, E. B., Bassfield, R. L., and Whidby, J. F., *J. Org. Chem.*, **46,** 3040 (1981).
(23) Ref. (*10*), p. 156.
(24) McKenna, J., *Top. Stereochem.*, **5,** 275 (1970).
(25) Jensen, F. R., and Bushweller, C. H., *Adv. Alicyclic Chem.* **3,** 140 (1971).
(26) Kwart, H., and Takeshita, T., *J. Amer. Chem. Soc.*, **86,** 1161 (1964).
(27) Eliel, E. L., and Biros, F. J., *J. Amer. Chem. Soc.*, **88,** 3334 (1966).
(28) Brown, D. R., Leviston, P. G., McKenna, J., McKenna, J. M., Melia, R. A., Pratt, J. C., and Hutley, B. G., *J. Chem. Soc., Perkin Trans.*, **2,** 838 (1976).
(29) McKenna, J., *Tetrahedron*, **30,** 1555 (1974).
(30) McKenna, J., *in* "Conformational Analysis, Scope and Present Limitations," (*Editor:* Chiurdoglu, G.), Academic Press, New York, **1971,** pp. 171.
(31) Baker, V. J., Blackburne, I. D., Katritzky, A. R., *J. Chem. Soc., Perkin Trans. 2*, 1557 (1974).
(32) Baker, V. J., Blackburne, I. D., Katritzky, A. R., Kolinski, R. A., Takeuchi, Y., *J. Chem. Soc., Perkin Trans. 2*, 1563 (1974).
(33) Seeman, J. I., Sanders, E. B., Farone, W. A., *Tetrahedron*, **36,** 1173 (1980).
(34) Ref. (*9*), p 27.
(35) Oki, M., *Acc. Chem. Res.*, **17,** 154 (1984).