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Analytical Solution to the Curtin–Hammett/Winstein–Holness Kinetic System[1]

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The analytical solution is presented for the kinetic scheme involving a starting material which exists in two isomeric forms, each of which reacts via first-order or pseudo-first-order kinetics to give a different product. This kinetic scheme has been approximated by the well-known Curtin–Hammett (C–H) principle (in terms of product ratios) and by the Winstein–Holness (W–H) equation (in terms of reaction rate). The versatility of the exact solution is discussed especially with regard to the range of validity of the C–H/W–H approximations.

Conformational analysis commands a central role in the understanding of the physical properties and the chemical reactivity of molecules.[2] Almost 25 years ago, Curtin and Hammett,[3] Winstein and Holness,[4] and Eliel and Ro[5] independently considered the chemical consequences of a system in which the starting material exists in two distinct equilibrating forms, each reacting to give a different product (Scheme I).[6]

Scheme I

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$
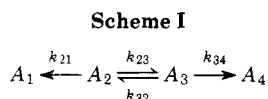
Two principles dealing with this kinetic scheme were advanced. The Curtin–Hammett (C–H) principle stated that the ratio of the products formed "depends only on the relative energy levels of the transition states by which the products are formed, provided that the activation energy for product formation is large compared to the activation energy for the interconversion of the isomeric starting materials"[7] (eq 1).[8] The Winstein–Holness (W–H) equation approximated the overall rate constant for total product formation as the time-independent quantity shown in eq 2.[4,5,9]

$$\frac{A_4}{A_1} = \frac{k_{23}}{k_{32}} \frac{k_{34}}{k_{21}} = K \frac{k_{34}}{k_{21}} \qquad (1)$$

$$k_{WH} = \frac{k_{34}K + k_{21}}{K + 1} \qquad (2)$$

The Winstein–Holness relationship and the Curtin–Hammett principle have been valuable approximations be-

cause they allow the use of simplified expressions to describe rate and product composition phenomena. The assumption used in both of these treatments is the same, that is, the rate constants for interconversion between the conformational isomers, k_{23} and k_{32}, are significantly larger than the rate constants for reaction, k_{21} and k_{34}.

While the W–H relationship refers to reaction rates and the C–H principle refers to product ratio composition, the two are indeed fundamentally related to each other. These relationships have been extensively used in the literature although only qualitative arguments have been proposed to support the decision to use, or not to use, these relationships for any particular chemical system. We now report the analytical mathematical solution[10] (eq 3–14) to Scheme I and an analysis of the range of validity of the C–H/W–H approximations. This exact solution allows the determination of the concentration of reactants and products (A_i) (C–H principle) and permits the calculation of the rates of formation of A_1 and A_4 (W–H equation), both as a function of time. The exact solution is valid for any system which is represented by Scheme I,[6a] and we will demonstrate its usefulness by delineating the range of k_{ij} which will result in C–H/W–H kinetics and by elucidating those parameters which control the observed kinetics.[11]

$$A_1(t) = bk_{21}e^{\alpha t}/\alpha + k_{21}Ce^{\beta t}/\beta$$
$$+ (A_{10} - bk_{21}/\alpha - k_{21}C/\beta) \quad (3)$$

$$A_2(t) = be^{\alpha t} + Ce^{\beta t} \quad (4)$$

$$A_3(t) = de^{\alpha t} + he^{\beta t} \quad (5)$$

$$A_4(t) = dk_{34}e^{\alpha t}/\alpha + hk_{34}e^{\beta t}/\beta$$
$$+ (A_{40} - dk_{34}/\alpha - k_{34}h/\beta) \quad (6)$$

$$\alpha = [-\Omega + (\Omega^2 - 4\Delta)^{1/2}]/2 \quad (7)$$

$$\beta = [-\Omega - (\Omega^2 - 4\Delta)^{1/2}]/2 \quad (8)$$

$$\Omega = k_{21} + k_{23} + k_{34} + k_{32} \quad (9)$$

$$\Delta = k_{21}k_{34} + k_{21}k_{32} + k_{23}k_{34} \quad (10)$$

$$d = bk_{23}/(\alpha + k_{34} + k_{32}) \quad (11)$$

$$h = Ck_{23}/(\beta + k_{34} + k_{32}) \quad (12)$$

$$C = [A_{30} - A_{20}k_{23}/(\alpha + k_{34} + k_{32})]/k_{23}[1/(\beta + k_{34} + k_{32}) - 1/(\alpha + k_{34} + k_{32})] \quad (13)$$

$$b = A_{20} - C \text{ where } A_{i0} = \text{initial concn of } i \quad (14)$$

The C–H/W–H approximations are valid when $A_3/A_2 = k_{23}/k_{32}$ and is time independent. This relationship implies both eq 1 and 2. The validity of either eq 1 or 2 also implies that A_3/A_2 is constant. More complex results are obtained for sets of k_{ij} for which these requirements are not met. For a system involving non-C–H kinetics, both A_4/A_1 and A_3/A_2 will be time dependent. Thus, a simple experimental test for C–H and W–H kinetics involves the examination of the time dependency of the product mixture and/or the ratio of starting isomers.[6b]

For the purpose of evaluating deviation from C–H kinetics, we have defined the terms Δ_{CH} (eq 15) and Δ_{WH} (eq 16).[6b]

$$\Delta_{CH} = \frac{K(k_{34}/k_{21}) - A_4/A_1}{A_4/A_1} \times 100 \quad (15)$$

$$\Delta_{WH} = \frac{k_{WH} - k_{obsd}}{k_{obsd}} \times 100 \quad (16)$$

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

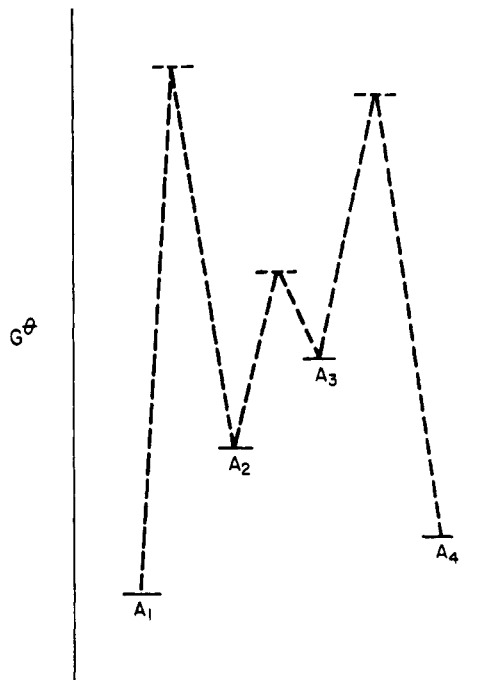For Scheme I kinetics, the absolute magnitude of Δ_{CH} and

Figure 1. The relative free energies of A_i and the free energies of activation per mole for Scheme I systems when $k_{21} < k_{23} < k_{32}$ and $k_{34} < k_{32}$ (case I).

Δ_{WH} either is close to zero at all times or increases in absolute magnitude monotonically to a limiting value with increasing reaction percentage. It is convenient to arbitrarily assign any value of $|\Delta_{CH}| \geq 5$ and any value of $|\Delta_{WH}| \geq 5$ as non-C–H and non-W–H, respectively. This value was based on a assumed experimental error of 5% expected for many reactions. The maximum value of Δ_{CH} is at reaction completion and was evaluated at infinite time in this work. However, Δ_{WH} is (1) meaningless at $t = \infty$ since the reaction is complete and (2) useless at $t = 0$ since it is exactly zero for all values of the rate constants at 0% conversion. This latter observation indicates that there is no deviation from W–H kinetics at $t = 0$, regardless of the values of k_{ij}, even though major deviations can occur as soon as the reaction begins.

The chemistry involved in Scheme I kinetics can be illustrated by examining the extreme kinetic situations as shown in Figures 1 and 8. These figures, patterned after the recent observations of Cruickshank et al.,[13] represent the free energy of 1 mol of each of the states concerned without reference to either reaction progress or time; i.e., the horizontal spacing is drawn as such for convenience only. Real chemical compounds are represented by solid lines while transition states are represented by broken lines.

Case I (Figure 1). When $k_{21} \lesssim k_{23} \lesssim k_{32}$ and $k_{34} \lesssim k_{32}$, then eq 3–14 can be used to calculate the reaction profile (cf. Figure 2) and it is possible to compare the results with those obtained using the C–H/W–H approximations. We choose a simplifying procedure to enable us to make these evaluations. A set of values for k_{23} and k_{32} was chosen; then, k_{21} and k_{34} were each varied over eight orders of magnitude in 32 steps. For each set of four rate constants, A_4/A_1 at $t = \infty$ and k_{obsd} at a predetermined reaction time were calculated using eq 3–14. The percentage reaction at this reaction time was also calculated. From these values, Δ_{CH} and Δ_{WH} were determined. These results were automatically tabulated or could be more conveniently displayed in a 40 × 40 matrix grid, the x and y coordinates being k_{21} and k_{34} and the out-of-plane z coordinate being either Δ_{CH} or Δ_{WH}.

For case I kinetics, as for most of the cases that follow Scheme I, certain sets of k_{ij} can result in $\Delta_{CH} \simeq 0$ although
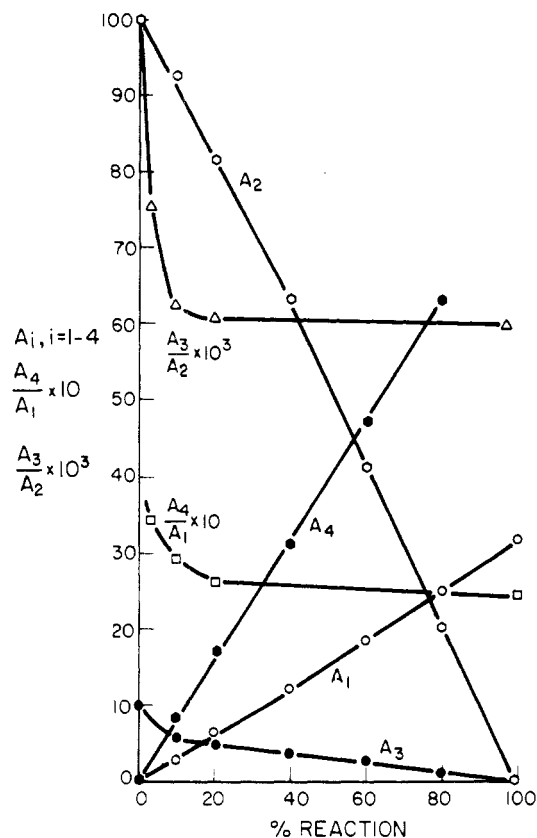
Figure 2. Values of A_i (i = 1–4), A_4/A_1, and A_3/A_2 as a function of percent reaction when $k_{21} = 1.0 \times 10^{-4}$, $k_{23} = 5.64 \times 10^{-4}$, $k_{32} = 5.64 \times 10^{-3}$, and $k_{34} = 4.0 \times 10^{-3}$. Note that A_3/A_2 and A_4/A_1 are both time dependent. The very low value of A_3 at >40% reaction indicates that A_4, which increases continuously throughout the course of the entire reaction, originates actually form A_2.

Figure 3. Δ_{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 Δ_{CH}.

one or more of the basic assumptions seems not to apply. For example, $\Delta_{CH} \simeq 0$ when $k_{21} \simeq k_{34}$, regardless of the values of k_{23} and k_{32}. In this situation the agreement with the C–H/W–H approximations is due to a mathematical degeneracy in the definition of Δ_{CH} and Δ_{WH} and not to a kinetic result which is consistent with the C–H/W–H postulates.

As seen in Figure 3, this results in the diagonal of the matrix becoming identically zero. Results similar to this for other choices of k_{ij} also have zero lines. The zero lines are not always along the diagonal of the matrix but always appear close to it (see below), due to the lack of symmetry caused by $k_{23} \neq k_{32}$ in these cases. The rate of change of Δ_{CH} perpendicular to the matrix diagonal is dependent on the location in the figure, being generally much smaller in absolute magnitude the closer to the upper left-hand corner. This is because the C–H approximation is valid in this region of k_{ij}'s. It should be noted that the values of Δ_{CH} and Δ_{WH} are not symmetrical with an interchange of variables due to the selection of the exact solution as the reference in eq 15 and 16.

For case I kinetics, examination of a wide range of values of $k_{23} = k_{32}$ as described above led to the interesting observation that $\Delta_{CH} < 5$ when $k_{23} > 10k_{21}$ (note that $k_{21} < k_{34}$). Figure 4 illustrates the maximum value of k_{21} as a function of Δ_{CH}. It is interesting that a series of parallel lines results, indicating that similar deviations from C–H kinetics will be obtained for a set of rate constants having the same relative magnitudes proportional to one another.

As k_{34} approaches k_{32} in magnitude, Δ_{CH} increases steadily. When $k_{34} > 0.1 k_{32}$, then $\Delta_{CH} > 5$. In conclusion, it generally *appears that when the rate of reaction from the less stable of the two isomers (A_2 or A_3) is greater than 0.1 times as fast as the rate of conversion of that compound to its isomer the*
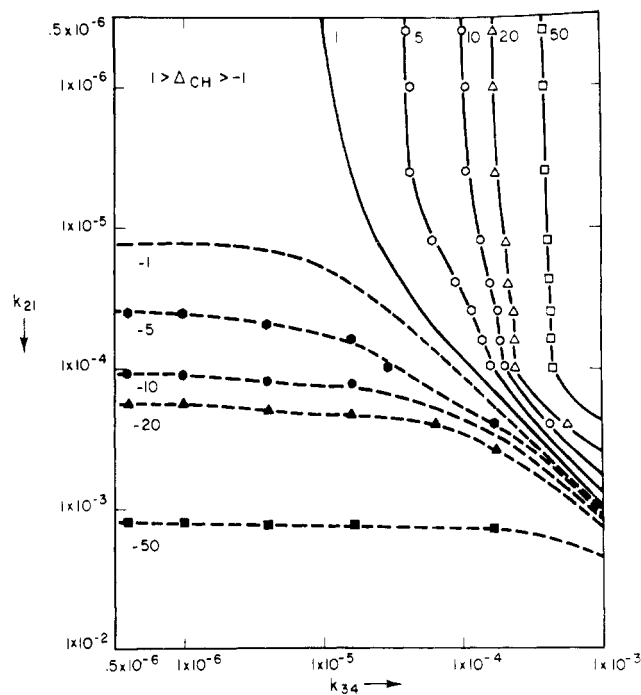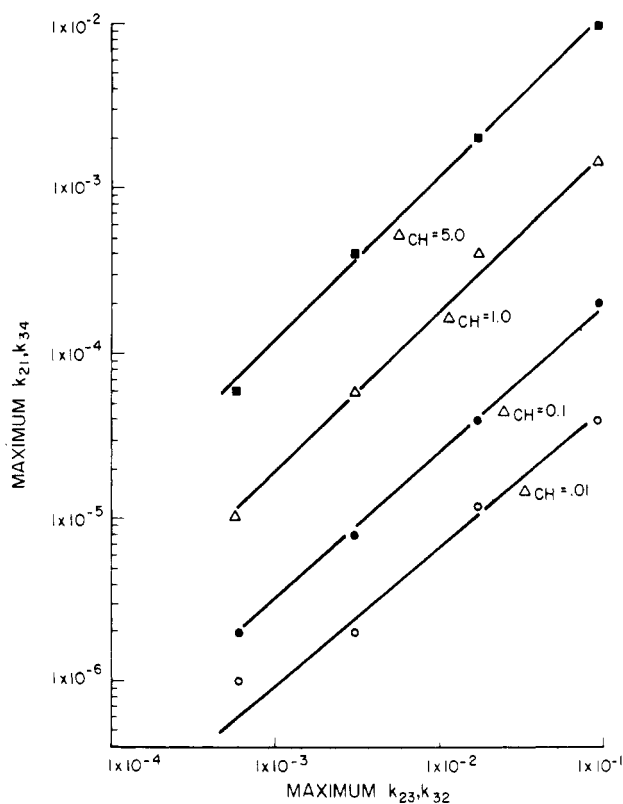
Figure 4. Maximum allowable values of k_{21} and k_{34} as a function of Δ_{CH} when $k_{23} = k_{32}$.

C–H/W–H kinetics will not approximate the actual chemistry observed. As k_{34} gets progressively smaller with respect to k_{32}, k_{21} can approach the value of k_{23} and still allow the resultant system to follow the C–H/W–H approximations.

It is interesting that the conclusions from the previous paragraph are valid even when k_{21} approaches, and in some cases is even greater than, k_{23}. This indicates the strong role
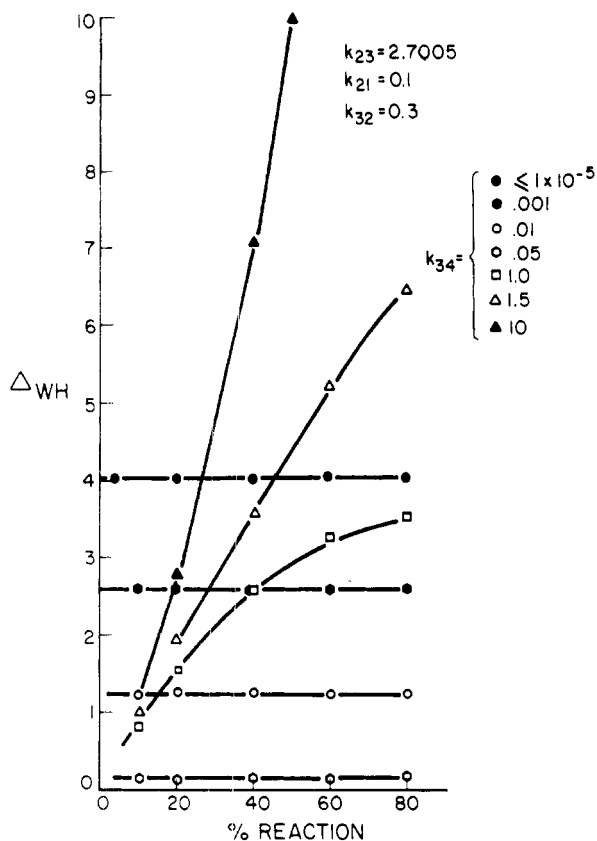
Figure 5. The dependency of Δ_{WH} as a function of reaction completion for sets of k_{ij}. Note that multiplication of all the k_{ij} by the same factor will not change the dependencies shown in this figure but will only change the relationship between percentage completion and time.

Figure 6. The dependency of Δ_{WH} as a function of reaction completion for sets of k_{ij}. Compare with Figure 5.

that the $A_3 \rightarrow A_4$ transformation exerts on the reaction profile under these special relationships between the k_{ij}'s. The larger k_{32} is with respect to k_{23}, the larger k_{21} can become with respect to k_{23} and still fall within the C–H/W–H approximations. This observation can be explained by realizing that significantly smaller amounts of A_3 with respect to A_2 are available for reaction.

As discussed above Δ_{WH} will be reaction percentage dependent, and this is illustrated in Figures 5 and 6 for sets of case I kinetics. A strong percentage reaction dependency does exist, and the greater the variation from W–H kinetics, the greater the dependency becomes. Thus, when the limiting value of Δ_{WH} is small, the asymptotic value is reached early in the reaction. This observation is a crucial simplifying factor in our comparison of Δ_{CH} and Δ_{WH} as criteria for the kinetic systems.

Since one of the major assumptions in the derivation of both C–H and W–H kinetics is that $k_{23}, k_{32} \gg k_{21}, k_{34}$, i.e., A_3/A_2 is constant throughout the reaction, it was expected that Δ_{CH} and Δ_{WH} would qualitatively mirror each other in response to variation in the choice of k_{ij}. Such a comparison, however, is complicated by the time dependency discussed at length above; nonetheless, Δ_{CH} and Δ_{WH} did match each others dependence on the set of k_{ij}.

Figures 5 and 6 represent cases having the same k_{23}, k_{32}, and k_{34}, but $k_{21} = 0.1$ in Figure 5 and $k_{21} = 1 \times 10^{-4}$ in Figure 6. Note that Δ_{WH} is independent of percent reaction for certain values of k_{ij}, indeed for those values which correspond to C–H kinetics. Also note the degeneracy found in Δ_{WH} (Figure 5), similar to the degeneracy found in Δ_{CH} and discussed above. Also, lowering k_{34} below a certain point in each of these cases has no effect on Δ_{WH}, i.e., Δ_{WH} reaches a limiting value. A comparison of Figures 5 and 6 indicates the important
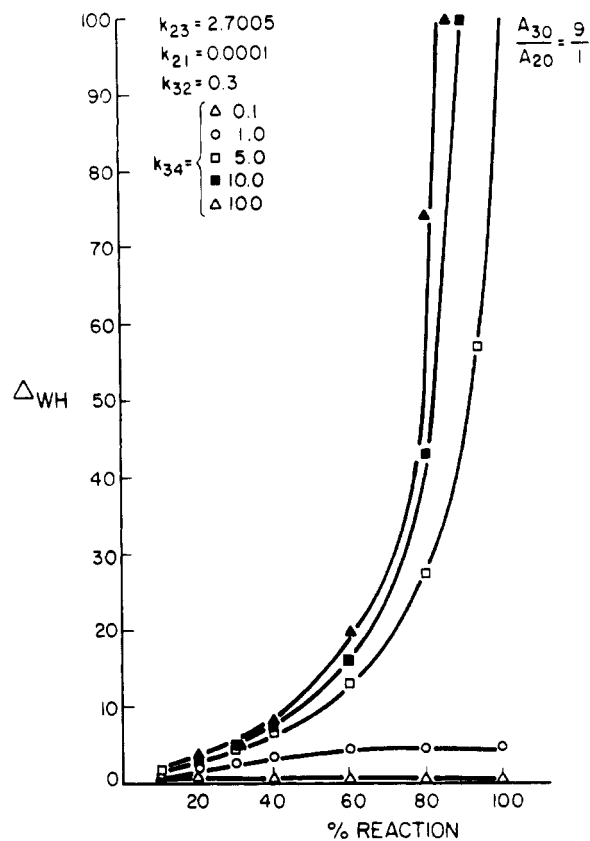
controlling features in W–H kinetics. For example, Figure 5 shows the degeneracy at $k_{34} \simeq 0.05$ (i.e., where Δ_{WH} reaches a minimum value) and the kinetics become strongly non-W–H for $k_{34} \simeq 1$. On the other hand, Figure 6 indicates the degeneracy at $k_{34} \simeq 1 \times 10^{-4}$ but the kinetics are well approximated by W–H for $k_{34} \simeq 1$. Clearly, Figure 6 kinetics are a closer fit to the W–H kinetics than Figure 5 kinetics. This is because the lower value for k_{21} in Figure 6 kinetics biases the system to favor the approximations made in deriving the C–H/W–H equations.

When Δ_{CH} and $\Delta_{WH} \gg 5$, these terms become quantitatively meaningless in a practical sense. The deviations from an assumed kinetics situation for sets of k_{ij} are so great that only qualitative meaning can be placed on large values of these terms. A detailed analysis of non-C–H/W–H kinetics can best be done by the examination of the dependency of A_i as a function of time (percent reaction).

A very large percentage of the literature which cites the Curtin–Hammett principle and/or the Winstein–Holness equation is related to kinetic systems illustrated by case I kinetics. For example, two conformations of the starting material having unequal free energies of formation each give a different product at rates significantly slower than their rates of interconversion. This is illustrated by considering the interconversion–alkylation of the nicotine analogue, 1-methyl-2-phenylpyrrolidine, shown in Scheme II.[14] If $k_{2\rightarrow3}, k_{3\rightarrow2} \gg k_{2\rightarrow1}, k_{3\rightarrow4}$, then [4]/[1] and [3]/[2] are expected to be constant throughout the course of the reaction and the C–H/W–H approximations are expected to be valid.

Estimates of the rates and barriers for the nitrogen inversions shown in Scheme II can be made on the basis of low-temperature NMR results and strong acid kinetic quenching of the $2 \rightleftarrows 3$ mixture. Kinetic studies of the iodomethylation of $2 \rightleftarrows 3$ using well-established conductometric techniques allow the determination of the overall pseudo-first-order rate constant for alkylation, and ^2H NMR analysis of the total
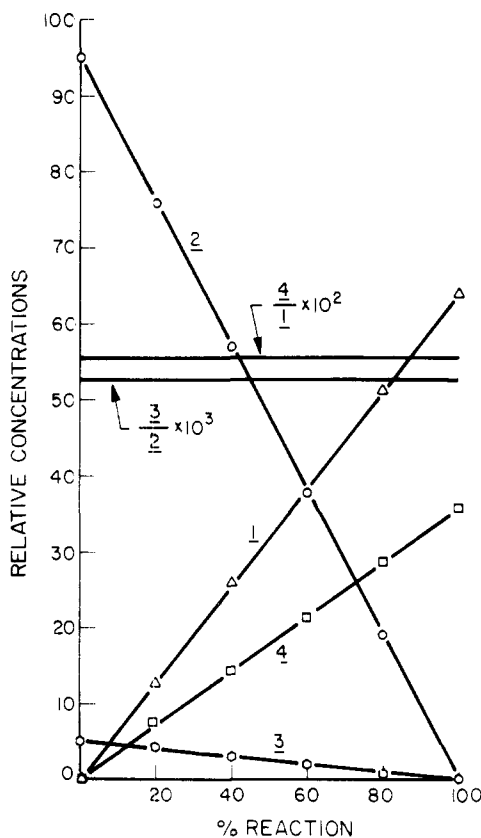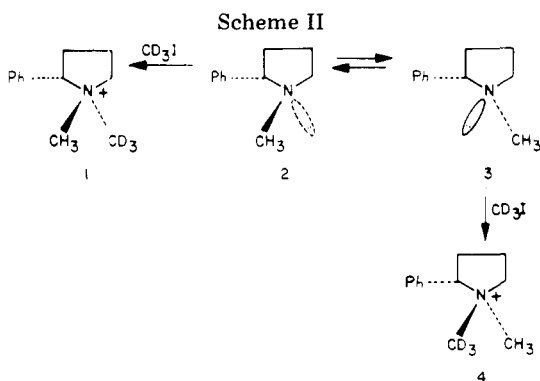
Figure 7. The relative concentrations of 1–4 (see Scheme II) and the ratios of starting materials (3/2) and products (4/1) where $k_{2\to1} = 3.24 \times 10^{-4}$, $k_{3\to4} = 3.45 \times 10^{-3}$, $K = k_{2\to3}/k_{3\to2} = 5.26 \times 10^{-2}$, and $k_{3\to2}/k_{3\to4} > 20$.

Scheme II

reaction mixture resulting from deuterioiodomethylation allowed the determination of the value of **4/1**. These determinations allowed the estimates for the rate constants shown in the caption of Figure 7.[14]

The rate constants and subsequent kinetic analysis using the exact solution for Scheme II are shown in Figure 7, which illustrates the compositions and ratios of conformers and products of Scheme II for 1–95% conversion representing over 60 h of reaction time. As expected, **3/2** and **4/1** are clearly time independent. While the rates of isomer interconversion are considerably greater than the rates of alkylation, a time dependency in both the product ratio **4/1** and the "overall rate constant" k_{WH} occurs only at *very low* conversion. This is reasonable, since a small time delay will be required following the initiation of the reaction to allow reequilibration of the isomers. The size of this time delay will be very dependent on the closeness to the C–H/W–H approximations. Thus, no sets of k_{ij} will exactly be described by the C–H/W–H approximations.

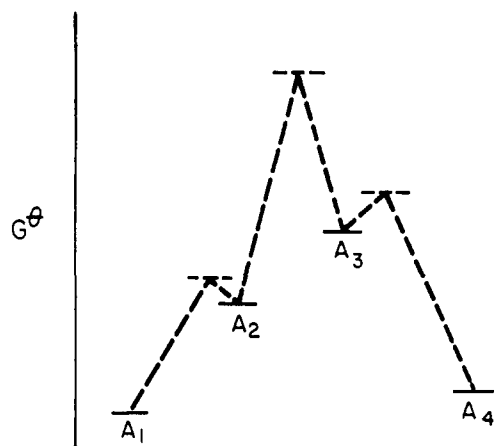A number of kinetic situations can be postulated which by

Figure 8. The relative free energies of A_i and the free energies of activation per mole for Scheme I systems when $k_{23} \leqslant k_{32} < k_{21}$ and k_{34} (case IV).

inspection fail to meet the C–H/W–H criteria. Included in these are case II ($k_{23} \leqslant k_{32} < k_{21}$ and $k_{34} < k_{32}$) and case III ($k_{21} < k_{23} < k_{32} < k_{34}$). Examples of cases II and III in chemical systems in which the $A_2 \rightleftharpoons A_3$ represents conformational interconversion are rare, and we will not examine these systems in detail. Suffice it to say that eq 3–14 can be used expeditiously to derive the k_{ij} from kinetic data in these cases. It should be pointed out that systems involving more complex chemical reactions between A_2 and A_3 can be solved exactly using eq 3–14 (see below).

Case IV (Figure 8; $k_{23} < k_{32} < k_{21}$ and k_{34}). In this case, both reaction rates are greater than the rates of interconversion, and non-C–H/W–H kinetics will be obtained. This case is particularly interesting in that it describes a number of important chemical situations generally labeled as "the fast chemical reaction technique".[15]

The object of this technique is often to determine the conformational equilibrium value for a compound existing in more than one form *and not* to analyze the compound's reactivity. Indeed, assumptions are made with respect to the compound's chemical reactivity and these are basic to the method.

McKenna has described five kinetic cases, three involving intermolecular reactions and two involving intramolecular reactions.[15b] The exact mathematical solution to Scheme I allows a more detailed examination of a number of McKenna's cases. For example, McKenna's case 5 is similar to our case IV in that one is dealing with an intramolecular reaction in which $k_{23}, k_{32} \ll k_{21}, k_{34}$ (often termed "diffusion controlled"). McKenna concludes that $A_4/A_1 = k_{32}/k_{23}$ even if $k_{21} \neq k_{34}$. An examination of Table I reveals how the exact solution of Scheme I places a more quantitative relationship between the rate constants involved in case IV kinetics.

Consider the situations involving conformational isomers having $\Delta H^{\ddagger}_{\text{inv}} = 6, 10$, and 18 kcal/mol being subjected under Scheme I. A number of observations can be made.[6b]

(1) When $\Delta H^{\ddagger}_{\text{inv}}$ is sufficiently small and $A_{23} = A_{32}$[6b] is sufficiently large so that $k_{23}, k_{32} > 10k_{21}, 10k_{34}$, then $A_4/A_1 = K(k_{34}/k_{21})$, exactly as expected under C–H conditions (see case I above). For example, the barrier of inversion for nicotine is ca. 6 kcal/mol.[14] According to Table I, lines 1–3, the C–H approximation is valid, A_4/A_1 is time independent, and a kinetic discrimination between the formation of A_1 and A_4 could be directly observed in the product ratio.

(2) When $k_{21}, k_{34} \gg k_{23}, k_{32}$ (Table I, lines 7–9), then the kinetic system behaves as if A_2 and A_3 are not interconvertible; i.e., the reaction to product occurs so quickly that any depletion of either A_2 (or A_3) would not be replenished from

Table I. Scheme I Kinetics under Fast Chemical Reaction Conditions[c]

Line	k_{21}	$k_{23}{}^a$	$k_{32}{}^a$	k_{34}	$E_{0,inv}$, kcal mol^{-1}	$A_4/A_1{}^b$ 10% rxn	50% rxn	94% rxn	100% rxn
1	1×10^{12}	1.15×10^{13}	1.03×10^{14}	1×10^{12}	6	0.111	0.111	0.111	0.111
2	2×10^{12}			1×10^{12}		0.056	0.056	0.056	0.056
3	1×10^{12}			2×10^{12}		0.222	0.222	0.222	0.222
4	1×10^{12}	1.31×10^{10}	1.18×10^{11}	1×10^{12}	10	0.111	0.111	0.111	0.111
5	2×10^{12}			1×10^{12}		0.056	0.065	0.090	0.105
6	1×10^{12}			2×10^{12}		0.211	0.171	0.124	0.118
7	1×10^{12}	1.71×10^4	1.54×10^5	1×10^{12}	18	0.111	0.111	0.111	0.111
8	2×10^{12}			1×10^{12}		0.057	0.065	0.092	0.111
9	1×10^{12}			2×10^{12}		0.212	0.170	0.118	0.111

^{a} Determined using eq 18 with $A = 1 \times 10^{15}$ at 298.16 K. Note that multiplication of all the k_{ij} by the same number changes the product composition with respect to time but not with respect to percent reaction. ^{b} $A_{30}/A_{20} = k_{23}/k_{32} = 0.11$. ^{c} Note ref 6.

A_3 (or A_2). Thus, even if $k_{21} \neq k_{34}$, kinetic discrimination will be observed, but only prior to reaction completion. It is interesting to note that A_4/A_1 will be time dependent but equal to $K = k_{23}/k_{32}$ at 100% reaction. Reactivity of this sort may be expected from isomers such as *cis-* and *trans-N*-alkyl-2-arylaziridines, known to have $\Delta H^{\ddagger}_{inv} = 18$ kcal/mol.

(3) When $k_{21}, k_{34} \sim k_{23}, k_{32}$ (Table I, lines 4–6), an intermediate kinetic response is obtained. Neither the C–H approximation nor the kinetic quenching formulation describe A_4/A_1. Here, a kinetic discrimination for reaction can be determined only by application of the exact solution to Scheme I kinetics. This would require, for example, the determination of $K = k_{23}/k_{32}$ and A_4/A_1 at 100% reaction. These experimental values and the application of a numerical technique such as the Newton–Raphson method for extracting roots of an equation would allow the evaluation of k_{34}/k_{21} for the intermediary case.

(4) It is interesting to note that for the examples shown in Table I, lines 1–9, A_4/A_1 at low (<10%) percentage reaction depends primarily on the ratios k_{21}/k_{34} and k_{23}/k_{32} and not on the relative magnitudes of k_{ij}; this is because any imbalance in A_3/A_2 which may occur during the course of the reaction has not yet been able to exert its influence.

(5) When $k_{21} = k_{34}$ for some of the cases in Table I (lines 1, 4, and 7), $A_4/A_1 = 0.111 = k_{23}/k_{32}$. These sets of k_{ij}'s fall along the zero line of the Δ_{CH} matrix, i.e., are degenerate.

(6) We have previously demonstrated that A_4/A_1 is not dependent on the magnitudes of the k_{ij}'s (as the time-percentage reaction dependency is) but only on their relative magnitudes. Thus, Table I is more generally applicable in that multiplication of the k_{ij}'s in one set by the same constant results in the same dependency of A_4/A_1 as a function of reaction percentage.

More complex kinetic schemes may be necessary to describe phenomena associated with biomolecular diffusion-controlled reactions. For example, substrate and reagent mixing and other solution inhomogeneity factors must be included. The treatment shown in Table I is the simplest exact solution possible. If Table I shows the results to be non-C–H, then all more complicated systems will be non-C–H unless there exist fortuitous balancing factors. Hence, the results shown in Table I can be used as approximations for more complex reacting systems.

Reaction Energetics

It must be noted that the C–H/W–H approximations are in terms of the k_{ij} and not activation energies (E_{ij}) and preexponential factors (A_{ij}).[6b] The Arhennius equation (eq 17) and the Eyring equation (eq 18) are the two relationships generally used to relate the rate constants of a reaction to energy and entropy parameters. These two equations are specific formulations of the more general Eyring equation (eq

Table II. Derivation of the Minimum E_{21} and E_{34} for C–H Acceptability When $E_{23} = E_{32} = 18$ kcal/mol (298 K)[a]

$A_{23}, A_{32}{}^{b,c}$	$k_{21}, k_{34}{}^{c,d}$	A_{21}, A_{34}	k_{21}/A_{21}, k_{34}/A_{34}	E_{21}, E_{34} for C–H acceptability,[a,d] kcal mol^{-1}
1×10^5	$<4 \times 10^{-10}$	1	$<4 \times 10^{-10}$	>12.8
		10	$<4 \times 10^{-11}$	>14.1
		1×10^2	$<4 \times 10^{-12}$	>15.5
		1×10^3	$<4 \times 10^{-13}$	>16.9
		1×10^4	$<4 \times 10^{-14}$	>18.2
		1×10^5	$<4 \times 10^{-15}$	>19.6
1×10^{10}	$<4 \times 10^{-5}$	1	$<4 \times 10^{-5}$	>6.0
		10	$<4 \times 10^{-6}$	>7.3
		1×10^2	$<4 \times 10^{-7}$	>8.7
		1×10^3	$<4 \times 10^{-8}$	>10.1
		1×10^4	$<4 \times 10^{-9}$	>11.4
		1×10^5	$<4 \times 10^{-10}$	>12.8
1×10^{15}	<4	1×10^2	$<4 \times 10^{-2}$	>1.9
		1×10^3	$<4 \times 10^{-3}$	>3.3
		1×10^4	$<4 \times 10^{-4}$	>4.6
		1×10^5	$<4 \times 10^{-5}$	>6.0

^{a} The Arrhenius equation is arbitrarily used in these calculations; e.g., $E_a = 18$ kcal/mol implies that $k/A = 5.64 \times 10^{-14}$ at 298 K. ^{b} $A_{23} = A_{32}$ since the same transition state is involved. ^{c} Multiplication of all the k_{ij} by the same number changes the product composition with respect to time but not with respect to percent reaction. ^{d} These are the maximum values possible for k_{21}, k_{34} such that $\Delta_{CH} < 5$. Note ref 6.

19). The appropriate rate equation for a particular reaction is dependent on the nature of the reaction, i.e., whether the reaction is unimolecular or bimolecular, whether the transition state complex is linear, nonlinear, etc.[16] In Scheme I, the interconversions $A_2 \rightleftarrows A_3$ signified a unimolecular conformational (or configurational) transformation, and as such eq 18 is suggested by theory.[16] The only assumption that has been made in the derivation of the exact solution in terms of the reactions $A_2 \rightarrow A_1$ and $A_3 \rightarrow A_4$ is that they obey first-order kinetics or pseudo-first-order kinetics. Theory suggests a wide range of values for n in eq 19 for reactions following this assumption, and for the calculation of Δ_{CH} and Δ_{WH} we have chosen[17] the value $n = 0$ as has often been done in the literature.

$$k = A \exp(-E_a/RT) \tag{17}$$

$$k = AT \exp(-E_0/RT) \tag{18}$$

$$k = AT^n \exp(-E_0/RT) \tag{19}$$

Tables II and III demonstrate the important observation that the preexponential factors play a determining role in

Table III.[a] **Derivation of the Minimum E_{21} and E_{34} for C–H Acceptability When $E_{23} = E_{32} = 6$ kcal/mol**[b]

A_{23}, A_{32}	k_{21}, k_{34}	A_{21}, A_{34}	$k_{21}/A_{21},$ k_{34}/A_{34}	E_{21}, E_{34} for C–H accept- ability,[a] kcal mol^{-1}
10	$<3 \times 10^{-1}$	1	$<3 \times 10^{-1}$	>0.71
		10	$<3 \times 10^{-2}$	>2.07
		1×10^{2}	$<3 \times 10^{-3}$	>3.43
		1×10^{3}	$<3 \times 10^{-4}$	>4.79
		1×10^{4}	$<3 \times 10^{-5}$	>6.15
		1×10^{5}	$<3 \times 10^{-6}$	>7.51
1×10^{10}	$<3 \times 10^{4}$	1×10^{5}	$<3 \times 10^{-1}$	>0.71
1×10^{15}	$<3 \times 10^{9}$	1×10^{10}	$<3 \times 10^{-1}$	>0.71

[a] See Table II footnotes. [b] $E_a = 6$ kcal/mol implies $k/A = 3.83 \times 10^{-5}$.

Figure 9. The minimum values of the activation energies E_{21} and E_{34} for C–H acceptability ($\Delta_{CH} < 5$) as a function of the activation energies for isomer interconversion ($E_{23} = E_{32}$). The family of lines represents different values of the preexponential factors $A_{21} = A_{34}$. Note that the free energies of A_2 and A_3 are equal and $A_{23} = A_{32} = 1 \times 10^{-10}$.

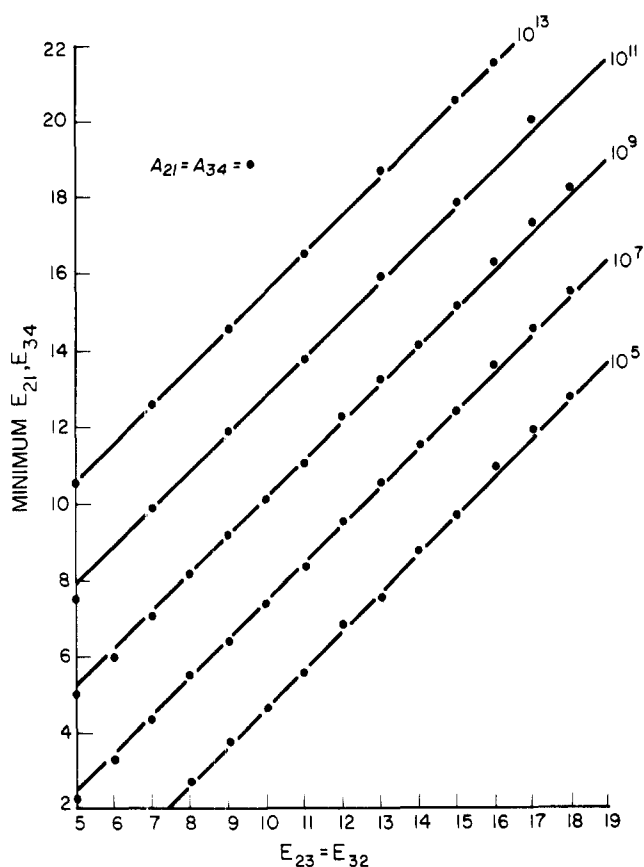**Figure 10.** The minimum values of the activation energies E_{21} and E_{34} for C–H acceptability ($\Delta_{CH} < 5$) as a function of the activation energy E_{23} for different values of $\Delta E = E_{23} - E_{32}$. $A_{23} = A_{32} = 1 \times 10^{-10}$; $A_{21} = A_{34} = 1 \times 10^{-5}$. In this figure, the free energy difference between A_2 and A_3 is varied; compare with Figure 9.

these kinetics. While significant statistical errors are associated with the experimental determination of the preexponential factor A, it is clear that the preexponential factors for typical unimolecular reactions[18] (e.g., conformational interconversion) are a number of orders of magnitude greater than the preexponential factors of bimolecular reactions.[19]

These points are illustrated by comparing the results for Scheme I kinetics when $E_a = 18$ kcal/mol (Table II) with those when $E_a = 6$ kcal/mol (Table III). The former is representative of the energy barrier of nitrogen inversion for aziridines[18] and the latter is representative of the inversion barrier of a hindered pyrrolidine, e.g., nicotine.[14] If we assume (1) that the

preexponential factor for inversion is 10^{10} and (2) the upper limit for any preexponential factor for the reactions $A_2 \rightarrow A_1$ and $A_3 \rightarrow A_4$ is 10^5, then any reaction having a barrier less than 12.8 kcal/mol will result in non-C–H/W–H kinetics for the aziridines ($\Delta H^{\ddagger}_0 = 18$ kcal/mol) while any barrier less than 0.71 kcal/mol for the substituted pyrrolidine would result in non-C–H/W–H kinetics. Consider the result if one assumes that the preexponential factor for nitrogen interconversion is 10^{15} rather than 10^{10}. Reaction barriers less than 6.0 kcal/mol for aziridines would result in non-C–H/W–H kinetics.

The influence of the preexponential factor in determining reaction profiles can be seen in Figure 9 which shows the minimum values of E_{21}, E_{34} for $\Delta_{CH} < 5$ for different values of $A_{21} = A_{34}$ assuming $A_{23} = A_{32} = 1 \times 10^{10}$. The parallel lines are not an obvious consequence of the exact solution (eq 3–14) but are related to the linear relationship found in Figure 4.

We also examined the minimum E_{21}, E_{34} allowable and still maintain $\Delta_{CH} < 5$ for sets of E_{23}, E_{32} having a constant energy difference $x = E_{23} - E_{32}$ as a function of E_{23} (Figure 10). A series of parallel lines resulted, thus indicating that the actual value of the energy difference between A_2 and A_3 is important for determining the minimum value of E_{21}, E_{32} but the location on the energy scale, in an absolute sense, is not.

It is important to stress at this stage that the kinetics are controlled by the rate constants which appear in the rate expressions, and it is from these rate constants measured at various temperatures that the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are calculated. We have attempted to use the designations of E_a, E_0, or $\Delta H^{\ddagger}$ corresponding to the individual author's use in the literature. In some literature cases, it is difficult to determine which equation (e.g., eq 17–19) the author used in derivation of his activation parameters. Although the relationship between these various parameters is well-known, considerable uncertainly exists in the usage of eq 17–19. For example, the value

Table IV.[a] **Calculated**[b] **Percentages of Hydroboration Products for Thujopsene (5) under the Assumption That the Minor Isomer**[c] **Reacts Faster Than the Major Isomer**[c]

$E_{HB,5s \to 6}$, kcal mol^{-1}	$E_{HB,5s \to 7}$, kcal mol^{-1}	$\dfrac{k_{5s \to 6}}{k_{5n \to 7}}$	$\dfrac{A_{inv}}{A_{HB}}$	% products 6	% products 7
3.7	9.1	1×10^4	1×10^3	96.6	3.4
3.7	9.1	1×10^4	1×10^4	98.8	1.2
5	9.5	2×10^3	1×10^7	95.2	4.8
9	14	4.8×10^3	1×10^3	97.9	2.1
8	13	4.8×10^3	1×10^3	97.9	2.1

[a] Subscripts "inv" and "HB" refer to the ring inversion processes and hydroboration reactions, respectively. [b] $E_{5s \to 5n} = 11$ kcal mol^{-1}. Calculations were based on eq 17 at 25 °C. Note that multiplication of all k_{ij} by the same number changes the product distribution with respect to time but not with respect to percent reaction. [c] $[k_{5s \to 5n}/k_{5n \to 5s} = 0.01]$.

of n in eq 19 is usually assumed to be 0 or 1, but other values are certainly possible and would dramatically effect the derived thermodynamic parameters. The value of κ is, by and large, indeterminate and is generally assumed to be 1, though theory suggests that κ can be considerably larger than 1 (e.g., in unimolecular processes). Tables II and III are meant to *illustrate* the controlling factors in C–H/W–H chemistry in terms of these more widely used activation parameters. Thus, whether or not an aziridine or any other molecule follows C–H/W–H kinetics will be best judged following the experimental determination of the k_{ij} and not by the hypothetical treatment shown in Tables II and III.

Additional Applications of the Exact Solution. Perhaps the ultimate use of the exact solution (eq 3–14) to Scheme I is the determination of all the rate constants from time–concentration data. The experimental difficulties in determining time–concentration data coupled with the previous unavailability of the exact solution to this kinetic scheme have encouraged various investigators either (1) to use the C–H/W–H approximations or (2) to intuitively cite the probable failure of these approximations for the treatment of their systems. We are unaware of any kinetic treatment of a Scheme I non-C–H/W–H kinetic system.

Numerous examples can be found in the literature in which the C–H/W–H approximations are utilized for various determinations. If appropriate upper (or lower) limits can be made for the reaction rate constants for a chemical system or interest, then the exact solution can predict the appropriateness or inappropriateness of the use of these approximations.

One continuing application of Scheme I kinetics involves the determination of the position of the $A_2 \rightleftharpoons A_3$ equilibrium, defined by $K = k_{23}/k_{32}$. For example, the early work on the quaternization of tropines incorporated the assumption that the product ratio A_4/A_1 was dependent only on the free energy difference between the reactant configurational isomers.[20] Such considerations led to incorrect deductions[20] of reactant isomer ratios, since the C–H approximation clearly indicates a dependency not only on K $[=k_{23}/k_{32} = \exp(-\Delta G^0/RT)]$ but also on the ratio of reaction rates k_{34}/k_{21} (see eq 1).

Indeed, numerous examples can be found in the chemical literature in which the C–H principle is interpreted by implying that "the ratio of the products so formed is independent of the relative energy levels of the various starting forms ...".[7] This interpretation is somewhat misleading as evidenced by eq 1. Indeed, the relative values of k_{23} and k_{32} are always reflected in the relative values of A_1 and A_4: (1) if $k_{21}, k_{34} \gg k_{23}, k_{32}$, then (kinetic quenching) $A_4/A_1 = A_3/A_2 = k_{23}/k_{32}$ at reaction completion; (2) if $k_{21}, k_{34} \ll k_{23}, k_{32}$ (C–H/W–H), then eq 1 is valid; and (3) if k_{21} and/or $k_{34} \sim k_{23}$ and/or k_{32}, then eq 3–14 are the simplest descriptors of $A_i(t)$,

Scheme III

and A_i are certainly dependent on the relative values of k_{ij}.

To exemplify these concepts, consider the attempt by Acharya and Brown to elucidate the conformational equilibrium position of (−)-thujopsene (5).[21,22] Acharya and Brown hypothesized that the steroidal 5s and nonsteroidal conformations 5n of (−)-thujopsene would stereospecifically yield alcohols 6 and 7, respectively, on hydroboration–peroxide oxidation. The isolation of a single alcohol identified as 6 in 96.3% yield formed the basis of their conclusion that thujopsene exists preferentially in the steroidal conformation 5s.[21]

An alternative hypothesis is that thujopsene exists preferentially (e.g., 100-fold greater) in the nonsteroidal conformation 5n but the hydroboration rate $k_{5s \to 6}$ of the steroidal conformer is considerably larger than the rate $k_{5n \to 7}$ of the nonsteroidal conformer. Utilizing the activation barriers for Scheme III suggested by Acharya and Brown,[21] one can apply eq 3–14 and examine the conditions under which isomer 6 is preferentially formed when conformer 5n predominates. The results of some of these calculations are illustrated in Table IV, which clearly indicates that if the ratio $k_{5s \to 6}/k_{5n \to 7}$ is sufficiently large, product from the "minor" isomer will predominate whether or not the kinetic system can be described by the C–H/W–H approximations. The major conclusion from this treatment is that detailed kinetic studies must be performed in any attempt to correlate product ratio with the equilibrium distribution of isomers.

Considerable interest has been shown for some years in the thermal chemistry of azoalkanes.[23] Engel et al.[23a] recently investigated the thermolysis of a number of *cis-* and *trans*-azoalkanes. They demonstrated that *trans*-dinorbornyldiazene (8t) decomposes giving nitrogen and unspecified hydrocarbons, while lower temperature thermolysis of the less stable cis isomer 8c leads only to the trans compound 8t. The possibility that some of the nitrogen from 8t was derived from prior isomerization to 8c was not mentioned. Equations 3–14, coupled with the thermodynamic parameters reported for these compounds, allow the calculation of the ratio of nitrogen coming directly from the trans isomer 8t vs. the nitrogen coming from the trans isomer via the cis isomer 8c (Table V). The relative times for 50% reaction completion are also shown in Table V and can serve as an additional experimental test for the kinetic parameters. Since a significant amount of product does indeed arise via the indirect pathway, the transition state parameters for the transformation of 8t to prod-

Table V. Calculated^a Reaction Profiles for the Thermal Decomposition of 8t

Temp, °C	$\dfrac{\text{Total N}_2 \text{ via } 8t}{\text{Total N}_2 \text{ via } 8c}$	Rel rxn times^b
400	1.35	1
300	1.39	1.3×10^3
200	1.53	3.8×10^7
100	1.72	2.5×10^{14}

^{a} Based on thermodynamic data cited in ref 23a,d using eq 18. This treatment assumes $A_{8t \rightarrow 8c} = A_{8c \rightarrow 8t}$ and $A_{8c \rightarrow \text{Pdt}} = A_{8t \rightarrow \text{Pdt}}$. ^{b} Relative times for 50% destruction of 8.

Table VI.^{a} Calculated^b Reaction Profiles for the Thermal Decomposition of 9c and 9t

$\Delta H^{\ddagger}_{9c \rightarrow 9t}$	$\Delta H^{\ddagger}_{9t \rightarrow 9c}$	$9c \rightarrow 9t \rightarrow N_2{}^{c,d}$ from -17 °C pyrolysis of 9c, %	$9t \rightarrow 9c \rightarrow N_2{}^{d,e}$ from 183 °C pyrolysis of 9t, %
20	42.3	96	0.241
21	43.3	89	0.234
22	44.3	54	0.215
23	45.3	14	0.172
24^{c,f}	46.3	2.2^{c,f}	0.107

^{a} The exact solution to Scheme I (eq 3–14) can also serve as the exact solution to lesser included kinetic schemes. In some cases, as exemplified in a number of the calculations performed for Table VI, sets of k_{ij} are obtained in which Scheme I can be approximated by simpler kinetics schemes, e.g., parallel or series first-order reactions (cf. ref 16, Chapter 8). ^{b} Based on the thermodynamic data cited in ref 23a, assuming $A_{9t \rightarrow 9c} = A_{9c \rightarrow 9t}$. ^{c} Experimentally, the conversion 9c → 9t at -17 °C was not observed. ^{d} Evaluated at infinite time. ^{e} The percentage of decomposition occurring via the indirect path ($9t \rightarrow 9c \rightarrow N_2$) compared with the direct path ($9t \rightarrow N_2$) at >180 °C was not discussed in the literature (cf. ref 23a). ^{f} Minimum value consistent with experimental data (see footnote c above) assuming an experimental error of 5%.

ucts should be reobtained from experiments that can distinguish these two pathways.

Thermolysis of either *cis*- or *trans-tert*-butyldiazene (9c and 9t) leads only to fragmentation; in neither case was cis–trans isomerization observed.[23a] Equations 3–14 can be utilized to determine the minimum activation enthalpies for cis–trans isomerization such that these processes not be observed; in addition, the likelihood of the sequence $9t \rightarrow 9c \rightarrow N_2$ can be evaluated. These results are shown in Table VI.

(structure diagram)

9t   9c
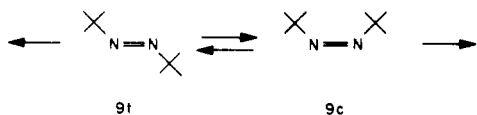
The exact solution for Scheme I kinetics has two additional versatilities: it can be used for systems (1) in which A_2 and A_3 do not necessarily represent conformational isomers but, in a less restrictive sense, interconverting compounds; and (2) in which the initial ratio of concentrations A_{30}/A_{20} is not equal to the equilibrium distribution.[24]

An interesting example incorporating both of these aspects can be found in the recent work of Dolbier and Enoch on the thermochemistry of *cis*- and *trans*-1,1-difluoro-2,3-dimethylcyclopropanes, 10c and 10t, respectively.[25] Analysis of this system using the published rate data and eq 3–14 indicates that C–H/W–H kinetics should be obtained if an equilibrium mixture of 10c and 10t were pyrolyzed; however, when 10c and 10t were pyrolyzed independently, non-C–H/W–H kinetics
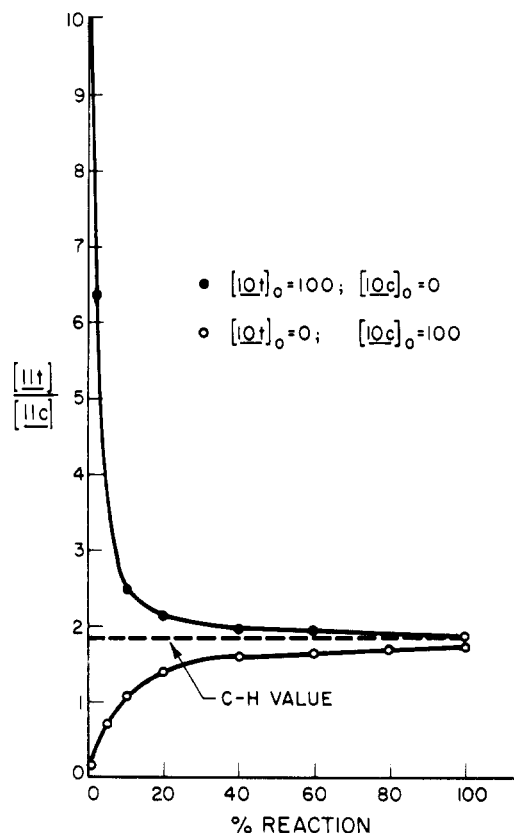

Figure 11. The calculated percentage reaction dependency of the product ratio [11t]/[11c] obtained in the independent pyrolyses of either 10t or 10c using rate data obtained from ref 25: $k_{10c \rightarrow 10t} = 3.96 \times 10^{-5}$; $k_{10t \rightarrow 10c} = 2.07 \times 10^{-5}$; $k_{10c \rightarrow 11c} = 1.2 \times 10^{-6}$; $k_{10t \rightarrow 11t} = 1.15 \times 10^{-6}$. The dashed line in the figure represents the C–H value.

should have been obtained (see Figure 11). Note that, as indicated in Figure 11, maximum deviation from C–H kinetics occurs early in the reaction. The use of the exact kinetic solution should allow the most accurate determination of the rate constants and other thermodyanmic properties of this system, as well as substantiate the system's presumed stereospecificity.
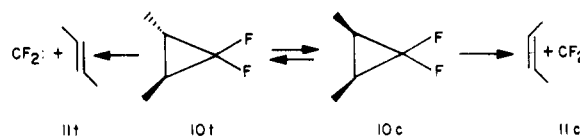
Summary and Conclusions

Equations 3–14 form the exact analytical solution to any chemical system represented by Scheme I. The solution can be applied regardless of the relative values of the rate constants k_{ij}. The species A_2 and A_3 can be conformational or configurational isomers or two compounds related by their mutual interconversion through more complex chemistry. Any initial values for the species A_1–A_4 may be used as input; e.g., the initial value A_{30}/A_{20} may not equal the equilibrium value K. If the reactions to A_1 and A_4 from A_2 and A_3, respectively, are bimolecular (or higher order) with respect to a particular reagent, then eq 3–14 can be used *only if* the reactions to product can be treated as pseudo-first-order. The reaction order to A_1 and A_4 need not be identical, however, as the appropriate transformations in the k_{ij} may be made.

Maximum utilization of these results can be had as in any kinetic study if time–concentration data are available. These data would allow the determination of the k_{ij}. However, if only

partial experimental information is available, upper and/or lower limits of some of the rate parameters may be estimated in many cases as described above.

A wide range of values of k_{ij} has been selected and the kinetic results have been evaluated (cases I–IV above). This has allowed the rough generalization that the Curtin–Hammett principle and the Winstein-Holness equation correctly approximate the exact solution *when* $k_{23}, k_{32} > 10k_{21}, 10k_{34}$. However, the more skewed the system, either by grossly differing values of the k_{21}, k_{34} or k_{23}, k_{32} pairs or by situations in which $A_{30}/A_{20} \approx k_{23}/k_{32}$, the greater the above inequality must be for C–H/W–H acceptability.

The relationships between the rate constants and the thermodynamic parameters (E_a, A, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) were examined for Scheme I kinetic systems. It was found that the preexponential factor plays a considerable role in determining the kinetic results. This observation was contrasted to the usual view that the activation energies alone controlled the kinetics. An important consequence of the dominating role of the preexponential factor is that chemical systems which undergo intramolecular conversion to product are more likely to be non-C–H/W–H. This is due to the significantly greater value of the preexponential factor for intramolecular processes than for intermolecular processes (from five to ten orders of magnitude larger).[6a,18,19]

The product ratio A_4/A_1 is always partially dependent on the relative energy levels of the starting forms. This dependency is manifested (albeit in a complex fashion) in the appearance of both k_{23} and k_{32} in eq 3–14. Under C–H/W–H conditions, this dependency is simply directly proportional to the ratio k_{23}/k_{32} (cf. eq 1).

It is hoped that these results will not only allow a better appreciation of the Curtin–Hammett and Winstein–Holness concepts but also serve as the basis for more detailed experimentation in complex chemical systems. We are currently examining the utility of the solution and anticipate that these results will indeed be put to significant use exceeding the simple, but important, analyses initially made possible by the long and well-used approximations of Curtin–Hammett and Winstein–Holness.[26,27]

Registry No.—1, 65414-58-6; 2/3, 938-36-3; 4, 65414-59-7; 5, 470-40-6; 6, 25966-77-2; 7, 26039-33-8; 8c, 59388-64-6; 8t, 59388-65-7; 9c, 24577-10-4; 9t, 15464-01-4; 10c, 694-20-2; 10t, 694-21-3; 11c, 590-18-1; 11t, 624-64-6.

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(6) (a) The treatment given herein is also applicable to kinetic systems in which the products are formed via a bimolecular or higher order reaction but follow pseudo-first-order kinetics. (b) Throughout this paper, A_i ($i = 1$–4) represents the concentration of the chemical entities involved in Scheme I with rate constants k_{ij} for the reaction $A_i \rightarrow A_j$; A_{i0} represents the initial value of A_i. E_{ij}, ΔH_{ij}, and A_{ij} represent the activation energy, the activation enthalpy, and the preexponential factor, respectively, for the $A_i \rightarrow A_j$ transformation.

(7) Reference 2c, p 28.

(8) (a) An extension of the Curtin–Hammett principle to chemical systems involving three or more very rapidly interconverting conformations each reacting slowly to give the same two products with independent rate constants has recently been made[cf. C. Alvarez-Ibarra, F. Fernández-González, A. Garcia-Martinez, R. Pérez-Ossorio, and M. L. Quiroga, *Tetrahedron Lett.*, 2715 (1973), and references cited therein]. (b) For an extension of the Curtin–Hammett principle to systems in which each conformer yields the same two products, see R. O. Hutchins, *J. Org. Chem.*, **42**, 920 (1977).

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(10) The method of solution for systems of equations such as these is given in, e.g., R. C. Buck and E. F. Buck, "Introduction to Differential Equations", Houghton Mifflin Co., Boston, Mass., 1976, Chapter 6; E. L. Ince, "Ordinary Differential Equations", Dover Publications, New York, N.Y., 1956, Chapter IX; I. S. Sokolnikoff and R. M. Redheffer, "Mathematics of Physics and Modern Engineering", McGraw-Hill, New York, N.Y., 1958, pp 95–106.

(11) The primary use of the W–H equation has been the extrapolation of k_{ax} and k_{eq} in a conformationally fixed system (e.g., *cis*- and *trans*-4-*tert*-butyl-cyclohexanol) to a compound (e.g., cyclohexanol) capable of existing in and reacting from two conformations. The inherent assumption in such an analysis is that only two *idealized* conformations are available to the reacting compound. This assumption has been the focus of considerable controversy due to the established importance of substituent-induced conformational changes.[12] Our manuscript does not deal with this extrapolative use of the W–H equation, although it can be used in some cases (i.e., when the W–H approximation to Scheme I fails) to determine the validity of the use of Scheme I to represent a particular chemical system's kinetics. Equations 3–14 will always allow one to derive k_{ij} from time-concentration data for Scheme I systems. However, extrapolations and other uses of these k_{ij} must be evaluated in terms of the assumptions made in the extrapolation procedure. These justifications are independent of the correct derivation of the k_{ij}. For a particularly interesting discussion on the problems that can occur in the extrapolative use of W–H concepts, see H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964).

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exactly (unpublished work). We thank Professor E. L. Eliel for bringing this work to our attention and for helpful discussions.

(27) **Note Added In Proof.** Following acceptance of this paper, N. S. Zefirov reported [*Tetrahedron*, **33**, 2719 (1977)] an analytical expression for A_4/A_1 for Scheme I at reaction completion. This expression does not include arbitrary initial conditions and does not describe the system as a function of time.

Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction. 3. Disubstituted Dienes

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Frontier molecular orbital theory is used to predict the regioselectivity in the Diels–Alder reactions of disubstituted butadienes. The primary orbital interactions which have been used by several investigators to predict the regioselectivity in the Diels–Alder reaction could not account for the regioselectivity observed with 1,2-disubstituted butadienes. When the secondary orbital interactions were included in the theory, the preferred regioisomer was predicted in every case. The frontier molecular orbitals of the dienes and dienophiles were determined by the CNDO/2, INDO, CNDO/S, and Hückel methods.

The regioselectivity of the Diels–Alder reaction has been successfully rationalized by considering only the interactions between the frontier molecular orbitals (FMO) of the diene and the dienophile.[1–5] This approach is based on the second-order perturbation equation for the energy change which accompanies the orbital interactions of the two molecules involved in a cycloaddition reaction.[6] From this theory several investigations[2–5] have used the following generalizations to predict the regioselectivity: (1) the principle stabilization of the transition state arises from the HOMO–LUMO interaction which is the closest in energy (when the FMO interactions have similar energy separations, both interactions are considered); (2) the larger primary orbital coefficient of the diene will bond preferentially with the larger primary orbital coefficient of the dienophile. In fact, Anh et al.[3] has recently applied this approach to approximately 100 examples of the Diels–Alder reaction.

In previous investigations we have found numerous cases in which this approach failed to predict the regioselectivity that was observed.[1] However, these discrepancies were eliminated when the secondary orbital interactions were considered. Consequently, we have added a third generalization in our approach which is as follows: (3) the secondary orbital coefficient of the dienophile will interact preferentially with the larger secondary orbital coefficient of the diene. By considering which regioisomers are favored by the interactions in generalizations 2 and 3 and the relative importance of these generalizations, the preferred regioisomer can be predicted.

In this paper the above theories have been applied to the uncatalyzed Diels–Alder reactions of disubstituted butadienes. In these cases generalizations 2 and 3 favor different regioisomers and the experimentally preferred regioisomer varies with the substituent combination, thereby allowing a critical evaluation of the two theoretical approaches.

Results and Discussion

CNDO/2 calculations predict that the energy separation between the HOMO of the diene and the LUMO of the dienophile is considerably smaller than the energy separation between the LUMO of the diene and the HOMO of the dienophile for all reactions that have been investigated. Thus, the principle stabilization of the transition state will result from the former MO interaction and the latter can be neglected. Consequently, in the frontier molecular orbital approach the second-order perturbation equation simplifies into eq 1 and 2 for the two possible endo approaches of the dienophile to the diene.[7] In the equations the γ_{cc} values are the atomic orbital transition state resonance integrals for the p_z carbon atomic orbitals. The c values are the atomic orbital coefficients in the respective molecular orbitals and the E values are the energies of the interacting frontier molecular orbitals.

Using CNDO/2 FMO energies and coefficients (Table I), the stabilization energy from the interaction of HOMO of the diene and the LUMO of the dienophile has been calculated for the various reactions. A resonance integral of 7 eV for the primary orbital interactions and a resonance integral of 2.8 eV for the secondary orbital interactions were used in the calculations. The value of 7 eV for the resonance integral of the primary orbital interactions was derived from the concerted transition state that ab initio calculations[8] predicted for the cycloaddition of ethylene to butadiene along with consideration for the narrowing of the FMO energy separation in the transition state and a larger than experimental CNDO/2 energy separation between the interacting MO's. The resonance integral for the secondary orbital interactions was assigned a smaller value because the geometry of the transition state favors the overlap between the primary orbitals at the