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STEREOCHEMICAL STUDIES—XXI

GENERAL EQUATION OF RELATIONSHIP BETWEEN PRODUCTS RATIO AND CONFORMATIONAL EQUILIBRIUM

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Abstract—The general equation has been derived relating the products ratio, $P_\infty = C_\infty/B_\infty$, with the rate constants of the reacting conformationally mobile system, $B \leftarrow X \rightleftarrows Y \rightarrow C$. The limiting cases (Curtin–Hammett and conformational equilibrium control) and consequences of this equation are discussed.

Conformational analysis is one of the most developed branches of modern organic chemistry. The ultimate goals of conformational analysis are: (1) to predict the relative stabilities of conformers and the barriers of interconversion and (2) to relate the conformational preferences or relative stability of stereoisomers to reactivity and product distribution.

The second problem is a matter of special interest to organic chemists. It would not be an overstatement to say that extremely wide extension of the conformational concepts is essentially due to their usefulness and productivity in solving problems of reactivity. However, the problem of the relationship between conformational equilibrium and distribution of the products in spite of its importance is far from a solution.[1-7]

Let us consider the present approach to this problem. Suppose that we have the conformational equilibrium of two conformers, $X \rightleftarrows Y$, of one structurally individual compound A. Also assume that each of the conformers, X and Y, produces its individual reaction product, B and C, correspondingly, via its own transition state, $B^{\neq}$ and $C^{\neq}$. Then the general relation of the interconversion in this system can be expressed by Scheme (**1**). The final ratio of the product, P_∞, is

$$A\left\{\begin{tikzcd} X \arrow[r, "k_3"] \arrow[d, shift left, "k_1"] & B \\ Y \arrow[u, shift left, "k_2"] \arrow[r, "k_4"] & C \end{tikzcd}\right. \qquad (1)$$

$$K_{eq} = \frac{k_1}{k_2} = \frac{[Y]_0}{[X]_0} \qquad (2)$$

$$P_\infty = \frac{C_\infty}{B_\infty} \qquad (3)$$

expressed by eqn (3).

Although the set of kinetic equations for system (**1**) can be solved in principle,[8] to the best of our knowledge, there is no such solution, and there is no discussion on this matter in stereochemical literature. In particular, there is no general consideration of the relationship between P_∞ and the values K_{eq} (eqn 2), k_3 and k_4. There are only two separate approaches dealing with two limiting cases.

In the first approach one assumes that conformational equilibrium is extremely rapid and that the concentrations of the conformers, [X] and [Y], are determined by K_{eq}. In other words, one assumes, that the conformational barrier is substantially lower than the reaction barriers, and, therefore, $k_1, k_2 \gg k_3, k_4$ (Case *a*, Figs. 1 and 2). In stereochemical literature this case is known as the "Curtin–Hammett principle".[1-5] According to this principle, the value P_∞ is determined by the difference between the free energies of transition states, $B^{\neq}$ and $C^{\neq}$ (*vide infra*). This assumption can also be used to derive eqn (4) which relates the effective rate constant, K_{eff}, to the partial rate constants of particular conformers.

$$k_{eff} = \Sigma\, n_i k_i \qquad (4)$$

$$k_{eff} = n_1 k_1 + n_2 k_2 \qquad (5)$$

$$k_{eff} = \frac{k_1 K_{eq} + k_2}{K_{eq} + 1} \qquad (6)$$

This relationship was first derived by Winstein and Holness in the form of eqn (5)[5] and by Eliel *et al.* in the form of eqn (6).[1,6]

In the second approach one assumes the opposite extreme, i.e. that the conformational barrier is substantially higher than the reactions barriers, which is expressed in the relationship $k_3, k_4 \gg k_1, k_2$. In this limiting case "... the conclusion would follow that the ratio

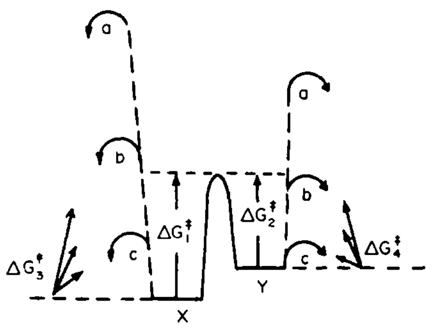


Fig. 1. Free energy diagram for Situation 1 (see text); (a) the Curtin–Hammett case, (b) the intermediate case, (c) the case of conformational equilibrium control.

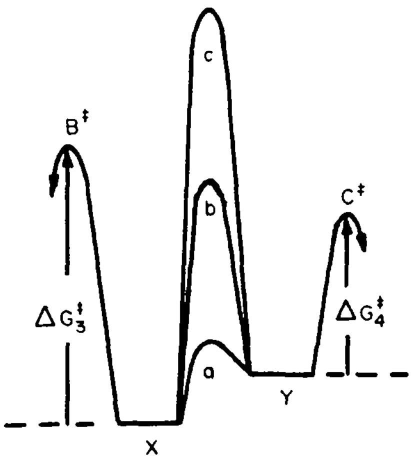


Fig. 2. Free energy diagram for Situation 2 (see text); (a) the Curtin–Hammett case, (b) the intermediate case, (c) the case of conformational equilibrium control.

of the products is equal to the ratio of the populations of the starting states"[1] (Case *c*, Figs. 1 and 2). For example, this limiting case has been used for a conformational equilibrium study of cyclic amines by a kinetically controlled protonation technique.[9] The purpose of this paper is to derive the general equation for P_∞ and thus to clarify the general relationship between P_∞ and rate constants.

RESULTS AND DISCUSSION

Let us accept the general kinetic scheme (1). We assume, therefore, that (i) each conformer gives only its own product, X→B and Y→C, and that (ii) the problem is treated in terms of a first-order model. The sketch of free energy relationships for system (1) is shown in Figs. 1 and 2. A description of the kinetic for the system (1) is given by first-order differential eqns 7–11.

$$\frac{d[X]}{dt} = -(k_1+k_3)[X] + k_2[Y] \tag{7}$$

$$\frac{d[Y]}{dt} = -(k_2+k_4)[Y] + k_1[X] \tag{8}$$

$$\frac{d[B]}{dt} = k_3[X] \tag{9}$$

$$\frac{d[C]}{dt} = k_4[Y] \tag{10}$$

$$\frac{d[A]}{dt} = -k_3[X] - k_4[Y] \tag{11}$$

Before proceeding further, we must evaluate the reality of the chosen model system (1) namely the two restrictions stated above. The first assumption requires that there be no interconversion of the reaction products, B$\rightleftarrows$C, and that the reactions yield different and relatively stable species. In other words we consider a system where a conformationally mobile reactant yields two isomeric (diastereomeric) products. For instance the elimination reaction of type (12) is an example of such a system because the interconversion of the unsaturated products requires the rotation about a double bond. Another example could be the addition of the substituted cyclohexene to the double bond (13), which leads to different configurational isomers for each of the conformers. (For a discussion of configurational relationships see Ref. 7).

The second assumption concerns the first-order model. If the reaction steps were of second order, the solution would become extremely difficult. Experimental conditions can be chosen, however, so as to make the reaction steps pseudo-first-order.[10] In this case the values k_3 and k_4 will be effective rate constants and will equal the product of true constants on the reactant concentration (in appropriate power).

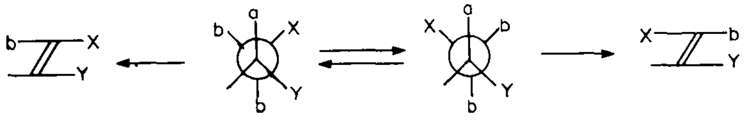
The solution of the set of eqns (7)–(11) is given in the Appendix. It permits us to find the values B_∞, C_∞ and P_∞. The value P_∞ is expressed by eqn (14); *equation* (14) *is the general relationship between the products ratio and the rate constants for system* (1).

$$P_\infty = K_{eq}\cdot\frac{k_4(k_1+k_2+k_3)}{k_3(k_1+k_2+k_4)} \tag{14}$$

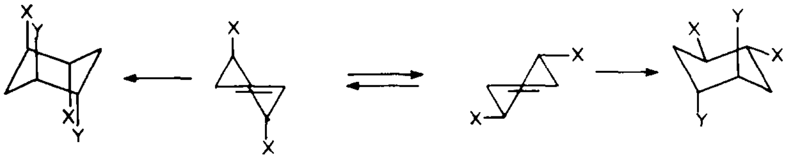
$$P_\infty = K_{eq}\cdot\frac{k_4}{k_3} \tag{15}$$

$$P_\infty = e^{(G_B^{\neq}-G_C^{\neq})/RT}. \tag{16}$$

In analyzing eqn (14), let us, consider the limiting cases. We shall first discuss the Curtin–Hammett case (Case *a*, Figs. 1 and 2). When k_1, $k_2 \gg k_3$, k_4 eqn (14) is simplified to eqn (15) which is one of the mathematical formulations of the Curtin–Hammett principle. It is easy to show (see, for example[1]) that (15) is precisely equivalent to the usual formulation of this principle, expressed by eqn (16). In this connection one widespread inexactitude in the verbal formulation of the Curtin–Hammett principle must be pointed out. In Ref. 5 this principle has been formulated as follows: . . ."the relative amounts of reaction through the transition states $e^{\neq}$ and $a^{\neq}$ (equivalent to $B^{\neq}$ and $C^{\neq}$ in the case discussed, N.Z.) are independent of A or relative proportions of the ground state conformations *e* and *a*, and they depend only on the free energy difference $A^{\neq}$ between the conformationally isomeric transition states $e^{\neq}$ and $a^{\neq}$."



(12)



(13)

Analogous definitions of this principle are widely used in the literature.[1,2] All of them have one feature in common: firstly they disclaim a relationship between P_∞ and K_{eq} and secondly they assert a relationship between P_∞ and $\Delta G^{\ddagger}_{B\text{-}C}$. However, if one uses eqn (16) for the verbal definition of the Curtin-Hammett principle, one has to make the second statement, without any reference to the relationship between P_∞ and K_{eq}. Indeed, the existence of *two* mathematical expressions (15 and 16), permits us to state two different verbal descriptions of the principle discussed. Taking eqn (15), one can say, that P_∞ depends on E_{eq} as well as on the ratio of partial rates, k_4/k_3. Furthermore, it is possible to imagine the following case: if the ratios of the reaction rates, k_4/k_3, are approximately equal for a set of compounds with changeable substituents, for example X for the cyclohexenes (13), the change of the products ratio, P_∞, in this entire set has to be determined solely by the changes of the K_{eq}'s, although the Curtin-Hammett condition, k_1, $k_2 \gg k_3$, k_4, holds.

Now, it is expedient to show, that the applicability of eqns (5) and (6) requires the implementation of the Curtin-Hammett condition. In general the rate of the conversion of compound A (Scheme 1) is completely dependent on the transient concentrations [X] and [Y]. However, if the assumption that this dependence has the effective first-order (eqn 17), is made it leads automatically to the Curtin-Hammett case. Indeed the rate

$$\frac{d[A]}{dt} = -k_{eff}[A] \qquad (17)$$

$$\frac{[Y]}{[X]} = \frac{k_3 - k_{eff}}{k_{eff} - k_4} = const. \qquad (18)$$

expressions are now given by eqns (11) and (17), from which it is easy to obtain eqn (18). Thus the above assumption leads to the conclusion that the ratio of the transient concentrations of conformers, [Y]/[X], does not depend on time. At time $t = 0$, this ratio is evidently equal to $[Y]_0/[X]_0 = K_{eq}$. Starting from this point we may reach two conclusions: it is easy to derive eqns (5) and (6), and it is evident that the ratio [Y]/[X] is the equilibrium one in the whole course of the reaction, which means that k_1, $k_2 \gg k_3$, k_4 and that Curtin-Hammett principle holds.

Consider now the second limiting case (Case *c*, Figs. 1 and 2). When k_3, $k_4 \gg k_1$, k_2 eqn (14) reduces to $P_\infty = K_{eq}$. Thus, this is the case of pure conformational equilibrium control because the product ratio is determined solely by the position of the equilibrium.

Consider finally the general case when the magnitudes of k_1 and k_2 on the one hand and of k_3 and k_4 on the other hand are of the same order. For this complex case we need to apply general eqn (14). To analyse this case we shall discuss two model situations:

Situation 1. We assume as constants (i) $\Delta G_{eq} =$ 1 kcal/mol, (ii) the activation barrier of conformational equilibrium ($\Delta G_1^{\neq} = 18$ kcal/mol) and (iii) the difference between activation free energies ($\Delta G_3^{\neq} - \Delta G_4^{\neq} =$ const.), and shall vary the magnitude $\Delta G_3^{\neq}$ (and consequently $\Delta G_4^{\neq}$). This situation is shown in Figs. 1 and 3.

Situation 2. We assume as constants (i) $\Delta G_{eq} =$ 1 kcal/mol, (ii) $\Delta G_3^{\neq} = 15$ kcal/mol and (iii) $\Delta G_4^{\neq} =$ *10 kcal/mol* and shall vary the barrier of conformational equilibrium. This situation is shown in Figs. 2 and 4.

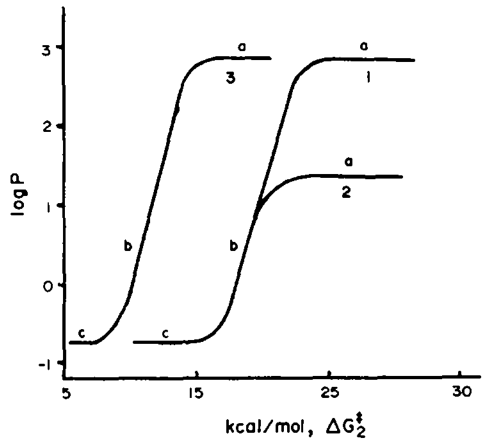


Fig. 3. Model calculations of Situation 1: curve $1 - \Delta G_1^{\neq} =$ 18 kcal/mol, $\Delta G_3^{\neq} - \Delta G_4^{\neq} = 5$ kcal/mol; curve $2 - \Delta G_1^{\neq} =$ 18 kcal/mol, $\Delta G_3^{\neq} - \Delta G_4^{\neq} = 3$ kcal/mol; curve $3 - \Delta G_1^{\neq} =$ 10 kcal/mol, $\Delta G_3 - \Delta G_4^{\neq} = 5$ kcal/mol; (a) the Curtin-Hammett plateau, (b) the intermediate region, (c) the plateau of conformational equilibrium control.

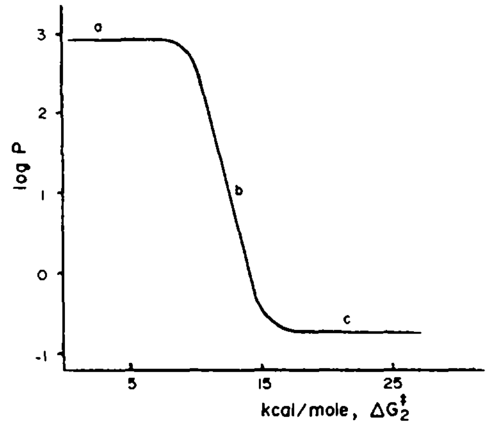


Fig. 4. Model calculation of Situation 2 using $\Delta G_{eq} = 1$ kcal/mol, $\Delta G_3^{\neq} = 15$ kcal/mol, $\Delta G_4^{\neq} = 10$ kcal/mol; (a) the Curtin-Hammett plateau, (b) the intermediate region, (c) the plateau of conformational equilibrium control.

Situation 2. We assume as constants (i) $\Delta G_{eq} =$ 1 kcal/mol, (ii) $\Delta G_3^{\neq} = 15$ kcal/mol and (iii) $\Delta G_4^{\neq} =$ 10 kcal/mol and shall vary the barrier of conformational equilibrium. This situation is shown in Figs. 2 and 4.

We first examine situation 1. For $\Delta G_3^{\neq} - \Delta G_4^{\neq} =$ 5 kcal/mol the dependence of log P_∞ on $\Delta G_3^{\neq}$ is represented by curve 1 in Fig. 3. This nice curve has two plateaux *a* and *c* in a wide range of $\Delta G_3^{\neq}$ and a relatively narrow intermediate region, *b*. Both plateaux correspond to the limiting cases discussed above namely the Curtin-Hammett case (*a*) and the conformational equilibrium control case (*c*). Decreasing the value of $\Delta G_3^{\neq} - \Delta G_4^{\neq}$ leads to a decrease in the range of log P_∞ values (Fig. 3, curve 2 for $\Delta G_3^{\neq} - \Delta G_4^{\neq} = 3$ kcal/mol). Lowering the conformational barrier shifts the picture on abscissa (Fig. 3, curve 3 for $\Delta G_1^{\neq} = 10$ kcal/mol) which leads to a narrowing of the plateau of conformational equilibrium control, *c*. This result, therefore, explains the wide application of the Curtin-Hammett principle for the usual conformational barriers observed in noncyclic systems.

Analogous results can be obtained in an examination of situation 2. The curve shown in Fig. 4 illustrates the dependence of log P_∞ on the conformational barrier in accordance with scheme depicted in Fig. 2. It contains again the two plateaux of the limiting cases, *a* and *c*, and the relatively narrow path (*b*) of a transition between them.

In conclusion one general remark is in order. Earlier one clear-cut tendency which could be observed was to use the kinetic approach for determining the position of conformational equilibria, K_{eq}. Now the conformers ratio may be obtained directly by physical, for example spectroscopic, methods. Therefore, the more attractive goal is on the contrary to determine the reactivity of individual conformers. Equation (14) permits us to find the dependence between k_3 and k_4 if the rates of equilibrium are known. However, the determination of k_3 and k_4 themselves requires the knowledge not only of the P_∞ but of the transient concentrations of the products, [B] and [C]. The set of differential equations of system (1) can be solved analytically,[11] but this problem is beyond the scope of the present work.

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[11] This subject will be discussed in separate publication (together with V. A. Palyulin).

APPENDIX

Let us derive eqn (14). Using the relationship [A] = [X] + [Y], eqns (7) and (11) can be transformed into eqns (19) and (20) correspondingly.

$$\frac{d[X]}{dt} = k_2[A] - (k_1 + k_2 + k_3)[X] \qquad (19)$$

$$\frac{d[A]}{dt} = -k_4[A] + (k_4 - k_3)[X]. \qquad (20)$$

Multiplying eqn (19) by k_4 and eqn (20) by k_2, and then adding them yields eqn (21):

$$\frac{k_2}{k_5} \cdot \frac{d[A]}{dt} + \frac{k_4}{k_5} \cdot \frac{d[X]}{dt} = [X], \qquad (21)$$

where the new constant $k_5 = k_2\,(k_4 - k_3) - k_4(k_1 + k_2 + k_3)$. Substituting for [X] eqn (21) in eqn (9) and integrating gives eqn (22):

$$\int_0^{B_\infty} d[B] = k_3 \left[\frac{k_2}{k_5} \int_{A_0}^{0} d[A] + \frac{k_4}{k_5} \int_{X_0}^{0} d[X] \right]. \qquad (22)$$

The result of integrating (22) is eqn (23):

$$B_\infty = -k_3 \left[\frac{k_2}{k_5} \cdot A_0 + \frac{k_4}{k_5} \cdot X_0 \right] \qquad (23)$$

$$A_0 = \frac{k_1 + k_2}{k_2} \cdot X_0 \qquad (24)$$

Using eqn (24), the B_∞ is expressed by eqn (25):

$$B_\infty = \frac{k_3(k_1 + k_2 + k_4)}{k_1k_4 + k_2k_3 + k_3k_4} X_0 \qquad (25)$$

Analogously, the C_∞ is expressed by eqn (26):

$$C_\infty = \frac{k_4(k_1 + k_2 + k_3)}{k_1k_4 + k_2k_3 + k_3k_4} Y_0. \qquad (26)$$

Finally, dividing eqn (26) by eqn (25) will result in the general eqn (14).