



Extending the Curtin–Hammett principle: the relative rates of intramolecular cyclisation versus intermolecular processes



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ABSTRACT

A common tactic for synthetic chemists is to employ high dilution to ensure cyclisation is favoured over intermolecular processes. This intuitive strategy is ubiquitous in synthesis, although a quantitative analysis of these systems has not previously been proposed. In this Letter a theoretical analysis of the Curtin–Hammett principle when applied to systems in which the two equilibrating reactive species each undergo reactions of different orders is reported. This quantitative analysis predicts that a change in product distribution will be observed over time (under fixed conditions). However, the product ratios may be controlled by the addition of excess reagent(s) or by altering their concentration(s), consistent with established best practice (i.e., high dilution to maximise the formation of cyclised products, and high concentrations of reagents to maximise the formation of products resulting from intermolecular reactions).

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Considering cyclisation processes in which conformationally labile substrates may undergo different reactions, synthetic chemists have routinely employed the tactic of high dilution to retard the rate of intermolecular processes and thus favour the formation of the desired cyclised products.^{1,2} In these systems unimolecular cyclisation proceeds via one reactive conformation whereas intermolecular displacement (i.e., a bimolecular process such as dimerisation or reaction with an external agent) may proceed via an alternative reactive conformation. The well-known Curtin–Hammett principle^{3,4} is concerned with the product ratios obtained from a reaction when there are two competing pathways each proceeding from one of two different interconverting species (e.g., intermediates, conformers or isomers). It is characterised by a constant product ratio being observed over time, and is frequently invoked when considering organic reaction mechanisms; several detailed analyses of the Curtin–Hammett principle have been reported over the years.^{5–10} For a system where two species A and B interconvert rapidly, the Curtin–Hammett principle states that the product ratios are not determined by the relative Gibbs energies of the two reactive species, rather it is the difference in activation Gibbs energy for the two pathways that determines the ratio of the products P₁ and P₂. The Curtin–Hammett principle is only

applicable for irreversible reactions of the same order where the activation Gibbs energy for interconversion of the two different species is far less than the activation Gibbs energy to form the different products. The requirements to satisfy the Curtin–Hammett principle are that k_{AB} and k_{BA} are both at least an order of magnitude greater than the larger of k_1 and k_2 , and that the equilibrium between the two species is no more than 10:1 in favour of either species (Fig. 1).^{11,12}

The Curtin–Hammett principle is routinely applied to systems in which the two interconverting species undergo the *same* mode of first-order reaction to give rise to two different products, and previous work has also examined the case where the interconverting species react via the *same* pathway under non-first-order kinetics.¹³ However, systems where the two interconverting species undergo *different* reaction pathways have not previously been rationalised by the Curtin–Hammett principle. Herein we describe a theoretical analysis of systems where alternative reaction manifolds may be accommodated within the Curtin–Hammett principle, leading to a prediction that a change in product distribution will be observed over time. In particular, we contrast reactions where species A and B undergo first order kinetics (as in Fig. 1) with the case where one undergoes second order kinetics but the other reacts via a first order pathway. Whilst the focus of this Letter is systems in which cyclisation is competing with intermolecular processes, this analysis is also applicable to other reaction manifolds of differing orders.

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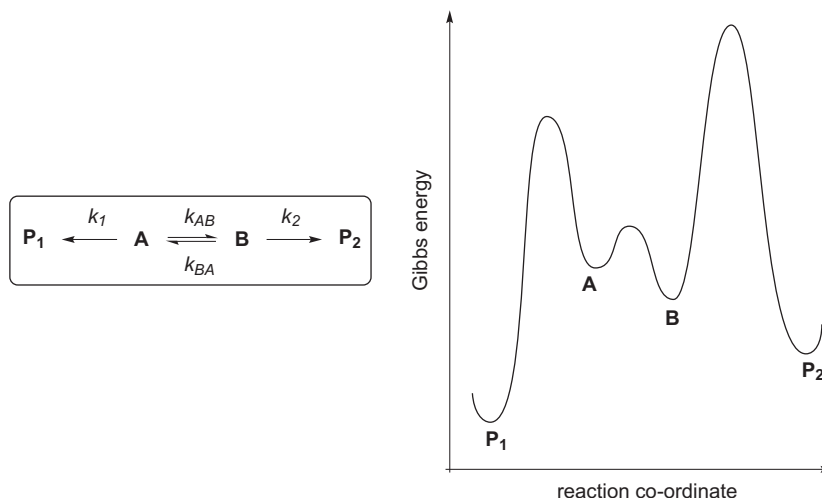
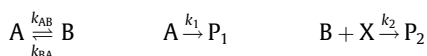


Figure 1. Reaction profile diagram demonstrating the Curtin–Hammett principle.

Theoretical analysis

We consider a system of two reactants, A and B, which rapidly interconvert. These reactants follow differing reaction pathways to form products: species A undergoes an irreversible unimolecular reaction to form product P₁ and species B undergoes an irreversible bimolecular reaction with species X to form product P₂. The overall reaction scheme is thus:



At this stage we may consider two limiting cases regarding the concentration of species X:

1. In the limit $C_X \gg C_B$ the bimolecular reaction between B and X is reduced to a pseudo-first order process and the system becomes equivalent to the classical Curtin–Hammett system.^{3,4} Thus the product distribution becomes independent of the position of equilibrium between A and B.
2. In the limit $C_X \ll C_B$ the supply of species X will be quickly exhausted. Consequently the conversion of B into P₂ will be limited and only P₁ can be formed via the conversion of A into B.

In between these two limits, we must solve the coupled rate equations in order to understand the product distribution. The gain and loss of each species is given by:

$$\frac{dC_A}{dt} = -k_1 C_A - k_{AB} C_A + k_{BA} C_B \quad (1)$$

$$\frac{dC_B}{dt} = -k_2 C_B C_X + k_{AB} C_A - k_{BA} C_B \quad (2)$$

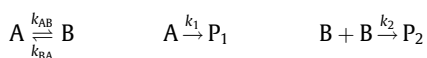
$$\frac{dC_X}{dt} = -k_2 C_B C_X \quad (3)$$

$$\frac{dC_{P_1}}{dt} = +k_1 C_A \quad (4)$$

$$\frac{dC_{P_2}}{dt} = +k_2 C_B C_X \quad (5)$$

Special case: species B reacts with itself

We now consider the special case in which species B reacts with itself such that:



since this is amenable to analytical solution.

The interconversion of A and B is rapid (i.e., $k_{AB}, k_{BA} \gg k_1, k_2$), thus we shall assume the reaction to be at equilibrium at all times. The concentrations of species A and B (denoted C_A and C_B , respectively) are therefore related via:

$$\frac{C_B}{C_A} = K = \frac{k_{AB}}{k_{BA}} \quad (6)$$

where K is the equilibrium constant for the interconversion reaction. Under such conditions the rate equations for this system are therefore:

$$\frac{dC_A}{dt} = -k_1 C_A \quad (7)$$

$$\frac{dC_B}{dt} = -k_2 C_B^2 \quad (8)$$

$$\frac{dC_{P_1}}{dt} = k_1 C_A \quad (9)$$

$$\frac{dC_{P_2}}{dt} = \frac{1}{2} k_2 C_B^2 \quad (10)$$

We may solve this system of equations by considering the combined rate of loss of reactants:

$$\frac{dC_A}{dt} + \frac{dC_B}{dt} = -k_1 C_A - k_2 C_B^2 \quad (11)$$

We now define the term C_{AB} :

$$C_{AB} = C_A + C_B \quad (12)$$

$$= C_A + K C_A \quad (13)$$

$$= C_A (1 + K) \quad (14)$$

which implies:

$$C_A = \left[\frac{1}{1 + K} \right] C_{AB} \quad (15)$$

$$C_B = \left[\frac{K}{1 + K} \right] C_{AB} \quad (16)$$

Substituting Eqs. 12, 15 and 16 into Eq. 11 we obtain:

$$\frac{dC_{AB}}{dt} = -k_a C_{AB} - k_b C_{AB}^2 \quad (17)$$

where k_a and k_b are constants given by:

$$k_a = k_1 \left[\frac{1}{1 + K} \right] \quad (18)$$

$$k_b = k_2 \left[\frac{K}{1 + K} \right]^2 \quad (19)$$

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