A Generalized Pre-Equilibrium Approximation in Chemical and Photophysical Kinetics

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For most mechanisms of chemical reactions and molecular photophysical processes the time evolution of the concentration of the intervening species cannot be obtained explicitly. The most commonly used methods to derive the approximate analytical expressions are the steady-state approximation and the pre-equilibrium approximation (PEA), also called the equilibrium approximation *(1–3)*. This last approximation is used when fast reversible reactions precede slower reactions in a mechanism *(1–3)*. General conditions for the applicability of the PEA, as well as the corresponding general solution, are not available in the literature, however several specific cases have been considered *(1–4)*.

In this article, we discuss two specific cases and then consider the more general situation. It is shown that the long-time behavior of systems subjected to pre-equilibration can be obtained by a simple kinetic reasoning. General expressions for the time evolution and respective rate constants are derived and some applications discussed.

Pre-Equilibrium Approximation: Specific Cases

Lindemann Scheme

The PEA is often described in textbooks in connection with the following mechanism *(1–4)*,

$$\mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \xrightarrow{k_3} \mathrm{C}$$

for which an exact explicit solution exists *(1–4)*. Since this mechanism is composed in its entirety of unimolecular steps, the solution can be obtained by the eigenvalue method *(1–3, 5)*. It can be shown that the time evolution of any of the participating species is given by a sum of three exponentials, whose arguments are the eigenvalues of the kinetic matrix. One of the eigenvalues, corresponding to the long-time limit (true equilibrium) is zero, while the other two are negative, and given by algebraic expressions involving the rate constants of the elementary steps *(1–4)*.

This mechanism applies to several real cases, namely acid–base equilibrium preceding a first-order or pseudo first-order step *(1, 2)*, and is also the simplest model for enzyme-catalyzed reactions and unimolecular reactions in the gas phase (Lindemann mechanism; ref *1, 3*). Conditions of applicability of the PEA approximation to this mechanism have been discussed in detail *(4)*. It was found that the PEA applies if $(k_1 + k_2) >> k_3$ and this only after an induction period (equilibration time) of $1/(k_1 + k_2)$. One frequently finds in the literature a conflicting (and incorrect) statement, namely that the PEA applies only if $k_2 >> k_3$. While this is an intuitive condition (several "pre-equilibrating" cycles A → B → A must occur before the reaction can proceed as B → C), a counter example shows it to be too restrictive. Consider the case where $k_2 << k_3$. From the general condition $(k_1 + k_2) >> k_3$ it follows that $k_1 >> k_3$ and therefore $k_1 >> k_2$. This implies that the equilibrium is shifted to the right. After the equilibration time (in this case, $1/k_1$), one has a practically complete conversion of A into B, before any significant quantity of C has been formed. No significant back reaction B → A is possible, since k_2 is small, but a quasi-equilibrium situation is nevertheless attained. In this case, the equilibration time is simply the time needed for almost complete conversion of A into B, by an essentially irreversible reaction. Strictly speaking, the condition $k_2 \neq 0$ should be specified, for an equilibrium, however shifted, to be possible, but it makes no difference, as shown. It is thus concluded that the condition $k_2 >> k_3$ is only necessary if k_1 is of the order or smaller than k_3.

Application of the PEA yields a common rate constant describing the long-time evolution of all three species A, B, and C,

$$[\mathrm{A}] = \frac{k_2}{k_1 + k_2}[\mathrm{A}]_0 e^{-kt} \qquad (1)$$

$$[\mathrm{B}] = \frac{k_1}{k_1 + k_2}[\mathrm{A}]_0 e^{-kt} \qquad (2)$$

$$[\mathrm{C}] = [\mathrm{A}]_0\left(1 - e^{-kt}\right) \qquad (3)$$

where,

$$k = \frac{k_1 k_3}{k_1 + k_2} \qquad (4)$$

assuming that $[\mathrm{B}]_0 = [\mathrm{C}]_0 = 0$. The overall rate constant k can be rewritten as

$$k = \frac{k_1}{k_1 + k_2} k_3 \qquad (5)$$

and viewed as the product of the molar fraction of reagent molecules (A and B) present in the reactive form (B), x_B, given by $k_1/(k_1 + k_2)$, times the intrinsic rate constant (k_3),

$$k = x_B k_3 \qquad (6)$$

It is of interest to note that under the conditions of applicability of the PEA, the two eigenvalues of the system are $-(k_1 + k_2)$ and $-k$. One has $(k_1 + k_2) >> k$, hence after a short period of time dominated by $k_1 + k_2$ and corresponding to pre-equilibration of A and B, the system slowly evolves according to the smaller (in modulus) eigenvalue, $-k$. It is under this regime that the PEA is valid.

Monomer–Excimer Scheme

A slightly more complex mechanism is

$$\mathrm{D} \xleftarrow{k_4} \mathrm{A} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \xrightarrow{k_3} \mathrm{C}$$

This mechanism applies, for instance, to monomer–excimer kinetics, where A is an excited monomer and B is an excimer. The exact, explicit solution is again known *(4, 6)*. Application of the PEA approximation now yields

$$[\mathrm{A}] = \frac{k_2}{k_1 + k_2}[\mathrm{A}]_0 e^{-kt} \tag{7}$$

$$[\mathrm{B}] = \frac{k_1}{k_1 + k_2}[\mathrm{A}]_0 e^{-kt} \tag{8}$$

$$[\mathrm{C}] = \frac{k_1 k_3}{k_1 k_3 + k_2 k_4}[\mathrm{A}]_0\left(1 - e^{-kt}\right) \tag{9}$$

$$[\mathrm{D}] = \frac{k_2 k_4}{k_1 k_3 + k_2 k_4}[\mathrm{A}]_0\left(1 - e^{-kt}\right) \tag{10}$$

where,

$$k = \frac{k_1 k_3 + k_2 k_4}{k_1 + k_2} \tag{11}$$

assuming that $[\mathrm{B}]_0 = [\mathrm{C}]_0 = [\mathrm{D}]_0 = 0$. In the monomer–excimer case, this situation corresponds to the so-called high-temperature behavior *(6)*, where a fast equilibrium in the excited state exists, and for which a single exponential decay (after a short induction period) with a common decay time for both monomer and excimer is predicted *(6)*. The equation for the rate constant k, given by eq 11, can be rewritten as

$$k = \frac{k_1}{k_1 + k_2}k_3 + \frac{k_2}{k_1 + k_2}k_4 \tag{12}$$

and it can be viewed as the weighted sum of the rate constants k_3 and k_4 of the two consumption paths, the weighting factors being the molar fractions of reactive molecules (B and A, respectively) in each of the paths,

$$k = x_\mathrm{B} k_3 + x_\mathrm{A} k_4 \tag{13}$$

Pre-Equilibrium Approximation: General Case

We now consider the general case of a fast pre-equilibrium (by means of unimolecular or pseudo-unimolecular *internal* steps) involving a number of species A_i (i = 1, 2, ..., n), each of which may in turn react to yield other species not participating in the fast pre-equilibrium, by means of *outgoing* steps, as shown in Scheme I.

It is assumed that the internal steps are of the type,

$$\mathrm{A}_i + \mathrm{B}_j \rightleftharpoons \mathrm{A}_k + \mathrm{B}_l$$

where the B_i are only involved in internal steps, and do not significantly change their concentrations with time, while the A_i also participate in outgoing steps of the type

$$\mathrm{A}_i \longrightarrow \mathrm{C}_j + \ldots$$

Based on the specific results discussed above, it seems reasonable to suppose that the general form of the long-time rate constant k obtained by the PEA will be,

$$k = \sum_{i=1}^{n} x_i \Gamma_i \tag{14}$$

where the x_i are the *equilibrium* molar fractions of the A_i,

$$x_i = \frac{[\mathrm{A}_i]}{\sum_{i=1}^{n}[\mathrm{A}_i]} \tag{15}$$

and the Γ_i are the respective rate constants for the outgoing, irreversible steps, as shown in Scheme 1. The molar fractions x_i can be related to the equilibrium constants of the internal steps.

A simple proof that eq 14 is correct is as follows: For any of the A_i (i = 1, 2, ..., n), the following rate equation holds,

$$\frac{\mathrm{d}[\mathrm{A}_i]}{\mathrm{d}t} = r_i - \Gamma_i[\mathrm{A}_i] \tag{16}$$

where r_i is the global rate for A_i resulting from all internal steps (unimolecular or pseudo-unimolecular). Summing all rate eqs 16, one gets

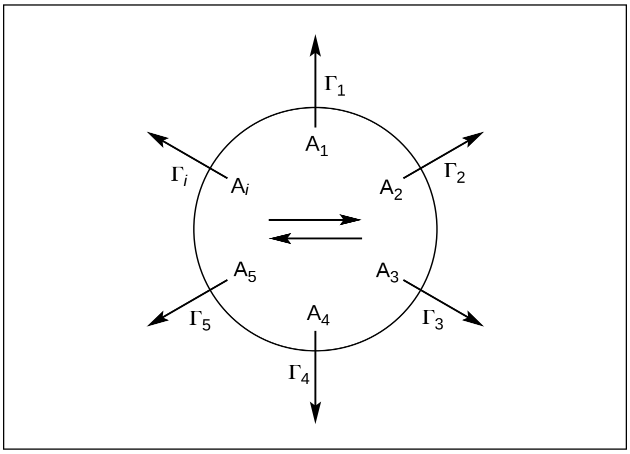
$$\frac{\mathrm{d}\sum_{i=1}^{n}[\mathrm{A}_i]}{\mathrm{d}t} = \sum_{i=1}^{n} r_i - \sum_{i=1}^{n}\Gamma_i[\mathrm{A}_i] \tag{17}$$

Now, $\sum_i r_i = 0$ for all times, since the total number of moles of the A_i is conserved for *internal* reactions, and eq 17 becomes

$$\frac{\mathrm{d}\sum_{i=1}^{n}[\mathrm{A}_i]}{\mathrm{d}t} = -\sum_{i=1}^{n}\Gamma_i[\mathrm{A}_i] \tag{18}$$

After the time lapse needed for equilibration, eq 15 must hold, and eq 18 becomes

$$\frac{\mathrm{d}\sum_{i=1}^{n}[\mathrm{A}_i]}{\mathrm{d}t} = -\left(\sum_{i=1}^{n} x_i\Gamma_i\right)\left(\sum_{i=1}^{n}[\mathrm{A}_i]\right) \tag{19}$$



Scheme I. Generalized scheme for the outgoing, irreversible steps, where Γ_i are the rate constants. The products are not shown.

Since the equilibrium molar fractions x_i are time-independent (this would not be true in general if the B_i significantly changed their concentrations with time), a single exponential decay of $\sum_i [A_i]$ follows from eq 19,

$$\sum_{i=1}^{n}[A_i] = \left(\sum_{i=1}^{n}[A_i]_{eq}\right)\exp(-kt) \tag{20}$$

where the rate constant k is given by eq 14, and $[A_i]_{eq}$ stands for the concentration of A_i upon full equilibration, *in the absence of outgoing steps*. Since, from eq 15, $[A_i]$ is proportional to $\sum_i [A_i]$, one finally has

$$[A_i] = x_i\left(\sum_{i=1}^{n}[A_i]_{eq}\right)\exp(-kt) \tag{21}$$

again with k given by eq 14. A more general derivation of eq 14 is given in ref *7*.

Note that one cannot assume that after the equilibration time one will have exactly $r_i = 0$ (i = 1, 2, ..., n) in eq 16, otherwise the equilibrium mole fractions would not be time-independent, since the disappearance rates Γ_i are in general different for each species. This observation serves to stress that the fast equilibration not only occurs at the early stages of the reaction, just before the PEA becomes valid, but keeps going at latter times, maintaining a state of (dynamic) equilibrium.

The validity of eq 21 rests on the assumption of a fast pre-equilibration process, with respect to the characteristic times of the outgoing processes. These are given by the inverse of the rate constants Γ_i. The internal pre-equilibrium must therefore be attained in a time considerably shorter than the smallest $1/\Gamma_i$.

A still more general situation can be envisaged if outgoing bimolecular steps of the following type

$$A_i + A_j \longrightarrow C_k + \ldots$$

are also allowed. In such a case eq 16 becomes

$$\frac{d[A_i]}{dt} = r_i - \left(\sum_{j=1}^{n}k_{ij}[A_j]\right)[A_i] - \Gamma_i[A_i] \tag{22}$$

and eq 17 becomes

$$\frac{d\sum_{i=1}^{n}[A_i]}{dt} = \sum_{i=1}^{n}r_i - \sum_{i=1}^{n}\sum_{j=1}^{n}k_{ij}[A_i][A_j] - \sum_{i=1}^{n}\Gamma_i[A_i] \tag{23}$$

Instead of eq 19, one now has,

$$\frac{d\sum_{i=1}^{n}[A_i]}{dt} = -\left(\sum_{i=1}^{n}\sum_{j=1}^{n}x_i x_j k_{ij}\right)\left(\sum_{i=1}^{n}[A_i]\right)^2 - \left(\sum_{n=1}^{n}x_i\Gamma_i\right)\left(\sum_{i=1}^{n}[A_i]\right) \tag{24}$$

whose solution is

$$[A] = \frac{[A]_{eq}}{\left(1 + \frac{k_2[A]_{eq}}{k_1}\right)\exp(k_1 t) - \frac{k_2[A]_{eq}}{k_1}} \tag{25}$$

where,

$$[A] = \sum_{i=1}^{n}[A_i];\quad [A]_{eq} = \sum_{i=1}^{n}[A_i]_{eq};$$

$$k_1 = \sum_{i=1}^{n}x_i\Gamma_i;\quad k_2 = \sum_{i=1}^{n}\sum_{j=1}^{n}x_i x_j k_{ij}$$

If $k_2 = 0$, eq 25 reduces to eq 20, which has the familiar form of the elementary first-order reaction $A \rightarrow P$. If, on the other hand, $k_1 = 0$, then eq 25 becomes,

$$[A] = \frac{[A]_{eq}}{1 + k_2[A]_{eq}t} \tag{26}$$

which has now the familiar form of the elementary second-order reaction $2A \rightarrow P$. The more general eq 25 corresponds to mixed first- and second-order kinetics, occurring for instance in triplet state decay kinetics in solution, where unimolecular decay and triplet–triplet annihilation compete *(6)*.

Discussion and Applications

A Probabilistic View

It is interesting to note that the form of eq 14 can be understood on the grounds of a simple probabilistic argument: In a situation of fast equilibration, each species A_i can be viewed as a specific state of an abstract entity A, that is continuously changing between these states and can be found in each with probability x_i. In this way, the rate constant for the decay of A (outgoing steps) will be the weighted sum of the decay rate constants of all states, the weighting factor being the respective probability.

In some cases, the species A is real, and the A_i are its states. For instance, in a gas phase unimolecular reaction, an energized molecule with a given vibrational energy content frequently redistributes this energy among the normal modes, sampling many isoenergetic vibrational states, each with a specific reaction rate *(1, 3)*. Also, in the computation of the rate constant of an elementary reaction, it is usually assumed that a Boltzmann distribution is maintained throughout the reaction; that is, that a fast equilibration with the thermal reservoir exists. In this case, a continuum of states is usually assumed, and the summation in eq 14 is replaced by an integral, as is done in the usual expression for the rate constant of an elementary bimolecular reaction according to the collision theory *(1–3)*.

The existence of a fast pre-equilibrium allows us therefore to qualitatively view the ensemble of the A_i species (i = 1, 2, …, n) as a single species, given their fast interconversion by means of unimolecular or pseudo-unimolecular steps. This imaginary species reacts according to familiar rate laws, eqs 20, 25, and 26, their form being dictated by the type of the outgoing elementary steps.

A Case with Unimolecular Outgoing Steps and Multiple Equilibria

As a specific application of eq 14, consider the simplest mechanism for noncompetitive enzyme inhibition *(8, 9)*,

$$\mathrm{E} + \mathrm{S} \rightleftharpoons \mathrm{ES} \qquad (K_\mathrm{S})$$

$$\mathrm{ES} + \mathrm{I} \rightleftharpoons \mathrm{ESI} \qquad (K_\mathrm{I})$$

$$\mathrm{ES} \xrightarrow{k_\mathrm{P}} \mathrm{E} + \mathrm{P}$$

where E is the free enzyme, S is the substrate, ES is the enzyme–substrate complex, I is the inhibitor, ESI is the enzyme–substrate–inhibitor complex, and P is the reaction product. The equilibrium constants K_S and K_I are given by

$$K_\mathrm{S} = \frac{[\mathrm{E}][\mathrm{S}]}{[\mathrm{ES}]} \tag{27}$$

$$K_\mathrm{I} = \frac{[\mathrm{ES}][\mathrm{I}]}{[\mathrm{ESI}]} \tag{28}$$

It is assumed, as usual, that the substrate concentration is much higher than the total enzyme concentration, [S] >> $[\mathrm{E}]_\mathrm{t}$ and that it does not change significantly in the time range of the kinetic experiment. Under the PEA assumption (which is not obeyed in some enzymatic systems), the species in fast internal equilibrium are S, ES, and ESI, and the unimolecular outgoing step is the last reaction of the mechanism. After the fast pre-equilibration period, and as long as [S] is essentially constant, the product concentration evolves with time according to

$$[\mathrm{P}] = [\mathrm{S}]\left(1 - e^{-kt}\right) \simeq [\mathrm{S}]kt \tag{29}$$

where the rate constant k is, from eq 14,

$$k = x_\mathrm{ES} k_\mathrm{P} \tag{30}$$

and x_ES is the fraction of substrate present as ES

$$x_\mathrm{ES} = \frac{[\mathrm{ES}]}{[\mathrm{S}]_t} \simeq \frac{[\mathrm{ES}]}{[\mathrm{S}]} \tag{31}$$

Since

$$[\mathrm{ES}] = x'_\mathrm{ES}[\mathrm{E}]_t \tag{32}$$

where x'_ES is the fraction of enzyme present as ES,

$$x'_\mathrm{ES} = \frac{[\mathrm{ES}]}{[\mathrm{E}]_t} \simeq \frac{1}{1 + \dfrac{K_\mathrm{S}}{[\mathrm{S}]} + \dfrac{[\mathrm{I}]}{K_\mathrm{I}}} \tag{33}$$

one finally gets for the rate constant

$$k = k_\mathrm{P} x'_\mathrm{ES}\frac{[\mathrm{E}]_t}{[\mathrm{S}]} = \frac{k_\mathrm{P}}{K_\mathrm{S} + [\mathrm{S}]\left(1 + \dfrac{[\mathrm{I}]}{K_\mathrm{I}}\right)}[\mathrm{E}]_t \tag{34}$$

and for the rate of product formation v,

$$v = k[\mathrm{S}] = \frac{k_\mathrm{P}}{K_\mathrm{S} + [\mathrm{S}]\left(1 + \dfrac{[\mathrm{I}]}{K_\mathrm{I}}\right)}[\mathrm{S}][\mathrm{E}]_t \tag{35}$$

This relation is also obtained by application of the steady-state approximation *(8)*, the only difference being that K_S is replaced by the Michaelis constant.

A Case with Bimolecular Outgoing Steps

As a specific application of eq 26, consider the mechanism for decomposition of hydroperoxyl radicals in aqueous solution *(10)*,

$$\mathrm{HO_2} \rightleftharpoons \mathrm{H^+} + \mathrm{O_2^-}$$

$$\mathrm{HO_2} + \mathrm{HO_2} \xrightarrow{k_a} \mathrm{H_2O_2} + \mathrm{O_2}$$

$$\mathrm{HO_2} + \mathrm{O_2^-} \xrightarrow{k_b} \mathrm{HO_2^-} + \mathrm{O_2}$$

where the acid–base equilibrium is fast compared to the disproportionation reactions *(10)*. The interconverting species are in this case the hydroperoxyl radical, $\mathrm{HO_2}$, and the superoxide radical, $\mathrm{O_2^-}$, by means of the first (reversible) reaction, and the two outgoing steps are the other two reactions, both bimolecular. The rate constant k_2 of eq 26 is now

$$k_2 = 2x_1^2 k_a + 2x_1 x_2 k_b = 2\frac{k_a + \dfrac{K}{[\mathrm{H^+}]}k_b}{\left(1 + \dfrac{K}{[\mathrm{H^+}]}\right)^2} \tag{36}$$

where x_1 and x_2 are the equilibrium mole fractions of $\mathrm{HO_2}$ and $\mathrm{O_2^-}$, respectively, and K is the acidity equilibrium constant

$$K = \frac{[\mathrm{H^+}][\mathrm{O_2^-}]}{[\mathrm{HO_2}]} \tag{37}$$

Conclusions

The pre-equilibrium approximation is one of several useful approximation methods that allow one to go from complex systems of differential equations (the kinetic rate equations) to simple explicit solutions. Its discussion in textbooks is usually limited to a few particular cases. This paper presents a more general view of the pre-equilibrium approximation, along with the respective solution. Apart from the examples chosen, many other situations, chemical or photophysical, can be envisaged where eqs 14, 21, and 25 will be useful.

Acknowledgment

This work was carried out within project POCTI 34400/QUI/2000 (FCT, Portugal).

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