KINETIC ASPECTS OF THE SYNTHESES USING SHORT-LIVED RADIONUCLIDES

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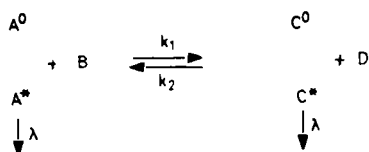Box 531, S-751 21 Uppsala (Sweden)*

In syntheses using short-lived radionuclides, such as ^{11}C, the reaction conditions are usually such that the concentrations of the reactants, except for the labelled reactant, can be considered constant during the reaction. Two kinetic models have been investigated — irreversible and reversible bimolecular elementary reactions. The influence of the rate constants, of the equilibrium constants, and of the ratio between the starting reactants on the yield of the labelled product has been studied. The results show that, even in cases with unfavourable equilibrium constants, high yields of the labelled products can be obtained if the rate constant for the forward reaction is large. In addition, the specific activity of the labelled product as a function of time has been studied for the irreversible bimolecular case.

Introduction

The significance of the rate constants for the yield of labelled products has been examined previously for a bimolecular irreversible reaction.[1,2] The importance of the equilibrium constant for the yield of the labelled products in different types of reactions has been stressed by others.[3] In the present investigation two types of elementary reactions
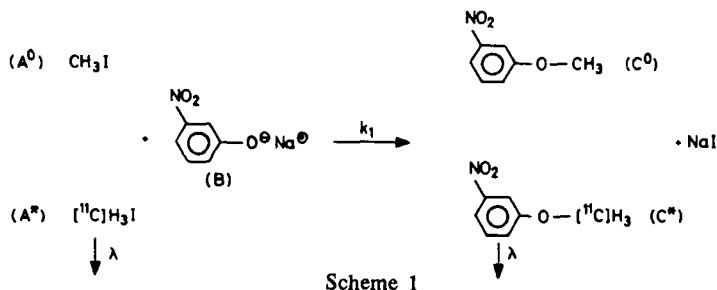
Scheme 1

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$$A^O \qquad\qquad C^O$$
$$+ \; B \;\; \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \;\; + \; D$$
$$A^* \qquad\qquad C^*$$
$$\downarrow \lambda \qquad\qquad\quad \downarrow \lambda$$

Scheme 2

of elementary reactions have been studied concerning the influence of rate constants, equilibrium constants and concentration of the starting reactants on the yield of the labelled product.

Materials and methods

Case A (a bimolecular irreversible elementary reaction)

An example of this type of reaction, the alkylation of sodium 3-nitrophenoxide with methyl iodide in dimethylformamide (Scheme 1) has previously been studied in some detail.[1] This type of reaction will give the rate equations shown below (the notations are according to Scheme 1, where B, A° and C° are the concentrations of the non-radioactive compounds).

$$dC^\circ/dt = k_1 \; BA^\circ \tag{1}$$

$$dA^\circ/dt = -k_1 \; BA^\circ \tag{2}$$

Assuming that $A^\circ = A_0^\circ - C^\circ$ and $B > A_0^\circ$ (A_0° = the concentration of A° at $t = 0$), equation (1), after integration and with the initial condition $C^\circ = 0$ at $t = 0$ gives:

$$C^\circ = -A_0^\circ \, e^{-k_1 Bt} + A_0^\circ \tag{3}$$

When A is a radioactive compound (A*), rate Eqs (4) and (5) (notations according to Scheme 1) are valid for A* and C* respectively, where $\lambda = \ln 2/t_{1/2}$ is the decay constant for ^{11}C.

$$dA^*/dt = -k_1 BA^* - \lambda A^* \tag{4}$$

$$dC^*/dt = k_1 BA^* - \lambda C^* \tag{5}$$

The decay of the labelled compounds A* and C* is expressed by:

$$d(A^* + C^*)/dt = -\lambda(A^* + C^*) \tag{6}$$

After integration, this equation gives:

$$A^* = (A^* + C^*)_0 e^{-\lambda t} - C^* \qquad (7)$$

If Eq. (7) is combined with Eq. (5), C^* is obtained on integration with $C_0^* = 0$:

$$C^* = (A^* + C^*)_0 \left[e^{-\lambda t} - e^{-(\lambda + k_1^*)t} \right] \qquad (8)$$

where $k_1^* = k_1 B$. By differentiating Eq. (8) and putting $dC^*/dt = 0$. Eq. (9) is obtained:

$$t_{max} = (1/k_1^*)\ln[(k_1^*/\lambda) + 1] \qquad (9)$$

where t_{max} is the time at which the maximum yield of the labelled product C is obtained. From Eq (8) and (9), Eq. (10) is then obtained:

$$C_{max}^*/A_0^* = [(k_1^*/\lambda) + 1]^{-\lambda/k_1^*} - [(k_1^*/\lambda) + 1]^{-[(\lambda/k_1^*) + 1]} \qquad (10)$$

where C_{max}^*/A_0^* is the maximum yield of the labelled product C^* related to A_0^*, the concentration of radioactive A^* at $t = 0$.

Specific activity as a function of time

The specific activity is defined as the rate of disintegration per unit mass of the element or of the molecule containing the radionuclide. The specific radio-activity of product C (Scheme 1) may thus be expressed as follows:

$$SA(C) = \lambda \, C^*/(C^* + C^0) \qquad (11)$$

If Eq. (3) and (8) are combined with Eq. (11), the following equation is obtained:

$$SA(C) = \lambda/[1 + (A_0^0/A_0^*)e^{\lambda t}] \qquad (12)$$

where A_0^0/A_0^* is the concentration ratio of stable and radioactive A at time $t = 0$. In the theoretical case with no isotopic dilution of stable molecules ($A_0^0 = 0$), the specific radioactivity will thus be constant with time. However, in the "Results and Discussion" section it is shown that there are differences in the specific radioactivity with time, depending on the isotopic dilution at time $= 0$.

Case B (a bimolecular reversible elementary reaction)

Scheme 2 shows a reversible bimolecular elementary reaction. The rate equations for A^o and C^o (notations according to Scheme 2) are as follows:

$$dA^o/dt = -k_1 A^o B + k_2 C^o D \tag{13}$$

$$dC^o/dt = k_1 A^o B - k_2 C^o D \tag{14}$$

At equilibrium, the classical equilibrium equation (15) is obtained by putting $dA^o/dt = 0$

$$K = k_1/k_2 = C_\infty^o D_\infty / A_\infty^o B_\infty \tag{15}$$

which gives $k_2 = k_1 K^{-1}$.

In the radioactive case, the rate equations for the radioactive starting compound A^* and the labelled product C^* are as follows:

$$dC^*/dt = k_1 BA^* - (k_1 K^{-1} D + \lambda)C^* \tag{16}$$

$$dA^*/dt = -(k_1 B + \lambda)A^* + k_1 K^{-1} DC^* \tag{17}$$

$$d(A^* + C^*)/dt = -\lambda(A^* + C^*) \tag{18}$$

After integration, Eq. (18) gives:

$$A^* = (A^* + C^*)_0 \, e^{-\lambda t} - C^* \tag{19}$$

where $(A^* + C^*)_0 = A_0^*$, the starting concentration of A^*. If Eq. (19) and (16) are combined, the following equation is obtained:

$$dC^*/dt = k_1 BA_0^* e^{-\lambda t} - [k_1 B + k_1 K^{-1} D + \lambda]C^* \tag{20}$$

In order to solve Eq. (20) we need to know the time dependence of D. From Scheme 2, the following rate equation of D is obtained:

$$dD/dt = k_1 BA^* - k_1 K^{-1} DC^* + k_1 BA^o - k_1 K^{-1} DC^o \tag{21}$$

This equation is simplified by disregarding the first two terms, since $A^* \ll A^o$ and $C^* \ll C^o$ (that is the common case). This gives:

$$dD/dt = k_1 BA^o - k_1 K^{-1} DC^o \tag{22}$$

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If now $C_0^o = D_0 = 0$ and $C^o = D$ (C^* and A^* are neglected) and $A^o = A_0^o - D$, Eq. (23) is obtained:

$$dD/dt = k_1 B(A_0^o - D) - k_1 K^{-1} D^2 \qquad (23)$$

On integration, Eq. (23) gives:

$$D = [A_0^o \{e^{2k_1 (BK^{-1})^{1/2} \{A_0^o + 1/4\, BK\}^{1/2} t} - 1\}]/$$

$$/(BK)^{-1/2} \{A_0^o + 1/4\, BK\}^{1/2}\; \frac{1}{2} + [(BK)^{-1/2} \{A_0^o + 1/4\, BK\} + \frac{1}{2}\quad \times$$

$$\times\; e^{2k_1 (BK^{-1})^{1/2} \{A_0^o + 1/4\, BK\}^{1/2} t} \qquad (24)$$

Eq. (24) is then used in a graphical solution of Eq. (20).

By data simulation of Eq. (8). (12), and (20), 3-dimensional plots using the DISSPLA plotting software[4] were obtained. In the investigation, kinetic isotope effects have been neglected.

Results and discussion

The yield of product C^*, related to A_0^*, was simulated as a function of time and rate constant k_1^* according to Eq. (8). In the 3-dimensional plot (Fig. 1), the function is visualized by keeping the decay constant $\lambda = 0.034145$ min^{-1}) fixed and allowing k_1^* to vary between $10^{-2} \lambda$ to $10^2 \lambda$ min^{-1}. The plot shows the importance of selecting fast reactions and of interrupting them at the time when the yield of the labelled product is highest. In cases where the concentration of the labelled reactant is small compared with that of the unlabelled precursor B, the kinetic is of pseudo-first order; it is then possible, since $k_1^* = k_1 B$, to influence the rate constant by increasing the concentration of the unlabelled reactant B. If the rate constant k_1^* is known, it can be used directly in Eq. (9) to calculate t_{max}. If, on the other hand, k_1^* is unknown, it might be estimated by taking a few samples and determining the concentration of the product at different times during a synthesis. The data obtained are then plotted to a curve set of C^*/A_0^* (t) [Eq. (8)], and the k_1^* thus obtained is then used in Eq. (9) to calculate t_{max}.
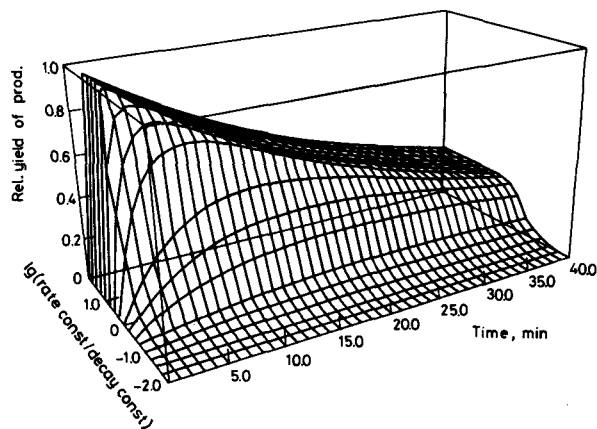
Fig. 1. A 3-D plot of C^*/A_0^* [obtained for the irreversible reaction. Eq. (8)] as a function of time (in min) and rate constants k_1^* (in units of λ, where $\lambda = 0.034145$ min^{-1})
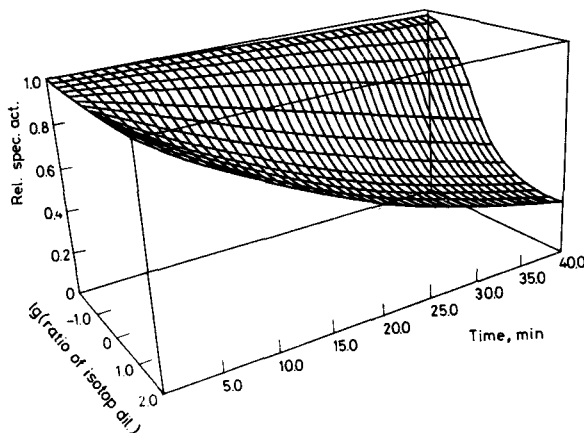

Fig. 2. A 3-D plot of the specific activity of product C as a function of time (in min) and the logarithm of isotopic dilution (A_0^o/A_0^*)

In Fig. 2, the specific activity of compound C is plotted as a function of time and isotopic dilution (A_0^o/A_0^*) using Eq. (12) related to the specific activity at time = 0. The results show that there is a variation in the specific activity with time, depending on the original specific activity. However, the most drastic changes are observed when the ratio A_0^o/A_0^* proceeds from 0.1 to 10^2. From Fig. 2 it can also be seen that, when the isotopic dilution is smaller than about 0.1 · the specific activity shows small variation with time. Thus the highest specific activity is obtained in the limit t = 0.
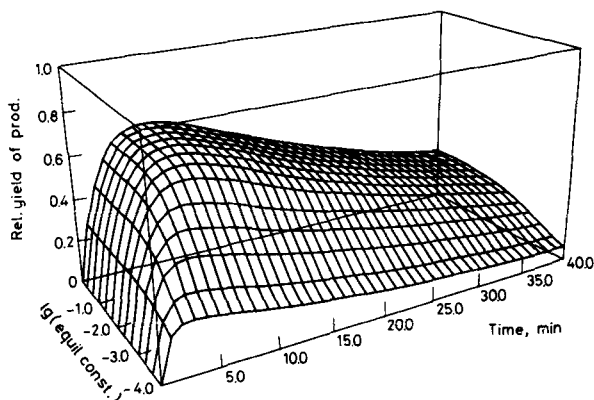
Fig. 3. A 3-D plot of C^*/A_0^* [obtained for the reversible reaction. Eq. (20)] as a function of time (in min) and the logarithm of the equilibrium constant, where $k_1 B = 10 \times \lambda$ ($\lambda = 0.034145$ min^{-1}) and $B/(A_0^O + A_0^*) = 10^3$

In the reversible reaction (Scheme 2), the concentration of the product C^* related to the starting concentration of A_0^* is calculated by using Eq. (24) and (20). Fig. 3 shows a 3-dimensional plot of C^*/A_0^* (t, K) for a given rate constant $k_1 B = 10 \times \lambda$ and for a decay constant $\lambda = 0.034145$ min^{-1}. The figure also shows that the influence of the equilibrium constant on the radiochemical yield of the product C is almost negligible[3] if K is in the range $1-10^{-2}$, and that the important factor is the size of the forward rate constant as shown previously. The figure also shows that, when the equilibrium constant K increases, the kinetics of the reversible reaction (the term $k_1 K^{-1} DC^*$ approaches zero for practical values of D and C^*) approaches that for the irreversible case.

In Fig. 4, the product C^*/A_0^* as a function of time and concentration ratio between the two starting reactants A and B is simulated. The figure clearly shows that, when the ratio between the reactants is of the order of 10^2 or larger, the yield of the product C^* will be very little effected.

In conclusion, it may be said that, for a bimolecular reaction, where one of the reactants is a molecule labelled with a short-lived radionuclide, such as ^{11}C having a specific activity of the order of $10-100$ mCi/μmole, and where one is working with activities resulting in a total concentration of the labelled reactants in the μmole scale, this discussion is applicable, if the unlabelled reactant is present in a 10^2-fold excess. In these cases one should look for fast reactions and not be concerned about the equilibrium constants in reversible reactions. This means that there might be a number of reactions which are of interest for labelling purposes but which are of no interest in conventional syntheses. The
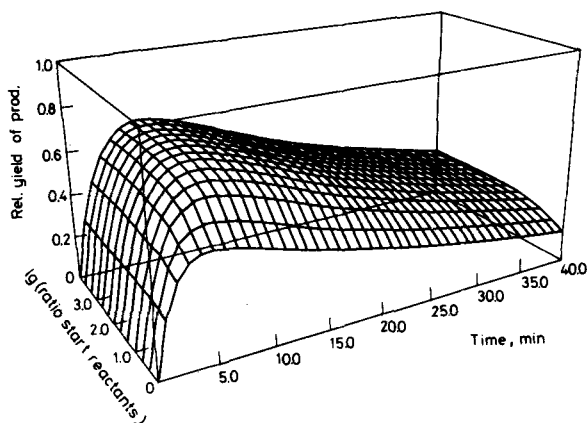
Fig. 4. A 3-D plot of C^*/A_0^* [obtained for the reversible reaction. Eq. (20)] as a function of time (in min) and the logarithm of the rate of starting reactants $B/(A_0^o + A_0^*)$, where $k_1 B = 10 \lambda$ $\lambda = 0.034145$ min^{-1}) and K = 1

large excess of the unlabelled reactant in the bimolecular reactions discussed here mostly favours the rate at which the labelled product is formed. However, situations arise where this large excess of one reactant is a problem — for example, the unlabelled reactant can react further with the primary product in a consecutive reaction. One such example where a consecutive reaction might occur is the reaction between [^{11}C] carbon dioxide and methyl magnesium halide reagents.[1] In this reaction, the products obtained after reduction and hydrolysis are ethanol and isopropanol, which indicates that excess Grignard reagent is added to the primary product, the salt of acetic acid.

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References

1. B. LÅNGSTRÖM, Doctoral Thesis, Acta Universitatis Upsaliensis, No. 555 (1980).
2. B. LÅNGSTRÖM, G. BERGSON, Radiochem. Radioanal. Lett., 43 (1980) 47.
3. G. BERGER, M. MAZIÈRE, J. M. GODOT, J. SASTRE, C. PRENANT, D. COMAR, Proc. 3rd Int. Symp. on Radiopharm. Chem. June 16–20, 1980 in St. Louis, USA, p. 5.
4. DISSPLA, a plotting software produced by ISSCO, 4186 Sorrento Valley Blvd, San Diego, CA 92121, USA.