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Computer-Controlled Reaction of Substituted N-(Carboxyalkyl)amino Acids

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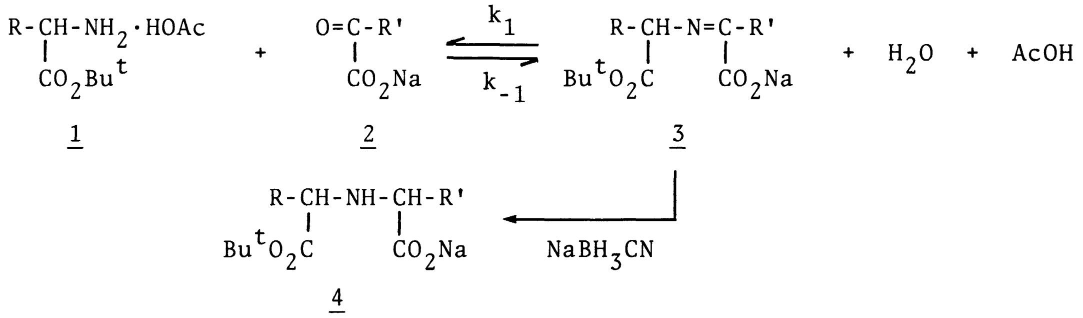
Kinetic equations for controlling the consecutive reactions in the reduction of a Schiff base, formed by the equilibrium reaction of an amino acid with a 2-keto acid, have been developed and applied to a computer-assisted automatic synthesis of substituted N-(carboxyalkyl)amino acids. The equations were especially useful for the prediction of optimum reaction conditions and on-line reaction control.

We have recently developed an automatic apparatus equipped with an artificial intelligence software, which can synthesize substituted N-(carboxyalkyl)amino acids.[1)] This paper deals with the development of a computer-assisted reaction control based on kinetic equations.

The reaction of an amino acid tert-butyl ester acetic acid salt (1) with a 2-keto acid sodium salt (2) produces an unstable intermediate, Schiff base (3), which is reduced with sodium cyanoborohydride to give a substituted N-(carboxyalkyl)amino acid tert-butyl ester sodium salt (4).

When the initial concentrations of 1 and 2 are identical, let their initial concentration be defined as A, the Schiff base concentration at time t be X, and E be defined as the concentration of the Schiff base at equilibrium. The kinetic equation for the Schiff base formation can then be written as Eq. 1.



$$\frac{2Ak_1}{\sqrt{K}} = \frac{1}{t} \ln \frac{1}{1+\sqrt{K}} \left(\frac{E+X}{E-X} + \sqrt{K} \right) \qquad (1)$$

Where k_1 and K are the rate constant in the forward direction and the equilibrium constant, respectively. Let concentrations of the Schiff base at time t_1 and t_2 be defined as X_1 and X_2, respectively. An equation can then be derived as follows:

$$t_2 \ln\left(\frac{E + X_1}{E - X_1} + \sqrt{K}\right) - t_1 \ln\left(\frac{E + X_2}{E - X_2} + \sqrt{K}\right) - (t_2 - t_1) \ln (1 + \sqrt{K}) = 0 \qquad (2)$$

Although the molar absorption coefficient of the Schiff base is unknown, it is possible to calculate the equilibrium constant using Eq. 2 based on measurement of optical absorbances as a function of reaction time. After K is calculated, k_1 can be obtained using Eq. 1. A computer program for calculating Eqs. 1 and 2 has also been developed.

Since the reaction rate of keto acids was slow, while that of the Schiff base was rapid compared to its formation rate, the formation of 4 may be controlled by the addition rate of sodium cyanoborohydride. Let the initial volume of the reaction mixture be defined as V_0, and the addition volumes in each aliquot of the reducing agent be V_1, V_2, and V_i, respectively. V_i can be formulated on the basis of the stoichiometry.

$$V_i = \frac{AV_0}{\beta y}\left(\frac{\alpha\sqrt{K}}{1 + \sqrt{K}}\right)\left(1 - \frac{\alpha\sqrt{K}}{1 + \sqrt{K}}\right)^{i-1} \qquad (3)$$

Where i denotes the number of the addition (for i=1 to n), y is the concentration of sodium cyanoborohydride, β is the ratio of the stoichiometric coefficient of reduction ($NaBH_3CN$/Schiff base) and α is defined as X/E. The total addition volume (V_t) of reducing agent is then represented by

$$V_t = \sum_{i=1}^{n} V_i \qquad (4)$$

The reaction time before the first addition of reducing agent, t_0, is derived from Eq. 1.

$$t_0 = \frac{\sqrt{K}}{2Ak_1} \ln \frac{1}{1 + \sqrt{K}}\left(\frac{1 + \alpha}{1 - \alpha} + \sqrt{K}\right) \qquad (5)$$

The addition interval (t_i) of the reducing agent is given by Eq. 6, which is corrected for the decreasing concentration of the reactants and the dilution caused by the addition of the reducing agent.

$$t_i = \frac{\sqrt{K}}{2Ak_1}\left(\frac{1 + \sqrt{K}}{1 + (1-\alpha)\sqrt{K}}\right)^i \left(1 + \frac{\sum_{i=1}^{n} V_i}{V_0}\right) \ln \frac{1}{1 + \sqrt{K}}\left(\frac{1 + \alpha}{1 - \alpha} + \sqrt{K}\right) \qquad (6)$$

The total reaction time (T) is then obtained by the summation of t_0 and t_i.

$$T = t_0 + \sum_{i=1}^{n} t_i \qquad (7)$$

After optical absorbances of the Schiff base formed were measured at 24°C

(UV-235 nm), K, k_1 and the dropping rate of reducing agent were calculated. The optimum mole ratio of $NaBH_3CN$: Schiff base for the reduction of Schiff base was found to be 2 : 3, and α was empirically set at 0.95 for convenience. It is not clear why the optimum ratio of $NaBH_3CN$: Schiff base differs from the stoichiometric ratio of 1 : 3. As a typical example, the computed result for the controlled reaction of norvaline tert-butyl ester acetic acid salt with 2-ketoisocaproic acid sodium salt in methanol is shown in Table 1.

Table 1. Reaction control table of norvaline tert-butyl ester acetic acid salt with 2-ketoisocaproic acid sodium salt in methanol

Input data	Calculation of dropping rate	
	Time/min	Reagent volume/mL
Equilibrium constant (K) : 0.25	4.7	4.3
Coefficient α (X/E) : 0.95	13.6	2.9
Forward rate constant (k_1) :	28.5	2.0
0.643 (L/mol.min)	52.4	1.4
Raw material	89.3	0.9
Initial concentration : 0.27 (mol/L)	145.2	0.6
Initial volume : 15 (mL)	229.1	0.4
Reducing agent	353.7	0.3
Concentration : 0.2 (mol/L)	528.2	0.2
Optimum mole ratio	810.0	0.1
($NaBH_3CN$/Schiff base) : 0.67		

To confirm the reaction control in Table 1, a rate study was carried out using an HPLC analytical procedure. Chemical yield curves of the product, N-(3-methyl-1-sodioxycarbonylbutyl)norvaline tert-butyl ester, under various reaction conditions are presented in Fig. 1.

The dotted line (c) indicates the chemical yield versus reaction time when sodium cyanoborohydride is added to the reaction mixture at a rate of 0.038 mL per 10 sec interval. The dotted line (d) shows the chemical yield versus reaction time when the reactants and sodium cyanoborohydride were mixed at once.[2] When the addition rate of sodium cyanoborohydride was rapid compared to the formation rate of the Schiff base, the yield (dotted line d) levelled off at relatively low value. This fact indicates that the formation of the Schiff base is interfered with by the large excess of sodium cyanoborohydride, and it is suggested that a competitive equilibrium with a kind of complex formed between the keto acid and the sodium cyanoborohydride may be responsible. However the yield curve for the reaction controlled by the kinetic approach in Table 1, the dotted line (b), was similar to the calculated yield presuming consumption of reducing agent, the solid line (a) in Fig. 1.

It is thus clear that the equations derived by a kinetic approach are of great use for the prediction of optimum reaction conditions and on-line reaction control.

The relationship between K (or k_1) and the steric constants of substituents for the reaction of 1 with 2 will be reported elsewhere. As an application of the on-line reaction control, the automated apparatus has been run continuously for 24 hours, giving an average synthetic rate of three compounds per day.

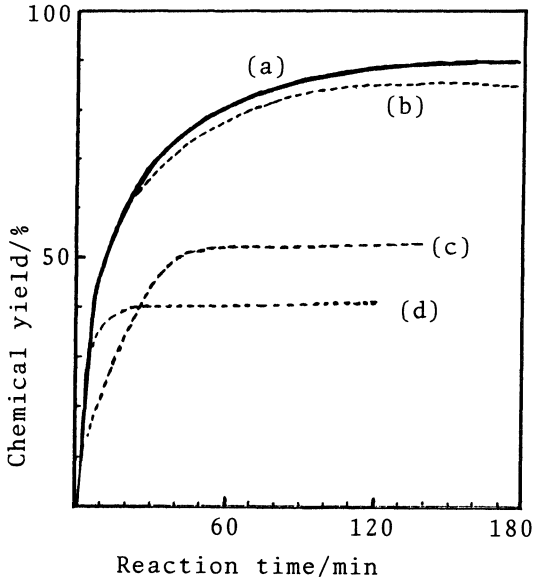


Fig. 1. Chemical yield curves under various reaction conditions for the reaction of norvaline tert-butyl ester acetic acid salt with 2-ketoisocaproic acid sodium salt.
Solid line (a) : calculated yield presuming consumption of reducing agent.
Dotted lines (b,c,d) : observed yields.

References
1) N. Hayashi, T. Sugawara, and S. Kato, in preparation.
2) Although the yield levelled off, it slowly increased while the reaction mixture was standing overnight : Y. Ohfune, N. Kurokawa, N. Higuchi, M. Saito, M. Hashimoto, and T. Tanaka, Chem. Lett., 1984, 441.

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