Is There a Time Lag Before Formation of Methyl Phenyl-O-Anisylphosphine and Methylcyclohexyl-O-Anisylphosphine Species? : A Kinetic Study of Multiple Reactions

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Abstract

The scheme of reactions underwent during the Hoffman-La-Rouche L-Dopa process by 6 species appears to be reactions in series as shown in Figure 1. The scheme of reactions during preparation of CAMP and diPAMP phosphines from methyl ester via series-parallel reactions of 6 species is shown in Figure 2.

The kinetic rate expressions for the reactions that occur in Hoffman-La Rouche L-Dopa process for 5 species, A, R, S, T and U can be modeled using the reactions in series scheme. There are 5 multiple reactions under this scheme. The kinetic rate expressions are made dimensionless by suitable transformations. The dimensionless kinetic rate equations were solved using second order Runge-Kutta method on a Hewlett Packard desktop computer using Microsoft Excel for Windows 2013. The computer has Intel ® Xeon ® CPU ES-2680 0 @ 2.7 GHz microprocessor speed with 2 GM RAM run using a 32-bit operating system. The ratios of the reaction rate constants used in the computer simulation are shown in Table 1. The dimensionless concentration of five species A, R, S, T and U are plotted in Figure 3. The species A falls exponentially from an initial concentration of CA0 or uA0 = 1 with an asymptotic limit of zero at infinite time. The species R and S are found to undergo A maxima in species concentration. The rise in concentration to maxima is seen to be rapid. The fall in concentration after reaching maxima was found to be gradual. There seen a right skew in the concentration vs time curves. The species T also underwent A maxima. The right skew was less and there was found a right tail. There was a period of gestation or time lag before species U began to form. The rise in concentration of U was convex at first and then became concave with a steep rise to a plateau concentration.

Keywords: Kinetic study; Phenylalanine; Multiple reactions; Amino acid

Introduction

Tyrosine is synthesized by mammalian species from phenylalanine. Phenylalanine is of the 20 aminoacids specified by the genetic code. Many proteins are enzymes that are found to catalyze biochemical reactions. Better understanding of reaction pathways that are found in metabolic activities can lead to sustainable production of useful chemicals. Phenylalanine is a non-polar aminoacid [1]. William Knowles, Monsanto Co., St. Louis, MO won the Nobel Prize for chemistry in 2001 for his work on chiral catalysis for asymmetric hydrogenation. L-Dopa may be used for curing Parkinson's disease. The structure of chiral ligand was found to be crucial to asymmetric hydrogenation. The price of phosphine is high. The half-life of phosphines during its pyramidal inversion was of the order of 100s of minutes at 46.1^{0}C. α-phenyl acrylic acid was transformed into the chiral ethyl propyl phenyl phosphine using the RhL^3 Cl catalyst. Monsanto had a dominant position in vanillin. Phenylalanine intermediate was used as a good test reaction. Hydrogen bonding site and steric hindrance was provided by introduction of o-anisyl group. Knowles [2] solved- what was considered in one of the toughest synthetic problems. Laureate obtained patents for use of chiral phosphines and rhodium as catalysts. They tried to scale-up the hydrogenation discovered into large scale production at a plant that was idle and provided the golden opportunity. The mole ratio of substrate to catalyst was 20,000:1. Racemic products are difficult to separate systems.

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Entrainer may be used. The kinetic expressions for the series-parallel reactions shown in Figure 2 are shown in Equation (1). These are the reactions that are involved in the formation of CAMP and diPAMP phosphines prepared from methyl ester. The kinetic rate expressions are made dimensionless by the transformation variables, u_A, u_R, u_S, u_u, u_T and u_v. The reaction rate constant ratios are ω, θ, ε and δ. The dimensionless time is in terms of the reaction rate constant of the first reaction step k_1. The kinetic rate expressions are converted into the Laplace domain. The inverse Laplace transforms can be found from the tables. Equations (1.49-1.54) are plotted in Figure 2. The ratios of reaction rate constants used in obtaining the 6 curves in Figure 2 are given in Table 1. The state space model for the kinetic rate expressions are given by Equation (1.49). The characteristic polynomial for the rate matrix K is given by Equation (1.59). It can be seen from Figure 2 that the fall of concentration in species A is exponential. The concentrations of species R, S and U are seen to undergo A maxima. There is a period of induction or time lag before species T begins to form for certain ratios of reaction rate constants. Species V is found to rise in concentration rapidly to the roof for the set of reaction rate constant ratios used in the simulation. The simulation was made using MS Excel 2013 in a desktop computer with Intel ® Xeon ® CPU ES-2680 0 @ 2.7 GHz microprocessor speed with 2 GM RAM run using a 32-bit operating system. Species T appears to reach a plateau at larger times. Evonik Degussa GmbH produces amino acids and its derivatives by chemical and biotechnological means. Verseck., *et al*. [3] reviewed the production of amino acids via bio catalysis and biotransformation.

Catalytic Racemization

L-Dopa was found to be useful in curing Parkinson's disease. Patients with Parkinson disease have two medicines to swallow. They are treated with a combination of L-Dopa and a Dopa carboxylate inhibitor such as carbidopa or benserazide.
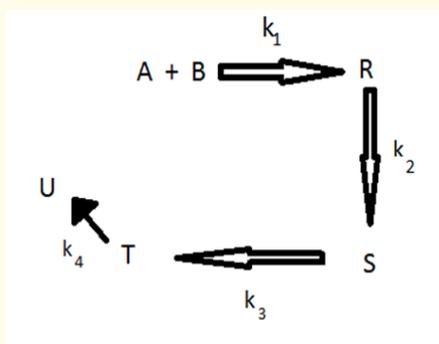

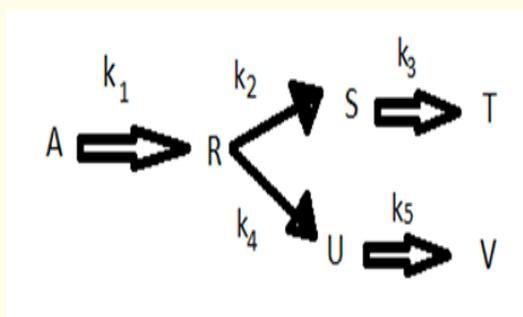*Figure 1:* Hoffman-La Rouche L-DOPA Process: Scheme of Reactions underwent by 6 Species.

Figure 2: CAMP and DIPAMP Phosphines Prepared from Methyl Ester via Series-Parallel Reactions.

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The condition of a patient deteriorates after a period of 2-5 years. This is the average initial period of stable and satisfactory benefit from L-DOPA. They develop complex dose-related and not predictable response fluctuations. Not favorable pharmacokinetic properties of L-Dopa such as poor solubility, poor bio-availability and short half-life were found to be causative in observed faulty absorption of L-Dopa. A correlation was found between the clinical fluctuations and the oscillations of L-Dopa plasma levels. The symptoms noted in patients are "on-off" oscillations in which diurnal motor activity in patients dominated by striking swings between off hours. During the off periods the patients are in capacitated, appear rigid like a log, sometimes speechless, experience difficulty swallowing. During the on periods the patients are responsive to L-Dopa. Metabolic product of L-Dopa methyl ester is menthol which has been shown to be toxic.

Knowles [2] in his Nobel lecture attributed the structure of the chiral ligand crucial to asymmetric hydrogenation. He realized that preparation of phosphines requires the chemical transformations that occur from multiple reactions. The series-parallel reactions that govern the formation of phosphine are shown in Figure 2. The price of phosphine is high. A 10 year supply is provided for by running a few plant-size batches. There are several allotropes of Phosphorous: (i) white solid; (ii) red solid; (iii) solid violet; (iv) black solid. White and yellow phosphorous are found to exhibit tetrahedral structure. The α form of phosphorous was found to have the FCC, Face Centered Cubic Lattice structure. The β form of phosphorous was found to have the hexagonal cubic crystal structure. Dextro and Levo forms of tetrahedral structured phosphorous are possible when different substituents are attached to it. Lone pair of electrons can be counted as a substituent in the case of phosphine. Phosphines were found to invert pyramidally and to have a half-live of 100s of minutes at 46.1^0C. Prochiral olefin was hydrogenated using a Wilkinson's catalyst with the triphenylphospine replaced with a chiral counterpart. Soluble hydrogenation catalysts for unhindered olefins were found to exhibit comparable rates with heterogeneous counterparts. Chlorotris (triphenyl-phosphine) Rhodium, $[RhCl (PPh_3)_3]$ was discovered by Professor Wilkinson. α-phenylacrylic acid was transformed into the chiral methyl-propyl-phenyl-phosphine using the RhL_3Cl catalyst. They established that the hydrogenation technique gave a definite asymmetric bias and was accomplished in solution. At the Welch foundation conference where the laureate presented the work, a latter paper discussed methyl-propyl-phenyl-phosphine on a substituted styrene.

Massive dose of L-DOPA was needed in treating Parkinson's disease. Monsanto had a dominant market position in vanillin. A racemic intermediate was custom manufactured. Hoffman-La Roche resolved and deblocked the racemic intermediate to L-DOPA. 3-4-dihydroxyl-phenyl functional group can be found in vanillin. The Erlenmeyer azlactone procedure found in organic synthesis laboratory manual was closely followed. Prochiral enamide was hydrogenated to block DL-DOPA. The scheme of reactions underwent in the Hoffman-La Roche process is shown in Figure 2. There was the golden opportunity to commercialize the technology where enamide is used. The Prochiral enamide precursor of α-aminoacid were found to hydrogenate at much faster rates compared with that of substituted olefin. The chiral results were found to be amenable to a structure vs activity study. Phenylalanine intermediate was used as a good test reaction. They searched for a proper structure of phosphine. They believed that the asymmetry had to be directly on the phosphorous to obtain high enantiomeric excess. Phosphines with chiral alkyl side chain were attempted at first. Enantiomeric excess was found in the range of 28-32% were found when the alkyl groups on the phosphorous were varied and the n-propyl converted to hindered isopropyl/cyclohexyl groups. Knowles [2] introduced the o-anisyl group in order to provide steric hindrance and hydrogen bonding site. They have achieved enzyme like selectivity using synthetic catalyst. This structure-activity study was an interesting example of confluential academic and industrial advancement. The ether linkages were stable through the rigors of phosphine synthesis. Enantiomeric excess of 58% was achieved when PAMP, methyl phenyl-o-anisylphosphine was made. CAMP, methylcyclohexyl-o-anisylphosphine was obtained from further modification of PAMP with an enantiomeric excess of 88%.

CAMP, methyl cyclohexyl-o-anisylphosphine, was prepared from phenyl-dichloro-phosphine via Mislow's menthyl ester. The o-anisyl group is introduced towards the conclusion of the procedure. The desired isomer was produced in small amounts. In order to seek a better outcome it was found mandatory to reverse the order of addition of aryl groups. Knowles [2] solved what was considered one of the toughest of synthetic problems. For a century the enzyme paradigm is what the chemists expected to rely on for synthesis of phosphines. The laureate obtained patents for use of chiral phosphines and rhodium as catalysts. They obtained the asymmetry from the menthol used in chiral phosphine synthesis. A small amount of L-menthol can lead to a large amount of chiral product. They were on their way in developing a commercial L-DOPA process.

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The management increased their manpower from underfunded and undirected research levels. They wanted to see the hydrogenation was done on a 50 gallon scale without incident. They tried to scale-up the hydrogenation discovered into large scale production. They had an idle plant that can be an opportunity for a retrofit project. The idle plant was due to Monsanto getting out saccharin manufacture. They used an *in situ* prepared catalyst [Rh (1,5-COD) L_2]+BF_4. The mole ratios of substrate to catalyst were about 20,000:1. Racemic products made needs to be separated. The boiling points of the compounds can be expected to be proportional to their molecular weights. The isomers can be expected to have boiling points close to each other. These systems can be expected to be difficult to separate systems. Methods used for azeotropic distillation such as use of entrainer may be applicable.

The formation of monosubstituted dimethyl bezylphosphonate needed large excess of trimethylphosphite. Crystalline phosphonic acid was isolated from the sequence of three products made. Acid chloride can be transformed into an 80/20 mix of S_p and R_p isomers. This meant that the menthol preferentially reacts with one form whereas the other form was seen to rapidly racemize. Catalyst preparation was facilitated by an asymmetric synthesis of its own directed by L-menthol. DIPAMP was made by chelation of biphosphine by dimerizing PAMP. CAMP and diPAMP were prepared from a mutual intermediate, methyl ester. CAMP was prepared by selective hydrogenation of methyl ester using a rhodium on carbon heterogeneous catalyst. The reaction needs to be monitored closely and quenched before the anisyl ring gets hydrogenated. R-CAMP was formed by reduction with tri-chlorosilane. The stereochemistry was not affected by the copper coupling step run with lithium di-isopropyl amide and CuCl. The kinetic rate expressions for the series-parallel reactions shown in Figure 2 are as follows:

$$r_A = -\frac{dC_A}{dt} = k_1 C_A$$

$$r_R = \frac{dC_R}{dt} = k_1 C_A - k_2 C_R - k_4 C_R$$

$$r_s = \frac{dC_S}{dt} = k_2 C_R - k_3 C_S$$

$$r_U = \frac{dC_U}{dt} = k_4 C_R - k_5 C_U \quad\quad\quad\quad\text{-------------------(1)}$$

$$r_T = \frac{dC_T}{dt} = k_3 C_S$$

$$r_V = \frac{dC_V}{dt} = k_5 C_U$$

$$\text{Let} \quad u_A = \frac{C_A}{C_{A0}}; \tau = k_1 t; \omega = \frac{k_2}{k_1}; \theta = \frac{k_3}{k_1}; \varepsilon = \frac{k_4}{k_1}; \delta = \frac{k_5}{k_1} \quad\quad\text{----------------(2)}$$

The kinetic expressions for the 6 species given by Equation (1) can be made dimensionless [4,5].

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$$\frac{du_A}{d\tau} = -u_A$$

$$\frac{du_R}{d\tau} = u_A - \omega u_R - \varepsilon u_R$$

$$\frac{du_S}{d\tau} = \omega u_R - \theta u_S$$

$$\frac{du_U}{d\tau} = \varepsilon u_R - \delta u_U \qquad \text{-------------(3)}$$

$$\frac{du_T}{d\tau} = \theta u_S$$

$$\frac{du_V}{d\tau} = \delta u_V$$

Obtaining the Laplace transforms of the dimensionless kinetic rate equations given in Equation (3) with the initial time condition of :

$$u_{A0} = 0; u_R = u_S = u_U = u_T = u_V = 0$$

$$u_A(s) = \frac{1}{(s+1)} \qquad \text{-------------(4)}$$

$$u_R(s) = \frac{1}{(s+1)(s+\omega+\varepsilon)} \qquad \text{-------------(5)}$$

$$u_S(s) = \frac{1}{(s+\theta)(s+1)(s+\omega+\varepsilon)} \qquad \text{-------------(6)}$$

$$u_U(s) = \frac{\varepsilon}{(s+\delta)(s+1)(s+\omega+\varepsilon)} \qquad \text{-------------(7)}$$

$$u_T(s) = \frac{\theta}{(s)(s+\theta)(s+1)(s+\omega+\varepsilon)} \qquad \text{-------------(8)}$$

$$u_V(s) = \frac{\delta\varepsilon}{(s)(s+\delta)(s+1)(s+\omega+\varepsilon)} \qquad \text{-------------(9)}$$

The inverse Laplace transforms of Equations (4-9) can be written as follows:

$$u_A(\tau) = e^{-\tau} \qquad \text{-----------(10)}$$

$$u_R(\tau) = \frac{1}{(\omega+\varepsilon-1)}\left(e^{-\tau} - e^{-(\omega+\varepsilon)\tau}\right) \qquad \text{-----------(11)}$$

$$u_S(\tau) = \frac{(\omega+\varepsilon-1)e^{-\theta\tau} + (\theta-\omega-\varepsilon)e^{-\tau} + (1-\theta)e^{-(\omega+\varepsilon)\tau}}{(\omega-\varepsilon-\theta)(\omega+\varepsilon-1)(1-\theta)} \qquad \text{-----------(12)}$$

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$$u_S(\tau) = \frac{(\omega+\varepsilon-1)e^{-\theta\tau} + (\theta-\omega-\varepsilon)e^{-\tau} + (1-\theta)e^{-(\omega+\varepsilon)\tau}}{(\omega-\varepsilon-\theta)(\omega+\varepsilon-1)(1-\theta)}$$ -----------(12)

$$u_U(\tau) = -\varepsilon\frac{\left((\omega+\varepsilon-1)e^{-\delta\tau} + (\delta-\omega-\varepsilon)e^{-\tau} + (1-\delta)e^{-(\theta)\tau}\right)}{(1-\delta)(\omega+\varepsilon-1)(\delta-\omega-\varepsilon)}$$ -----------(13)

$$u_T(\tau) = \omega\frac{\theta(\theta-1)\left(1-e^{-(\omega+\varepsilon)\tau}\right) - (\omega+\varepsilon)(\omega+\varepsilon-1)\left(1-e^{-\theta\tau}\right) + \theta(\omega+\varepsilon)(\theta-\omega-\varepsilon)\left(1-e^{-\tau}\right)}{(\omega+\varepsilon)(\theta-1)(\omega+\varepsilon-1)(\theta-\omega-\varepsilon)}$$ -----------(14)

$$u_V(\tau) = \varepsilon\frac{\left((\omega+\varepsilon)(\omega+\varepsilon-1)\left(1-e^{-\delta\tau}\right) - \delta(\omega+\varepsilon)(\delta-\omega-\varepsilon)\left(1-e^{-\tau}\right) - \delta(1-\delta)\left(1-e^{-(\omega+\varepsilon)\tau}\right)\right)}{(\omega+\varepsilon)(1-\delta)(1-\omega-\varepsilon)(\delta-\omega-\varepsilon)}$$ -----------(15)

Equations (10-15) are plotted in Figure 3. The ratios of reaction rate constants used in obtaining the 6 curves in Figure 3 are as follows:

ω	1.5
ε	2.5
θ	0.333
δ	0.333
ω+θ-1	0.833
δ-ω+θ	-0.834
δ-1	-0.667
1-ω-θ	-0.833
ω+ε-1	3
1-θ	0.667
θ-ω-ε	-3.667
ω+ε	4
ω-ε-θ	-1.333
δ-ω-ε	-3.667
ω+θ	1.833
δ-ω-q	-1.5
Ut - Denominator	10.66933
Uv - Denominator	29.35067

Table 1*: Reaction Rate Constants used to Obtain Figure 2.*

It can be seen from Figure 3 that the fall of concentration in species A is exponential. The concentrations of species R, S and U are seen to undergo A maxima. There is a period of induction or time lag before species T begins to form for certain ratios of reaction rate constants. Species V is found to rise in concentration rapidly to the roof for the set of reaction rate constant ratios used in the simulation. The simulation was made using MS Excel 2013 in a desktop computer with Intel ® Xeon ® CPU ES-2680 0 @ 2.7 GHz microprocessor speed with 2 GM RAM run using a 32-bit operating system. Species T appears to reach a plateau at larger times. The kinetic rate expressions given by Equation (16) in Eigen matrix form can be written as follows:

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$$\frac{d}{d\tau}\begin{pmatrix} u_A \\ u_R \\ u_S \\ u_U \\ u_T \\ u_V \end{pmatrix} = \begin{pmatrix} -1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -(\omega+\varepsilon) & 0 & 0 & 0 & 0 \\ 0 & \omega_R & -\theta & 0 & 0 & 0 \\ 0 & \varepsilon & 0 & \delta & 0 & 0 \\ 0 & 0 & \theta & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta \end{pmatrix}\begin{pmatrix} u_A \\ u_R \\ u_S \\ u_U \\ u_T \\ u_V \end{pmatrix} \qquad\text{----------(16)}$$

The Eigen equation can be obtained from the Eigen rate matrix which can be written as follows:

$$K = \begin{vmatrix} -(1+\lambda) & 0 & 0 & 0 & 0 & 0 \\ 1 & -(\omega+\varepsilon+\lambda) & 0 & 0 & 0 & 0 \\ 0 & \omega_R & -(\theta+\lambda) & 0 & 0 & 0 \\ 0 & \varepsilon & 0 & -(\delta+\lambda) & 0 & 0 \\ 0 & 0 & \theta & 0 & -\lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & -(\delta+\lambda) \end{vmatrix}\begin{pmatrix} u_A \\ u_R \\ u_S \\ u_U \\ u_T \\ u_V \end{pmatrix} \qquad\text{----------(17)}$$

The characteristic polynomial can be written as follows:

$$-(1+\lambda)(-(\omega+\varepsilon+\lambda)-(\delta+\lambda)(-\lambda-(\delta+\lambda)))=0 \qquad\text{----------(18)}$$

The Eigen values are:

$$\begin{aligned} \lambda_1 &= -1 \\ \lambda_2 &= -(\omega+\varepsilon) \\ \lambda_3 &= -\theta \\ \lambda_4 &= -\delta \\ \lambda_5 &= 0 \\ \lambda_6 &= -\delta \end{aligned} \qquad\text{----------(19)}$$
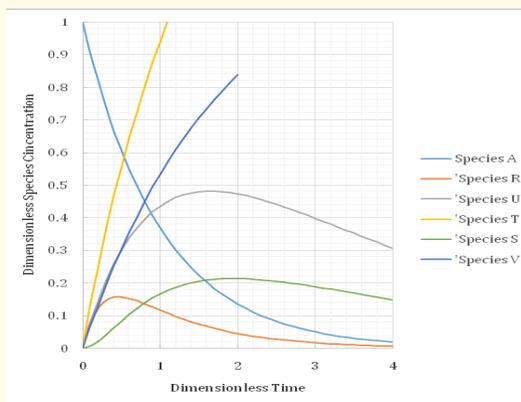

***Figure 3:** Dimensionless Concentration vs Dimensionless Time for 6 Species.*

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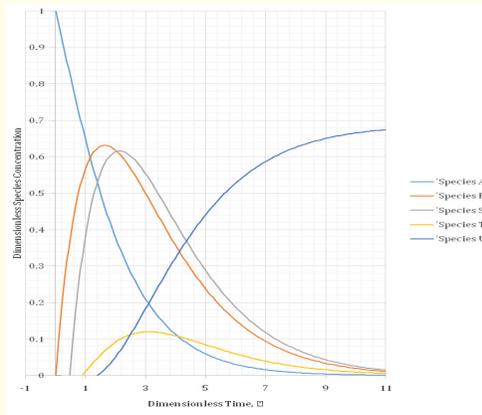**: A Kinetic Study of Multiple Reactions**

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Figure 4: *Dimensionless Concentration with Dimensionless Time for Five Species.*

The kinetic rate expressions for the reactions that occur in Hoffman-La Rouche L-Dopa Process can be written as follows. The scheme of reactions underwent by 5 species A, R, S, T and U is shown in Figure 1. The reactions are assumed to be irreversible and obey the first order reaction rate. There are 5 multiple reactions in this scheme.

$$
\begin{aligned}
r_A &= -\frac{dC_A}{dt} = k_1 C_A \\
r_R &= \frac{dC_R}{dt} = k_1 C_A - k_2 C_R \\
r_S &= \frac{dC_S}{dt} = k_2 C_R - k_3 C_S \qquad \text{----------(20)} \\
r_T &= \frac{dC_T}{dt} = k_3 C_S - k_4 C_T \\
r_U &= \frac{dC_T}{dt} = k_4 C_T
\end{aligned}
$$

The species concentration, reaction rate constants and time are made dimensionless by the following substitutions:

$$
u_A = \frac{C_A}{C_{A0}} ; u_R = \frac{C_R}{C_{A0}} ; u_S = \frac{C_S}{C_{A0}} ; u_T = \frac{C_T}{C_{A0}} ; u_U = \frac{C_U}{C_{A0}} ; \tau = k_1 t ; \omega = \frac{k_2}{k_1} ; \theta = \frac{k_3}{k_1} ; \varepsilon = \frac{k_4}{k_1} \quad \text{----------(21)}
$$

Substituting Equation (21) in Equation (20) the dimensionless rate expressions can be written as follows:

$$
\frac{du_A}{d\tau} = -u_A \qquad \text{----------(22)}
$$

$$
\frac{du_R}{d\tau} = u_A - \omega u_R \qquad \text{----------(23)}
$$

$$
\frac{du_S}{d\tau} = \omega u_R - \theta u_S \qquad \text{----------(24)}
$$

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$$\frac{du_T}{d\tau} = \theta u_S - \varepsilon u_T \qquad \text{----------(25)}$$

$$\frac{du_U}{d\tau} = \varepsilon u_T \qquad \text{----------(26)}$$

Equations (22-26) were solved using second order Runge-Kutta method on a Hewlett Packard desktop computer using Microsoft Excel for Windows 2013. The computer has Intel ® Xeon ® CPU ES-2680 0 @ 2.7 GHz microprocessor speed with 2 GM RAM run using a 32-bit operating system. The ratios of the reaction rate constants used in the computer simulation are shown below in Table 2.

ε	1.2
ω	0.6
θ	0.8

Table 2*: Ratios of Reaction Constants.*

The dimensionless concentration of five species A, R, S, T and U are plotted in Figure 4. The species A falls exponentially from an initial concentration of C_{A0} or u_{A0} = 1 with an asymptotic limit of zero at infinite time. The species R and S are found to undergo A maxima in species concentration. The rise in concentration to maxima is seen to be rapid. The fall in concentration after reaching maxima was found to be gradual. There was seen a right skew in the concentration vs time curves. The species T also underwent A maxima. The right skew was less and there was found a right tail. There was a period of gestation or time lag before species U began to form. The rise in concentration of U was convex at first and then became concave with a steep rise to a plateau concentration. The second order Runge-Kutta method used in the analysis is given in Chapra and Canale [6]. The recursive relation used and weights used are according to the Ralston's method and are given as follows:

$$y_{i+1} = y_i + h(a_1 k_1 + a_2 k_2)$$
$$k_1 = f(x_i, y_i)$$
$$k_2 = f(x_i + p_i h, y_i + q_{11} k_1 h) \qquad \text{--------(26.0)}$$
$$a_2 = \frac{2}{3}; a_1 = \frac{1}{3}; p_1 = q_{11} = \frac{3}{4}$$

Enzymes and whole cell biocatalysts are used for the production of enantiomerically pure proteinogenic and non-proteinogenic L and D-amino acids and derivatives. These chemicals are used as building blocks for pharmaceuticals, cosmetics and agriculture products. Single enantiomers of chiral active ingredients are of increased interest. Recent advances in molecular biological methods like recombinant enzyme expression, high through put DNA sequencing and enzyme evolution technologies have provided impetus to the production of aminoacids by bio-transformations. Reactions were found to be chemo, region or entantioselective. Enantiomeric pure intermediates are used in the production of pharmaceuticals. "Designer cells" are microbial whole cell biocatalysts. Enzymes from different sources can be used. All the required enzymes can be produced in one fermentation and cell disruption can be made to come about. Separation of biocatalyst after biotransformation can be achieved by flocculation and filtration of the biomass. EMR, enzyme membrane reactor is used for the production of L-methionine at a production rate of several tons per year. Acylases are available for purchase/Tjeu is made from porcine kidneys and from the fungi *Aspergillus Oryzae* and *Aspergillus Melleus*. This first generation process in order to produce L-/erMeucine is based on purified leucine dehydrogenase (LeuDH) from Bacillus cereus and formate dehydrogenase (FDH) from Candida boidinii. A broad range of aminoacids are accessible in substantial yields and with higher enantioselectivities. L-neopentylglycine was produced in the pilot scale. The substrate concentration was 42 g/L, The whole-cell LeuDH/GDH biocatalyst reaching >95% conversion within one

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day. It had an optical purity of more than 99.8% enantiomeric selectivity. The starting material α-keto acid is readily accessible through condensation of pivalaldehyde with hydantoin and successive hydrolysis.

Aspartame is a sweetener. It was made in large quantities. L-aspartic acid is formed by addition of NH3, ammonia to fumaric acid. This reaction is catalyzed by aspartase. L-aspartate is formed and is transformed into aspartame. L-alanine can also be produced from L-aspartate. Racemic β-phenylalanines are transformed into β-aminoacid. The reactions are reversible. Racemic β-phenylalanines can be obtained by the condensation of substituted benzaldehyde with malonic acid and ammonium acetate. N-Proponol can be used for esterification. Resulting esters are cleaved with lipase in a biphasic solvent system in order to produce the enantiomerically pure β-aminoacids. The process can be used in order to produce desired products with enantiomeric selectivity of greater than 99%. High substance concentration of 250 g/l and high space-time-yield of the synthesis was seen. New classes of industrial products were made in large quantities with better quality in a profitable manner.

Conclusion

Multiple reactions are encountered in the Hoffman La Rouche process. The scheme of reactions underwent during the Hoffman-La-Rouche L-Dopa process by 6 species appears to be reactions in series as shown in Figure 1. The scheme of reactions during preparation of CAMP and diPAMP phosphines from methyl ester via series-parallel reactions of 6 species is shown in Figure 2. The kinetic rate expressions for the reactions that occur in Hoffman-La Rouche L-Dopa process for 5 species, A, R, S, T and U can be modeled using the reactions in series scheme. There are 5 multiple reactions under this scheme. The kinetic rate expressions are made dimensionless by suitable transformations. The dimensionless kinetic rate equations were solved using second order Runge-Kutta method on a Hewlett Packard desktop computer using Microsoft Excel for Windows 2013. The computer has Intel ® Xeon ® CPU ES-2680 0 @ 2.7 GHz microprocessor speed with 2 GM RAM run using a 32-bit operating system The ratios of the reaction rate constants used in the computer simulation is shown in Table 1. The dimensionless concentration of five species A, R, S, T and U are plotted in Figure 3. The species A falls exponentially from an initial concentration of C_{A0} or u_{A0} = 1 with an asymptotic limit of zero at infinite time. The species R and S are found to undergo a maxima in species concentration. The rise in concentration to maxima is seen to be rapid. The fall in concentration after reaching maxima was found to be gradual. There was seen a right skew in the concentration vs time curves. The species T also underwent a maxima. The right skew was less and there was found a right tail. There was a period of gestation or time lag before species U began to form. The rise in concentration of U was convex at first and then became concave with a steep rise to a plateau concentration.

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