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Manufacture of Propanediol: Kinetic Parameter Evaluation of Dykat dynamic Kinetic Asymmetric Transformation Processes, Separation of Stereo isomers by Liquid Extraction

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Abstract

More interest is seen in technology development of energy sustainable solution to chemical production. A and B in Figure 1.0 can be dextro lactic acid and levo lactic acid. The artificial pathway in *Escherichia Coli* can be the biocatalyst used in order to produce the R-1-propanediol as P and s-1, 2-propanediol as Q in Figure 1.0. The scheme of catalytic reactions are shown in Figure 1.0 and is classified as DYKAT I reactions. The kinetics of these reactions was studied using computer simulations. A set of 5 ODEs were solved for numerically using the method of Runge-Kutta of the fourth order in a MS Excel for Windows 2013. Results are shown for some values of reaction rate constant ratios as graphs. The results depend on the reaction rate constant ratios ε, κ, δ, ω and θ as defined by Equation 8. It appears that although for high values of reaction rate constant ratio, ε when high reversible formation of reactant B can be expected according to the reaction scheme in Figure 1.0 and the computer simulations predict formation of B it is something that needs to be verified experimentally. If confirmed reactant B is being made from reactant A and products P and Q for certain values of reaction rate constants. For higher reaction rate constant ratio κ, the decay of reactant A and reactant B are non-intersecting. For smaller values of reaction rate constant, κ the decay of reactant A and reactant B undergoes a "cross-over". This could mean that the rate of B participation in the reaction is greater than rate of participation at longer times. The concentration of catalyst C_{cat} under goes a maximum in all the graphs Figures 2.0-5.0. For hight values of reaction rate constant ratios omega and Δ compared with θ, ε and κ, the product P can be recovered in a tower reactor at earlier location and product Q can be recovered in the same tower reactor at a later location.

Keywords: *DYKAT Reactions; Runge-Kutta Method; Solution of 5 Simultaneous ODEs; D- Lactic Acid; L-Lactic Acid; R-1-Propanediol; s-1,2-propanediol; Cross-Over; Reversible Reactions*

Nomenclature

A: reactant A such as dextro Lactic Acid

B: starting material B such as leveo Lactic Acid

C_A: concentration of species A ($mol.lit^{-1}$)

C_{cat}: concentration of Intermediate Catalytic Complex ($mol.lit^{-1}$)

C_B: concentration of species B ($mol.lit^{-1}$)

C_p: concentration of species P ($mol.lit^{-1}$)

C_Q: concentration of species Q ($mol.lit^{-1}$)

k_1: forward reaction rate constant from A to Ccat(h^{-1})

k_2: reverse reaction rate constant Ccst to A (s^{-1})

k_3: forward reaction rate constant from B to Ccat (h^{-1})

k_4: reverse reaction rate constant from Ccat to B (h^{-1})

k_5: reaction rate constant from Ccat to Q (h^{-1})

k_6: reaction rate constant from Ccat to P (h^{-1})

P: product P such R – 1 propanediol

Q: product Q such as s 1, 2, propanediol

r_A: rate of reaction of species A (mol.lit.-1h^{-1})

r_B: rate of reaction of species B (mol.lit-1.h^{-1})

r_{cat}: rate of reaction of Catalytic Intermediate Complex (mol.lit.-1.h-1)

r_p: rate of formation of product P (mol.lit.-1.h^{-1})

r_Q: rate of formation of product Q (mol.lit.-1.h^{-1})

u_A: dimensionless concentration of species A defined as $u_A = \frac{C_A}{C_{A0}}$ in Eq. (7)

u_B: dimensionless concentration of species B defined as $u_B = \frac{C_B}{C_{A0}}$

u_{cat}: dimensioless concentration of intermediate catalytic complex defined as $u_{cat} = \frac{C_{cat}}{C_{A0}}$

u_p: dimensionless concentration of product P defined as $u_p = \frac{C_p}{C_{A0}}$

u_Q: dimensionless concentration of product Q defined as $u_Q = \frac{C_Q}{C_{A0}}$

Greek

τ : dimensionless time, $\tau = k_1 t$

ω : dimensionless reaction rate contant ratio, $\omega = \frac{k_2}{k_1}$

δ : dimensionless reaction rate constant ratio, $\delta = \frac{k_6}{k_1}$

θ : dimensionless reaction rate constant ratio, $\theta = \frac{k_5}{k_1}$

ε : dimensionless reaction rate constant ratio, $\varepsilon = \frac{k_4}{k_1}$

κ : dimensionless reaction rate constant ratio, $\kappa = \frac{k_3}{k_1}$

Background

Products such as clothing, diapers, athletic shoes and automobile tires made from petrochemicals are going to be manufactured from raw materials that stems from botanical plants. Principles of enzyme catalysis are used in this endeavor. The PCR study of microorganism or host cell or polynucleotide that serves as catalyst can be performed using microarray analysis [1]. Cloning can be confirmed using sequencing studies. Mutagenesis and molecular cloning methods needed to achieve the desired outcome of higher yields can be designed using the information using microarray analysis. Engineered microbes and development of biocatalysts has lead to the commercialization of bio based polymers. The environmentalists' concerns about air and water pollution can be allayed using manufacturing processes that are scaled-up from tube studies of bioprocess technologies. Plants can be used as source of raw materials for common polymers such as polyester, spandex, synthetic rubber and nylon. Energy sustainability is another benefit obtained using this route. A plant as a source for raw materials makes them renewable feed stocks.

In vista and Genomatica [2] have made the News for the investments in setting up manufacturing plants in order to prepare nylon intermediates from sugar. Acrylic acid for superabsorbent polymers is going to be manufactured using a bio based method by BASF, Cargill and Novozymes. A 100% bio based soda bottle is under development at Coca Cola and its partner Virent is going to supply the raw material. p-xylene is used as a precursor to terephthalic acid that is used in condensation polymerization with ethylene glycol in order to make PET, polyethylene terepthalate. Raw material supply and cost can be a critical factor in determination of the Present Worth of these manufacturing plants. Invista's Lycra brand spandex is 70% from dextrose that is derived from corn. The CO_2 emissions from these processes are low. These fibers are stretchy. Bioprocess based BDO was sourced from BASF. BASF had licensed this technology from Genomatica. Genomatica has demonstrated a bioprocess route to butadiene the monomer that is used to make poly butadiene that is used to make automobile tires. Engineered microbes have been developed in order to make caprolactum used in the preparation of nylon 6 and adipic acid and hexamethylenediamine used in nylon 6, 6. Virent has the technology that can be used to convert sugars catalytically into gasoline and diesel. Virent along with Shell has a vision to build bio refineries. A product from bio refineries is expected to become attractive by cost when the oil reserves become depleted. Acrylic acid production by biotechnology is a goal of a partnership of conglomerates such as BASF, Cargill and Novozymes, in the fields of agriculture, enzymes and chemicals. The group earlier this 2014 year reported 3-hyroxypropionic acid from sugar. 3-Hp was converted to glacial acrylic acid. This is used in order to make a diaper that is superabsorbent. Commercial bio based produced is likely in the next decade to make:

1. Succinic acid, fumaric acid, malic acid from bacterial fermentation of glucose, chemical oxidation of 1,4-butanediol
2. 2-5-Furandicarboxylic acid from chemical dehydration of glucose, oxidation of 5-hydroxymethylfurfural
3. 3-hydroxypropionic acid from glycerol or glucose by bacterial fermentation
4. Glycerol from vegetable oils by catalytic transesterification
5. Sorbitol from glucose from corn syrup by hydrogenation of xylose
6. Xylitol from xylose by bacterial fermentation. Downstream chemicals of these products include 1,4 butanediol, THF, tetrahydrofuran, γ-butyrolactone, maleic anhydride, pyrrolidones, 1,3-propanediol, acrylic acid, methyl acrylate, acrylamide, propylene glycol, ethylene glycol, 1,3-propanediol, glyceric acid, lactic acid, acetol, acrolein, epichlorohydrin, isosorbide, propylene glycol, ethylene glycol, glycerol, lactic acid, alkenes, propylene glycol, ethylene glycol, glycerol, xylaric acid, furfural, 2,5-dihydroxymethylfuran.

Invista is setting up a $100 million manufacturing plant at Orange, TX in order to make AND, adiponitrile using next generation technology. They also have novel biotechnology process to make butadiene a raw material in the manufacture of automobile tires. Genomatica has posted on their websites 18 proprietary patents on biobased polymer technology. They prepare 6-ACA, 6 – aminocaproic acid from 5-formylvaleric acid [3] using a biocatalyst. The 6-ACA is then converted into -caprolactum. They discuss a host cell or polynucleotide used to catalyze the reaction. Nylon 6 can be made from caprolactum. Nylon 6, 12 is a copolymer of caprolactum and laurolactum. Caprolactum has been made from compounds obtained from mineral oil in current industrial practice. Plasmids carrying the different genes were identified by genetic, biochemical and phenotypic means. PCR diagnostic analysis of transformed or purified plasmid DNA and DNA sequence analysis may be used. The genes that encode the biocatalyst were amplified from g DNA using PCR methods.PCR reactions were analyzed using agarose gel electrophoresis. PCR products were purified and cloned. The sequence of genes cloned by PCR

was verified by DNA sequencing. *Escherichia Coli* was grown in 96 well plates with 940 µl media containing 0.02% L-arabinose. Protein expression was studied. Cells for small scale growth were obtained by centrifugation and supernatant was decanted. Centrifugation of 6000g was operated at 4 °C for 20 minutes.

A cell in living species contains many chemical compounds. How the chemicals are manufactured, how some reactants combine at moderate temperature and pressure, how some decompose is governed by enzyme catalysis. Enzymes are globular proteins. They have been found to catalyze more than 5000 bio chemical reactions types. Buchner first extracted certain enzymes from living cells in 1897. E. Fisher in 1894 proposed that both the enzyme and substrate take complementary geometric shapes that fit into each other admirably and presented their 'lock and key' model. One weakness of this model is it does not explain the intermediates that are now known to form in different pathways. The set of enzymes made in a cell can determine which metabolic pathways occur in that cell. Enzymes are said to convert substrates into products. They act as a catalyst. A catalyst, by definition, is a substance that is known to increase the rate of a chemical reaction without undergoing permanent chemical change. It affects the rate of the reaction. It does not affect the chemical equilibrium of the reactants and products. During enzymatic action the activation energy of the reaction undergoes a reduction in value. This can be seen in the synthesis of glucose 6 phosphate from glucose 1 phosphate. The number of 'hot molecules' that can participate in the reaction [4] is larger when the activation of energy of the reactions in lowered on account of enzymatic action.

Catalysts that are found to be active within the living cell can be made to be active outside the living cell such as in a bioreactor. Sumner isolated the first enzyme in 1926. Since then the number of known enzymes are greater than 1500. Microarray analysis and next-generation sequencing machines NGS [1] (Sharma, 2015) can be used to study gene transcription and gene translation processes and other biochemical reactions with increased accuracy. Potentially 3000-4500 enzymes may be present in the human anatomy. Enzyme Commission, EC, identified 6 classes of reactions that are known to be catalyzed by enzymes. These are:

1. Hydrolases
2. Transferases
3. Lyases
4. Ligases
5. Oxidoreductases
6. Isomerases

The enzyme *urease* for example catalyzes the decomposition of urea. Oxidative dehydrogenation of alcohol is catalyzed by *alchohol dehydrogenase*, Familiar names among enzymes are pepsin, *trypsin* that are found in the human digestive tract, *rennin* used in cheese factories and '*old yellow enzyme*' causes browning of slices apples.

Often times the reaction mechanism occurring within the cell is not well known. Experiments are conducted. At first, a guess is Mande of the elementary reactions taking place. The reaction intermediates that are formed are noted. Then an expression for the overall reaction rate is developed. This expression is checked against the experimental observations made. The iterative process of guess and estimation and verification can continue till a reasonable fit is obtained. Cofactors add on to apoenzyme that are not active and become catalytically active halo enzyme active complex. Metals and coenzymes can be cofactors. The Michaelis and Menten kinetics discussed in earlier section is applicable in order to describe enzymatic processes.

Computer Simulation of Kinetics of Dykat I Reactions

An example of reactions that can conform to the scheme shown in Figure 1.0 is the bio catalytic synthesis of propanediol from lactic acid. More interest is seen in technology development of energy sustainable solution to chemical production. A and B in Figure 1.0 can be dextro lactic acid and leveo lactic acid. The artificial pathway in *Escherichia Coli* can be the biocatalyst used in order to produce the R-1-propane diol as P and s-1, 2-propanediol as Q in Figure 1.0.

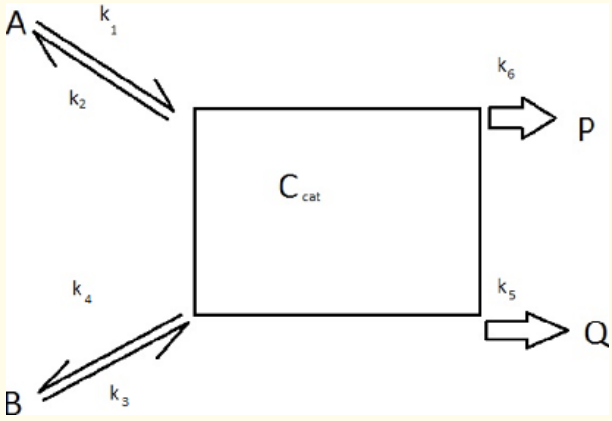

Figure 1: *Scheme of Reactions during Enzyme Catalysis.*

Dykat I Process

[5] defined what are called DYKAT processes. DYKAT, Dynamic kinetic asymmetric transformation processes are *the desymmetrization of racemic or diastereomeri mixtures involving interconverting diastereomeric intermediates* there are four types of DYKAT reactions [6]. Deracemization of enantiomers can be represented using DYKAT I and DYKAT II types. The scheme shown in Figure 61.0 can be used to characterize race mates by diastereoisomeric intermediates. C_{cat} in Figure 61.0 is a chiral intermediate-catalyst complex.

Numerical Solution to Five Simultaneous odes

The kinetics of DYKAT I reactions that obey the scheme shown in Figure 1.0 were studied. An earlier study of intermediate product yield improvement by mass transfer of intermediate was presented by [7]. The kinetic rate expressions in terms of elementary first order rates for each reaction in Figure 1.0 can be written as follows;

$$r_A = -\frac{dC_A}{dt} = k_1 C_A - k_2 C_{cat} \qquad (1)$$

$$r_B = -\frac{dC_B}{dt} = k_3 C_B - k_4 C_{cat} \qquad (2)$$

$$r_{cat} = -\frac{dC_{cat}}{dt} = (k_5 + k_6 + k_2 + k_4) C_{cat} - k_1 C_A - k_3 C_B \qquad (3)$$

$$r_p = \frac{dC_p}{dt} = k_6 C_{cat} \qquad (4)$$

$$r_Q = \frac{dC_Q}{dt} = k_5 C_{cat} \qquad (5)$$

$$u_A = \frac{C_A}{C_{A0}}; u_B = \frac{C_B}{C_{A0}}; u_{cat} = \frac{C_{cat}}{C_{A0}}; u_p = \frac{C_p}{C_{A0}}; u_Q = \frac{C_Q}{C_{A0}}; \tau = k_1 t \quad (7)$$

$$\omega = \frac{k_2}{k_1}; \kappa = \frac{k_3}{k_1}; \varepsilon = \frac{k_4}{k_1}; \theta = \frac{k_5}{k_1}; \delta = \frac{k_6}{k_1} \quad (8)$$

The set of 5 simultaneous ODES with constant coefficients were solved for by the Runge-Kutta method of the fourth order as discussed in [8] on a HP Compaq Elite 8300 Computer. The weighting factors used in the simulation are given as follows:

$K_1 = f(x_i, y_i)$ (8a)

$K_2 = f(x_i + h/2, y_i + K_1 h)$ (8b)

$K_3 = f(x_i + h/2, y_i + k_2 h/2)$ (8c)

$K_4 = f(x_i + h, y_i + K_3 h)$ (8d)

$y_{i+1} = y_i + h/6\,(K_1 + 2K_2 + 2K_3 + K_4)$ (8e)

Results

The results are presented in Figures 2.0 - 5.0. At higher values of κ the decay of species B and A are monotonic and falls without crossing each other as can be seen in Figure 3.0 and 4.0. The cross over in amount of decay of reactant A and amount of reactant B can be seen in Figure 2.0 for κ = 0.5. In Figure 5.0 it appears as though some species B is being made! These can be expected according to the simulation results at high values of κ. This needs to be verified experimentally as it may involve a stereo isomeric shift. Both θ and δ have to be low. The C_{cat} a potential substrate-catalyst complex rises and falls in concentration as can be seen in all the Figures. The values of the maxima depend on the reaction rate ratios.

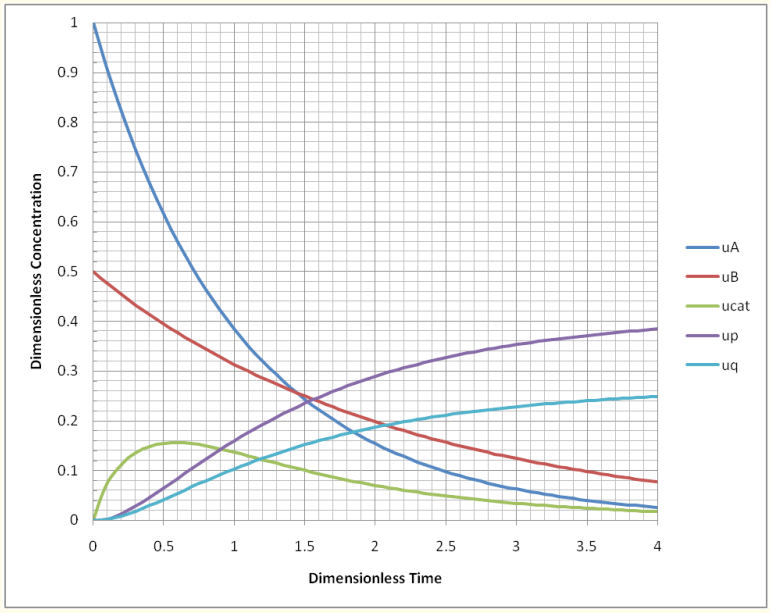

Figure 2: *Dimensionless Concentrations u_A, u_B, u_{cat}, up and uq as a Function of Dimensionless Time, τ from Simulations using Fourth Order Runge-Kutta Method .*

The values of ratios of reaction rate constants used in the computer simulation are as follows:

$\omega = 0.2$; $\varepsilon = 0.1$; $\kappa = 0.5$; $\theta = 1.2$; $\delta = 1.8$

$u_{A0} = 1.0$; $u_{B0} = 0.5$

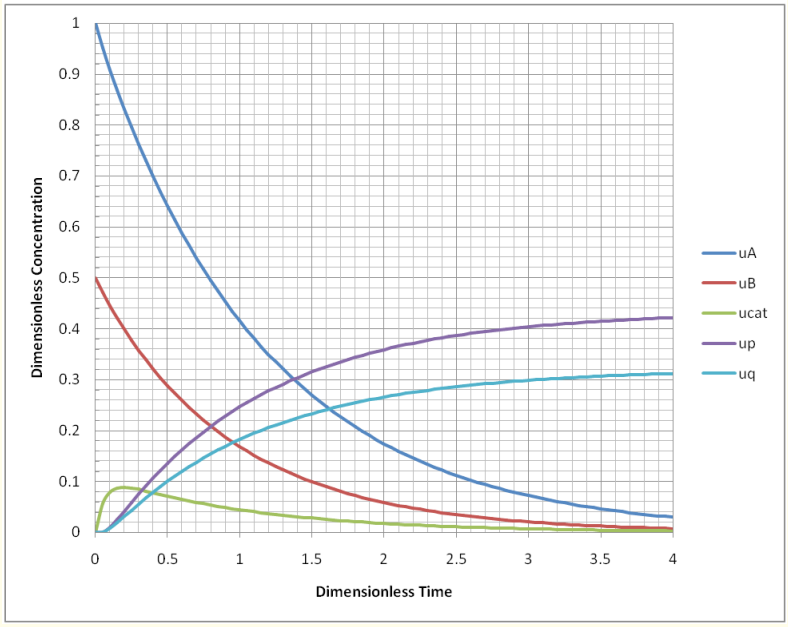

Figure 3: *Dimensionless Concentrations u_A, u_B, u_{cat}, u_p and u_q as a Function of Dimensionless Time, τ from Simulations using Fourth Order Runge-Kutta Method on a HP Compaq Elite 8300 Computer.*

The values of ratios of reaction rate constants used in the computer simulation are as follows;

$\omega = 1.2$; $\varepsilon = 0.5$; $\kappa = 1.2$; $\theta = 4.0$; $\delta = 5.0$

$u_{A0} = 1.0$; $u_{B0} = 0.5$

B Participation, High κ

The values of ratios of reaction rate constants used in the computer simulation are as follows:

$\omega = 0.1$; $\varepsilon = 0.2$; $\kappa = 5$; $\theta = 1.7$; $\delta = 1.2$

$u_{A0} = 1.0$; $u_{B0} = 0.5$

REVERSIBILITY EFFECTS, HIGHε

Species is made in the reactor at high ε!

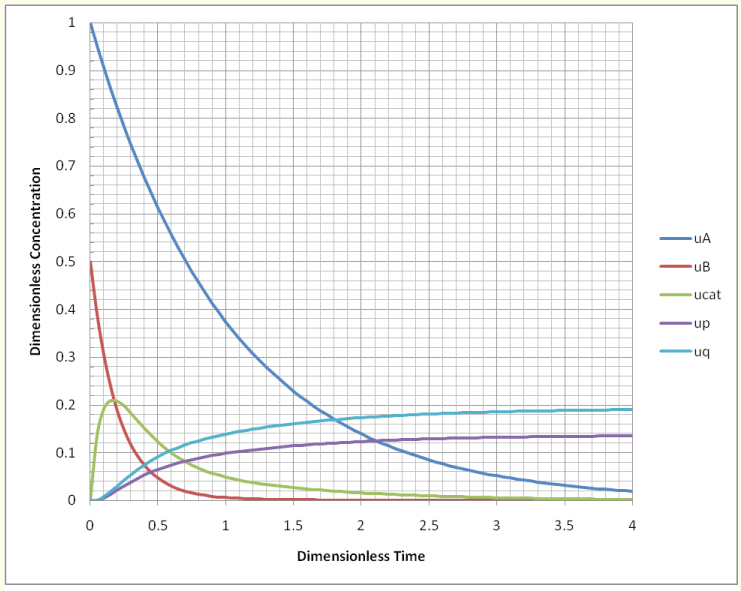

Figure 4: *Dimensionless Concentrations u_A, u_B, u_{cat}, u_p and u_q as a Function of Dimensionless Time, τ from Simulations using Fourth Order Runge-Kutta Method on a HP Compaq Elite 8300 Computer.*

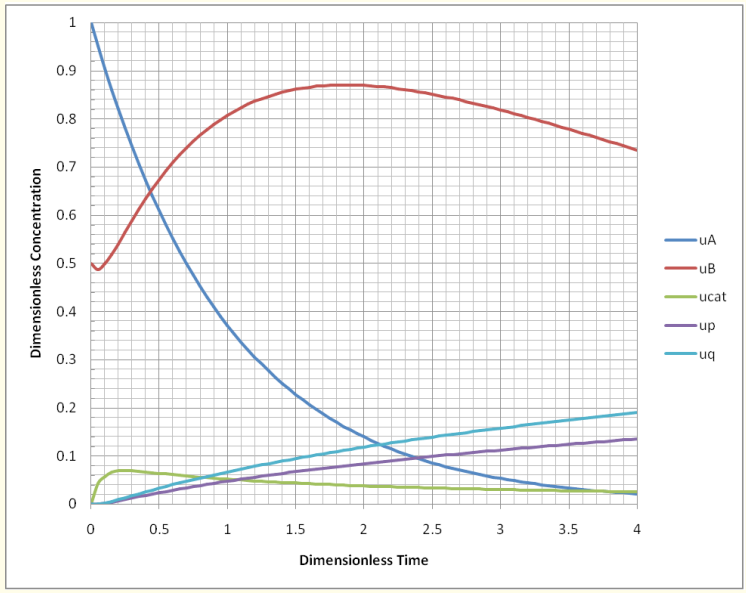

Figure 5: *Dimensionless Concentrations u_A, u_B, u_{cat}, u_p and u_q as a Function of Dimensionless Time, τ from Simulations using Fourth Order Runge-Kutta Method on a HP Compaq Elite 8300 Computer.*

The values of ratios of reaction rate constants used in the computer simulation are as follows;
$\omega = 0.1$; $\varepsilon = 11$; $\kappa = 0.5$; $\theta = 1.7$; $\delta = 1.2$
$u_{A0} = 1.0$; $u_{B0} = 0.5$

The kinetics of reaction scheme shown in Figure 1.0 was simulated on the computer. Numerical solution of 5 simultaneous ODEs with constant coefficients were obtained using the Runge-Kutta Method of the fourth order. Results are shown for some kinetic parameters. A graph showing the entire parametric space can be prepared depending on interest. Liquid extraction can be used for the separation of structural isomers. Ethyl acetate is a suitable solvent.

Conclusion

There is increased interest in the industry in order to manufacture products from raw materials that stem from botanical plants. Principles of enzyme catalysis are used in design of these processes. Stereo isomer products R and S Propanediol can be manufactured from L a D lactic acid. The scheme of catalytic reactions are shown in Figure 1.0 and is classified as DYKAT I reactions. The kinetics of these reactions was studied using computer simulations. A set of 5 ODEs were solved for numerically using the method of Runge-Kutta of the fourth order in a MS Excel Spread sheet. The weighting factors and recursive relation used as shown in Equations: (8a-8e). Results are shown for some values of reaction rate constant ratios as graphs. The results depend on the reaction rate constant ratios ε, κ, δ, ω and θ as defined by Equation: (8). It appears that although for high values of reaction rate constant ratio, ε when high reversible formation of reactant B can be expected according to the reaction scheme in Figure 1.0 the computer simulations predict formation of B it is something that needs to be verified experimentally. If confirmed reactant B is being made from reactant A and products P and Q for certain values of reaction rate constants. For higher reaction rate constant ratio, κ, the decay of reactant A and reactant B are non-intersecting. For smaller values of reaction rate constant, κ the decay of reactant A and reactant B undergoes a "cross-over". This could mean that the rate of B participation in the reaction is greater than rate of A participation at longer times. The concentration of catalyst C_{cat} undergoes a maximum in all the graphs Figures 2.0 -5.0. At high values of reaction rate constant ratio, κ reactant B gets depleted more rapidly than reactant A.

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