

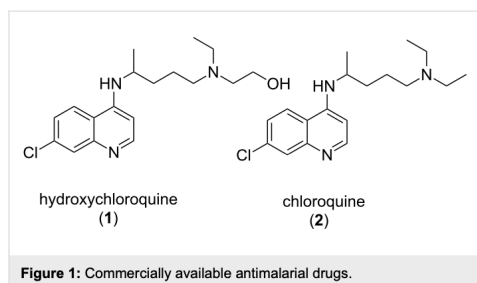
CBE 40445
Fall 2020
Test #1
9/4/20

1. Continuous manufacture of hydroxychloroquine (60 points)



High-yielding continuous-flow synthesis of antimalarial drug hydroxychloroquine

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It is more than a little surprising that ~8 months into the epidemic, conclusions regarding the efficacy of *hydroxychloroquine* for COVID19 patients remain sharply divided. *Hydroxychloroquine* has been used as an anti-malarial agent since the 1940's and more recently as an anti-inflammatory for Lupus and rheumatoid arthritis. Thus the "safe" dosage range is well - established and should not be controversial (but safety is questioned...). Its use in the current epidemic stems from previous apparent successes for

"SARS". *Hydroxychloroquine* is described by Bayer Corporation as having broad-spectrum antiviral properties (...of course they manufacture it...). If it were effective, then it would be widely available for all who need it in contrast to more "modern" drugs such as Remdesivir which are in short supply.

Let's first analyze CSTR's for first and 2nd order kinetics.

- a. Consider a CSTR with first order kinetics. Find an expression for the exit concentration, C_A in terms of the feed concentration, C_{A0} , the residence time ($\tau = V/q$) and the rate constant, k .
- b. Compare this to a CSTR with 2nd order kinetics of the form $r = k C_A^2$ but the same feed concentration, flowrate and volume from part a. Find an expression for the exit concentration in terms of the feed concentration, C_{A0} , the residence time ($\tau = V/q$) and the rate constant, k .
- c. In general, which order reaction gives a lower exit concentration of C_A ?

Now let's look at manufacture of hydroxychloroquine.

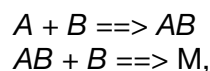
The synthesis takes many steps which are outlined in the above paper. The authors have developed a "continuous" (at least most of the steps can be done continuously) synthesis procedure.

For the purposes of this test question, we focus just one step, compound "11" (an "oxime" being converted to "12", an amine).

We can take compound 11 as "A", the hydrogen¹ is "B" and we will take compound 12 as M .

Most simplistically we could write

¹ In almost all cases, when hydrogen is a reactant with a liquid phase reactant, the process is done under elevated pressure. This allows the reaction to proceed with either enough or excess hydrogen. If the pressure were only 1 ATM, the H₂ molar concentration in the liquid would be much less than the molar concentration of the other reactant and thus hydrogen would limit the rate and extent of reaction.

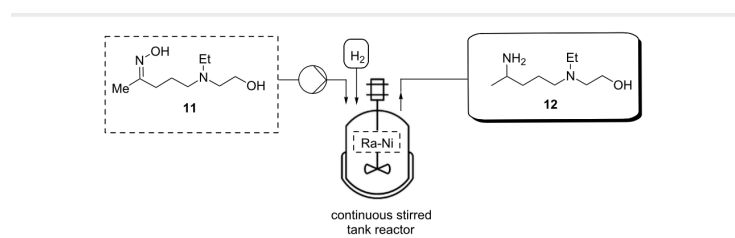


since two hydrogens are needed to balance the reaction. Note that the oxime is dissolved in *tetrahydrofuran* (THF) and a “Raney-nickel” catalyst is present and kept confined in the CSTR.

d. Given no other information, what would you expect the form of the kinetic rate expression to be for the first reaction $A + B \implies AB$?

e. With reference to the footnote on the previous page that the reactor is run with hydrogen in great excess, would the kinetic expression simplify? To what?

The data for the continuous flow reactor that is converting 11(oxime) to 12 is given in the following table. Note that t_R in the table is $V/q \implies \tau$, residence time



entry	oxime [concentration]	temp. (°C)	pressure (bar)	t_R = hours	conv. of 12 (%) ^a
1	0.05 M	80	10	4	94%
2	0.25 M	80	10	4	96%
3	0.5 M	80	10	4	97%
4	2.0 M	80	10	4	98%
5	2.0 M	80	10	2	56%
6	2.0 M	80	10	1	46%

^aConversion determined by GC-MS and ¹H NMR. ^bIsolated yield.

f.

Note that in the table above, the right-most column is defined as $(C_{A0} - C_A)/C_{A0}$.

f. Based on the bottom row of data, what is the first order rate constant for this reaction?

g. Based on the bottom row of data, if the feed concentration is $C_{A0} = 2$ moles/liter, what values of q and V would be needed to manufacture 100 moles in 24 hours.

h. Is this reaction really first order in A?

2. Comparison of different reactor configurations. (30 points)

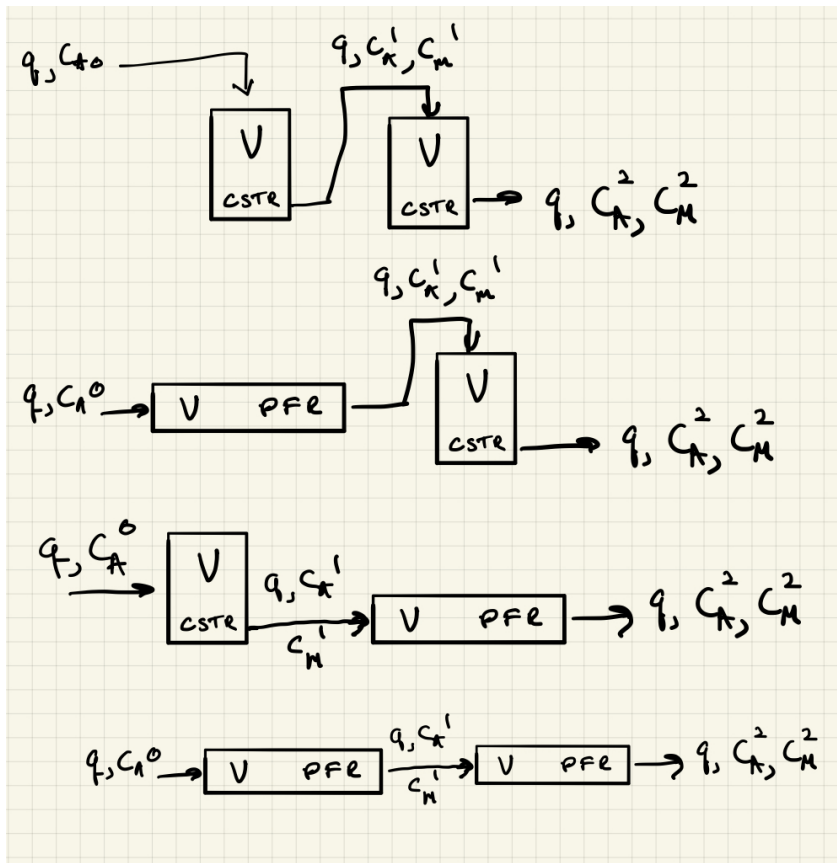
Consider the reaction $A \rightarrow M$ with first order kinetics.

The feed concentration is C_{A0} and the volumetric flow rate is q . Each reactor has total volume V .

- A. Find an expression for the ratio of the exit concentration of the 2nd reactor C_A^2 , to the feed concentration, C_{A0} , for the following reactor configurations.

Note that the superscripts denote the composition in reactor 1 or 2.

- B. Which configuration gives the the highest conversion (smallest C_A^2) at the exit of the second reactor? Explain why this is so.



3. Temperature dependence of Enzyme production. (10 points)



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Thermostable α -amylase and α -galactosidase production from the thermophilic and aerobic *Bacillus* sp.JF strain

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In this paper, Jin et al. report data for the growth of a strain of *Bacillus* sp.JF that is being used to produce the enzyme α -amylase. They provide the concentration of the substrate “S” (“total sugar”) and cell mass as a function of time (at 60 C) and the apparent first order rate constants k , for other temperatures.

From just these data: what is the expected rate constant for 50C?

Temp C		k (1/hr)
	55	0.0659
	58	0.074
	60	0.0805

Note that it is interesting that the peak in the data are at 60 C and the rate actually decreases (not shown here) when the temperature is increased to just 62 C. Such behavior would not be expected for a chemical reaction of just small molecules.

Potentially useful formulae:

$$\Delta G - \Delta G^0 = R_g T \sum_{i=1}^{NCOMP} \nu_i \ln a_i = R_g T \ln \left(\prod_i a_i^{\nu_i} \right) \quad \Delta G^0 = -R_g T \ln \left[\frac{a_W^w a_S^s \dots}{a_A^a a_B^b \dots} \right] = -R_g T \ln K_a$$

Equilibrium constant:

$$\left[\frac{\partial (\ln K_a)}{\partial T} \right]_P = \frac{\Delta H^0}{R_g T^2} \quad K_a = \exp \left[-\Delta G^0 / (R_g T) \right]$$

$$a = \bar{f}_i / \bar{f}_i^0 \quad \bar{f}_i = X_i \bar{\phi}_i P \quad K_a = \left[\frac{X_W^w X_S^s \dots}{X_A^a X_B^b \dots} \right] \left[\frac{\bar{\phi}_W^w \bar{\phi}_S^s \dots}{\bar{\phi}_A^a \bar{\phi}_B^b \dots} \right] P^{w+s+\dots-a-b-\dots}$$

The fractional conversion is defined as:

$$f(t) = \frac{\Phi(t)}{\Phi_{\max}} \quad (1.2.9)$$

and can be calculated from Equations (1.2.3) and (1.2.8):

$$f_\ell = (-\nu_\ell) \frac{\Phi}{n_\ell^0} = 1 - \frac{n_\ell}{n_\ell^0} \quad (1.2.10)$$

Equation (1.2.10) can be rearranged to give:

$$n_\ell = n_\ell^0 (1 - f_\ell) \quad (1.2.11)$$

where $0 \leq f_\ell \leq 1$. When the thermodynamics of the system limit Φ such that it cannot reach Φ_{\max} (where $n_\ell = 0$), Φ will approach its equilibrium value Φ^{eq} ($n_\ell \neq 0$ value of n_ℓ determined by the equilibrium constant). When a reaction is limited by

This expression is either positive or equal to zero if the system has reached equilibrium. The reaction rate, like Φ , is an extensive property of the system. A specific rate called the *volumic rate* is obtained by dividing the reaction rate by the volume of the system, V :

$$r = \frac{1}{V} \frac{d\Phi}{dt} \quad \left(\frac{\text{mol}}{\text{time} \cdot \text{volume}} \right) \quad (1.3.2)$$

Differentiation of Equation (1.2.3) gives:

$$dn_i = \nu_i d\Phi \quad (1.3.3)$$

Substitution of Equation (1.3.3) into Equation (1.3.2) yields:

$$r = \frac{1}{\nu_i V} \frac{dn_i}{dt} \quad (1.3.4)$$

tion (1.2.1), then the number of moles of component A_i at any time t will be given by the equation:

$$n_i(t) = n_i^0 + \nu_i \Phi(t) \quad (1.2.3)$$

that is an expression of the *Law of Definitive Proportions* (or more simply, a mole balance) and defines the parameter, Φ , called the *extent of reaction*. The extent of reaction is a function of time and is a natural reaction variable.

concentrations, C_i , is desired. Since $C_i = n_i/V$, Equation (1.3.4) can be written as:

$$r = \frac{1}{\nu_i V} \frac{d}{dt} (C_i V) = \frac{1}{\nu_i} \frac{dC_i}{dt} + \frac{C_i}{\nu_i V} \frac{dV}{dt} \quad (1.3.6)$$

Note that only when the volume of the system is constant that the volumic rate can be written as:

$$r = \frac{1}{\nu_i} \frac{dC_i}{dt}, \text{ constant } V \quad (1.3.7)$$

When it is not possible to write a stoichiometric equation for the reaction, the

Rule II

The rate of an irreversible (one-way) reaction can generally be written in the form:

$$r = k(T) \bar{F}(C_i, T) \quad (1.4.1)$$

where $\bar{F}(C_i, T)$ is a function that depends on the composition of the system as expressed by the concentrations C_i .

Rule III

The rate constant generally depends on the absolute temperature, T , following the law first proposed by Arrhenius in 1889:

$$k = \bar{A} \exp \left[\frac{-E}{R_i T} \right] \quad (1.4.2)$$

Rule IV

Frequently, the function $\bar{F}(C_i)$ in the expression $r = k \bar{F}(C_i)$ can approximately be written as:

$$\bar{F}(C_i) = \prod_i C_i^{\alpha_i}$$

Consider the unimolecular reaction:



Using the Guldberg-Waage form of the reaction rate to describe this reaction gives:

$$r = kC_A \quad (1.5.2)$$

From Equations (1.3.4) and (1.5.2):

$$r = \frac{1}{v_i V} \frac{dn_i}{dt} = \frac{-1}{V} \frac{dn_A}{dt} = kC_A$$

$$\frac{dn_A}{dt} = -kn_A \quad (\text{variable } V) \quad (1.5.3)$$

$$\frac{df_A}{dt} = k(1 - f_A) \quad [\text{using Equation (1.2.11)}] \quad (1.5.4)$$

Consider the bimolecular reaction:



Using the Guldberg-Waage form of the reaction rate to describe this reaction gives:

$$r = kC_A C_B \quad (1.5.8)$$

$$r = \frac{1}{v_i V} \frac{dn_i}{dt} = \frac{-1}{V} \frac{dn_A}{dt} = kC_A C_B$$

$$r = \left(\frac{\bar{k}T}{h} \right) \exp\left[\frac{\Delta S_0^\ddagger}{R_g} \right] \exp\left[\frac{-\Delta H_0^\ddagger}{R_g T} \right] C_A C_B$$

$$\frac{dn_i}{dt} = 0 - 0 + (v_i r V)$$

accumulation input output amount produced by reaction

The material balance can also be written in terms of the fractional conversion and it is:

$$n_i^0 \frac{df_i}{dt} = -(v_i r) V^0 (1 + \varepsilon_i f_i) \quad \text{with } f_i = 0 @ t = 0 \quad (3.2.2)$$

where $|\varepsilon_i| > 0$ for nonconstant volume.

Since the reactor is at steady-state, the difference in F_i^0 (input) and F_i (output) must be due to the reaction. (In this text, the superscript 0 on flow rates denotes the input to the reactor.) The material balance on a CSTR is written as:

$$0 = F_i^0 - F_i + (v_i r) V \quad (3.3.1)$$

accumulation input of i output of i amount produced by reaction

$$V \frac{dC_i}{dt} = q_i C_{i0} - q C_i + v_i r V$$

$$f_i = \frac{n_i^0 - n_i}{n_i^0} = \frac{F_i^0 - F_i}{F_i^0}$$

3.2.4) into Equation (3.2.2) yields:

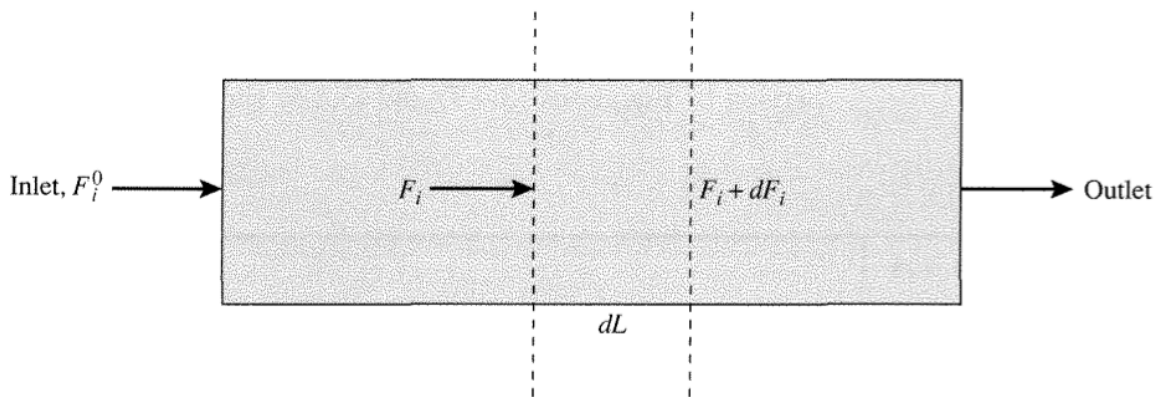


Figure 3.4.1 |
Tubular reactor.

$$0 = F_i - (F_i + dF_i) + v_i r A_C dL \quad (3.4.1)$$

(accumulation) = (input) - (output) + (amount produced by reaction)

where A_C is the cross-sectional area of the tube. Also, $A_C dL = dV_R$, so Equation (3.4.1) can be written as:

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$$\frac{dF_i}{dV_R} = v_i r \quad (3.4.2)$$

or

$$F_i^0 \frac{df_i}{dV_R} = -v_i r \quad (3.4.3)$$

Integration of Equation (3.4.3) gives:

$$\frac{V_R}{F_i^0} = \int_{f_i^0}^{f_i^{\text{outlet}}} \frac{df_i}{(v_i r)} \quad \text{or} \quad \tau = \frac{V_R}{v} = C_i^0 \int_{f_i^0}^{f_i^{\text{outlet}}} \frac{df_i}{(v_i r)} \quad (3.4.4)$$

If changes in volume due to reaction are negligible, then $[F_i = C_i v; \text{ moles of } i/\text{time} = (\text{moles of } i/\text{volume}) (\text{volume}/\text{time})]$:

$$\frac{dC_i}{d\tau} = \frac{dC_i}{d(V_R/v)} = v_i r \quad (3.4.5)$$

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$-\int_{C_{A0}}^{C_A} \frac{1}{\xi^2} d\xi = \frac{1}{C_A} - \frac{1}{C_{A0}}$$

$$\int_{x_0}^x \frac{1}{(\xi - \alpha)} d\xi = \ln \left(\frac{x - \alpha}{x_0 - \alpha} \right)$$

$$\int_{x_0}^x \frac{1}{\xi} d\xi = \ln \left(\frac{x}{x_0} \right)$$

Periodic table of the elements

group	1*	2											13	14	15	16	17	18
period 1	1 H																	2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg	3	4	5	6	7	8	9	10	11	12	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 Ac	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Nh	114 Fl	115 Mc	116 Lv	117 Ts	118 Og
lanthanoid series 6	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu				
actinoid series 7	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr				

*Numbering system adopted by the International Union of Pure and Applied Chemistry (IUPAC).

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UNITS

Mass	1 kg = 1000 g = 0.001 metric ton = 2.20462 lb _m 1 lb _m = 16 oz = 5E-4 ton = 453.59 g = 0.45359 kg
Length	1 m = 100 cm = 1000 mm = 1E6 μm = 1E9 nm = 39.370 in = 3.2808 ft = 1.0936 yd 1 ft = 12 in = 0.30480 m = 30.480 cm 1 in = 2.5400 cm
Volume	1 m ³ = 1000 L = 1E6 cm ³ = 1E6 ml = 35.315 ft ³ = 264.17 gal 1 ft ³ = 1728.0 in ³ = 7.4805 gal = 0.028317 m ³ = 28.317 L = 28317 ml
Force	1 N = 1 kg·m/s ² = 1E5 dynes = 1E5 g·cm/s ² = 0.22481 lb _f 1 lb _f = 32.174 lb _m ·ft/s ² = 4.4482 N
Pressure	1 atm = 1.01325E5 N/m ² (Pa) = 1.01325 bar = 760 mmHg at 0°C = 33.9 ftH ₂ O at 4°C 1 atm = 14.696 psia 1 bar = 0.1 MPa = 0.98692 atm = 14.504 psia = 750.06 mmHg at 0°C = 10.197 mH ₂ O at 4°C
Energy	1 J = 1 N·m = 1 MPa·cm ³ = 1 kgm ² /s ² = 0.23901 cal = 0.73756 ft·lb _f 1 J = 1E7 ergs = 1E7 g·cm ² /s ² 1 kJ = 0.94781 Btu ^(see note 1) = 2.7778E-4 kW·h = 0.23901 food calorie
Power	1 W = 1 J/s = 0.2390 cal/s ^(see note 2) = 0.73756 ft·lb _f /s = 3.4121 Btu/h ^(see note 1) 1 hp = 550 ft·lb _f /s = 0.70726 Btu/s ^(see note 1) = 0.74570 kW
Gas Constant, <i>R</i>	= 8.31447 J/mole·K = 8.31447 cm ³ ·MPa/mole·K = 8.31447 m ³ ·Pa/mole·K = 8,314.47 cm ³ ·kPa/mole·K = 83.1447 cm ³ ·bar/mole·K = 1.9859 Btu/lbmole·R ^(see note 1) = 82.057 cm ³ ·atm/mole·K = 1.9872 cal/mole·K ^(see note 2) = 10.731 ft ³ ·psia/lbmole·R
Gravitational Constants at sea level	$g = 9.8066 \text{ m/s}^2$ $g/g_c = 9.8066 \text{ N/kg}$ $g_c = 1 \text{ (kg·m/s}^2\text{)/N}$ $g = 32.174 \text{ ft/s}^2$ $g/g_c = 1 \text{ lb}_f\text{/lb}_m$ $g_c = 32.174 \text{ (lb}_m\text{·ft/s}^2\text{)/lb}_f$
Faraday's Constant	$F = 96,485 \text{ J/V}$
IUPAC Standard Conditions of Temperature and Pressure	$T = 0^\circ\text{C} = 273.15 \text{ K}$; $P = 0.1 \text{ MPa}$; $V(\text{ideal gas}) = 22711 \text{ cm}^3\text{/mole}$; $\rho(\text{water}) = 0.99984 \text{ g/cm}^3 = 8.3441 \text{ lb}_m\text{/gal}$

1. The International Steam Table (IT) BTU.
2. The thermochemical calorie.

