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Reactive Extraction of Penicillin G: Selection of Volume Ratios between Phases and Optimum Carrier Concentration

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ABSTRACT

Reactive extraction of penicillin G at pH 5 and reextraction at pH 7–8 were performed using Amberlite LA-2 (carrier) in *n*-butyl acetate. The volume ratios of aqueous feed phase to organic extract phase in extraction and organic extract phase to aqueous strip phase in reextraction were varied, and the effects on the degree of extraction and enrichment were studied. The effects of initial concentration ratio of carrier to penicillin G were also investigated. It was found that there existed an optimum carrier concentration giving the maximum degree of extraction and enrichment. Procedure for the selection of volume ratios and concentration ratio at a desired degree of extraction and enrichment was described for initial penicillin G concentration of 10 mmol·dm^{-3}, and generalized to be applicable for any concentrations of penicillin G. Finally, sodium carbonate solution was successfully applied as an aqueous strip phase on behalf of buffer solution in reextraction to avoid the disadvantages of using buffer solution and to shorten the reextraction time.

1. INTRODUCTION

A series of studies on the reactive extraction of penicillin G was performed by Schügerl and his colleagues (1–12) beginning in 1984. Their

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purposes were to reduce the penicillin loss during recovery, which was larger than 10% in conventional solvent extraction, and thereby to enhance the degree of extraction and to investigate the applicability to pilot plant.

In conventional solvent extraction of penicillin G, which is a weak acid ($pK_a = 2.75$), the pH has to be reduced below the pK_a value in order to increase the fraction of the free acid that is only soluble in organic solvent (e.g., *n*-butyl acetate). At this low pH value, however, penicillin G is unstable; therefore, the extraction is carried out at 0°C. In spite of low temperature and short contact time, the loss of penicillin G during recovery is considerable. Thus, to avoid the loss, reactive extraction by secondary amines was employed (1–12). The extraction and reextraction were carried out at pH 5 and 7.5, respectively. In this pH range, penicillin G is relatively stable, and the loss of penicillin G could be reduced to below 1%. Equilibrium (1, 2) and kinetic (3) studies as well as a feasibility study in a bench-scale Karr column (4) and its modeling (5) have already been dealt with. A scale-up study in a pilot plant Karr column (6–8) and comparison with other extraction columns were discussed (9). Reactive extraction of penicillin G was also performed in a mixer-settler (10), in a centrifugal extractor (11), and in a countercurrent extraction decanter (12).

Though a series of studies on the reactive extraction of penicillin G were performed, concentration ratio effects of carrier to penicillin G and the volume ratio effects of the aqueous (organic) phase to the organic (aqueous) phase have not been studied. Therefore, in this study we investigated the effects of volume ratio of the aqueous feed phase to organic extract phase in extraction and the organic extract phase to aqueous strip phase in reextraction. Also the method for selecting the above volume ratios and the optimum concentration ratio of carrier to penicillin G were studied. In addition, sodium carbonate solution was applied as an aqueous strip phase in reextraction to avoid the disadvantages of using buffer solutions and to shorten the extraction time.

2. THEORY

2-1. Partition Coefficient and Physical Extraction

Penicillin G, HP, dissociates in aqueous phase to give penicillin acid anion, P^-, and proton as follows:

$$HP = H^+ + P^- \tag{1}$$

The dissociation constant is given by

$$K_a = C_P C_H / C_{HP} \tag{2}$$

where the charge of the ions is omitted for simplicity.

The partition coefficient is defined as the ratio of the free acid concentration in the organic phase to that in the aqueous phase:

$$C = C_{HP}^E / C_{HP}^F \tag{3}$$

In physical extraction, the degree of extraction depends only on the partition coefficient and the pH value of the aqueous phase, because the undissociated free acid can only be extracted by an organic phase and the amount of free acid is related to the pH value as shown in Eq. (2).

The degree of extraction is defined as the fraction of free acid extracted in the organic phase to the overall concentration:

$$Y = \frac{C_{HP}^E V^E}{C_{HP}^E V^E + C_{HP}^F V^F + C_P^F V^F} \times 100 \tag{4}$$

From Eqs. (2) and (3), Eq. (4) becomes

$$Y = \frac{1}{1 + (1 + 10^{pH - pK_a})/C} \times 100 \tag{5}$$

where pK_a is defined as $-\log_{10}(K_a)$. When the volume of aqueous feed phase is different to that of organic extract phase, Eq. (5) is given by:

$$Y = \frac{1}{1 + V_{R1}(1 - 10^{pH - pK_a})/C} \times 100 \tag{6}$$

where V_{R1} is the volume ratio of aqueous feed phase to organic extract phase:

$$V_{R1} = V^F / V^E \tag{7}$$

In reextraction, Eq. (6) can be expressed as

$$Y = \frac{100}{1 + (1 + 10^{pH - pK_a})/C/V_{R2}} \tag{8}$$

where V_{R2} is the volume ratio of organic extract phase to aqueous strip phase:

$$V_{R2} = V^E / V^S \tag{9}$$

2.2. Reactive Extraction and Reextraction

The mechanism for the reactive extraction of penicillin G with Amberlite LA-2 in *n*-butyl acetate is obtained by (1, 13)

$$\text{A(org)} + \text{P}^-\text{(aq)} + \text{H}^+ = \text{AHP} \tag{10}$$

Reaction (10) is instantaneous, and the equilibrium constant is given by

$$K_{eq} = C_{AHP}/C_A C_P C_H \tag{11}$$

In reactive extraction, penicillin G is recovered simultaneously by physical and chemical extraction as shown in Fig. 1. At equilibrium, the overall mass balance is

$$C^F_{P,0} = C^F_P + C^F_{HP} + (C^E_{HP} + C_{AHP})/V_{R1} \tag{12}$$

Rearranging Eq. (12) with the aid of Eqs. (2) and (3) leads to

$$C_{AHP} = V_{R1}(C^F_{P,0} - C^F_P) - (V_{R1} + C)C^F_P \times 10^{-pH+pK_a} \tag{13}$$

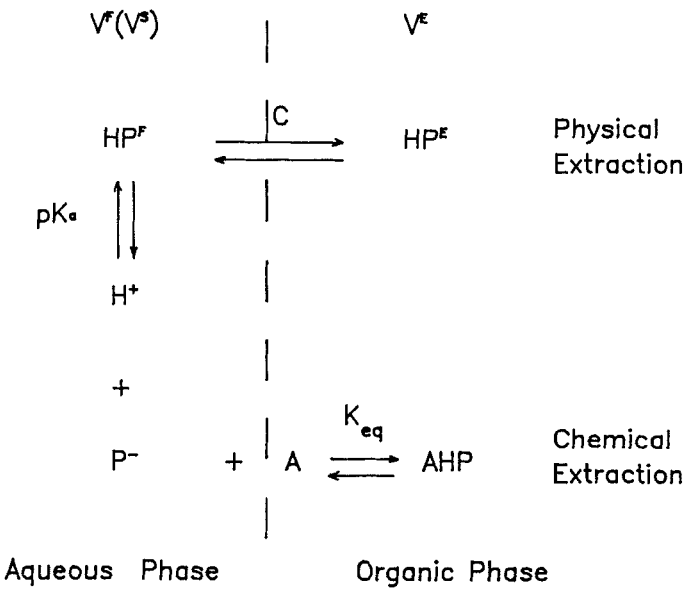

FIG. 1 Schematic diagram of reactive extraction of penicillin G.

The carrier concentration at equilibrium can also be derived by a material balance:

$$C_A = C_{A,0} - C_{AHP} \tag{14}$$

Substituting Eqs. (13) and (14) into Eq. (11) gives the penicillin G concentration in aqueous feed phase at equilibrium:

$$\frac{C_P^F}{C_{P,0}^F} = \frac{1}{2}\left[- \left(\frac{1}{K_{eq}C_H^F C_{P,0}^F} + \frac{C_E^*/V_{R1} - 1}{Z_1}\right) + \sqrt{\left(\frac{1}{K_{eq}C_H^F C_{P,0}^F} + \frac{C_E^*/V_{R1} - 1}{Z_1}\right)^2 + \frac{4}{Z_1 K_{eq} C_H^F C_{P,0}^F}}\right] \tag{15}$$

where C_E^* is the initial concentration ratio of carrier to penicillin G:

$$C_E^* = C_{A,0}/C_{P,0}^F \tag{16}$$

and Z_1 is represented by

$$Z_1 = 1 + (1 + C/V_{R1}) \times 10^{-pH^F + pK_a} \tag{17}$$

Therefore, the degree of extraction becomes:

$$Y_{EX} = \left[1 - \frac{C_P^F(1 + 10^{-pH^F + pK_a})}{C_{P,0}^F}\right] \times 100 \tag{18}$$

In the reextraction of penicillin G, the overall material balance at equilibrium can be written as

$$V_{R2}C_{AHP,0} = C_P^S + C_{HP}^S + (C_{HP}^E + C_{AHP})V_{R2} \tag{19}$$

where $C_{AHP,0}$ is given by

$$C_{AHP,0} = \frac{Y_{EX}C_{P,0}^F V_{R1}}{100} \tag{20}$$

The reextraction of penicillin G from the organic phase into the aqueous strip phase can be thought as a process of penicillin G extraction where the initial concentrations of penicillin G and carrier are $V_{R2}C_{AHP,0}$ and $C_{A,0}$, respectively, because reactive extraction is an equilibrium process, and the concentrations of carrier, penicillin, and the carrier–penicillin complex are the same at equilibrium. Rewriting this gives

$$\begin{aligned} C_{P,i0}^S &= V_{R2}C_{AHP,0} \\ &= \frac{Y_{EX}C_{P,0}^F V_{R3}}{100} \end{aligned} \tag{21}$$

where V_{R3} is the overall volume ratio of aqueous feed to strip phase:

$$\begin{aligned} V_{R3} &= V_{R1}V_{R2} \\ &= V^F/V^S \end{aligned} \tag{22}$$

Following the same procedure in reactive extraction, the penicillin G concentration in the aqueous strip phase at equilibrium becomes

$$\frac{C_P^S}{C_{P,i0}^S} = \frac{1}{2}\left[- \left(\frac{1}{K_{eq}C_H^S C_{P,i0}^S} + \frac{C_{RE}^* V_{R2} - 1}{Z_2}\right) + \sqrt{\left(\frac{1}{K_{eq}C_H^S C_{P,i0}^S} + \frac{C_{RE}^* V_{R2} - 1}{Z_2}\right)^2 + \frac{4}{Z_2 K_{eq} C_H^S C_{P,i0}^S}}\right] \tag{23}$$

where C_{RE}^* is the imaginary ratio of the initial concentrations of carrier and penicillin G in reextraction:

$$C_{RE}^* = C_{A,0}/C_{P,i0}^S \tag{24}$$

and Z_2 is represented by

$$Z_2 = 1 + (1 + CV_{R2}) \times 10^{-pH^S + pK_a} \tag{25}$$

The enrichment of penicillin G in reactive extraction and reextraction is defined as the ratio of penicillin G concentration in the aqueous strip phase to that in the aqueous feed phase:

$$E = \frac{C_P^S(1 + 10^{-pH^S + pK_a})}{C_{P,0}^F} \tag{26}$$

The overall degree of extraction of penicillin G is given by

$$Y_{OV} = \frac{E}{V_{R3}} \times 100 \tag{27}$$

If all of the penicillin G in the aqueous feed phase is recovered into the aqueous strip phase, E is equal to V_{R3}. However, because of the limitation by equilibrium between the two phases, Y_{OV} is much less than 100.

2.3. Kinetic in Reextraction

To study the applicability of sodium carbonate solution as a strip phase in reextraction, a kinetic study was performed. The kinetic model of Reschke and Schügerl (3) is given by

$$-\frac{dC_P^S}{dt} = k_p a_p \left[C_p^S + \frac{1}{2}\left(\frac{k_A}{k_{AHP} K_{eq} C_H} + \frac{k_A C_A}{k_p} - C_P^S \right) \right.$$

$$\left. - \left\{ \frac{1}{4}\left(\frac{k_A}{k_{AHP} K_{eq} C_H} + \frac{k_A C_A}{k_p} - C_P^S \right)^2 + \frac{k_A C_P^S}{k_{AHP} K_{eq} C_H} + \frac{k_A C_{AHP}}{k_p K_{eq} C_H} \right\}^{1/2} \right] \quad (28)$$

where k_p, k_A, and k_{AHP} are the mass transfer coefficients of penicillin G, carrier, and penicillin–carrier complex, respectively, and a_p is the specific interfacial area. In Eq. (28), C_{AHP} is a function of C_p and can be derived from Eq. (19):

$$C_{AHP} = C_{AHP,0} - \left[\frac{1}{V_{R2}} + \left(C + \frac{1}{V_{R2}} \right) \times 10^{-pH^S + pK_a} \right] C_P^S \quad (29)$$

C_A is given by Eq. (14), and the pH change of aqueous strip phase can be obtained from the ionic balance (14):

$$C_H^5 + C_1 C_H^4 + C_2 C_H^3 + C_3 C_H^2 + C_4 C_H + C_5 = 0 \quad (30)$$

$$C_1 = K_a + K_w/K_{b2} + 2C_b \quad (31)$$

$$C_2 = \frac{K_w^2}{K_{b1} K_{b2}} + \frac{K_w K_a}{K_{b2}} + \frac{K_w C_b}{K_{b2}} + 2K_a C_b - K_w - K_a C_P^S \quad (32)$$

$$C_3 = \frac{K_w^2}{K_{b1} K_{b2}} K_a + \frac{K_w}{K_{b2}} K_a C_b - \frac{K_w^2}{K_{b2}} - K_a K_w - \frac{K_w}{K_{b2}} K_a C_P^S \quad (33)$$

$$C_4 = -\frac{K_w^3}{K_{b1} K_{b2}} - \frac{K_w^2 K_a}{K_{b2}} - \frac{K_w^2 K_a}{K_{b1} K_{b2}} C_P^S \quad (34)$$

$$C_5 = -\frac{K_w^3 K_a}{K_{b1} K_{b2}} \quad (35)$$

Equations (28) and (30) were solved numerically by the FORTRAN Subroutine IVPAG and ZPORC available from the International Mathematical and Statistical Library (IMSL) MATH/LIBRARY (Problem Solving Software Systems).

3. EXPERIMENTAL

3.1. Partition Coefficient and Physical Extraction

The potassium salt of penicillin G (3–10 mmol·dm^{-3}, Sigma Chemical Co.) was dissolved in a buffer solution of citric acid (Shinyo Pure Chemical

Co.) and sodium citrate (Shinyo Pure Chemical Co.) in a 100-cm^3 flask whose temperature was controlled to 20°C. *n*-Butyl acetate (Junsei Chemical Co.), 10 cm^3, was poured into the flask and stirred vigorously with a magnetic stir bar for at least 20 minutes. After the termination of mixing, the mixture was poured into a separation funnel and left to be separated into two phases for 30 minutes. The aqueous phase was filtered through a filter paper, and the concentration of penicillin G and the pH were measured. The partition coefficient was calculated from Eq. (6). The volume of the aqueous feed phase was varied from 10 cm^3 (V_{R1} = 1) to 50 cm^3 (V_{R1} = 5). In reextraction, the volume of the aqueous strip phase was set to 10 cm^3 and the volume of *n*-butyl acetate was varied from 20 cm^3 (V_{R2} = 2) to 50 cm^3 (V_{R2} = 5).

3.2. Equilibrium Constant

An equal volume of penicillin G (3–10 mmol·dm^{-3}) dissolved in citrate buffer and *n*-butyl acetate with Amberlite LA-2 (3–20 mmol·dm^{-3}, Sigma Chemical Co.) as a carrier was stirred in a 100-cm^3 flask with a magnetic stir bar for at least 20 minutes. After termination of mixing, the mixture was poured into a separation funnel and left to be separated into two phases for 30 minutes. The penicillin G concentration and the pH were measured from the filtered-through aqueous phase. The equilibrium constant was calculated from Eq. (15), and an average of 40 measurements was used.

3.3. Reactive Extraction and Reextraction

The potassium salt of penicillin G (10 mmol·dm^{-3}) dissolved in 200 cm^3 citrate buffer solution (0.5 mol·dm^{-3}, pH 5.0) was prepared in a batch-type stirred glass reactor of 9 cm inner diameter and 18 cm deep. The vessel was fixed with stainless steel baffles and thermostatted at 20°C. The stirrer was a six-flat-blades turbine impeller, each 5.5 cm in diameter. The stirrer speed was 400 rpm. The organic extract phase of *n*-butyl acetate with Amberlite LA-2 as a carrier was dispersed in the aqueous solution. The mixing time was 20 minutes. Separation and analysis were the same as in physical extraction.

Reextraction was performed in the same reactor used in extraction. Instead of citrate buffer, a phosphate buffer of pH 7.0 to 8.0 was used as the buffer solution. The mixing and separation conditions were the same as in extraction.

3.4. Kinetic

In the reextraction experiment, samples were taken at intervals, and the filtered-through solution was analyzed.

3.5. Analysis

All the concentrations were measured by a UV/VIS spectrophotometer (Phillips) at 247 nm.

4. RESULTS AND DISCUSSION

4.1. Partition Coefficient and Physical Extraction

The mean value of 30 experimental runs for the partition coefficient was 52.0, which was somewhat larger than the 48 of Reschke and Schügerl (2). Using the partition coefficient measured, the degree of extraction was

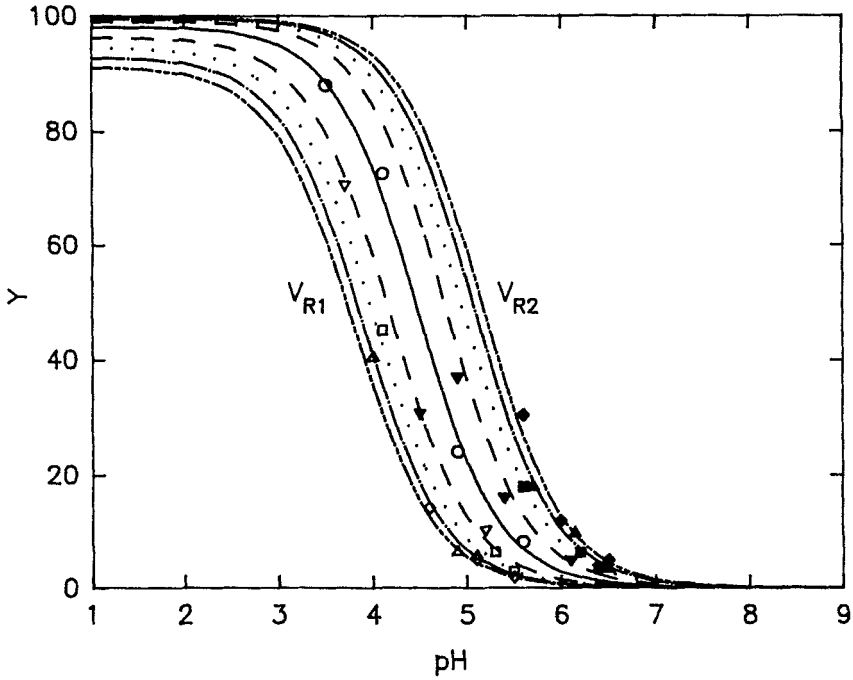

FIG. 2 Degree of extraction as a function of pH value for the extraction and reextraction of penicillin G with *n*-butyl acetate. V_R = 1 (○, ——); V_R = 2 (▽, ▼, - -); V_R = 3 (□, ■, ···); V_R = 4 (△, ▲, -·-); V_R = 5 (◇, ◆, -···-). The symbols are the results of experiments.

calculated from Eqs. (6) and (8) at various volume ratios of the aqueous (organic) phase to the organic (aqueous) phase and the pH. Agreement between the measured and calculated values was excellent, as shown in Fig. 2. It is plausible to extract at pH below 3.0 and reextract at pH above 7.0 with a high degree of overall extraction and enrichment. However, penicillin G is so unstable that it decompose at pH below 5.0 and above 8.0; therefore, it is uneconomical to extract penicillin G in the unstable pH range. In this respect, reactive extraction has advantages since it is operated in a stable pH range.

4.2. Reactive Extraction and Reextraction

4.2.1. Equilibrium Constant

The equilibrium constant, K_{eq}, of Eq. (11) was evaluated as 1.36×10^8 $dm^6 \cdot mol^{-2}$, which is slightly higher than the 1.25×10^8 $dm^6 \cdot mol^{-2}$ of

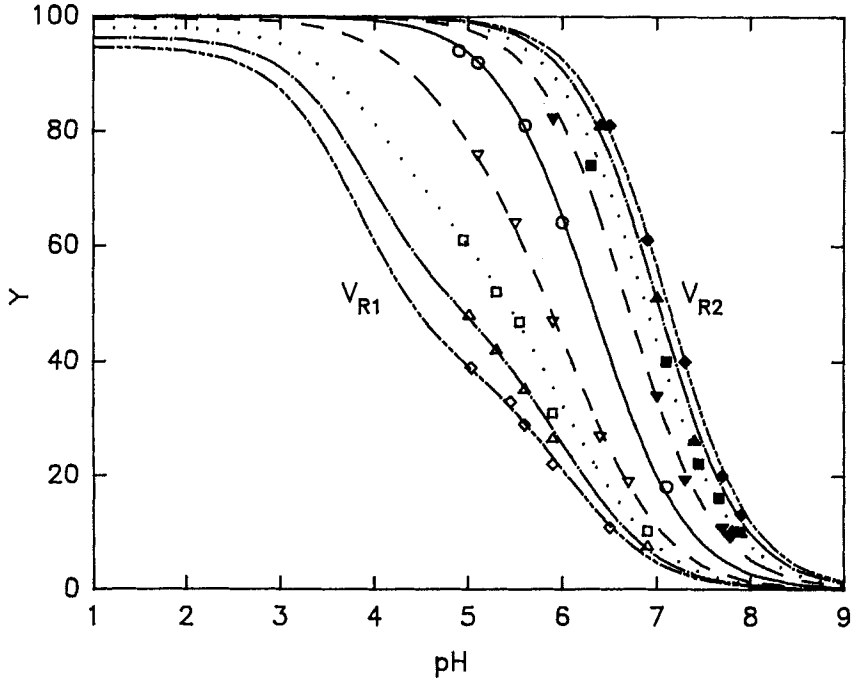

FIG. 3 Degree of extraction as a function of pH value for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate. $C_E^* = 2$, $C_{F,0}^E = 10$ mmol·dm^{-3}. $V_R = 1$ (○, ——); $V_R = 2$ (▽, ▼, - -); $V_R = 3$ (□, ■, ···); $V_R = 4$ (△, ▲, -·-); $V_R = 5$ (◇, ◆, -···-). The symbols are the results of experiments.

Reschke and Schügerl (2) and the 9.0×10^7 $dm^6 \cdot mol^{-2}$ of Hano et al. (13).

4.2.2. Volume Ratio Effects on the Degree of Extraction and Enrichment

In Figs. 3–5 the degree of extraction is depicted as a function of pH at various volume ratios of the aqueous (organic) phase to the organic (aqueous) phase. It can be seen that the degree of extraction was reduced as either V_{R1} or V_{R2} was increased at a given pH, while the penicillin G concentration was increased with an increase of V_{R1} or V_{R2}, although this is not clearly knowable from the figures. As the initial concentration ratio of carrier to penicillin G, C_E^*, was increased from 2 to 5, the lines in Fig. 3 shifted to the right, as shown in Fig. 4. If we further increase C_E^* from 5 to 10, the lines in Fig. 4 also shifted to the right (see Fig. 5), but the

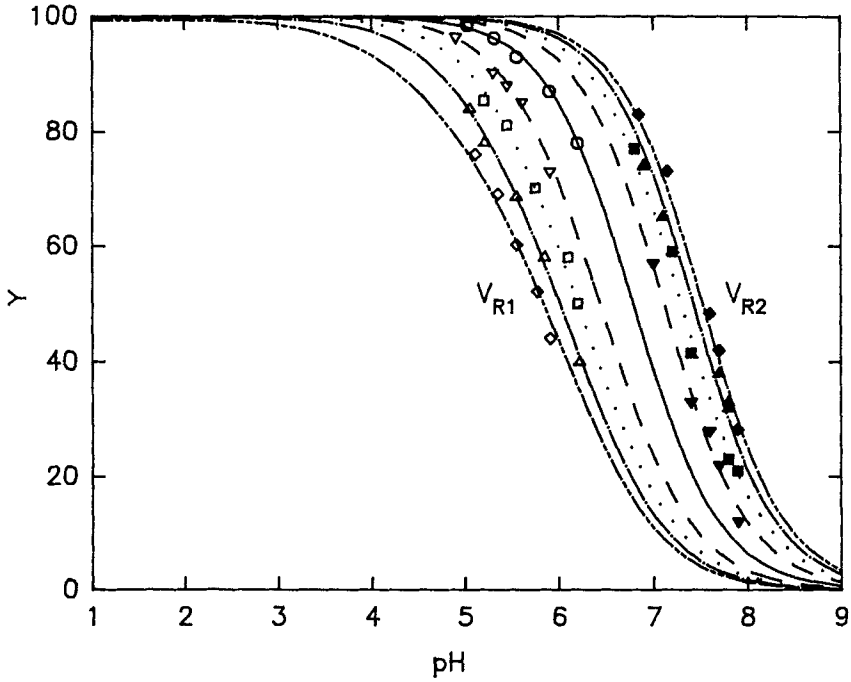

FIG. 4 Degree of extraction as a function of pH value for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate. $C_E^* = 5$, $C_{E,0}^E = 10$ mmol·dm^{-3}. $V_R = 1$ (○, ——); $V_R = 2$ (▽, ▼, - -); $V_R = 3$ (□, ■, ···); $V_R = 4$ (△, ▲, -·-); $V_R = 5$ (◇, ◆, -···-). The symbols are the results of experiments.

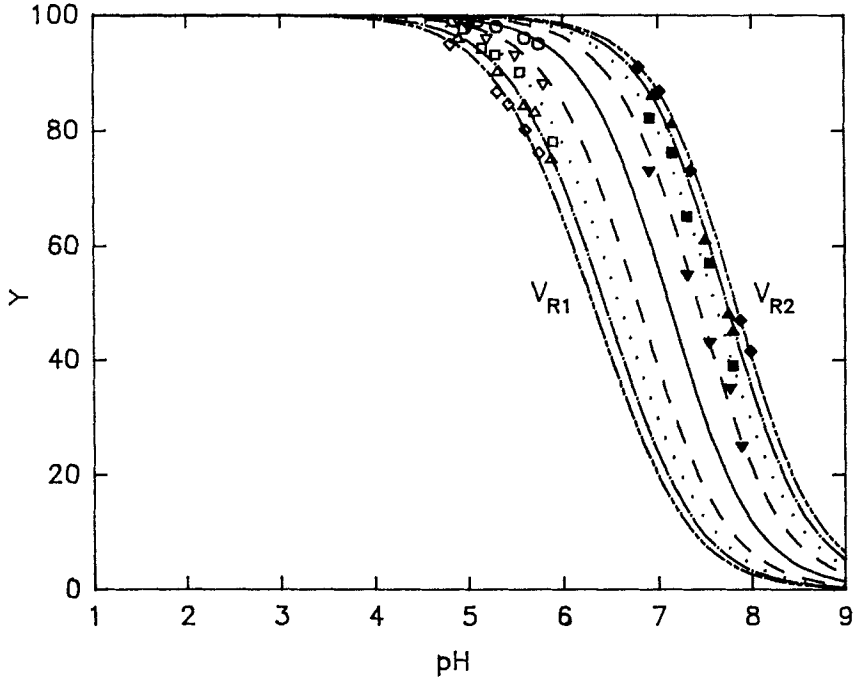

FIG. 5 Degree of extraction as a function of pH value for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate. $C_E^* = 10$, $C_{F,0}^F = 10$ mmol·dm^{-3}. $V_R = 1$ (○, ——); $V_R = 2$ (▽, ▼, - -); $V_R = 3$ (□, ■, ···); $V_R = 4$ (△, ▲, -·-); $V_R = 5$ (◇, ◆, -···-). The symbols are the results of experiments.

displacement is negligible. A further increase of C_E^* caused no line displacement. This implies that there is an optimum value of C_E^*, as will be seen later.

As mentioned above, the volume ratio of the aqueous (organic) to the organic (aqueous) phase has adverse effects on the degree of extraction and enrichment. Figures 6–8 show the overall degree of extraction and enrichment at various volume ratios. The trends for the adverse effects can be seen, i.e., as the volume ratio was increased, the enrichment went up and the overall degree of extraction came down. This trends were unchanged for a higher initial ratio of carrier to penicillin G concentration; however, the changes of the overall degree of extraction and enrichment were not remarkable. In some cases they decreased when C_E^* was increased from 5 to 10 (i.e., see Figs. 7a and 8a). This also shows that there should be an optimum C_E^* in reactive extraction and reextraction.

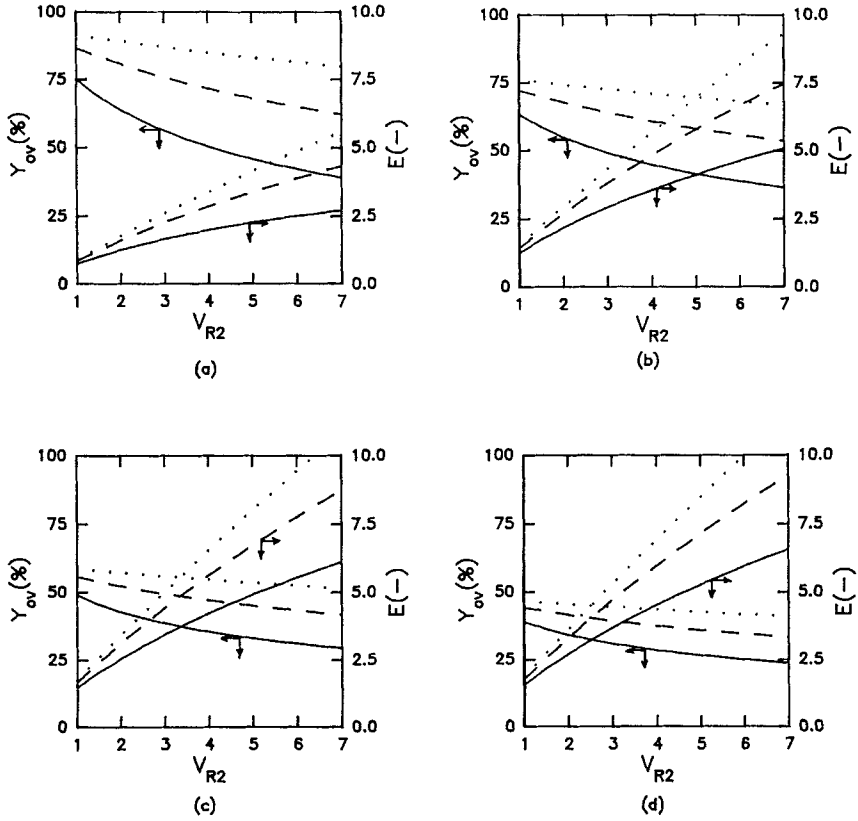

FIG. 6 Overall degree of extraction and enrichment for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of volume ratio of organic extract phase to aqueous strip phase. $C_{\bar{E}}^{*} = 2$, $C_{\bar{P},0}^{E} = 10$ mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) $V_{R1} = 1$, (b) $V_{R1} = 2$, (c) $V_{R1} = 3$, (d) $V_{R1} = 4$.

4.2.3. Effects of Initial Concentration Ratio of Carrier to Penicillin G

To confirm the existence of an optimum $C_{\bar{E}}^{*}$, the overall degree of extraction was plotted as a function of $C_{\bar{E}}^{*}$ with various volume ratios as parameters in Figs. 9–11. There clearly exists an optimum initial concentration ratio of carrier to penicillin G, and this provided a method for the selection of $C_{\bar{E}}^{*}$. That is, the initial concentration of carrier to penicillin G should be determined based on the volume ratio of the aqueous (organic) to the organic (aqueous) phase. The one thing to be considered here is the selection of V_{R1} and V_{R2} so they have the same value as V_{R3}. For

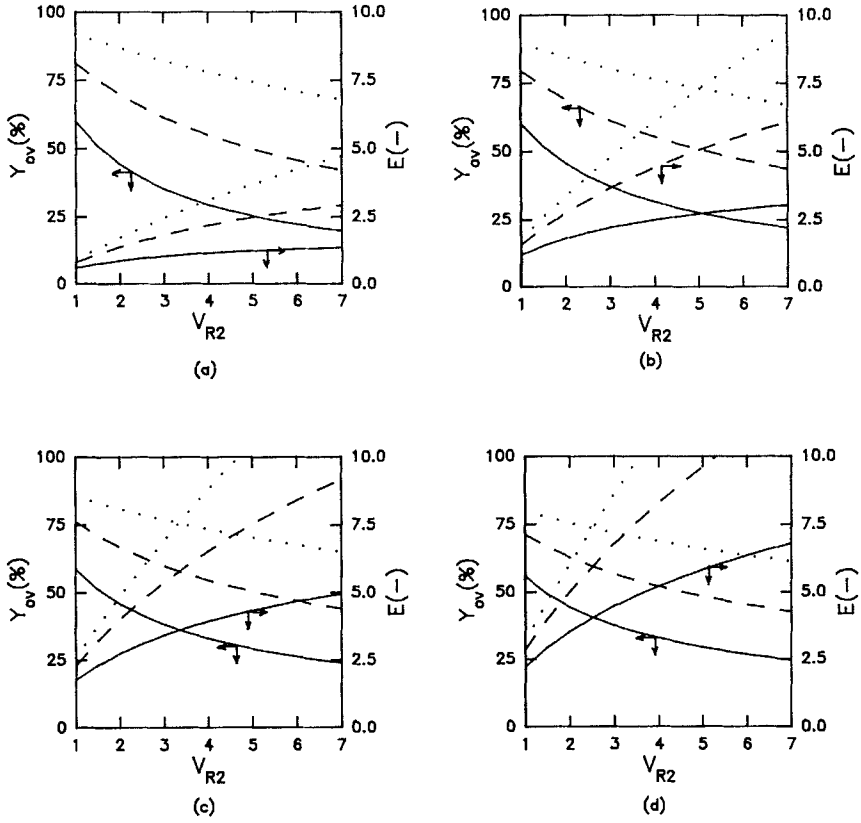

FIG. 7 Overall degree of extraction and enrichment for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of volume ratio of organic extract phase to aqueous strip phase. $C_E^* = 5$, $C_{P,0}^E = 10$ mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) $V_{R1} = 1$, (b) $V_{R1} = 2$, (c) $V_{R1} = 3$, (d) $V_{R1} = 4$.

example, if we determine V_{R3} to be 8, V_{R1} and V_{R2} could be 1 and 8, 2 and 4, 4 and 2, and so on. However, the maximum degree of overall extraction and enrichment were nearly the same in all cases. This was proven for all possible cases. The maximum degrees of extraction are nearly the same in Figs. 9(c) and 11(a). Nonetheless, the combination of a lower V_{R1} and a higher V_{R2} (Fig. 9c) gives a smaller C_E^* value than that of a higher V_{R1} and a lower V_{R2} (Fig. 11a). Of course, the absolute amount of carrier should be considered. In any combinations of V_{R1} and V_{R2} which have the same value as V_{R3}, the absolute amount of carrier was diminished, although nearly the same as V_{R1} was decreased. Therefore, it is

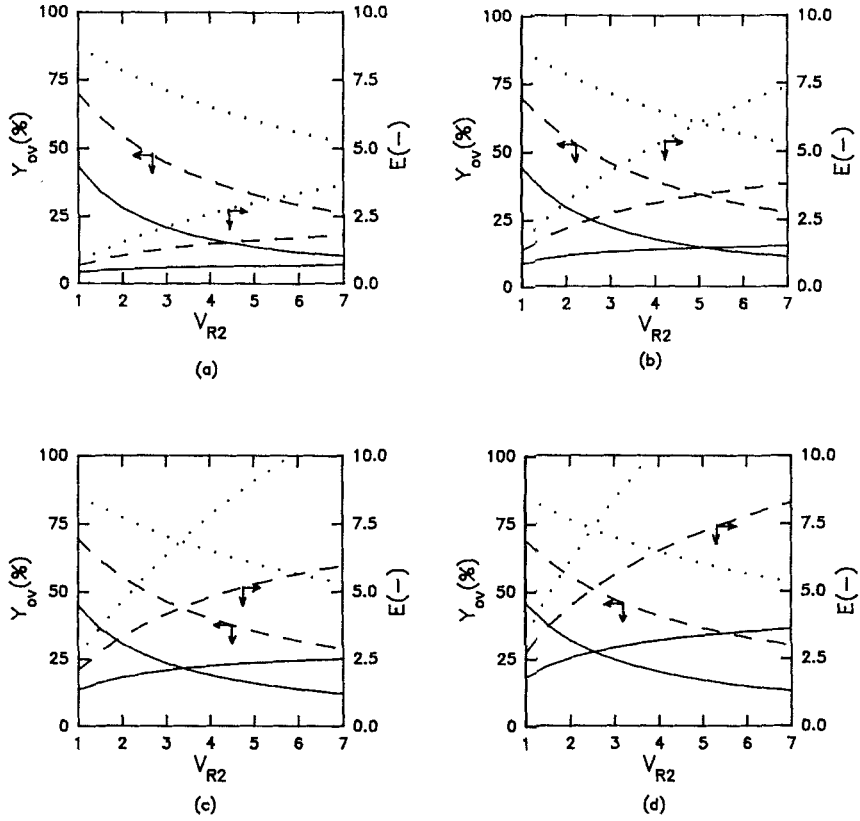

FIG. 8 Overall degree of extraction and enrichment for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of volume ratio of organic extract phase to aqueous strip phase. $C_E^* = 10$, $C_{E,0}^F = 10$ mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) $V_{R1} = 1$, (b) $V_{R1} = 2$, (c) $V_{R1} = 3$, (d) $V_{R1} = 4$.

desirable to select V_{R1} as low as possible. However, a lower V_{R1} needs a larger amount of solvent, and a higher value of V_{R2} needs a higher concentration of buffer solution to keep the pH value unchanged. In addition, phase separation was retarded if V_{R1} or V_{R2} was greater than 4.

4.2.4. Selection of Volume Ratios and Carrier Concentration

To summarize the procedure discussed in Section 4.2.3, the maximum degree of extraction and enrichment were plotted as a function of V_{R3} in

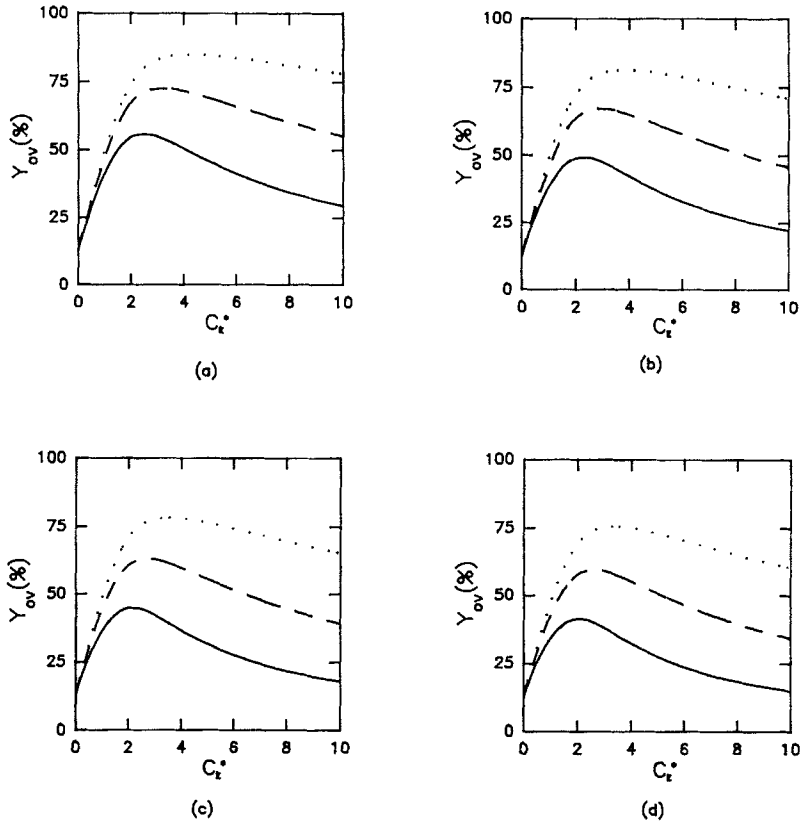

FIG. 9 Overall degree of extraction for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of concentration ratio of carrier to penicillin G. $C_{F,0}^F$ = 10 mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) V_{R1} = 2, V_{R2} = 2; (b) V_{R1} = 2, V_{R2} = 3; (c) V_{R1} = 2, V_{R2} = 4; (d) V_{R1} = 2, V_{R2} = 5.

Fig. 12. The first thing to determine is the desired degree of extraction, enrichment, and pH value of the aqueous strip phase. If this is done, the overall volume ratio, V_{R3}, is determined automatically and the selection of V_{R1} and V_{R2} follows. It is recommended that neither V_{R1} nor V_{R2} be greater than 4, as described in Section 4.2.3. With the selection of V_{R1} and V_{R2}, the initial concentration ratio of carrier to penicillin G, C_E^*, is determined from Fig. 13 for a pH value of 7.5 in reextraction, and this ends the selection procedure. For other pH values or other V_{R1} and V_{R2} values, C_E^* can be easily obtained by following the procedure described in the Appendix.

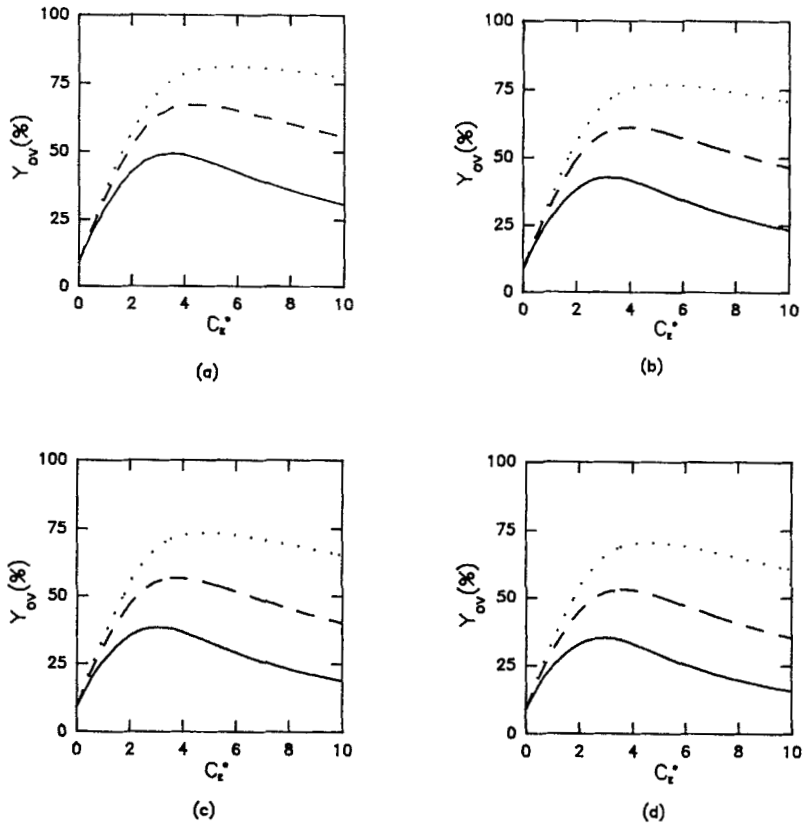

FIG. 10 Overall degree of extraction for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of concentration ratio of carrier to penicillin G. $C_{P,0}^F$ = 10 mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) V_{R1} = 3, V_{R2} = 2; (b) V_{R1} = 3, V_{R2} = 3; (c) V_{R1} = 3, V_{R2} = 4; (d) V_{R1} = 3, V_{R2} = 5.

Reviewing Fig. 12, it is impossible to recover 90% of penicillin G with an enrichment value over 3 even at pH 8, which seems to be the upper limit of the stable range. If we want to maintain the overall degree of extraction over 80%, the possible enrichment is about 5.6 when V_{R3} is 7.5 and the pH of the aqueous strip phase is 8.

In Fig. 12, experimental results are also plotted and show fairly good agreement. Most of the data points are under the calculated line. This resulted from a pH shift, and the deviation became larger as V_{R1} or V_{R2} became larger.

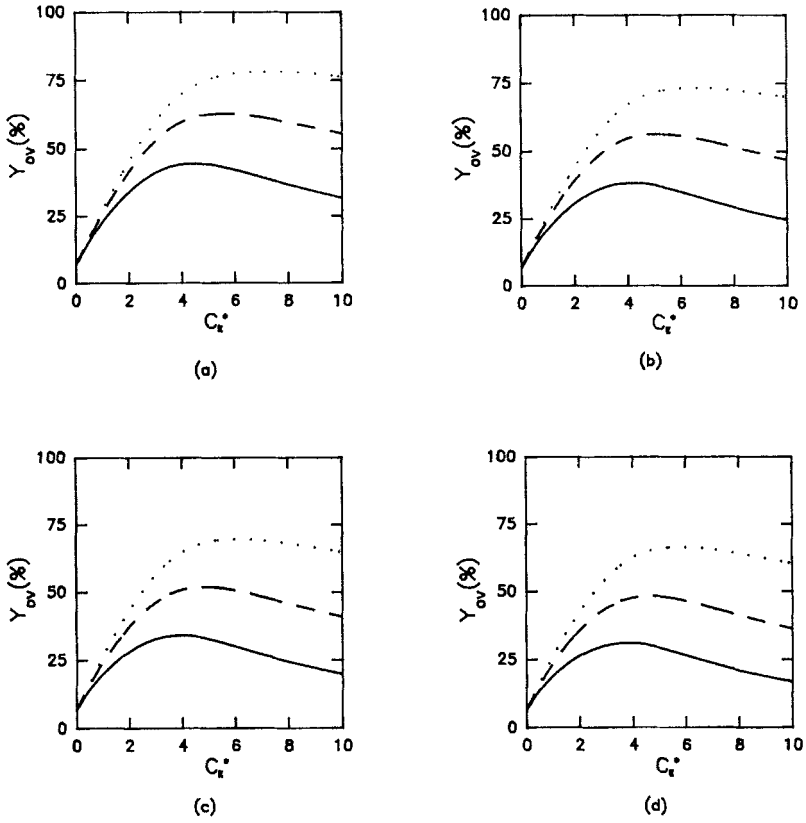

FIG. 11 Overall degree of extraction for the extraction and reextraction of penicillin G with Amberlite LA-2 and *n*-butyl acetate as a function of concentration ratio of carrier to penicillin G. $C_{P,0}^E$ = 10 mmol·dm^{-3}. pH 7 (——), pH 7.5 (- -), pH 8 (···). (a) V_{R1} = 4, V_{R2} = 2; (b) V_{R1} = 4, V_{R2} = 3; (c) V_{R1} = 4, V_{R2} = 4; (d) V_{R1} = 4, V_{R2} = 5.

4.2.5. Generalization of the Selection Method

So far we have discussed only the case for an initial penicillin G concentration of 10 mmol·dm^{-3} and an aqueous feed phase of pH 5. The overall degree of extraction and enrichment for the other cases are straightforward and follow Section 2.2. The selection of the initial concentration ratio, C_E^*, for a given V_{R1} and V_{R2} can be obtained by differentiating Eq. (26) by trial and error with respect to C_E^* to find that C_E^* value which makes the differential equation zero, described in detail in the Appendix.

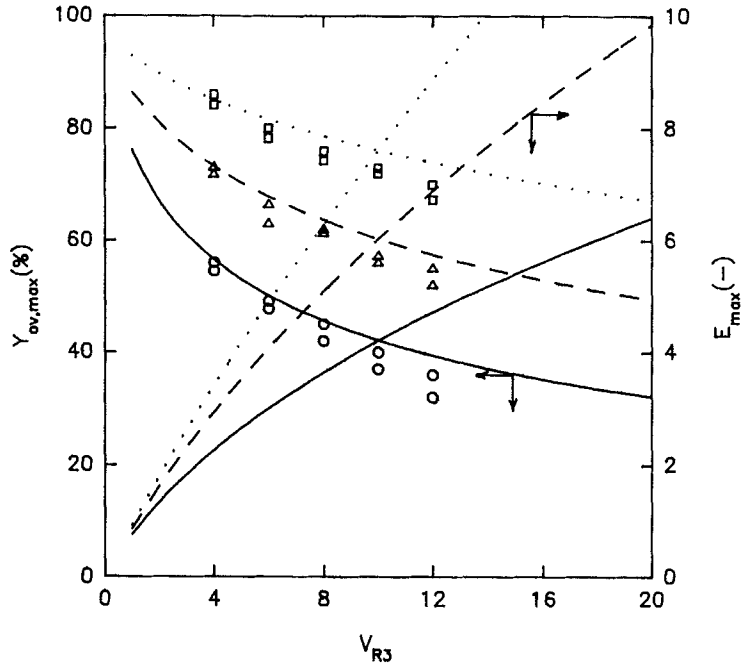

FIG. 12 Maximum degree of overall extraction and enrichment as a function of volume ratio of aqueous feed phase (pH 5) to aqueous strip phase. pH 7 (○, ——); pH 7.5 (△, - -); pH 8 (□, ···). The symbols are for experiments.

Substituting C_E^* obtained into Eqs. (26) and (27) then gives the maximum degree of extraction and enrichment.

4.3. Applicability of Sodium Carbonate Solution as an Aqueous Strip Phase: Kinetic

A buffer solution is used to keep the pH value of an aqueous feed or strip phase constant. However, pH change is inevitable, and a higher concentration is required if a greater volume ratio of V_{R1} or V_{R2} is used.

In order to lessen the quantity of chemicals used in the buffer solution and to shorten the reextraction time, sodium carbonate solution was applied as a strip phase. In Fig. 14, the penicillin G concentration in the aqueous strip phase is plotted as a function of time, which shows good agreement with the experimental results. It should be remembered that $C_{P,i0}^S$ is not the initial concentration of the aqueous strip phase but just

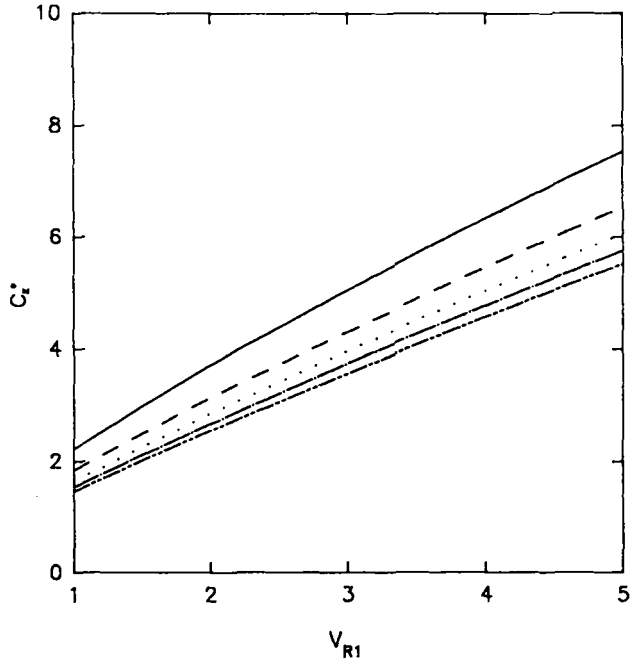

FIG. 13 Selection of optimum concentration ratio of carrier to penicillin G with V_{R1} and V_{R2} as parameters. pH of phosphate buffer solution: 7.5 V_{R2} = 1 (——), V_{R2} = 2 (- -), V_{R2} = 3 (···), V_{R2} = 4 (-·-), V_{R2} = 5 (-···-).

an imaginary one whose meaning is described in Eq. (21). When sodium carbonate solution was used as a strip phase, penicillin G was recovered more quickly. This is remarkable because V_{R2} increases. (Not shown here.) The mass transfer coefficients for penicillin G, carrier, and penicillin–carrier complex used were 4.5×10^{-6}, 1.0×10^{-5}, and 6.5×10^{-6} $m \cdot s^{-1}$, respectively (3). The specific surface area, a_p, was determined as the value which gave the optimum curve fit for the first kinetic experiment. The value for a_p so obtained was 12.7 dm^{-1}. The concentration of the sodium carbonate solution was adjusted to be pH 7.5 at equilibrium. This may be cumbersome. However, the concentration of the sodium carbonate solution can be easily calculated by using Eq. (30). The initial pH value of the sodium carbonate solution is about 11. At this pH, penicillin G is highly unstable. However, as penicillin G is stripped into the aqueous strip phase, the pH comes down sharply to the stable range because of co-stripping of the hydrogen ion. Therefore, the contact time at a high

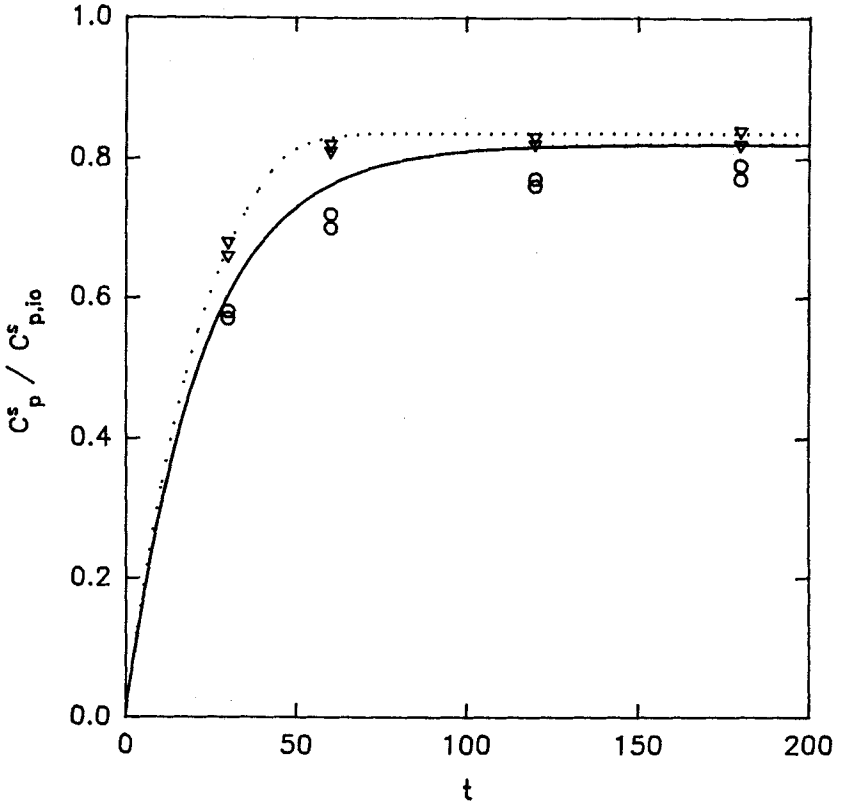

FIG. 14 Dimensionless penicillin G concentration in aqueous strip phase as a function of time. Phosphate buffer solution of pH 7.5 (——). $V_{R2} = 2$. Sodium carbonate solution (0.03 mol·dm^{-3}) (- -). (○) Phosphate buffer. (△) Sodium carbonate solution. The symbols are for experiments.

pH value is so short that the degree of decomposition is negligible, which was proved theoretically (15).

These facts imply that a sodium carbonate solution can be used as the strip phase. In addition, there is no problem of coextraction of anions such as may arise in using a buffer solution as a strip phase (2).

5. CONCLUSION

The volume ratio effects of the aqueous feed phase to the organic extract phase (V_{R1}) and of the organic extract phase to the aqueous strip phase

(V_{R2}) were investigated in the reactive extraction and reextraction of penicillin G. An increase of either V_{R1} or V_{R2} increases enrichment but decreases the degree of extraction. The overall degree of extraction and enrichment are nearly the same in any combinations of V_{R1} and V_{R2} that make the same volume ratio of aqueous feed phase to aqueous strip phase, V_{R3} ($= V_{R1} \times V_{R2}$). However, there exists an optimum value for the concentration ratio of carrier to penicillin G, C_E^*, in each combination of V_{R1} and V_{R2} that gave the maximum degree of overall extraction and enrichment. This value of C_E^* decreases as V_{R1} decreases, and the absolute amount of carrier also decreases although not by much. If the desired degree of overall extraction and enrichment is determined, V_{R3} is determined automatically. This is followed by the selection of V_{R1} and V_{R2} to determine the concentration ratio of carrier to penicillin G.

Finally, to avoid the disadvantages of using a buffer solution and to shorten the reextraction time, sodium carbonate solution was successfully applied to the aqueous strip phase in the reextraction of penicillin G.

APPENDIX: SELECTION OF AN OPTIMUM CONCENTRATION RATIO

The optimum concentration ratio of carrier to penicillin G for a given V_{R1} and V_{R2} can be obtained by differentiating Eq. (26) or (27):

$$\partial E/\partial C_E^* = 0 \tag{A-1}$$

$$\partial Y_{OV}/\partial C_E^* = 0 \tag{A-2}$$

Assuming constant pH in the aqueous strip phase, Eq. (A-1) becomes

$$\partial C_P^S/\partial C_E^* = 0 \tag{A-3}$$

From Eq. (23), C_P^S can be rewritten as

$$C_P^S = \frac{1}{2}(-Q + \sqrt{Q^2 + R}) \tag{A-4}$$

where

$$Q = \frac{1}{K_{eq}C_H^S} + \frac{C_{A,0}V_{R2} - C_{P,i0}^S}{Z_2} \tag{A-5}$$

$$R = \frac{4C_{P,i0}^S}{Z_2 K_{eq} C_H^S} \tag{A-6}$$

Using Eqs. (18) and (21), Eqs. (A-5) and (A-6) can be derived by

$$Q = \frac{1}{K_{eq}C_H^S} + \frac{C_{P,0}^F}{Z_2}\left[C_E^* V_{R2} - \left\{1 - \frac{C_P^F}{C_{P,0}^F}(1 + 10^{-pH^F + pK_a})\right\} V_{R3}\right] \tag{A-7}$$

$$R = \frac{4\{C_{P,0}^F - C_P^F(1 + 10^{-pH^F + pK_a})V_{R3}}{Z_2 K_{eq} C_H^S} \tag{A-8}$$

Substituting Eq. (A-4) into Eq. (A-3) and rearranging gives

$$\{(Q^2 + R)^{1/2} - Q\}\frac{\partial Q}{\partial C_E^*} = \frac{1}{2}\frac{\partial R}{\partial C_E^*} \tag{A-9}$$

Differentiating Eqs. (A-7) and (A-8) with respect to C_E^* and substituting into Eq. (A-9) leads to

$$\frac{\partial C_P^F}{\partial C_E^*} = \frac{\{Q - (Q^2 - R)^{1/2}\}C_{P,0}^F V_{R2}}{V_{R3}(1 + 10^{-pH^F + pK_a})\{(Q^2 + R)^{1/2} - Q + 2/K_{eq}C_H^S\}} \tag{A-10}$$

The left side of Eq. (A-10) can also be derived from Eq. (15):

$$\frac{\partial C_P^F}{\partial C_E^*} = \frac{C_{P,0}^F}{2Z_1 V_{R1}}\left[\left\{\left(\frac{1}{K_{eq}C_H^F} + \frac{C_E^*/V_{R1} - 1}{Z_1} C_{P,0}^F\right)^2 + \frac{4C_{P,0}^F}{Z_1 K_{eq} C_H^F}\right\}^{-1/2}\left(\frac{1}{K_{eq}C_H^F} + \frac{C_E^*/V_{R1} - 1}{Z_1} C_{P,0}^F\right) - 1\right] \tag{A-11}$$

Finding an optimum C_E^* is to find a value which makes Eqs. (A-10) and (A-11) equal. It cannot be solved explicitly. Equating Eqs. (A-10) and (A-11) and rearranging gives

$$f(C_E^*) = f_A(C_E^*) - f_B(C_E^*) = 0 \tag{A-12}$$

where

$$f_A(C_E^*) = \left\{\left(\frac{1}{K_{eq}C_H^F} + \frac{C_E^*/V_{R1} - 1}{Z_1} C_{P,0}^F\right)^2 + \frac{4C_{P,0}^F}{Z_1 K_{eq} C_H^F}\right\}^{-1/2}\left(\frac{1}{K_{eq}C_H^F} + \frac{C_E^*/V_{R1} - 1}{Z_1} C_{P,0}^F\right) - 1 \tag{A-13}$$

$$f_B(C_E^*) = \frac{2Z_1\{Q - (Q^2 + R)^{1/2}\}}{(1 + 10^{-pH^F + pK_a})\{(Q^2 + R)^{1/2} - Q + 2/K_{eq}C_H^S\}} \tag{A-14}$$

Equation (A-12) can be solved by the FORTRAN Subroutine ZREAL which uses Muller's method and is available from IMSL.

NOTATION

A	amine or carrier in the membrane phase
AHP	amine–penicillin complex
a_p	specific interfacial area (dm^{-1})
aq	aqueous phase
C	partition coefficient (dimensionless)
C_1, C_2, C_3, C_4, C_5	defined in Eqs. (31)–(35)
C_A	concentration of amine as a carrier ($mol \cdot dm^3$)
C_b	concentration of sodium carbonate solution ($mol \cdot dm^{-3}$)
C_{AHP}	concentration of amine–penicillin complex ($mol \cdot dm^{-3}$)
C_E^*	concentration ratio of carrier and penicillin G in extraction
C_H	concentration of hydrogen ion ($mol \cdot dm^{-3}$)
C_{HP}	concentration of penicillin acid ($mol \cdot dm^{-3}$)
C_P	concentration of penicillin anion ($mol \cdot dm^{-3}$)
C_{RE}^*	concentration ratio of carrier to penicillin G in reextraction
E	enrichment, defined in Eq. (26) (dimensionless)
f, f_A, f_B	defined in Eqs. (A-12)–(A–14)
H^+	proton
HP	penicillin G acid
k_A	mass transfer coefficient of carrier ($m \cdot s^{-1}$)
k_{AHP}	mass transfer coefficient of penicillin–carrier complex ($m \cdot s^{-1}$)
k_p	mass transfer coefficient of penicillin ion ($m \cdot s^{-1}$)
K_a	Dissociation constant of penicillin G ($mol \cdot dm^{-3}$)
K_{b1}	base dissociation constant, $[HCO_3^-][OH^-]/[CO_3^{2-}]$ ($mol \cdot dm^{-3}$)
K_{b2}	base dissociation constant, $[H_2CO_3][OH^-]/[HCO_3^-]$ ($mol \cdot dm^{-3}$)
K_{eq}	equilibrium constant $[(dm^3)^2 \cdot mol^{-2}]$
K_w	dissociation constant of water $[mol^2 \cdot (dm^{-3})^2]$
org	organic phase
P^-	penicillin acid anion
Q,R	defined in Eqs. (A-5) and (A-6)
t	time (seconds)

V	volume (dm^3)
V_R	volume ratio, V_{R1} or V_{R2}
V_{R1}	volume ratio of aqueous feed phase to organic extract phase
V_{R2}	volume ratio of organic extract phase to aqueous strip phase
Y	degree of extraction (%)
Z_1	defined in Eq. (17)
Z_2	defined in Eq. (25)

Subscripts and Superscripts

i0	imaginary initial value defined in Eq. (21)
0	initial value
E	organic extract phase
EX	extraction
F	aqueous feed phase
OV	overall
S	aqueous strip phase

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