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Distribution of Penicillin G from the Aqueous Phase to the Organic Phase Using Amberlite LA-2 Extractant in Different Diluents

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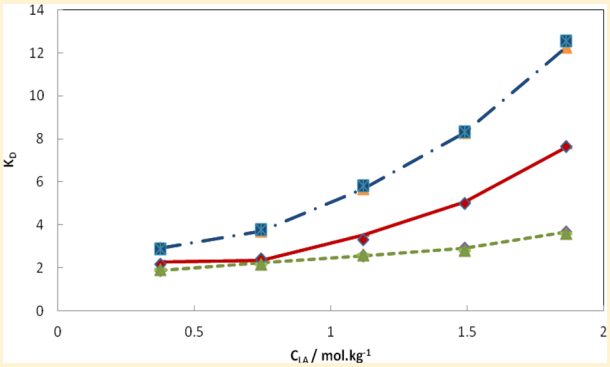
ABSTRACT: Benzyl penicillin, known as penicillin G (PG), is a β-lactam antibiotic and also a weak monocarboxylic acid. The penicillin G extraction from aqueous solution by Amberlite LA-2 in different diluents, that is, octan-1-ol, nonan-1-ol, 3-methyl-1-butanol, ethyl ethanoate, propyl ethanoate, 4-methylpentan-2-one, octan-2-one, octane, and decane has been studied. According to experimental results, some thermodynamic parameters, such as distribution coefficients (K_D), loading factors (Z), and the extraction efficiency or degree (E), were calculated. The best extraction efficiency, distribution coefficient, and loading factor were determined using 3-methyl-1-butanol diluent as values of 92.63, 12.25, and 0.195, respectively. The linear solvation energy relationship (LSER) model was regressed for the experimental results of the distribution coefficient with the regression coefficient (R^2) as 0.96. Besides, the equilibrium model for the extraction degree of alcohols has been applied and compared with experimental data.



1. INTRODUCTION

Penicillin G is a weak monocarboxylic acid, and its pK_a is equal to 2.75. Penicillin G (PEN G), used for curing bacterial diseases such as angina, bacterial pneumonia, and lung infections, is a class of β-lactam antibiotic.[1,2] In addition, it has served as the raw material of semisynthetic penicillin.[3]

Penicillin G is produced from fermentation broth of *Penicillium chrysogenum*. The conventional process for a fermentation bioproduct like penicillin G involves fermentation, extraction, product recovery, and purification.[4] Capital investment is necessary to run these steps because process depends on huge and highly complex fermenters.[5,6] Especially, downstream purification cost in fermentation process represents more than 60 % of the total production cost.[7] It is of great importance to develop an economical process.

Through our literature survey, solvent extraction has been a widely used method to recover penicillin G.[8] Although *n*-butyl acetate as solvent has been preferred for solvent extraction, an emulsion problem occurred.[9] In addition to this method, there are many drawbacks such as low extraction efficiency and high solvent losses, and also penicillin G decomposes at a low pH.[10−12] Therefore, the product cost is relatively expensive. Recently, novel separation methods such as ultra filtration, nanofiltration, liquid surfactant membranes, and reactive extraction have been examined to overcome these above problems encountered while using solvent extraction.[13−16]

The reactive extraction method using amines as an extractant has been used to increase the extraction yield and selectivity for fermentation bioproducts.[17] Various authors studied the reactive extraction of penicillin G with different extractants and different solvents. Yang and Cussler[14] extracted Penicillin G in hallow-fiber liquid−liquid fiber using Amberlite LA-2 as the amine. Likidis and Schügerl[18] extracted penicillin to recover it from fermentation broth with Amberlite LA-2 in *n*-butyl acetate at pH 5.0 using a laboratory countercurrent mixer−settler. In another study of Likidis et al.[19] studied Penicillin G recovery from mycel-containing fermentation broth using Amberlite LA-2 and DITDA as carriers. Lee et al.[20] examined penicillin G recovery through a supported liquid membrane with Amberlite LA-2 dissolved in 1-decanol, supported on a microporous polypropylene membrane. Cascaval et al. conducted reactive extraction of Penicillin G with Amberlite LA-2 using a modified extraction cell of Lewis type.[21] Ren et al.[22] compared different separation techniques to each other such as reactive extraction, bulk liquid membrane, and hollow fiber renewal liquid membrane to recover penicillin G from fermentation broth with TBP as a carrier and kerosene as the dilute. They showed that the reactive extraction efficiency was up to 85 % under at room temperature with pH of 3.05 and o/a = 1:1. In another research, they used various amines such as di-*N*-octylamine, tri-*N*-octylamine, as extractants with *N*-butyl acetate, kerosene, and *n*-heptane as diluents to seek the effects of organic solutions on the stability and extraction equilibrium of penicillin G. Besides, they investigated the effects of the experimental factors such as organic composition, pH, temperature, and so forth on the stability and extraction

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equilibrium of penicillin G. Their results showed that increasing the temperature results in decreasing the stability of penicillin G. Moreover, they found that, when they used amine-based extractants instead of phosphorus acid, the stability of penicillin G was better. Furthermore, they stated that increasing the pH, temperature, and initial concentration of penicillin G in aqueous solution results in decreasing the distribution coefficient under their experimental conditions.[23]

The main objective of this research was to investigate the reactive extraction of penicillin G from aqueous solutions by Amberlite LA-2 in two different acetates (ethyl ethanoate and propyl ethanoate), three different alcohols (octan-1-ol, nonan-1-ol, and 3-methyl-1-butanol), two different ketones (octan-2-one and 4-methylpentan-2-one), and two different alkanes (octane, decane).

2. CHEMICALS AND METHODS

2.1. Chemicals. Amberlite LA-2 which is a secondary amine and anion exchange extractant was purchased from Merck Co. (purity is greater than 0.99 in wt). Amberlite LA-2 is a colorless liquid and having a 353.67 g·mol^{-1} molecular weight. Benzyl penicillin sodium salt (penicillin G) [Sigma (CAS: 69-57-8) > 0.99 % in wt, molecular weight: 353.37, pK_a = 2.75]. Alcohols [octan-1-ol (CAS: 111-87-5), nonan-1-ol (CAS: 143-08-8), 3-methyl-1-butanol (CAS: 123-51-3)], alkanes [octane (CAS: 111-65-9), decane (CAS: 124-18-5)], acetates [ethyl acetate (CAS: 141-78-6) and propyl acetate (CAS: 109-60-4)], and ketones [4-methylpentan-2-one (MIBK) (CAS: 108-10-1) and octan-2-one (111-13-7)] have been supplied from Sigma-Aldrich and Fluka. Purities of all chemicals used in this study are above 0.98 % in wt.

2.2. Methods. 0.084 mol·kg^{-1} of aqueous solution penicillin G was prepared as the initial concentration. Five constant concentrations of Amberlite LA-2 were prepared by mixing diluents (octan-1-ol, nonan-1-ol, 3-methyl-1-butanol, ethyl ethanoate, propyl ethanoate, 4-methylpentan-2-one, octan-2-one, octane, and decane). Prepared concentrations of Amberlite LA-2 are 0.374 mol·kg^{-1}, 0.744 mol·kg^{-1}, 1.117 mol·kg^{-1}, 1.489 mol·kg^{-1}, and 1.862 mol·kg^{-1}. These (Amberlite LA-2 + diluents) mixtures help to find the optimum concentration of amine.

Equal volumes of an aqueous penicillin G and prepared organic solution of LA-2 have been mixed in Erlenmeyer flaks. These prepared two-phase systems have been shaken in a temperature-controlled shaker at 50 rpm and 25 °C for 3 h. After equilibration, both phases have been separated. The amounts of penicillin G in the aqueous phase after extraction have been analyzed by an equipment UV−visible spectrophotometer at 258 nm, and the quantity in the organic phase has been calculated using a mass balance. Each measurement was carried out in duplicate. The initial aqueous solution pH was adjusted about with adding HCl and NaOH for the acidic form of PG. The pH value of the aqueous phase was measured by pH meter (Mettler Toledo pH meter model S40). The determination of relative uncertainty in the aqueous phase was 1 %. The deviation of the amount of acid in both phases was in 1 %. Solvents were recycled by BAYGEN Solvent Recyle (BSR) equipment.

3. RESULTS AND DISCUSSION

3.1. Equilibrium Results. Reactive extraction of penicillin G has been studied in respect to distribution coefficient (D), loading factor (Z), and extraction efficiency (E).

The values of distribution coefficient[2] (D) are described by the ratio of the concentration of PG in the organic phase to the concentration of PG in the aqueous phase

$$K_D = \frac{C_{PG,org}}{C_{PG,aq}} \quad (1)$$

In eq 1, $C_{PG,org}$ is the concentration of penicillin G in the organic phase, and $C_{PG,aq}$ is the concentration of penicillin G in the aqueous phase. The extraction of the undissociated molecules of penicillin G in acidic form benzyl penicillin acid with amine extractant has been observed more at low pH values.[21] The ratio of dissociated to undissociated molecules changes with increasing pH. Therefore, pH is the most effective parameter for the concentration of undissociated acid. The penicillin G is stable and present a dissociated form at a pH range from 5.0 to 8.0. It presented the undissociated (acidic) form at low pH values.[21] Figure 1 shows the conversion of the penicillin salt acidic form at low pH.

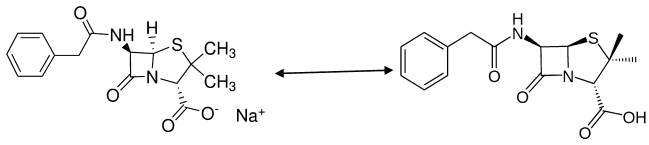

Figure 1. Conversion of penicillin salt to acidic form.

The efficiency of extraction, E, is expressed as

$$E = \left(1 - \frac{C_{PG,aq}}{C_{PG,in}}\right) \cdot 100 \quad (2)$$

In eq 2, after the extraction, $C_{PG,in}$ is the PG concentration at initial present in the aqueous phase. E gives information about the amount of acid removed from the aqueous phase to the organic phase after extraction.

Reactive extraction results were presented in Tables 1 to 4. As seen from tables, when the amount of Amberlite LA-2 increases in the organic phase, the extraction power increases to the maximum amine concentration of 1.862 mol·kg^{-1}. According to the results of diluents in the distribution coefficient, they varied between 12.57 and 0.87. At the highest concentration 1.862 mol·kg^{-1} of Amberlite LA-2, the highest value of distribution coefficients is 12.57, 7.70, and 3.59, and the extraction efficiency (E) is 92 %, 88 %, and 78 % for 3-methyl-1-butanol, octan-1-ol, and nonan-1-ol, respectively. These results may be explained by solvation power of diluents to Amberlite LA-2. This solvation power depends on its polarity, and also polarity depends on the dielectric constant of diluents. In this work used diluents (3-methyl-1-butanol, octan-1-ol, and decan-1-ol) have dielectric constant values of 15.3, 10.3, and 8.6, respectively. The polarity, which is the related dielectric constant, of 4-methylpentan-2-one is 13.1, whereas the polarity of octan-2-one is 10.3. The same situation has been observed in aliphatic solvents and ester; the polarities are 1.96, 2, 6.02, and 6.3 for octane, decane, ethyl ethanoate, and propyl ethanoate, respectively.

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Table 1. Results for the Extraction of Penicillin G with the Amberlite LA-2 + Alcohol System at T = 298 K[a]

solvents (alcohols)	ν	C_{LA} mol·kg^{-1}	$C_{PG,aq}$ mol·kg^{-1}	K_D	K_D^M	100 E	Z
octan-1-ol	0.828	0.374	0.0266	2.15	2.28	68.33	0.153
	0.656	0.744	0.0247	2.40	2.33	70.59	0.079
	0.493	1.117	0.0194	3.32	3.54	76.90	0.057
	0.327	1.489	0.0140	5.00	5.05	83.33	0.047
	0.163	1.862	0.0097	7.65	7.61	88.45	0.039
nonan-1-ol	0.837	0.374	0.0287	1.92	1.89	65.83	0.147
	0.675	0.744	0.0265	2.16	2.25	68.45	0.077
	0.500	1.117	0.0233	2.60	2.54	72.26	0.054
	0.342	1.489	0.0220	2.81	2.93	73.80	0.041
	0.166	1.862	0.0183	3.59	3.66	78.21	0.035
3-methyl-1-butanol	0.832	0.374	0.0216	2.88	2.92	74.28	0.166
	0.665	0.744	0.0176	3.77	3.71	79.04	0.089
	0.499	1.117	0.0123	5.82	5.69	85.35	0.064
	0.332	1.489	0.0090	8.33	8.30	89.28	0.050
	0.166	1.862	0.0062	12.54	12.25	92.61	0.041

[a] C_{LA} is the equilibrium concentration of amine in the organic phase, $C_{PG,aq}$ is the concentration in the aqueous phase after extraction, K_D is the distribution coefficient, Z is the loading factor, E is the extraction efficiency, and K_D^M is the distribution coefficients from the LSER model. The uncertainty for the experimental values was 1 %.

Table 2. Results for the Extraction of Penicillin G with the Amberlite LA-2 + Ketone System at T = 298 K[a]

solvents (ketones)	C_{LA} mol·kg^{-1}	$C_{PG,aq}$ mol·kg^{-1}	K_D	100 E	Z
4-methylpentan-2-one	0.374	0.0314	1.67	62.61	0.140
	0.744	0.0270	2.11	67.85	0.076
	1.117	0.0242	2.47	71.19	0.053
	1.489	0.0228	2.68	72.85	0.041
	1.862	0.0214	2.92	74.52	0.033
octan-2-one	0.374	0.0357	1.35	57.50	0.129
	0.744	0.0316	1.65	62.38	0.070
	1.117	0.0282	1.97	66.42	0.049
	1.489	0.0263	2.19	68.69	0.038
	1.862	0.0225	2.73	73.21	0.033

[a] C_{LA} is the equilibrium concentration of amine in the organic phase, $C_{PG,aq}$ is the concentration in the aqueous phase after extraction, K_D is the distribution coefficient, Z is the loading factor, and E is the extraction efficiency. The uncertainty for the experimental values was 1 %.

Table 3. Results for the Extraction of Penicillin G with the Amberlite LA-2 + Ester System at T = 298 K[a]

solvents (esters)	C_{LA} mol·kg^{-1}	$C_{PG,aq}$ mol·kg^{-1}	K_D	100 E	Z
ethyl ethanoate	0.374	0.0289	1.90	65.59	0.147
	0.744	0.0263	2.19	68.69	0.077
	1.117	0.0231	2.63	72.50	0.054
	1.489	0.0225	2.73	73.21	0.041
	1.862	0.0196	3.28	76.66	0.034
propyl ethanoate	0.374	0.0397	1.11	52.73	0.118
	0.744	0.0320	1.62	61.90	0.069
	1.117	0.0319	1.63	62.02	0.046
	1.489	0.0280	2.00	66.66	0.037
	1.862	0.0243	2.45	71.07	0.032

[a] C_{LA} is the equilibrium concentration of amine in the organic phase, $C_{PG,aq}$ is the concentration in the aqueous phase after extraction, K_D is the distribution coefficient, Z is the loading factor, and E is the extraction efficiency. The uncertainty for the experimental values was 1 %.

In all of the diluents, categories used in this study for the extraction degree of PG with LA-2 have been determined in the following orders (Tables 1 to 4):

In Alcohols: 3-methyl-1-butanol > nonan-1-ol > decan-1-ol

In Acetates: ethyl ethanoate > propyl ethanoate

In Ketones: 4-methylpentan-2-one > octan-2-one

In Alkanes: octane > decane

The loading factor[2] (Z) is described by the ratio of the concentration of acid in the organic phase and the concentration of amine in the organic phase.

$$Z = \frac{C_{PG,org}}{C_{LA}} \quad (3)$$

In eq 3, $C_{PG,org}$ is the concentration of PG in the organic phase, and C_{LA} is the concentration of amine in the organic phase.

Tables 1 to 4 present loading factor values for all diluents. As seen from tables and Z values are gradually decreasing by the increase of the concentration of Amberlite LA-2. Overloading is described as bigger than unity (>1). This shows that the

Table 4. Results for the Extraction of Penicillin G with the Amberlite LA-2 + Alkane System at T = 298 K[a]

solvents (alkanes)	C_{LA} mol·kg^{-1}	$C_{PG,aq}$ mol·kg^{-1}	K_D	100 E	Z
octane	0.374	0.0405	1.07	51.78	0.116
	0.744	0.0361	1.32	57.02	0.064
	1.117	0.0330	1.54	60.71	0.045
	1.489	0.0291	1.88	65.35	0.036
	1.862	0.0279	2.01	66.78	0.030
decane	0.374	0.0450	0.86	46.42	0.104
	0.744	0.0436	0.92	48.09	0.054
	1.117	0.0393	1.13	53.21	0.040
	1.489	0.0361	1.32	57.02	0.032
	1.862	0.0317	1.64	62.26	0.028

[a] C_{LA} is the equilibrium concentration of amine in the organic phase, $C_{PG,aq}$ is the concentration in the aqueous phase after extraction, K_D is the distribution coefficient, Z is the loading factor, and E is the extraction efficiency,

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Table 5. Equilibrium Model Results[a]

diluent	a	b	c	d	K_e	K_E	χ
nonan-1-ol	0.255	0.659	0.372	0.510	$4.244\cdot10^{-2}$	$2.805\cdot10^{-1}$	8.92
octan-1-ol	0.344	0.403	0.310	0.427	$6.208\cdot10^{-1}$	$6.075\cdot10^{-1}$	6.34
3-methyl-1-butanol	0.144	0.320	0.064	0.251	$3.541\cdot10^{-1}$	$1.0146\cdot10^{2}$	5.11

[a] a, b, c, and d are the reaction coefficients; K_e is the physical extraction equilibrium constant, K_E is the chemical equilibrium constant, and χ is the deviation.

complexes have more than one acid per amine. For systems with only one amine per complex, it can be seen that no effect of total amine concentration on the loading. In these experimental studies, overloading has been observed at 0.374 mol·kg^{-1} and 0.744 mol·kg^{-1} amine concentrations. This situation can be explained by the formation of complexes between acid and amine. The loading factors for the used diluent in this study were observed decreasing from 0.028 to 0.195 by increasing of amine concentration from 0.374 mol·kg^{-1} to 1.862 mol·kg^{-1}.

3.2. Model Results. *3.2.1. Equilibrium Model.* Reschke and Schuégerl[24−26] described that Amberlite LA-2 (LA) reacted with a hydrogen ion (H) and penicillin acid anion to form a complex. There are many mathematical equilibrium models to calculate the extraction degree in the literature. Lee[27] described an equilibrium model for reactive extraction of PG for active diluents with amine extractant. In this situation, physical and reactive extraction can be considered together. In the case of physical extraction,

$$a(\mathrm{PG})_{aq} + bS \overset{K_e}{\leftrightarrow} (\mathrm{PG})_a S_b \qquad K_e = \frac{C_{(\mathrm{PG})_a(S)_b}}{C^a_{\mathrm{PG}_{aq}} \cdot C^b_s} \tag{4}$$

In eq 4, (PG) is penicillin G in the aqueous phase, S is the solvent in the organic phase, a and b are reaction coefficients, and K_e is the physical extraction equilibrium constant.

In the case of reactive extraction,

$$c(\mathrm{PG})_{aq} + d(\mathrm{LA}) \overset{K_E}{\leftrightarrow} (\mathrm{PG})_c(\mathrm{LA})_d \qquad K_E = \frac{C_{(\mathrm{PG})_c(\mathrm{LA})_d}}{C^c_{\mathrm{PG}_{aq}} \cdot C^d_{\mathrm{LA}}} \tag{5}$$

In eq 5, (LA) is the Amberlite LA-2 in the organic phase, c and d are reaction coefficients, and K_E is the chemical equilibrium constant.

The overall material balances of PG and LA can be expressed with combinated eqs 4 and 5.

$$\bar{C}_{\mathrm{PG}} = C_P + C_{\mathrm{PG,org}} + aC_{(\mathrm{PG})_a(S)_b} + cC_{(\mathrm{PG})_c(\mathrm{LA})_d} \tag{6}$$

$$\bar{C}_{\mathrm{LA}} = C_{\mathrm{LA}} + dC_{(\mathrm{PG})_c(\mathrm{LA})_d} \tag{7}$$

In eqs 6 and 7, $\bar{C}_{\mathrm{PG}}$ is the overall penicillin G concentration, C_P is the penicillin anion concentration, $\bar{C}_{\mathrm{LA}}$ is the overall amine concentration, and C_{LA} is the amine concentration in the organic phase.

Extraction degree (E_M) is given by,

$$E_M = \frac{aK_e \cdot C^a_{\mathrm{PG}_{aq}} \cdot C^b_s + cK_E \cdot C^c_{\mathrm{PG}_{aq}} \cdot C^d_{\mathrm{LA}}}{\bar{C}_{\mathrm{PG}}} \tag{8}$$

The obtained data for alcohols (3-methyl-1-butanol, octan-1-ol, nonan-1-ol) from experimental results were used to calculate the extraction degree.

The deviations χ were calculated according to eq 9. The Matlab used to solve nonlinear least-squares and the deviations and coefficients (a,b,c,d) were presented in Table 5.

$$\chi = \sqrt{\frac{1}{N}\sum_{i=1}^{n}(E - E_M)} \tag{9}$$

where E is the experimental extraction degree and E_M is the calculated extraction degree. N is the number of experimental data.

The comparison of calculated and experimental results in extraction degree was presented in Figure 2. Similar trends and close results have been obtained.

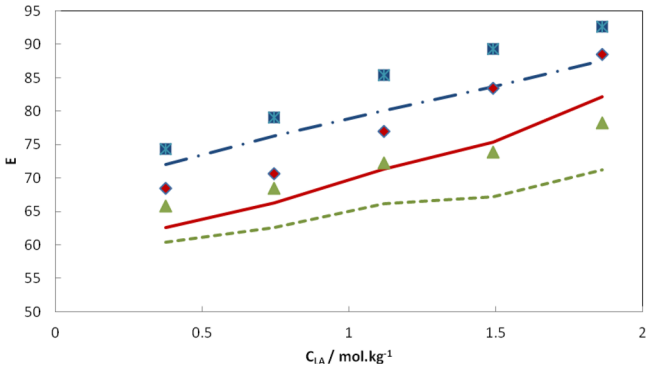

Figure 2. Comparison of extraction degrees between experimental results and equilibrium model results. ▲, nonan-1-ol; ----, nonan-1-ol model; ◆, octan-1-ol; ——, octan-1-ol model; ■, 3-methyl-1-butanol; — — —, 3-methyl-1-butanol method.

3.2.2. Linear Solvation Energy Relationship (LSER) Model Application. Some properties of extraction according to hydrogen bond formation of between acid and amine can be estimated by the linear solvation energy relationship model (LSER) based on the solvatochromic approach. For the equilibrium of an amine/diluents/acid system in the reactive extraction, a new LSER model was given by Bizek et al.,[28] and detailed information was given by Kamlet et al.[29]

The influence of solvent effects on a single solute is shown in eq 5, whereby XYZ resembles the property to be correlated.

$$XYZ = (XYZ)^0 + m(vV_m/100) + s(v\pi^* + dv\delta) + av\alpha + bv\beta \tag{10}$$

where $(XYZ)^0$ is a property relating to a standard process, π^* is the dipole−dipole interaction, and δ is dipole−induced dipole interaction. The solvatochromic parameter α term is of solvent HBD (hydrogen-bond donor) acidities. This explains the ability of the solvent to donate a proton from a solvent−solute hydrogen bond. The β term is of solvent HBA (hydrogen-bond acceptor) basicities. The β term is a measure of the solvent's ability for accepting a proton from a solute−solvent hydrogen

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bond. V_m is the solute volume. The coefficients *s*, *d*, *a*, and *b* include the solute properties that come from regression.[29] *v* is the mole fraction of solvent used in the study. The solvatochromic parameters were taken from literature and presented in Table 6.[29,30]

Table 6. Solvatochromic Parameters[31,a]

Kamlet solvatochromic parameters					
diluent	π^*	δ	β	α	V_m/cc·mol^{-1}
3-methyl-1-butanol	0.40	0	0.84	0.84	109.4
octan-1-ol	0.40	0	0.81	0.77	157.7
nonan-1-ol	0.40	0	0.81	0.74	180.5

[a] V_m is the solute volume; π^* is the dipole−dipole interaction; δ is the dipole−induced dipole interaction. The β term is of solvent HBA (hydrogen-bond acceptor) basicities; the α term is of solvent HBD (hydrogen-bond donor) acidities.

LSER model regressed experimental data to predict distribution coefficients (K_D) as eq 11

$$\log K_D^M = \log K_D^0 + m(vV_m/100) + s(v\pi^* + d v\delta) + av\alpha + bv\beta \quad (11)$$

In eq 11, the coefficients *m*, *s*, *a*, *b*, and *d* are determined from linear regression. The log K_D^0 term intercept comes from the regression of the experimental data.

The distribution coefficients (K_D) of each diluents calculated from experimental results were used in the LSER model.[31] LSER model results were presented in Table 1 as K_D^M. The new LSER equation was obtained as eq 12:

$$\log K_D^M = 6.537 + 14.102(vV_m/100) + (-9.003)(v\pi^* + 0.v.\delta) + 9.507v\alpha + (-3.498)v\beta \quad (12)$$

As seen from Table 2 and Figure 3, the LSER model predicts close results to experimental data with an R^2 of 0.96.

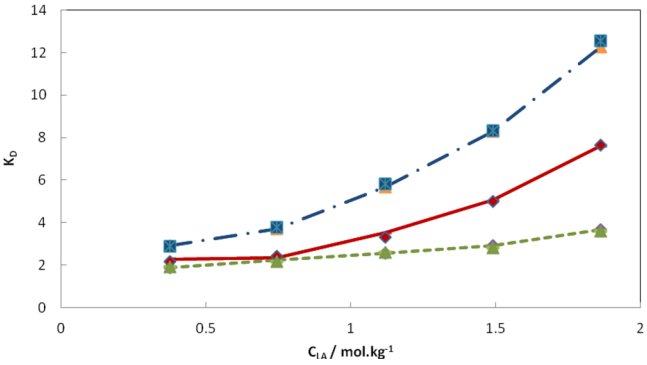

Figure 3. Comparison of distribution ceofficients between experimental results and LSER model results. ▲, nonan-1-ol; ----, nonan-1-ol model; ◆, octan-1-ol; —, octan-1-ol model; ■, 3-methyl-1-butanol; − − −, 3-methyl-1-butanol method.

3. CONCLUSION

Reactive extraction experiments for physical extraction and reactive extraction of penicillin G were carried out in a batch extraction system with three different solvent categories such as alcohols, ketones, esters, and alkanes. A total of 92 % of acid from aqueous solution was removed to the organic phase with LA-2 in 3-methyl-1-butanol at maximum concentration (1.862 mol·kg^{-1}). The equilibrium and LSER models reflecting solute solvent interactions gave good effective results for alcohols. The overall equilibrium constants were determined. The LSER model showed close results to the experimental data with an R^2 of 0.96.

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