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Separation of the Mixture of Mandelonitrile and Mandelonitrile Acetate by Solvent Extraction

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Abstract: In this paper, a solvent extraction system is applied to separate the mixture of mandelonitrile (MN) and mandelonitrile acetates (MA) for the first time. The basic consistence of the system is water and n-hexane with the phase ratio of 1.0. Operation parameters such as temperature, the pH value in the aqueous phase, and the concentration of the mixture and benzaldehyde were investigated to find the optimal conditions. When the temperature was 30°C and the pH value in the aqueous phase was 2.0, a three-stage extraction was performed. The purity of MA in the organic phase was more than 99% (wt) with the yield of 87.7%. And the purity of MN in the aqueous phase was 98.8 % (wt) with the yield of 92.6%. This extraction system can separate the mixture of MN and MA efficiently.

Keywords: Separation, solvent extraction, mandelonitrile, mandelonitrile acetate

INTRODUCTION

Cyanohydrins, especially aromatic cyanohydrins, are useful building blocks for the organic synthesis. And their derivatives, such as α-hydroxy acids, α-hydroxy ketone and β-hydroxy amines can serve as important synthetic intermediates for the production of drugs and agrochemicals (1–3). Mandelonitrile (MN) is one of the most important cyanohydrin. Consequently the enantioselective synthesis of MN has attracted considerable attention. Optically active MN have been prepared by chemical methods using chiral catalysis (4, 5).

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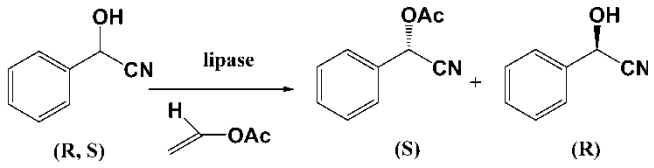
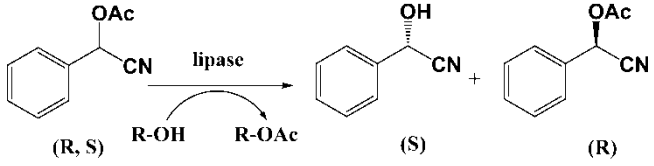


(a) the transesterification of cyanohydrin



(b) the alcoholysis of cyanohydrin acetate

Scheme 1.

Meanwhile, the enzymatic approaches have been investigated by Hydroxynitrile lyase (6, 7). However, these methods all have problems and cannot achieve both high yields and excellent e.e. values in a reasonable amount of time. The method of lipase-catalyzed asymmetric alcoholysis of mandelonitrile acetates (MA) or transesterification of MN in organic media (Scheme 1) was developed to obtain the satisfied products (1, 8). In order to get the enantiopure MN, the separation of the mixture of MN and MA must be performed.

At present, there have been very few investigations of the separation of MN and MA. Ulf Hanefeld et al. (9) purified the mandelonitrile (MN) by silica gel column chromatography, but the purity of the final production was not mentioned. In addition, the technology is difficult to be applied in industry.

Solvent extraction is a very common method in industrialization production, supported by the large variety of pure or mixed solvents with broad solubility and selectivity ranges (10, 11). The objectives of this work were to establish an efficient extraction system by screening the solvent and to make use of the system to separate the mixture of MN and MA. In this work, *rac*-MN and *rac*-MA were used to study the extraction progress.

EXPERIMENTAL

Chemicals

MN and MA were provided by Changzhou Kangmei Chemical Industry Co., Ltd. Solvents were commercially available and of analytical grade. High-performance liquid chromatography (HPLC) grade n-hexane, 1,2-dichloroethane, and ethanol were supplied by Tedia.

Experimental Method

The extractions were performed in 1.5 cm diameter × 20 cm long glass tubes with a lower-to-upper phase volume ratio of 1 : 1 and total liquid volume was 20 mL. The molar ratio of MN to MA was 1 in the mixture. The capped tubes were placed in a lab oven set to 30 ± 1°C to maintain a constant extraction temperature. The filled tubes, when fully equilibrated with the temperature of the oven, were shaken vigorously for 10 min to completely emulsify the lower and upper layers. The layers were then allowed to settle for 60–90 min with the tubes in a vertical position. This process of emulsification and settling was repeated 3 times at a constant temperature, to ensure that the extraction system had reached equilibrium. After the extraction was completed, the phases were separated by gravity. The concentrations of MN and MA were determined in both phases by HPLC.

Distribution coefficients and separation factors were calculated from data at a given extraction temperature. The equilibrium distribution coefficient for MN is defined as the ratio of the concentration of MN in the lower phase (L) to the concentration of MN in the upper phase (U). The equilibrium distribution coefficient for MA and benzaldehyde are defined similarly. The separation factor, α, is defined as the ratio of the MN distribution coefficient to that of MA.

$$K_{MN} = \frac{[MN]_U}{[MN]_L} \tag{1}$$

$$K_{MA} = \frac{[MA]_U}{[MA]_L} \tag{2}$$

$$K_{benzaldehyde} = \frac{[benzaldehyde]_U}{[benzaldehyde]_L} \tag{3}$$

$$\alpha = \frac{K_{MA}}{K_{MN}} \tag{4}$$

In order to get both MN and MA, one of the values of the K_{MN} and K_{MA} needs to be less than 1 and the other larger than 1. If α is larger than 1, then the larger α is, the higher the degree of separation will be achieved. On the contrary, if α is less than 1, then the smaller α is, the higher the degree of separation will be achieved.

Analytical Method

An analysis of MN and MA were performed by HPLC (Agilent 1100). A SUMICHIRAL OA-4400 column was used. Samples were diluted with the ethanol if necessary. 87% n-hexane, 10% 1,2-dichloroethane, and 3% ethanol were used as eluents and the flow rate is 1 mL/min. The wavelength of the detector was 254 nm. Retention times: benzaldehyde 4.3 min, MA 5.1 min, (S)-MN 18.4 min, (R)-MN 19.8 min.

RESULTS AND DISCUSSION

Choice of Extraction Systems

The selection of a suitable extraction solvent is the pivotal challenge, because the structure of MN and MA is similar. First, different organic solvents that can form two phases were selected as the extractant. The separation factor and the distribution coefficient of MN and MA are displayed in Table 1. These results show that under these conditions a majority of MN and MA were distributed into the lower phase with greater polarity. These systems cannot meet the needs of separation.

Then, the systems with one organic phase and one aqueous phase were selected to separate the mixture of MN and MA. The results are listed in Table 2. From the results it is clear that the system consisting of n-hexane and water is the best one to efficiently separate the mixture of MN and MA. Therefore, this extraction system was selected in the following study.

Effect of the pH Value in Aqueous Phase

The pH value of the aqueous phase is an important parameter for the extraction equilibrium. The pH was adjusted by HCl. This effect is shown in Table 3 from which it can be seen that K_{MN} decreases slowly when the pH value is less than 2 and deceases rapidly along with increasing pH value in the range of pH 2-5.

In order to demonstrate whether Cl^- affect the distribution of MN, NaCl was added into the tubes. The molar of NaCl equated to the molar of HCl. The results are shown in Table 4. It can be seen that the concentration of Cl^- is not the reason for the change of K_{MN}.

In the experiment, we found that the pH can affect the stability of MN. When the pH is increasing, the MN will decompose and produce

Table 1. Extraction of the mixture of MN and MA by the system with two organic solvents

	Extraction system				
Upper phase	n-Hexane	Cyclohexane	n-Hexane	Iso-octane	n-Hexane
Lower phase	Dimethyl sulfoxide	Dimethyl sulfoxide	Acetonitrile	Acetonitrile	Nitroethane
K_{MN}	0	0.005	0.007	0.015	0.083
K_{MA}	0.012	0.039	0.032	0.051	0.345
α	–	7.8	4.4	3.4	4.2

–denoted that the concentration of MN in upper phase was to low too be determined, so K_{MN} and α cannot be calculated.

Table 2. Extraction of the mixture of MN and MA by system with aqueous and organic phase

Extraction system					
Upper phase	Ethyl acetate	n-Hexane	Benzene	Xylene	Water
Lower phase		Water		Dichloromethane	
K_{MN}	55.556	0.039	5.988	1.481	0.136
K_{MA}	250.000	22.727	38.462	48.455	0.035
α	4.5	582.7	6.4	30.7	0.3

benzaldehyde and HCN. We determined the concentration of benzaldehyde in the organic phase. The results shown in Fig. 1 indicate that the concentration of benzaldehyde rose quickly with the increase of the pH value.

We also studied the distribution of benzaldehyde in the system and the effect of benzaldehyde on the distribution of MN. The concentration of benzaldehyde was defined as the molar of benzaldehyde to the volume of hexane. The results are shown in Table 5. It indicates that benzaldehyde is distributed in the organic phase and it does not affect the distribution of MN. Thus, the decomposition of MN is not the reason for the change of the distribution of MN with the rising of pH value, and the best pH range for the extraction of the mixture of MN and MA should be less than 2. From Table 5 it also appears that the system can separate the mixture of MN and benzaldehyde.

Effect of the Concentration of the Mixture

The effect of the concentration of the mixture of MN and MA was studied. The concentration of the mixture was defined as the weight of the mixture to the total volume of two phases. The experimental results are shown in Table 6. It can be seen that the concentration has little influence on K_{MA}. But K_{MN}

Table 3. Effect of the pH in aqueous phase on extraction distribution

	pH				
	1	2	3	4	5
K_{MN}	0.035	0.036	0.041	0.165	0.175
K_{MA}	14.493	18.519	21.739	13.699	13.698
α	414.1	514.4	530.2	83.0	78.3

Table 4. Effect of NaCl in different pH of aqueous phase on extraction distribution

	pH				
	1	2	3	4	5
K_{MN}	0.034	0.037	0.043	0.143	0.163
K_{MA}	13.889	19.625	22.048	14.949	13.127
α	408.5	530.4	512.7	104.5	80.5

changes greatly. The lower concentration will have a better distribution coefficient.

Effect of Temperature

Temperature affects not only the extraction equilibrium, but also the physical properties of the two phases. The effect of temperature on the extraction distribution is presented in Table 7. From the data in Table 7, we can see that there is no obvious effect of temperature on the distribution coefficient. However, with the temperature rising, the mandelonitrile decomposes greatly. The concentration of benzaldhyde in the organic phase was determined (see Fig. 2). The extraction should be operated at less than 40°C.

Multi-stage Extraction of the Mixture of MN and MA

The extraction experiment was carried out in a separatory funnel. The conditions used throughout the experiment were as follows the total volume of

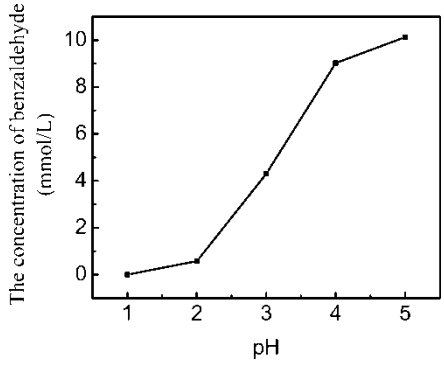


Figure 1. Effect of pH value on decomposition of mandelonitrile in extraction process.

Table 5. Distribution and effect of benzaldehyde on extraction distribution

	Concentration of benzaldehyde (mmol/L)				
	5	10	15	20	25
$K_{benzaldehyde}$	8.745	9.009	8.772	8.928	8.772
K_{MN}	0.031	0.030	0.030	0.028	0.031

the extractant was 600 mL, the phase ratio was 1.0, the weight of the mixture of MN and MA was 11.0 g, the ratio of the molar of MN to that of MA was 0.75, the temperature was 30°C, the pH value of the aqueous phase was 2.0. The steps of extraction were as follows:

(1) 600 mL extractant and 11 g mixture were placed in the separatory funnel. Then the funnel was shaken for 15 min and settled at 30°C in a thermostat for 1 hr.

(2) The lower phase was collected in a second separatory funnel containing 300 mL n-hexane, and the funnel was shaken for 15 min, then settled at 30°C in the same thermostat for 1 hr. 300 mL water was added into the first separatory funnel, and the funnel was shaken for 15 min, then settled at 30°C in the thermostat for 1 hr.

(3) Step (2) was repeated twice. Samples of each stage were withdrawn for HPLC analysis. The extraction process and experimental data was shown in Fig. 3.

According to the data in Fig. 3, K_{MN} and K_{MA} in every stage were calculated. K_{MN} and K_{MA} changed greatly in different stages. It indicated that the distribution coefficient can change along with the change of the concentration of the mixture. Moreover, the proportion of the mixture also can affect the distribution coefficient. We cannot get any result by a simple calculation from the first extraction.

Table 6. Effect of the concentration of the mixture of MN and MA on extraction distribution

	Concentration (g/L)				
	7.5	10	12.5	15	17.5
K_{MN}	0.019	0.026	0.039	0.044	0.067
K_{MA}	18.182	19.231	20.000	20.408	21.277
α	956.9	739.7	512.8	463.8	317.6

Table 7. Effect of temperature on extraction distribution

	t (°C)			
	20	30	40	50
K_{MN}	0.019	0.021	0.023	0.024
K_{MA}	16.129	17.241	19.231	19.608
α	848.9	821.0	836.1	817.0

The purity of MN or MA is defined as follows:

$$\text{The purity of MN} = \frac{\text{MN (mol)}}{\text{MA (mol)} + \text{MN (mol)}} \quad (5)$$

$$\text{The purity of MA} = \frac{\text{MA (mol)}}{\text{MA (mol)} + \text{MN (mol)}} \quad (6)$$

It can be seen from the Fig. 3 that after three-stage extraction the purity of MA in the organic phase is more than 99% (wt) and the yield reaches 87.7%. And the purity of MN in the aqueous phase is 98.8% (wt) and the yield reaches 92.6%. MN and MA remained in the raffinates can be recycled. No obvious decomposition of MN to benzaldehyde was observed throughout the extraction process.

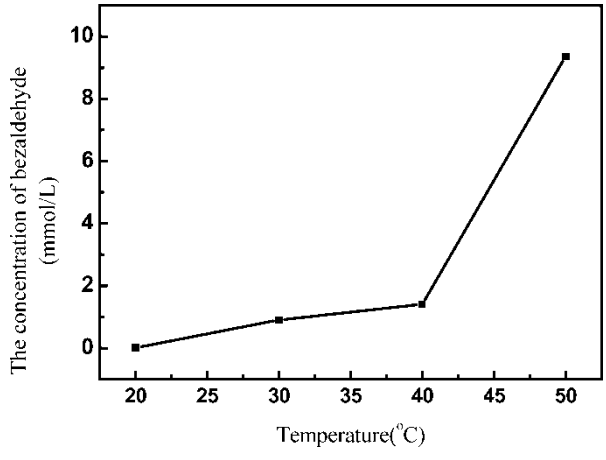


Figure 2. Effect of temperature on decomposition of mandelonitrile in extraction process.

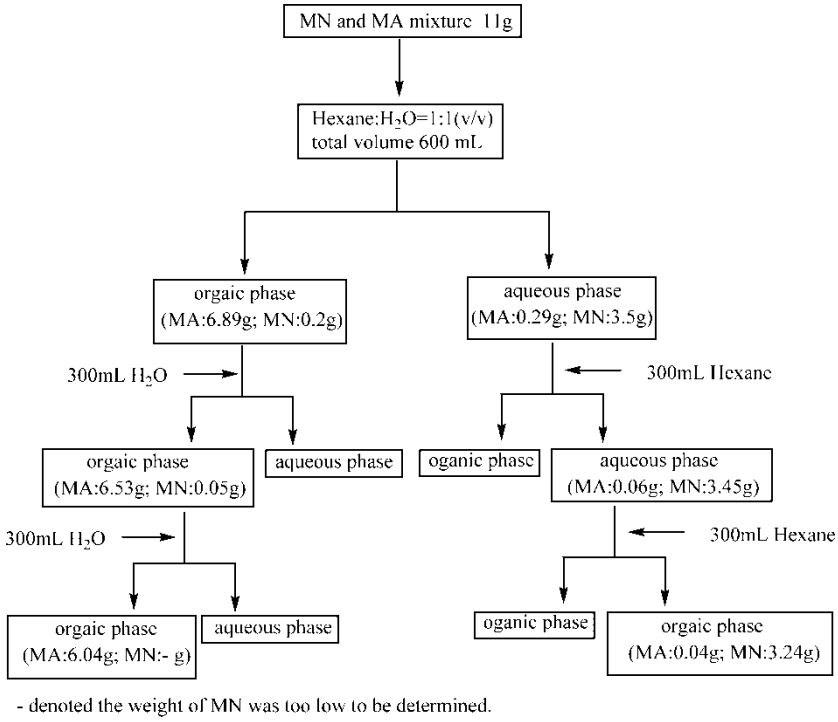


Figure 3. The process of multi-stage extraction of the mixture of MN and MA.

CONCLUSION

In this work, the solvent extraction system, consisting of water and n-hexane, was established to separate the mixture of mandelonitrile and mandelonitrile acetates. The effects of pH value of the aqueous phase, the concentration of the mixture, and temperature on the extraction distribution coefficient were studied. The mixture of MN and MA was separated with the system by multi-stage extraction. After the three-stages, the purities of MN and MA were more than 98% (wt). Thus, this study clearly indicated that the system with water and n-hexane can efficiently extract and separate the mixture of mandelonitrile and its acetate, which can meet the needs of industrial production.

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