

Computer Aided Solvent Scanning for the Separation of 2-Methoxynaphthene and 2-Acetyl-6-methoxynaphthalene

Yueqiang Zhao,* Shilong Xiao, Weiwei Liu, and Zhengming Wu

Department of Chemical Engineering, Jiangsu Key Laboratory of Marine Biotechnology, Huaihai Institute of Technology, Lianyungang 222005, Jiangsu, People's Republic of China

ABSTRACT: The solvents for the separation of 2-methoxynaphthene and 2-acetyl-6-methoxynaphthalene were screened by computer using the solid–liquid equilibrium equation based on modified UNIFAC; according to the predicted values of separation factor and selection principles of suitable solvent, the promising candidates of appropriate solvents were determined as hexane, heptane, cyclohexane, and octane. The solubility and separation factor data of the two solid solutes in corresponding appropriate solvents were measured by static equilibrium method, and the average absolute value of relative deviation between the calculated separation factor values and experimental data is 8.1%, which indicates that the solid–liquid equilibrium equation based on modified UNIFAC is suitable for the separation solvents scanning of solid solute mixtures having similar molecular stereoscopic structures. Determination the appropriate separating solvents by the combination of computer high-throughput scanning and experimental verification can save the manpower, material, and financial resources as much as possible.

INTRODUCTION

2-Acetyl-6-methoxynaphthalene (2A-6MN) is a very important pharmaceutical intermediate for the synthesis of naproxen; which is a nonsteroidal anti-inflammatory drug used for relief of pain, fever, inflammation, and stiffness.^{1–5} Nan¹ used bromine to protect the 1-site of 2-methoxynaphthene (2MN) and made the acetyl enter into the 6-site quantitatively in the Friedal-Crafts acylation reaction and then removed the 1-bromo from resultant product, in which the crude product (composed of unreacted 2MN and 2A-6MN) was purified by recrystallization using methanol as solvent. In order to separate the unreacted raw material (2MN) from the product, the vacuum fractionation was used in refs 2 and 3, which may cause solidification and possible blocking in the condenser. In ref 4, the crude product was refined by recrystallization in petroleum ether to give 2A-6MN. Selvaraj et al.⁵ purified the crude product by preparative thin layer chromatography (TLC) using dichloromethane (mole fraction = 0.9385) + ethyl acetate (mole fraction = 0.0615) as eluent to obtain 2A-6MN. The preparative TLC and column chromatography usually used in laboratory have the disadvantages of large time and solvent consumption and low yield of target product, which are not suitable for industrial scale separation. The crystallization process is usually used in the chemical industry for the separation of solid organic mixtures,^{6–12} in which an appropriate solvent can improve the separation efficiency and reduce the equipment size and solvent consumption remarkably; thus, the key issue in the process research and design of crystallization is the solvent selection. The solubility and separation factor data of 2MN and 2A-6MN in different solvents are nearly unavailable in the literature, which are essential for the size design and solvent consumption calculation of industrial crystallization process.

Until now, there are two methods in solvent selection:^{8–12} experimental test and computer aided solvent scanning. The large number of solvents¹¹ makes it a very time and solvent consuming task to select appropriate solvents by experimental test. The computer aided solvent scanning method^{8–10} is the combination

of high-throughput computer solvent scanning and experimental verification, which could find out the suitable separation solvents rapidly and save the manpower, reagents and money remarkably.

In this work, the appropriate solvents for the separation of 2MN and 2A-6MN were determined by computer aided solvent scanning method, the solubility and separation factor data of the two compounds in corresponding suitable solvents were measured by static equilibrium method.

THEORETICAL CALCULATIONS

1. Prediction of the Selectivity of Solvents. The equation of solid–liquid equilibrium (SLE) for the solute (component 2) is¹³

$$\ln(\gamma_2 x_2) = -\frac{\Delta H_m}{RT} \left(1 - \frac{T}{T_m}\right) \quad (1)$$

where γ_2 is the activity coefficient of solute in the solution, which reflects the interactions between the solute and solvent molecules and can be calculated by modified UNIFAC^{14–18} model, x_2 is the solute solubility (mole fraction), ΔH_m and T_m are enthalpy of fusion and the melting point of the solid solute, respectively, R is the gas constant, and T is the system temperature. Equation 1 can be used to predict the solubility of solid solute (component 2) in a solvent (component 1).

When the system temperature T is fixed, the activity coefficient of solute $\gamma_2(x_2, T)$ is only a function of solute solubility x_2 . Then eq 1 becomes a nonlinear equation of x_2

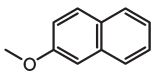
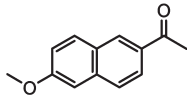
$$f(x_2) = (\gamma_2 x_2) / \exp \left[-\frac{\Delta H_m}{RT} \left(1 - \frac{T}{T_m}\right) \right] - 1 = 0 \quad (2)$$

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Table 1. Physical Property of Solutes

solute	2-methoxynaphthene (A)	2-acetyl-6-methoxynaphthalene (B)
molecular formula	C ₁₁ H ₁₀ O	C ₁₃ H ₁₂ O ₂
structural formula		
group assignment	7 ACH, 3 AC, 1 CH ₃ O	6 ACH, 4 AC, 1 CH ₃ O, 1 CH ₃ CO
T_m / K	343.15 to 346.15 ^a	380.15 to 382.15 ^a
$\Delta H_m / \text{kJ}\cdot\text{mol}^{-1}$	20.966 ^b	24.479 ^b
$M / \text{g}\cdot\text{mol}^{-1}$	158.19	200.24

^aExperimental value of ref 3. ^bEstimated value by the method in ref 19, with an uncertainty of $\pm 0.76 \text{ kcal}\cdot\text{mol}^{-1}$.

For given parameter range ($0 < x_2 < 1$) and allowable error ($|f(x_2)| \leq \varepsilon$, i.e., $\varepsilon = 0.001$), eq 2 can be solved readily by numerical methods (i.e., bisection method).

The separation factor β is defined by¹⁰

$$\beta = x_A/x_B \quad (3)$$

When the solubility of two compounds (A and B) in the same solvent is known, then the separation factor β can be obtained by eq 3. In this work, A and B represent 2MN and 2A-6MN, respectively.

2. High-Throughput Computer Solvent Scanning. The physical properties of solutes are listed in Table 1. The separation factor values of 2MN relative to 2A-6MN in more than 80 different solvents have been calculated at 298.15 K and part of the results are shown in Table 2.

The principles of selecting an appropriate solvent^{11,12} are as follows: the bigger the value of separation factor deviates from unity, the better the solvent will be; it should not react with the separating compounds; and its normal boiling point should not too low or too high. In selecting a solvent for crystallization, a number of other factors are also considered, including availability, cost, corrosivity, thermal stability, heat of vaporization, toxicity, safety, and ease of recovery for recycle.¹² As shown in Table 2, the separation factor values in pentane ($\beta = 51.3$), 2-methylbutane ($\beta = 51.3$), hexane ($\beta = 45.7$), cyclopentane ($\beta = 43.7$), heptane ($\beta = 42.1$), cyclohexane ($\beta = 40.6$), and octane ($\beta = 39.6$) are much greater than unity, but pentane ($T_b = 309.15 \text{ K}$) and 2-methylbutane ($T_b = 303.15 \text{ K}$) have too low normal boiling point and tend to evaporate at ambient temperatures. Cyclopentane is reactively unstable compared with other solvents; therefore, the three solvents seems inappropriate for the separation of 2MN and 2A-6MN. Based on the above analysis, we could choose the promising candidates of appropriate solvents as hexane, heptane, cyclohexane, and octane.

EXPERIMENTAL VERIFICATION

1. Materials. 2MN (mass fraction purity >0.99) and 2A-6MN (mass fraction purity >0.99) were purchased from the Beijing Hwrk Chemistry Reagent Company of China. The organic solvents used (hexane, heptane, cyclohexane, and octane) were analytical grade reagents (mass fraction purity >0.995) and were

Table 2. Some Solvent Scanning Results (with an Uncertainty of 31.9 % (Relative Error) for Solute Solubility) at 298.15 K

solvent	T_b (K)	$x_A \times 10^2$	$x_B \times 10^2$	β
methanol	338.55	7.23	2.99	2.4
ethanol	351.15	5.49	1.19	4.6
propanol	370.15	7.17	1.25	5.7
formic acid	374.15	38.3	19.8	1.9
acetic acid	391.15	13.9	5.10	2.7
propionic acid	414.15	17.6	5.99	3.0
ethyl formate	326.15	31.4	12.3	2.6
ethyl acetate	347.05	32.0	8.49	3.8
diethyl ether	307.75	20.5	1.41	14.5
dipropyl ether	362.15	19.1	1.23	15.6
1,1'-dimethyldiethyl ether	341.65	16.3	0.79	20.6
propionaldehyde	321.15	30.2	8.97	3.4
butyraldehyde	348.15	30.0	7.96	3.8
methyl trichloride	334.15	57.7	36.6	1.6
carbon tetrachloride	349.65	34.6	3.58	9.7
acetone	329.15	29.9	11.9	2.5
2-butanone	353.15	30.5	10.8	2.8
cyclohexanone	428.15	31.4	10.7	2.9
pentane	309.15	6.67	0.130	51.3
2-methylbutane	303.15	6.67	0.130	51.3
hexane	342.15	7.27	0.159	45.7
heptane	371.15	7.68	0.183	42.1
octane	399.15	8.01	0.202	39.6
cyclopentane	323.15	12.1	0.278	43.7
cyclohexane	353.85	10.4	0.256	40.6
benzene	353.15	34.1	11.0	3.1
methylbenzene	384.15	32.8	8.07	4.1
ethylbenzene	409.35	29.0	4.07	7.1
propylbenzene	432.15	27.2	3.14	8.7
acetonitrile	354.65	28.7	16.9	1.7
propionitrile	370.15	32.9	16.8	2.0
dimethyl sulfoxide	462.15	8.58	6.22	1.4
water	373.15	0.000479	0.000158	3.0

purchased from Tianjin Fuchen Chemicals Company. 2MN, 2A-6MN, and the organic solvents were used as received.

Table 3. Solubility of 2-Methoxynaphthene (A) and 2-Acetyl-6-methoxynaphthalene (B) in Different Solvents

solvent	T	experimental value ^a			calculated value by modified UNIFAC model		
	K	$x_A \times 10^2$	$x_B \times 10^2$	β	$x_A \times 10^2$	$x_B \times 10^2$	β
hexane	283.15	2.813	0.05882	47.8	3.35	0.068	49.3
	288.15	3.526	0.07265	48.5	4.31	0.091	47.5
	293.15	4.101	0.09656	42.5	5.57	0.121	46.3
	298.15	4.501	0.1224	36.8	7.27	0.159	45.7
	303.15	5.803	0.1385	41.9	9.61	0.209	45.9
	308.15	8.241	0.1470	56.1	13.0	0.273	47.6
heptane	283.15	3.243	0.07074	45.8	3.61	0.078	46.3
	288.15	3.930	0.09697	40.5	4.63	0.104	44.4
	293.15	5.129	0.1200	42.7	5.95	0.138	43.0
	298.15	5.990	0.1563	38.3	7.68	0.183	42.1
	303.15	7.921	0.1752	45.2	10.0	0.240	41.8
	308.15	10.76	0.2002	53.8	13.3	0.314	42.4
octane	283.15	4.569	0.09488	48.2	3.83	0.086	44.2
	288.15	4.855	0.1177	41.3	4.88	0.115	42.3
	293.15	6.176	0.1605	38.5	6.24	0.153	40.7
	298.15	7.791	0.2024	38.5	8.01	0.202	39.6
	303.15	10.08	0.2336	43.2	10.3	0.266	39.0
	308.15	12.04	0.2630	45.8	13.5	0.347	39.0
cyclohexane	283.15	2.987	0.06429	46.5	4.62	0.109	42.5
	288.15	4.395	0.1007	43.6	6.00	0.146	41.2
	293.15	5.760	0.1358	42.4	7.85	0.194	40.6
	298.15	7.213	0.1670	43.2	10.4	0.256	40.6
	303.15	9.713	0.2033	47.8	14.0	0.338	41.6
	308.15	12.77	0.2902	44.0	19.4	0.445	43.7

^a The expanded uncertainty of solute solubility was $\pm 1.2\%$ (relative error).

2. Methods. The wavelength range of larger absorption for 2MN and 2A-6MN were determined by wavelength scanning as (200 to 339) nm and (200 to 360) nm, respectively. A series of standard solutions of known molarities were prepared by dissolving desired amounts of solute in a solvent, and then working curves of 2MN and 2A-6MN were obtained by measuring the ultraviolet absorbance of standard solutions at (330 and 343) nm, respectively.

The solubility data of 2MN and 2A-6MN in four appropriate solvents were measured by static equilibrium method.⁶ Excess solute and solvent were added to a vessel which was placed inside the thermostatic water bath, and then the mixture was stirred continuously for 2 h⁷ at constant temperature (with an uncertainty of ± 0.05 °C). Subsequently the agitation was stopped, and the mixture was settled for 45 min to separate the undissolved solid solute from the solution adequately. The upper transparent saturated solution was withdrawn and diluted for UV absorbance analysis. On the basis of the working curves and UV absorbance value of diluted sample solution, the solubility of a solute in a solvent can be determined. At each temperature point, the experiments were repeated three times, and the solubility for a given mixture was reproducible with an uncertainty of $\pm 0.5\%$ (relative error).

The solubility of naphthalene in acetone at different temperatures was measured to verify the reliability of this method;¹⁰ the average absolute value of relative deviation between the experimental solubility values and that of ref 13 is 3%, which shows that this method is reliable.

3. Results and Discussion. The experimental measured values of solute solubility as well as the predicted values are listed in Table 3, which show that the average absolute value of relative deviations between the predicted values of solute solubility and experimental data for 2MN and 2A-6MN are 28.7 % and 31.9 %, respectively. This indicates that the SLE equation based on modified UNIFAC could generate large deviations in predicting the solubility of aromatic compounds, which was also reported in refs 20 and 21. The reason for this case may lie in three aspects: (1) modified UNIFAC model does not take into account the stereoscopic structure effects of the whole molecule on the activity coefficient;^{20,21} (2) the SLE equation (eq 1) neglects the heat capacity term and pressure term in its expression,^{22,23} which will influence the prediction accuracy of solute solubility accordingly; (3) the fusion enthalpy values of the two solutes used in eq 1 to predict solubility were estimated by the method in ref 19, which have an uncertainty of 15.4 %.

It is interesting that the average absolute value of relative deviation between the calculated separation factor values and that of experimental data is only 8.1 % (Table 3), which is much less than that of solute solubility. The reason for this case may be that 2MN and 2A-6MN have similar molecular stereoscopic structures and the separation factor is a ratio of solubility for the two compounds; thus, the molecular steric structure contribution to activity coefficient may be canceled out in the value of separation factor. This indicates that it is feasible to predict the separation factor by SLE equation based on modified UNIFAC

and to select the suitable solvents for the separation of solid mixtures having similar molecular stereoscopic structures.

CONCLUSIONS

In summary, the appropriate solvents for the separation of 2-methoxynaphthene and 2-acetyl-6-methoxynaphthalene were determined by computer aided solvent scanning method as hexane, heptane, cyclohexane, and octane. The solubility and separation factor data of the two compounds in corresponding appropriate solvents were measured by static equilibrium method. The average absolute value of relative deviation between the calculated separation factor values and that of experimental data is 8.1 %, which indicates that SLE equation based on modified UNIFAC is reliable for the prediction of separation factor values and selection of suitable solvents for the separation of solid mixtures having similar molecular stereoscopic structures. Determination the suitable separating solvents by the combination of computer high-throughput scanning and experimental verification can save the time, reagent and money consumption as much as possible.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zyqlyg@hhit.edu.cn; zyqlyg@yahoo.com.cn.

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