Physicochemical Properties and the Crystallization Thermodynamics of the Pure Enantiomer and the Racemate for *N*-Methylephedrine

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The binary melting point phase diagram of (+)- and (−)-*N*-methylephedrine was determined. It was shown that (±)-*N*-methylephedrine is a racemic conglomerate. The enthalpies of fusion of (+)-*N*-methylephedrine and of (±)-*N*-methylephedrine and the entropy of mixing of (+)- and (−)-*N*-methylephedrine were calculated using the thermal data. The nature of the (±)-*N*-methylephedrine crystalline racemate was also confirmed by means of comparison of solid-state infrared spectra and powder X-ray diffraction patterns of the racemic mixture with those of one of the enantiomers. The solubility and supersolubility diagrams of (±)-*N*-methylephedrine in a mixed solvent of 2-propanol and water were determined over the temperature range (7 to 30) °C. The ternary phase diagram of (+)- and (−)-*N*-methylephedrine with the mixed solvent was constructed at (15, 20, 25, and 30) °C.

Introduction

Chirality plays an important role in biological activities. Enantiomers are related to each other in that they are nonsuperimposable mirror images. As such, opposite enantiomers of a given molecule exhibit identical physical and chemical properties in an achiral environment. However, they will differ on interaction with chiral influences.[1] For example, enantiomers rotate plane polarized light in opposite directions and can react with chiral reagents at different rates. It is well established that the physiological activity of organic drug compounds can be dramatically affected by their chirality.[2] If the binding site is chiral in nature, the lock-and-key visualization of drug action suggests that one enantiomer of a drug molecule will fit better into the chiral binding site than will the other enantiomer of the same molecule.[1]

N-Methylephedrine belongs to the class of ephedrines which are potential central nervous stimulant drugs.[3] *N*-Methylephedrine is also widely used as a chiral resolving agent, a precursor to chiral supporting electrolytes, a phase-transfer catalyst, and a reducing agent. This use for ephedrine and its derivatives has increased rapidly in recent years. Both synthetic forms and products obtained from botanical sources are used. Manufacture of enantiomers can embrace two different technologies, namely, chiral separation and chiral synthesis. Chiral separation mainly includes crystallization, chromatography, chiral solvent extraction, and kinetic resolution. Although revolutionary advances have been achieved in enzymatic kinetic resolutions and catalytic asymmetric synthesis, racemate resolution by crystallization techniques is still the most important method in both small and large scale production of pure enantiomers. Moreover, they are not restricted to the resolution of racemates but can also be used for further purification of partially resolved substances prepared by other techniques.[4−6] It is well-known that characterization of racemate types is the prerequisite to successful selection of a crystallization method.

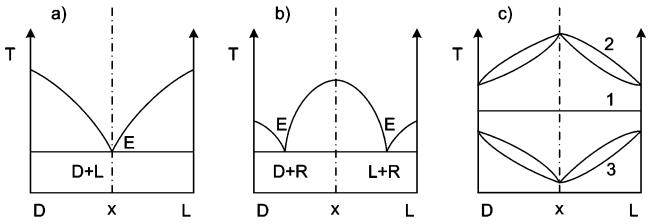

Figure 1. Typical binary phase diagrams of various racemic species.

Racemate crystals can be divided into three types: racemic compounds, racemic conglomerates, or pseudoracemates (solid solutions). The three types of racemates are readily distinguished by reference to their melting point diagrams, as shown in Figure 1.[7,8] For the unambiguous identification of racemic species, experimentalists have agreed on employing additional techniques, such as powder X-ray diffraction patterns, solid-state infrared spectra, or nuclear magnetic resonance spectra.[9] The spectra of enantiomers are identical to that of the racemic conglomerate but different from that of a racemic compound.[4,7] The prerequisite for crysallization from solution is the knowledge of the solid−liquid equilibrium of the two enantiomers in a solvent. Representing the data in a triangular diagram is helpful for the crystallization process design.[10−12]

For the study of crystallization processes, it is useful to determine the solubility (saturation limit) and supersolubility (supersaturation limit) diagram. According to the corresponding diagram, appropriate methods including temperature change, evaporation of solvent, changing

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solvent composition, and precipitation can be chosen to generate the supersaturated solution for further crystallization. Crystallization processes can take place only in the supersaturated phase. The rate of crystal nucleation and growth, as well as the crystal size distribution, is affected by the degree of supersaturation.[12,13] In the case of resolution of a conglomerate by the preferential crystallization method, the metastable zone width is especially important for controlling product quality. In this region, spontaneous nucleation does not occur, supersaturated solutions may exist, and the crystal growth process prevails upon the presence of a seed crystal surface. Accordingly, the optimal operation region for well-controlled crystallization should be within the metastable zone.

In this work, we identified the racemic species of (±)-*N*-methylephedrine using the melting point phase diagram, the infrared spectra, and the powder X-ray diffraction patterns. It was shown that (±)-*N*-methylephedrine is a racemic conglomerate. The enthalpies of fusion of (+)-*N*-methylephedrine and of (±)-*N*-methylephedrine and the entropy of mixing of (+)- and (−)-*N*-methylephedrine were calculated using thermal data. The solubility and supersolubility diagrams of (±)-*N*-methylephedrine in a mixed solvent of 2-propanol and water were determined over the temperature range (7 to 30) °C. The ternary phase diagram of (+)- and (−)-*N*-methylephedrine with the mixed solvent was constructed at (15, 20, 25, and 30) °C.

Experimental Section

Materials. (+)- and (−)-*N*-methylephedrine were purchased from Sigma-Aldrich Company. They were used without further purification. The racemic mixture (±)-*N*-methylephedrine was prepared by dissolving equimolar quantities of the two enantiomers in methanol and allowing the solvent to evaporate completely at room temperature. Analytical grade 2-propanol was purchased from Fisher Scientific Pte Ltd. Ultrapure water was prepared using a Millipore purification system.

Apparatus and Procedures

Differential Scanning Calorimetry, Powder X-ray Diffraction, Fourier Transform Infrared Spectroscopy, and Polarimetry. Enthalpies of fusion and melting points of the pure enantiomer and of the racemate *N*-methylephedrine were determined using a Mettler Toledo DSC 822e differential scanning calorimeter. The samples were scanned from (25 to 95) °C at the different heating rates (2, 5, and 10) K min^{-1} under a nitrogen atmosphere. The samples were cooled to room temperature and reweighed. No weight loss was detected, indicating that the volatility of *N*-methylephedrine did not pose a problem in the temperature range of the DSC experiment. The DSC curves were recorded and analyzed using the STARe software.

Experimental PXRD patterns of both the racemate and (+)-enantiomer for *N*-methylephedrine were determined at room temperature using a Bruker D8 Advance diffractometer with Cu Kα radiation at 40 mA, 40 kV. The samples were packed into an aluminum holder and scanned with the diffraction angle 2θ increasing from (5 to 70)°, with a step size of 0.02° for 1 s. All diffraction patterns were collected at ambient temperature (24 °C).

FTIR spectra of (±)-*N*-methylephedrine and (+)-*N*-methylephedrine were obtained in the range (400 to 4000) cm^{-1} with a Bio-Rad FTS 135 FTIR spectrometer using the KBr disk method. The scans were performed with a resolution of 4 cm^{-1}, and the number of scans is 40. All spectra were collected at ambient temperature.

The optical rotation of *N*-methylephedrine was measured at 589 nm using a JASCO P-1030 digital polarimeter equipped with a quartz cell of 1 cm path length at ambient temperature.

Solubility and Supersolubility of N-Methylephedrine in the Mixed Solvent of 2-Propanol and Water. The selection of the suitable solvent for a given crystallization operation is crucial. Many factors must be considered. The solute to be crystallized should be readily soluble in the solvent. It should also be easily deposited from the solution in the desired crystalline form after cooling, evaporation, or salting-out with an additive. A mixture of two or more solvents is sometimes found to possess the best properties for a particular crystallization purpose. In this study, the mixture of 2-propanol and water in a volumetric ratio of 1:3 was used as the solvent. Five samples of different composition, with the enantiomeric excess (ee) ranging from 0 (racemic mixture) to 100% (pure enantiomer), were prepared by weighing the pure enantiomers in a 50 cm^3 double-walled flask. The enantiomeric excess (ee) is calculated using eq 1, where x is the mole fraction

$$\mathrm{ee} = 2x - 1 \tag{1}$$

of the more abundant enantiomer in a mixture of the two enantiomers.

A known volume of solvent was added, not sufficient to dissolve the solute at the highest temperature of interest (30 °C). The solutions were stirred with a magnetic stir bar, and the temperatures were maintained by water circulating through the jacket of the flasks. Subsequently, solvent is added in intervals of at least 4 h, at the end decreasing additions to 0.2 cm^3, until all of the solute was dissolved. The solubility was calculated accordingly, and an error propagation was accomplished. The error of the experimental solubility data is less than 2%.

To determine the supersolubility, the transparent saturated solutions were cooled from their equilibrium saturation temperature T_0 with a cooling rate of 1 K h^{-1}. The temperature T at which turbidity was first observed was the supersolubility temperature; the metastable zone width (MSZW) was calculated as[12]

$$\Delta T = T_0 - T \tag{2}$$

To determine the solubility at lower temperatures, the same solutions were brought to the new temperatures of interest (15, 20, and 25) °C and the procedure to determine the solubility and supersolubility, as described above, was repeated.

The solubility of pure (+)-*N*-methylephedrine at (15 and 20) °C was verified by a different method. Solvent was added to pure (+)-*N*-methylephedrine, not sufficient to dissolve all of the solute. The solution was stirred for 48 h, and then the stirrer was switched off to settle the excess solid. After 8 h, an appropriate portion of the solution was pipetted from the flask, avoiding contamination by the solid, and analyzed in the polarimeter using the same mixed solvent as above. The determined optical rotation was converted to concentration using a calibration curve which was recorded before with different solutions of the pure enantiomer. The results determined by the two methods are in good agreement.

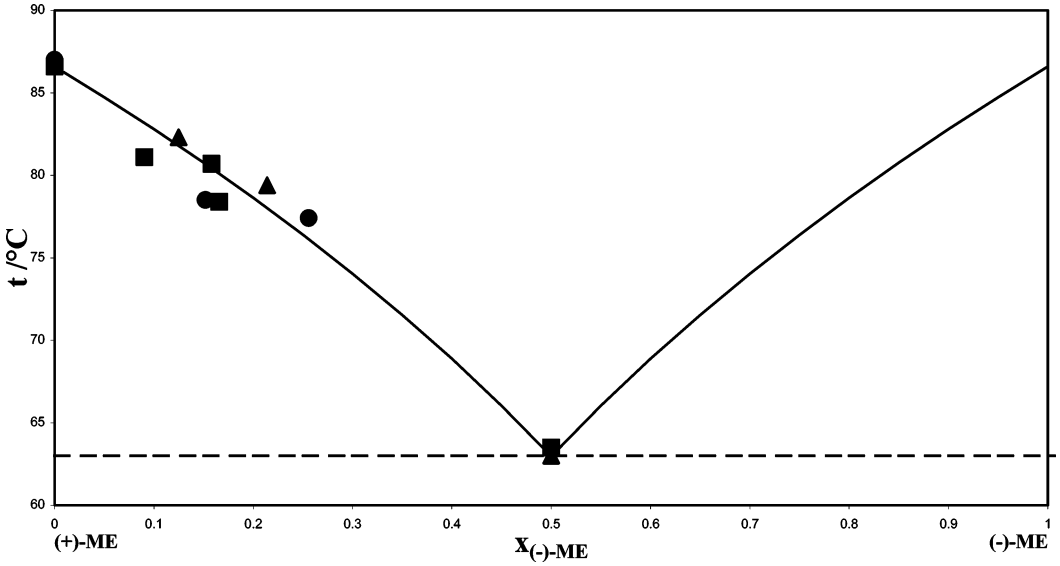

Figure 2. Binary phase diagram (melting point diagram) of *N*-methylephedrine: ▲, heating rate 2 K min^{-1}; ■, heating rate 5 K min^{-1}; ●, heating rate 10 K min^{-1}; —, simplified Schröder−Van Laar equation (liquidus line); - - -, solidus line.

Table 1. Melting Points and Enthalpies of Fusion of (+)-*N*-Methylephedrine and (±)-*N*-Methylephedrine

T_R^f / K	T_A^f / K	$T_A^f - T_R^f$ / K	ΔH_R^f / J mol^{-1}	ΔH_A^f / J mol^{-1}	$\Delta H_A^f - \Delta H_R^f$ / J mol^{-1}	ΔS_l^m / J mol^{-1} K^{-1}
336.65	359.75	23.10	26 576	30 531	3955	5.44

Table 2. Temperature of Fusion of *N*-Methylephedrine Determined with Differential Scanning Calorimetry (DSC) with Heating Rates (HRs) of (2, 5, and 10) K min^{-1}

HR = 2 K min^{-1}		HR = 5 K min^{-1}		HR = 10 K min^{-1}	
$x_{(+)\text{-ME}}$	T^f/K	$x_{(+)\text{-ME}}$	T^f/K	$x_{(+)\text{-ME}}$	T^f/K
0	359.95	0	359.75	0	360.15
0.125	355.45	0.0905	354.25	0.152	351.65
0.214	352.55	0.158	353.85	0.256	350.55
0.5	336.15	0.166	351.55		
		0.5	336.65		

Results and Discussion

Melting Point Phase Diagram of N-Methylephedrine. The binary melting point phase diagram of (+)- and (−)-*N*-methylephedrine is given in Figure 2. From the diagram, we can find the eutectic composition is the racemic composition (mole ratio: (+)/(−) = 0.5/0.5). This indicates that (±)-*N*-methylephedrine is a conglomerate. The liquidus curve is also calculated from the melting point and the enthalpy of fusion of the pure enantiomer shown in Table 1 using the simplified Schröder−Van Laar equation (eq 3),

$$\ln x = \frac{\Delta H_A^f}{R}\left(\frac{1}{T_A^f} - \frac{1}{T^f}\right) \tag{3}$$

where x is the mole fraction of the more abundant enantiomer of a mixture whose melting terminates at T^f. ΔH_A^f and T_A^f are the enthalpy of fusion and the melting point of the pure enantiomers, respectively. R is the gas constant (R = 8.314 J mol^{-1} K^{-1}).

The experimental results shown in Table 2 are in good agreement with the calculated curve.

Enthalpies of Fusion of (+)-N-Methylephedrine and of (±)-N-Methylephedrine: Entropy of Mixing of (+)- and (−)-N-Methylephedrine. Experimental and calculated results of thermal analysis by DSC are given in Table 1.

The thermodynamic cycle for the system is shown below:[7]

$$D_s + L_s \xrightarrow{\Delta H_A^f} D_l + L_l \xrightarrow{\Delta H_l^m} DL_l \qquad (\text{at } T_A^f)$$

$$C^s(T_A^f - T_R^f) \uparrow \qquad\qquad \downarrow C^l(T_R^f - T_A^f)$$

$$D_s + L_s \xleftarrow{-\Delta H_s^m} DL_s \xleftarrow{-\Delta H_R^f} DL_l \qquad (\text{at } T_R^f)$$

In this cycle, D and L represent the pure enantiomers, and DL represents the racemate. C^s and C^l represent the heat capacities of the solids and liquids, respectively. T_R^f represents the fusion point of the racemate. ΔH_l^m and ΔH_s^m represent the enthalpies of mixing of the enantiomers in the liquid and solid states, respectively.

If the enantiomers are perfectly immiscible in the solid state and if their mixture is ideal in the liquid state, then ΔH_s^m and ΔH_l^m equal zero. We may then write

$$\Delta H_s^m = 0 = C^s(T_A^f - T_R^f) + \Delta H_A^f + C^l(T_R^f - T_A^f) - \Delta H_R^f$$

$$\Delta H_A^f - \Delta H_R^f = (C^l - C^s)(T_A^f - T_R^f) \tag{4}$$

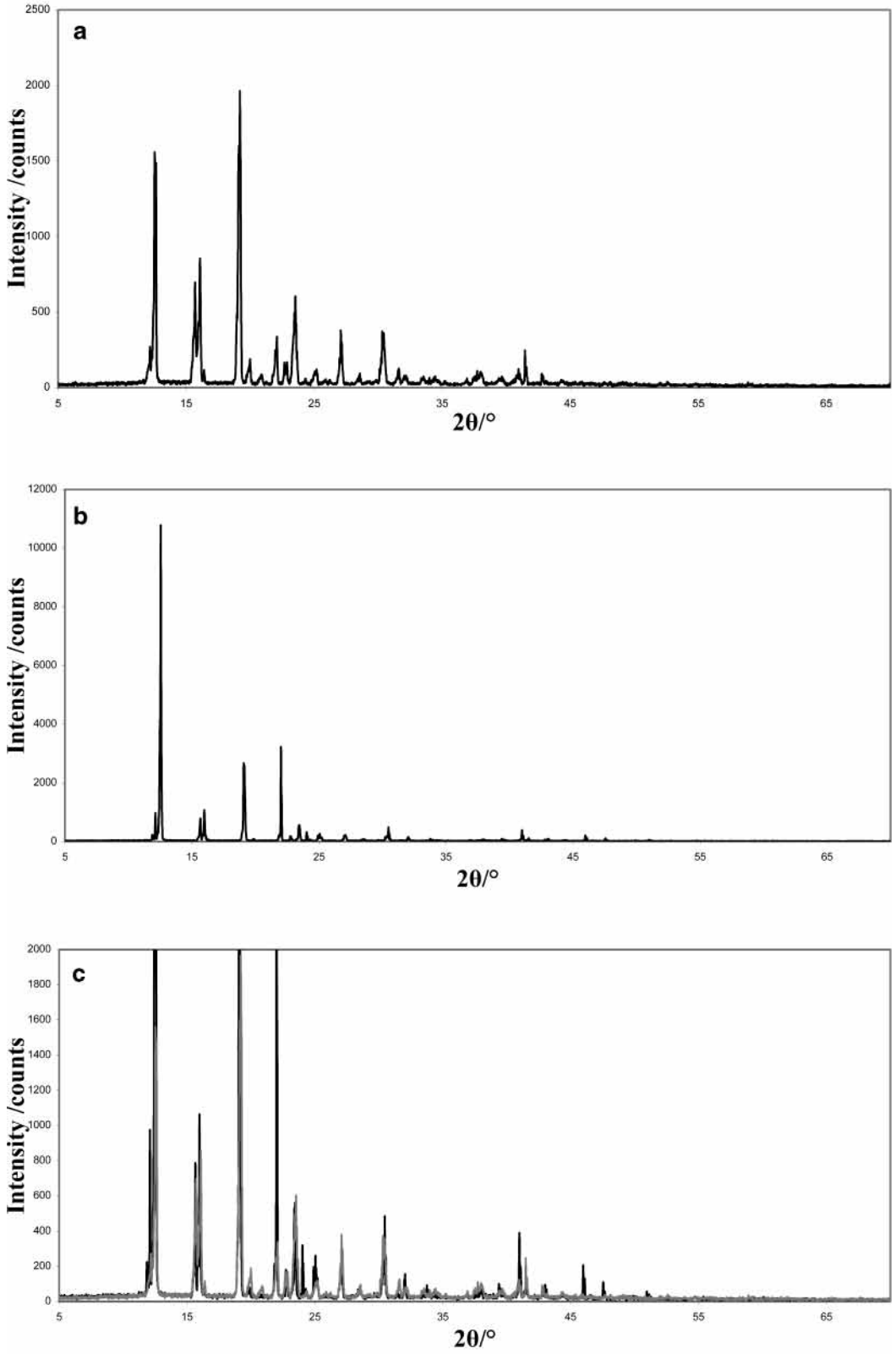

Figure 3. (a) Powder X-ray diffraction patterns of (+)-*N*-methylephedrine. (b) Powder X-ray diffraction patterns of (±)-*N*-methylephedrine. (c) Powder X-ray diffraction patterns of (+)-*N*-methylephedrine and (±)-*N*-methylephedrine.

Since $C^l > C^s$ and $T_A^f > T_R^f$, it follows that $\Delta H_A^f > \Delta H_R^f$. Typically the difference $C^l - C^s$ has a magnitude of (80 to 170) J mol^{-1} K^{-1} and $T_A^f - T_R^f$ is of the order of (20 to 30) K.[7] Therefore, the difference in the enthalpies of fusion lies between (1600 and 5100) J mol^{-1} for a conglomerate forming system. This is in fact what is observed in Table 1.

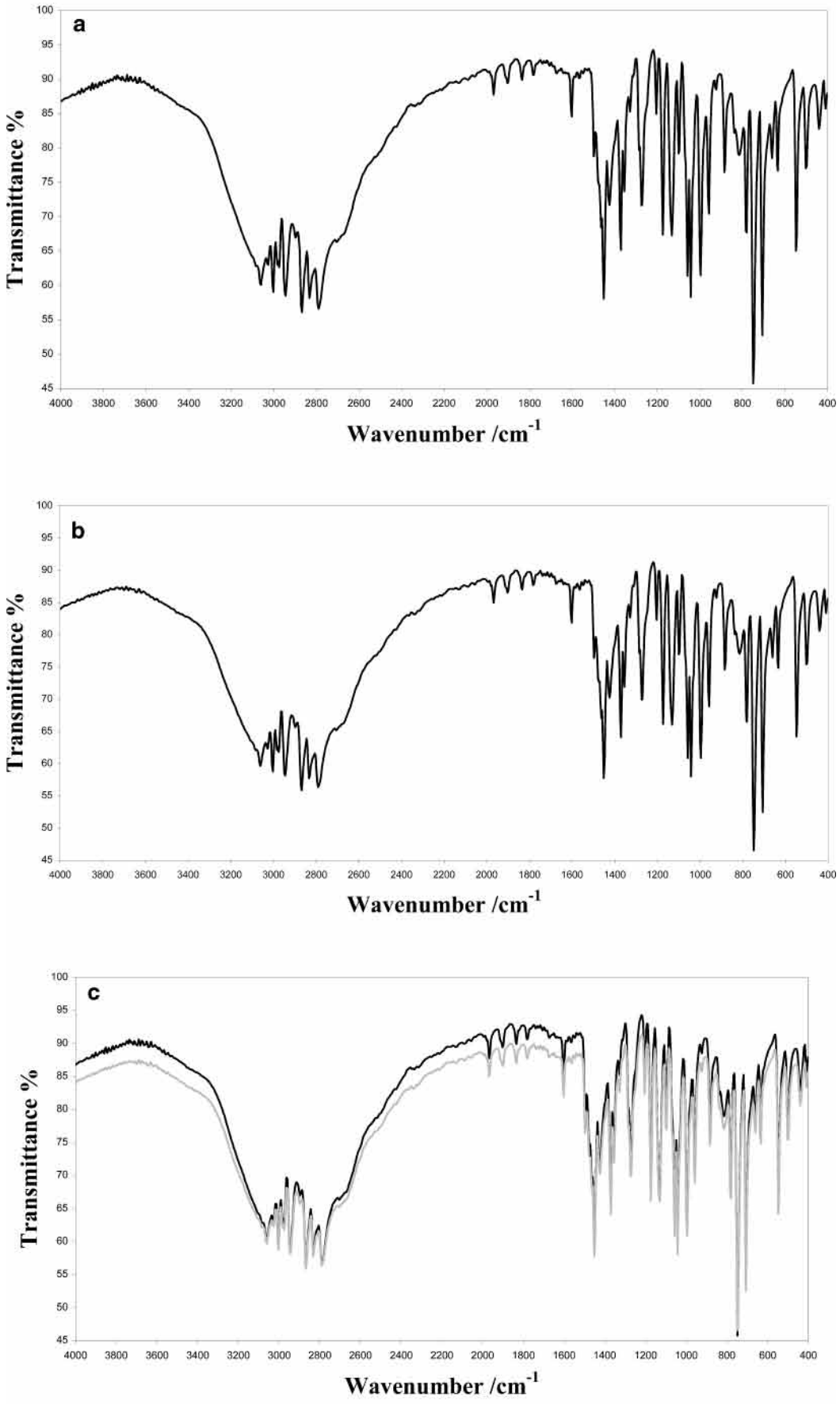

Figure 4. (a) Fourier transform infrared spectra of (+)-*N*-methylephedrine. (b) Fourier transform infrared spectra of (±)-*N*-methylephedrine. (c) Fourier transform infrared spectra of (+)-*N*-methylephedrine and (±)-*N*-methylephedrine.

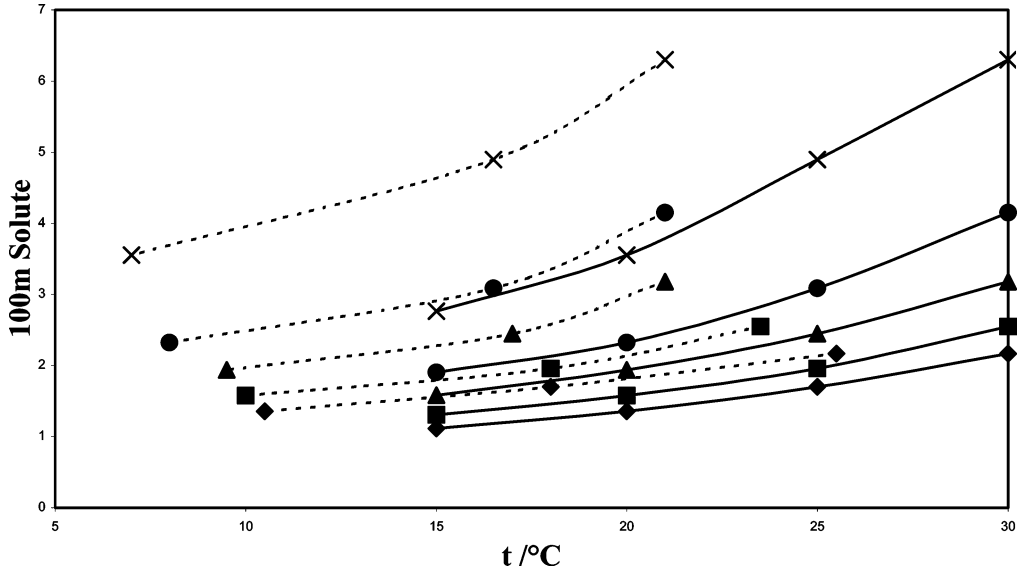

Figure 5. Solubility and metastable zone width of *N*-methylephedrine in a 1:3 (vol) mixture of 2-propanol and water: × , ee = 0%; ●, ee = 25%; ▲, ee = 50%; ■ ee = 75%; ◆ ee = 100%; —, solubility; - - -, metastable zone width.

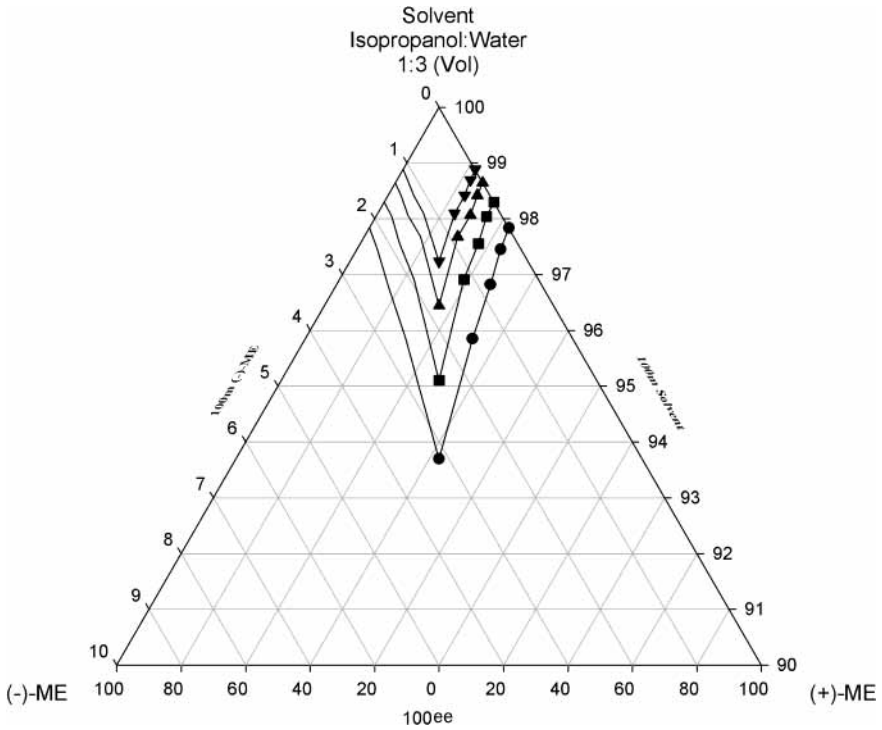

Figure 6. Ternary phase diagram of *N*-methylephedrine and a 1:3 (vol) mixture of 2-propanol and water: ●, t = 30 °C; ■, t = 25 °C; ▲, t = 20 °C; ▼, t = 15 °C.

Likewise, the changes in entropy can be determined with the thermodynamic cycle shown below:

$$D_s + L_s \xrightarrow{\Delta S_A^f} D_l + L_l \xrightarrow{\Delta S_l^m} DL_l \qquad (\text{at } T_A^f)$$

$$C^s \ln\frac{T_A^f}{T_R^f} \uparrow \qquad\qquad \downarrow C^l \ln\frac{T_R^f}{T_A^f}$$

$$D_s + L_s \xleftarrow{-\Delta S_s^m} DL_s \xleftarrow{-\Delta S_R^f} DL_l \qquad (\text{at } T_R^f)$$

In this cycle, ΔS_l^m and ΔS_s^m represent the entropies of mixing of the enantiomers in the liquid and solid states, respectively. For a conglomerate, DL_s exists in the form of two separate phases, D_s and L_s, which are present as a mechanical mixture.[7] Consequently, $\Delta S_s^m = 0$ and $\Delta S_l^m = R \ln 2 = 5.77$ J mol^{-1} K^{-1} if the system behaves ideally. We may then write

$$\Delta S_s^m = 0 = C^s \ln\frac{T_A^f}{T_R^f} + \Delta S_A^f + \Delta S_l^m + C^l \ln\frac{T_R^f}{T_A^f} - \Delta S_R^f$$

$$-\Delta S_l^m = \frac{\Delta H_A^f}{T_A^f} - \frac{\Delta H_R^f}{T_R^f} - \frac{\Delta H_A^f - \Delta H_R^f}{T_A^f - T_R^f}\ln\frac{T_A^f}{T_R^f} \qquad (5)$$

The value of ΔS_l^m calculated with eq 5 is shown in Table 1. It is close to the value expected from theory, which indicates that (±)-*N*-methylephedrine is a conglomerate.

Powder X-ray Diffraction Patterns and Fourier Transform Infrared Spectra. The PXRD patterns and FTIR spectra of the pure enantiomers and the racemic

Table 3. Solubility and Metastable Zone Width Data of *N*-Methylephedrine in a 1:3 (vol) Mixture of 2-Propanol and Water

100ee	$100m_{solute}$	$100m_{(+)\text{-ME}}$	$100m_{(-)\text{-ME}}$	$100m_{solvent}$	MSZW/°C
		$t = 30$ °C			
100	2.166	2.166	0.000	97.834	4.5
75	2.548	2.229	0.318	97.452	6.5
50	3.182	2.386	0.795	96.818	9.0
25	4.150	2.594	1.556	95.850	9.0
0	6.302	3.151	3.151	93.698	9.0
		$t = 25$ °C			
100	1.701	1.701	0.000	98.299	7.0
75	1.958	1.713	0.245	98.042	7.0
50	2.446	1.834	0.611	97.554	8.0
25	3.089	1.930	1.158	96.911	8.5
0	4.896	2.448	2.448	95.104	8.5
		$t = 20$ °C			
100	1.356	1.356	0.000	98.644	9.5
75	1.578	1.381	0.197	98.422	10.0
50	1.936	1.452	0.484	98.064	10.5
25	2.324	1.453	0.872	97.676	12.0
0	3.554	1.777	1.777	96.446	13.0
		$t = 15$ °C			
100	1.117	1.117	0.000	98.883	na
75	1.305	1.142	0.163	98.695	na
50	1.581	1.186	0.395	98.419	na
25	1.905	1.191	0.714	98.095	na
0	2.763	1.381	1.381	97.237	na

mixture are shown in Figures 3 and 4, respectively. The peak positions in the recorded PXRD patterns and FTIR spectra are the same for the racemic mixture and the pure enantiomers. This would be the case if the two separate enantiomers are present as a mechanical mixture, which confirms that (±)-*N*-methylephedrine is a racemic conglomerate.

Solubility and Supersolubility of (+)- and (−)-N-Methylephedrine in the Mixed Solvent of 2-Propanol and Water. The solubility and supersolubility of (+)- and (−)-*N*-methylephedrine in the mixture of 2-propanol and water are shown in Figure 5. It is found that both the solubility and supersolubility of *N*-methylephedrine increased appropriately with temperature (Table 3). The metastable zone width is (4.5 to 13) °C across the experimental temperature range. These results suggest the feasibility of decreasing the temperature to generate a supersaturated solution for crystallization operations.

Ternary Phase Diagram. The ternary solubility phase diagram of (+)- and (−)-*N*-methylephedrine for the temperatures (15, 20, 25, and 30) °C is shown in Figure 6. The shape of the solubility line in the phase diagram resembles the liquidus line in the binary phase diagram shown in Figure 1a.[7] The construction of the ternary phase diagram is useful for the crystallization process design. Combining the results of solubility and supersolubility of (+)- and (−)-*N*-methylephedrine, the starting and ending operative crystallization conditions can be inferred for different initial material compositions.

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