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# Diastereomeric salts of lactic acid and 1-phenylethylamine, their structures and relative stabilities

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Crystal structures have been determined for the two diastereomeric salts formed between *S*-lactic acid (*S*-LA) and 1-phenylethylamine (PEA). The relative stabilities of the salts have been investigated by differential scanning calorimetry and solubility measurements in acetonitrile. The less soluble salt obtained from water, (*R*-PEA)(*S*-LA), is the less dense. It belongs to the orthorhombic space group $P2_12_12_1$, $Z = 4$. The more soluble salt, (*S*-PEA)(*S*-LA)$\cdot$H$_2$O, crystallized from ethanol is monoclinic, space group $P2_1$, $Z = 2$. The crystal structure showed that the water molecule is well integrated into the hydrogen-bond network in the more soluble salt, which explains the fruitless attempts made to obtain the corresponding unhydrated salt. The lactate ion adopts different conformations in the two salts. The relative energies were investigated by Hartree–Fock calculations, showing that the lactate ion is in a conformation with higher energy in the more soluble salt. The difference in solubility between the two salts can be attributed to an interplay of enthalpy and entropy effects.

## 1. Introduction

The preparation of pure chiral compounds is of the utmost importance for their use as drugs, herbicides and pesticides. In this aspect, chemists have not reached the perfection that nature has accomplished with its development of enzymes capable of performing stereospecific reactions. Often a chemical synthesis results in a racemic mixture, which subsequently has to be resolved into its enantiomers. Despite the focus on the methods that can be used to isolate the enantiomers from a racemic mixture, there is still no thorough understanding of the structural and physicochemical factors that ensure a successful resolution. The classical method for resolving a racemate is through the formation of diastereomeric salts by reacting the racemate with a suitable chiral compound. If the resolution is successful, the resulting diastereomeric salts differ sufficiently in their solubilities or other physicochemical properties to enable an efficient resolution. Tartaric and mandelic acid are widely used to successfully resolve racemic amines, and we have previously investigated diastereomeric mandelate salts (Larsen *et al.*, 1994*b*). Lactic acid (2-hydroxypropionic acid) is one of the simplest naturally occurring chiral acids, but it is rarely used for resolution experiments. To elucidate its properties as a resolving agent and contribute to the understanding of factors that are responsible for a successful resolution by the formation of diastereomeric salts, we have determined the structures and investigated the properties of the diastereomeric salts formed of lactic acid and 1-phenylethylamine, a base extensively used in the resolution of racemic acids.

## 2. Experimental

### 2.1. Preparation

The chemicals were purchased from Aldrich, *S*-lactic acid as an 85+% aqueous solution, racemic 1-phenylethylamine 96% pure and the two enantiomers 99% pure. All crystallization experiments were performed at room temperature.

**2.1.1. *R*-1-Phenylethylammonium *S*-lactate**. (*R*-PEA)(*S*-LA) was prepared by dissolving 0.6267 g (0.0059 mol) of *S*-lactic acid in 5 ml of water and adding 0.6949 g (0.0057 mol) of *R*-1-phenylethylamine. The crystals formed were removed by filtration. Recrystallization from water gave crystals suitable for X-ray diffraction study.

**2.1.2. *S*-1-Phenylethylammonium *S*-lactate monohydrate**. (*S*-PEA)(*S*-LA)·$H_2O$ was prepared from a mixture of 0.2582 g (0.0024 mol) of *S*-lactic acid and 0.3047 g (0.0024 mol) of *S*-1-phenylethylamine in 96% ethanol. Slow evaporation of the solvent resulted in crystals suited for crystal structure determination.

**2.1.3. *S*-1-Phenylethylammonium *S*-lactate**. Different approaches were taken to obtain (*S*-PEA)(*S*-LA) from the monohydrate (*S*-PEA)(*S*-LA)·$H_2O$ as outlined below. The products were characterized by differential scanning calorimetry (DSC) and by elemental microanalysis for C, H and N.

0.1 g of (*S*-PEA)(*S*-LA)·$H_2O$ was placed in a desiccator over approximately 5 g of $P_4O_{10}$ and the desiccator was evacuated using a water aspirator. (An oil-sealed mechanical pump caused the sample to sublimate and be removed from the desiccator because the pressure became too low.) After one week, the chemical composition of the sample, determined from the elemental analysis, had changed in accordance with a removal of 80% of the crystal water. The DSC curve (Fig. 1*c*) shows two peaks: one at the melting point of (*S*-PEA)(*S*-LA)·$H_2O$ and one approximately 17 K higher, probably corresponding to the melting of (*S*-PEA)(*S*-LA). Further desiccator experiments did not improve this result.

Both Kugelrohr sublimation and azeotrope distillation with toluene were employed in our attempts to dehydrate the sample; however, these experiments led to an oily product rather than a crystalline material.

**2.1.4. Resolution of racemic 1-phenylethylamine by lactic acid**. 0.5285 g (0.0050 mol) of *S*-lactic acid was added to a solution of 0.5705 g (0.0047 mol) of racemic 1-phenylethylamine in 96% ethanol. Crystals formed after slow evaporation of the solvent and were removed by filtration. The crystalline material was characterized by X-ray powder diffraction. The recorded diagram corresponds to the pattern of (*R*-PEA)(*S*-LA).

### 2.2. Thermochemical measurements

**2.2.1. Differential scanning calorimetry**. DSC experiments were performed with a Polymer Laboratories DSC equipped with *PLus V* software version 5.33. Samples of 2–5 mg were placed in sealed crucibles and heated at a rate of 5 K $\min^{-1}$. The melting points and melting enthalpies of (*R*-PEA)(*S*-LA) and (*S*-PEA)(*S*-LA)·$H_2O$ (Table 1) were determined from bulk samples. In addition, DSC measurements were performed for the different products obtained in the attempts to produce the non-hydrated (*S*-PEA)(*S*-LA) (Fig. 1).

**2.2.2. Determination of solubilities**. Samples of (*R*-PEA)(*S*-LA) (0.2 g) and (*S*-PEA)(*S*-LA)·$H_2O$ (0.4 g) were added to 10 ml of acetonitrile and thermostated at 297 K for 48 h under constant stirring. Undissolved salt was removed by filtration, and 5 ml of the solution was diluted to 25 ml. The concentration of the salt in the final solution was determined by spectrophotometry by exploiting the absorption of 1-phenylethylamine at $\lambda = 258$ nm ($\epsilon_{258} = 170\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$). The solubilities are listed in Table 1.

### 2.3. X-ray crystallography

Both (*R*-PEA)(*S*-LA) and (*S*-PEA)(*S*-LA)·$H_2O$ formed crystals suitable for structure determination. Diffraction data were collected on a CAD-4 diffractometer using graphite-monochromated Cu $K\alpha$ radiation on crystals cooled to 122.4 (5) K with an Oxford Cryosystem. The $\omega$–$2\theta$ scan mode was employed with a maximum scan time of 60 s, and the orientation of the crystal was checked after every 600 measured reflections. The data reductions were conducted in similar ways for both compounds using the *DREADD* program package (Blessing, 1987). Corrections for background, Lorentz and polarization effects were included. The structures were determined by direct methods in *SHELXS* (Sheldrick, 1990) and refined by least-squares minimization of $\sum w(|F_o| - |F_c|)^2$ using *SHELXL*97 (Sheldrick, 1997). Assignment of the absolute configurations was made in agreement with the known configurations of the participating ions. This assignment was confirmed by the refined Flack parameter (Flack, 1983). For both compounds, correction of

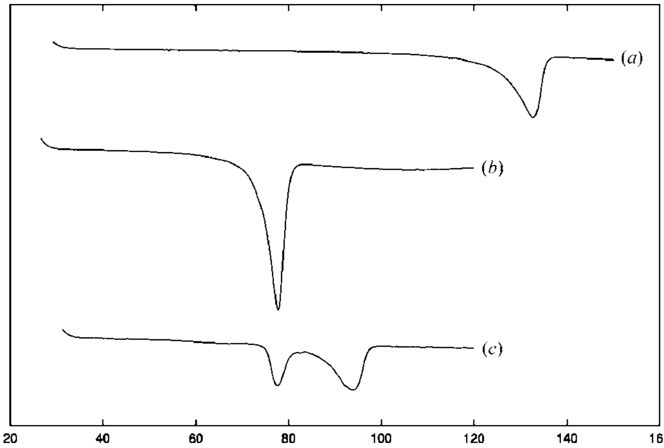

**Figure 1**
DSC curves (heat flow as a function of temperature in K) of (*a*) (*R*-PEA)(*S*-LA) (4.116 mg), (*b*) (*S*-PEA)(*S*-LA)·$H_2O$ (3.535 mg) and (*c*) approximately 80% dehydrated (*S*-PEA)(*S*-LA)·$H_2O$ (4.198 mg) all recorded with a heating rate of 5 K $\min^{-1}$.

**Table 1**
Experimental details.

| | ($R$-PEA)($S$-LA) | ($S$-PEA)($S$-LA)·$H_2O$ |
|---|---|---|
| Crystal data | | |
| Chemical formula | $(C_8H_{12}N)^+(C_3H_5O_3)^-$ | $(C_8H_{12}N)^+(C_3H_5O_3)^-$-·$H_2O$ |
| Chemical formula weight | 211.26 | 229.27 |
| Melting point | 398.9 (6) | 346.8 (4) |
| $\Delta H_{fus}$ (kJ mol$^{-1}$) | 18.8 (2) | 28.8 (8) |
| Solubility in acetonitrile (mol L$^{-1}$) | 0.011 (1) | 0.021 (1) |
| Space group | Orthorhombic, $P2_12_12_1$ | Monoclinic, $P2_1$ |
| $a$, $b$, $c$ (Å) | 6.8465 (10), 6.9702 (7), 24.248 (4) | 8.0795 (18), 5.8794 (9), 12.852 (2) |
| $\beta$ (°) | | 94.53 (2) |
| $V$ (Å$^3$) | 1157.1 (3) | 608.6 (2) |
| $Z$ | 4 | 2 |
| $D_x$ (Mg m$^{-3}$) | 1.213 | 1.251 |
| Radiation type | Cu $K\alpha$ | Cu $K\alpha$ |
| No. of reflections for cell parameters | 25 | 25 |
| $\theta$ range (°) | 39.85–42.19 | 39.46–42.24 |
| $\mu$ (mm$^{-1}$) | 0.721 | 0.786 |
| Temperature (K) | 122.0 (5) | 122.0 (5) |
| Crystal form, colour | Plate, colourless | Plate, colourless |
| Crystal size (mm) | 0.48 × 0.21 × 0.12 | 0.50 × 0.25 × 0.16 |
| | | |
| Data collection | | |
| Diffractometer | Enraf–Nonius CAD-4 | Enraf–Nonius CAD-4 |
| Data collection method | $\omega$–$2\theta$ scans | $\omega$–$2\theta$ scans |
| No. of measured, independent and observed reflections | 8032, 2384, 2342 | 5053, 2505, 2503 |
| Criterion for observed reflections | $I > 2\sigma(I)$ | $I > 2\sigma(I)$ |
| $R_{int}$ | 0.0214 | 0.0289 |
| $\theta_{max}$ (°) | 74.94 | 74.80 |
| Range of $h$, $k$, $l$ | $0 \rightarrow h \rightarrow 8$<br>$0 \rightarrow k \rightarrow 8$<br>$-29 \rightarrow l \rightarrow 30$ | $-10 \rightarrow h \rightarrow 10$<br>$-7 \rightarrow k \rightarrow 7$<br>$0 \rightarrow l \rightarrow 16$ |
| No. and frequency of standard reflections | 5 every 167 min | 5 every 167 min |
| Intensity decay (%) | 9.2 | 2.3 |
| | | |
| Refinement | | |
| Refinement on | $F^2$ | $F^2$ |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.0281, 0.0765, 1.029 | 0.0274, 0.0732, 0.970 |
| No. of reflections and parameters used in refinement | 2384, 205 | 2505, 222 |
| H-atom treatment | All H-atom parameters refined | All H-atom parameters refined |
| Weighting scheme | $w = 1/[\sigma^2(F_o^2) + (0.057P)^2 + 0.081P]$ where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.0614P)^2 + 0.0408P]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| $(\Delta/\sigma)_{max}$ | 0.000 | 0.001 |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 0.24, −0.208 | 0.303, −0.216 |
| Extinction method | *SHELXL* | *SHELXL* |
| Extinction coefficient | 0.0116 (10) | 0.169 (6) |
| Absolute structure (Flack, 1983) | | |
| Flack parameter | 0.03 (14) | −0.02 (10) |

Computer programs used: *CAD*-4 (Enraf–Nonius, 1989), *DREADD* (Blessing, 1987), *SHELXS*97 (Sheldrick, 1990), *SHELXL*97 (Sheldrick, 1997).

the data for extinction was considered necessary. After refining the heavy-atom positions and anisotropic displacement parameters, the difference density maps clearly showed all H atoms. Both positional and isotropic displacement parameters for the H atoms were included in the refinement. A summary of crystal data, data collection and structure refinement results is presented in Table 1.[1]

### 2.4. Powder diffraction

X-ray powder diffraction experiments were conducted at 294 K using a Stoe powder diffractometer. The diagrams were recorded in transmission mode using Cu $K\alpha_1$ radiation obtained from a curved Ge(111) monochromator. A position-sensitive detector covering 7° in $2\theta$ was used in $2\theta$ step scan mode with steps of 0.1° and a step time of 120 s. Powder diagrams were recorded for the diastereomeric salts obtained from the preparations of the pure enantiomers and for the crystals obtained by the resolution experiment.

### 2.5. Theoretical calculations

Hartree–Fock calculations were conducted for an isolated lactate ion using the *Gamess*97 program (Schmidt *et al.*, 1993) employing the 6-311G(d,p) basis set. A geometry optimization was carried out. The energy was also calculated for the lactate ion as observed in the crystal structures of ($R$-PEA)($S$-LA) and ($S$-PEA)($S$-LA)·$H_2O$ after the O—H and C—H distances had been adjusted to values from neutron studies.

## 3. Results and discussion

### 3.1. Description of the crystal structures

Figs. 2 and 3 show the 1-phenylethylammonium cations and lactate anions as they are found in the crystal structures of ($R$-PEA)($S$-LA) and ($S$-PEA)($S$-LA)·$H_2O$. The two cations are almost perfect mirror images of one another with identical bond lengths and angles (Table 2). The only small deviation is in the torsion angle that defines the conformation of the cation, N—C5—C6—C7, which is 62.03 (13)° in the $R$-PEA salt and −73.20 (10)° in the $S$-PEA salt. The variation in the geometry of 1-phenylethylammonium ions has been investigated previously (Larsen *et al.*, 1994*a*), and the bond lengths and angles as well as the conformation observed in the present structures correspond well to the most abundant and therefore presumably most stable conformation of this cation.

It is evident from Fig. 3 that the conformation of the lactate ion in the two salts is significantly different, as exemplified by the torsion angle O1—C1—C2—C3 being 87.55 (11)° in ($R$-PEA)($S$-LA) and 121.36 (9)° in ($S$-PEA)($S$-LA)·$H_2O$. This difference in the conformation of the lactate ion projects into the bond lengths and angles (Table 3), which vary much more than is the case for the cation, with the O3—C2—C3 angle being the most prominent example. The variation of the C—O distances of the carboxylate group is also noteworthy. The C—O distance involving the O1 oxygen adjacent to the alcohol group is the shortest in the $R$-PEA salt and the longest

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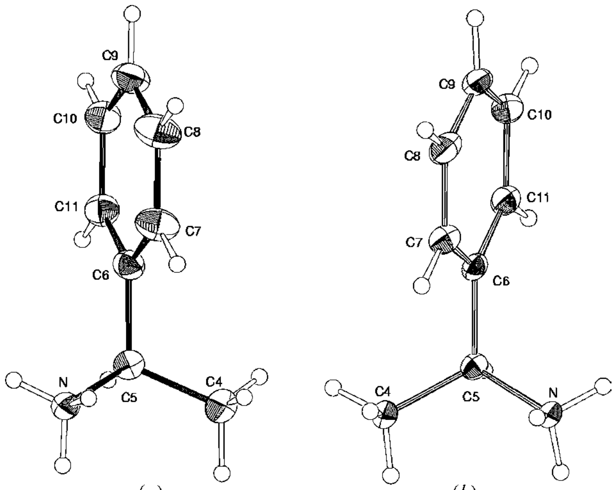
[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS0096). Services for accessing these data are described at the back of the journal.

**Table 2**
Geometry of the 1-phenylethylammonium ions (units are Å and °).

| | (*R*-PEA)(*S*-LA) | (*S*-PEA)(*S*-LA)·$H_2O$ |
|---|---|---|
| N—C5 | 1.5009 (12) | 1.4999 (12) |
| C4—C5 | 1.5227 (15) | 1.5213 (13) |
| C5—C6 | 1.5171 (13) | 1.5164 (13) |
| C6—C7 | 1.3883 (16) | 1.3985 (15) |
| C7—C8 | 1.3939 (16) | 1.3920 (16) |
| C8—C9 | 1.3845 (18) | 1.3909 (18) |
| C9—C10 | 1.3834 (17) | 1.3868 (19) |
| C10—C11 | 1.3944 (15) | 1.3963 (17) |
| C11—C6 | 1.3904 (15) | 1.3942 (13) |
| | | |
| N—C5—C4 | 109.70 (8) | 108.98 (7) |
| N—C5—C6 | 109.65 (8) | 109.43 (8) |
| C4—C5—C6 | 112.75 (8) | 113.96 (8) |
| C5—C6—C7 | 121.46 (9) | 121.41 (8) |
| C6—C7—C8 | 120.68 (11) | 120.52 (10) |
| C7—C8—C9 | 120.13 (11) | 120.25 (11) |
| C8—C9—C10 | 119.84 (10) | 119.68 (10) |
| C9—C10—C11 | 119.77 (11) | 120.14 (10) |
| C10—C11—C6 | 120.99 (10) | 120.64 (11) |
| C11—C6—C7 | 118.58 (9) | 118.77 (9) |
| C11—C6—C5 | 119.95 (9) | 119.82 (9) |
| | | |
| N—C5—C6—C7 | 62.03 (13) | −73.20 (10) |
| N—C5—C6—C11 | −118.51 (10) | 106.21 (10) |
| C4—C5—C6—C7 | −60.50 (13) | 49.08 (12) |
| C4—C5—C6—C11 | 118.96 (11) | −131.51 (9) |

in the *S*-PEA salt as a consequence of the hydrogen-bonding interactions (Tables 4 and 5). The variations in the geometry of the lactate ion are due to the differences in intermolecular interactions in the two salts. The stereo pairs in Fig. 4 illustrate the packing in the two salts. Stacking of phenyl groups and hydrogen bonding appear to be factors important for the crystal packing. Both crystal structures show a similar arrangement of the phenyl groups as shown in Fig. 4. Phenyl groups related by the symmetry of a twofold screw axis form a herringbone arrangement with almost perpendicular rings. The interatomic distances are all larger than the sum of the van der Waals radii. We conclude that the differences in the interactions of the phenyl groups cannot account for the energy difference.



(*a*) (*b*)

**Figure 2**
1-Phenylethylammonium ions for (*a*) *R*-PEA and (*b*) *S*-PEA.

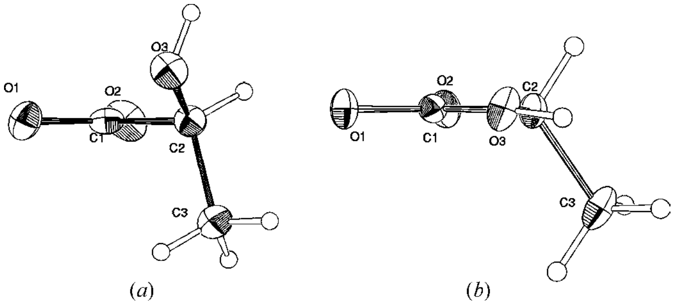
**Table 3**
Geometry of the lactate ions (units are Å and °).

| | (*R*-PEA)(*S*-LA) | (*S*-PEA)(*S*-LA)·$H_2O$ |
|---|---|---|
| O1—C1 | 1.2488 (13) | 1.2676 (12) |
| O2—C1 | 1.2677 (12) | 1.2527 (12) |
| C1—C2 | 1.5283 (14) | 1.5335 (13) |
| C2—C3 | 1.5207 (14) | 1.5312 (13) |
| O3—C2 | 1.4233 (12) | 1.4113 (12) |
| | | |
| O1—C1—O2 | 124.90 (10) | 124.47 (9) |
| O1—C1—C2 | 119.15 (9) | 118.06 (8) |
| O2—C1—C2 | 115.95 (9) | 117.47 (8) |
| C1—C2—C3 | 109.24 (8) | 109.80 (8) |
| C1—C2—O3 | 111.00 (8) | 109.24 (7) |
| O3—C2—C3 | 108.82 (9) | 111.66 (8) |
| | | |
| O1—C1—C2—O3 | −32.44 (12) | −1.40 (11) |
| O1—C1—C2—C3 | 87.55 (11) | 121.36 (9) |
| O2—C1—C2—O3 | 148.46 (8) | 179.47 (8) |
| O2—C1—C2—C3 | −91.55 (11) | −57.76 (11) |

The features of the hydrogen-bond interactions are listed in Tables 4 and 5. In both structures, the hydroxy group is connected to the carboxylate group of another lactate ion, related either by the twofold screw axis along *b* in (*R*-PEA)(*S*-LA) or by translational symmetry along the 5.87 Å *b* axis in (*S*-PEA)(*S*-LA)·$H_2O$. In the latter salt, each cation is hydrogen bonded to two different anions and a water molecule. In (*R*-PEA)(*S*-LA), each cation is connected by hydrogen bonds to three different anions, and we note that the shortest N—H···O hydrogen bond has the largest N—H distance. One of the interactions is a bifurcated hydrogen bond to O3 and O1 of the same anion. The water molecule in the structure of (*S*-PEA)(*S*-LA)·$H_2O$ accepts a proton from a cation and serves as a donor to two anions related by the twofold screw axis, making it well integrated into the crystal packing. The result is a more dense structure than that of the (*R*-PEA)(*S*-LA) salt (Table 1).

### 3.2. Relative stability of the diastereomeric salts

The resolution of the racemic 1-phenylethylamine in ethanol showed that the crystals precipitated first are exclusively (*R*-PEA)(*S*-LA) as verified by the powder diffraction experiments. The solubility experiments in acetonitrile confirmed that this salt is the less soluble, the solubility of (*S*-PEA)(*S*-LA)·$H_2O$ being twice as large. Furthermore the



(*a*) (*b*)

**Figure 3**
*S*-Lactate ions from the salt with (*a*) *R*-PEA and (*b*) *S*-PEA.

**Table 4**
Hydrogen bonds in (*R*-PEA)(*S*-LA).

| $D-\mathrm{H}$ | $A$ | $D-A$ (Å) | $D-\mathrm{H}$ (Å) | $\mathrm{H}-A$ (Å) | $D-\mathrm{H}-A$ (°) |
|---|---|---|---|---|---|
| N—H12*A* | O1$^{\mathrm{i}}$ | 2.8093 (12) | 0.898 (14) | 1.931 (13) | 166.5 (13) |
| N—H12*B* | O1 | 2.9234 (12) | 0.876 (16) | 2.234 (14) | 135.6 (12) |
| N—H12*B* | O3 | 2.9220 (12) | 0.876 (16) | 2.149 (14) | 147.0 (12) |
| N—H12*C* | O2$^{\mathrm{ii}}$ | 2.7670 (12) | 1.019 (17) | 1.757 (14) | 169.9 (14) |
| O3—H2O | O2$^{\mathrm{iii}}$ | 2.7037 (11) | 0.887 (15) | 1.831 (13) | 168.0 (13) |

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (ii) $x, y+1, z$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$.

**Table 5**
Hydrogen bonds in (*S*-PEA)(*S*-LA)·$H_2O$.

| $D-\mathrm{H}$ | $A$ | $D-A$ (Å) | $D-\mathrm{H}$ (Å) | $\mathrm{H}-A$ (Å) | $D-\mathrm{H}-A$ (°) |
|---|---|---|---|---|---|
| N—H12*A* | O2 | 2.7605 (12) | 0.893 (16) | 1.881 (15) | 167.6 (15) |
| N—H12*B* | O1$^{\mathrm{i}}$ | 2.8343 (13) | 0.890 (18) | 1.946 (17) | 174.4 (16) |
| N—H12*C* | O(aq)$^{\mathrm{ii}}$ | 2.7510 (13) | 0.875 (19) | 1.875 (17) | 176.9 (15) |
| O3—H2O | O2$^{\mathrm{iii}}$ | 2.7743 (16) | 0.87 (2) | 1.912 (18) | 173.4 (16) |
| O(aq)—H1(aq) | O1$^{\mathrm{iv}}$ | 2.8282 (12) | 0.850 (19) | 2.005 (18) | 163 (2) |
| O(aq)—H2(aq) | O1 | 2.7001 (12) | 0.82 (2) | 1.91 (2) | 152 (2) |

Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+2$; (ii) $x+1, y+\frac{1}{2}, -z+2$; (iii) $x, y+1, z$; (iv) $-x+2, y-\frac{1}{2}, -z+2$.

melting point of (*R*-PEA)(*S*-LA) is 52 K higher than that of (*S*-PEA)(*S*-LA)·$H_2O$; thus we conclude that (*R*-PEA)(*S*-LA) must be the thermodynamically more stable of the two diastereomeric salts.

(*R*-PEA)(*S*-LA) was obtained from an aqueous solution, whereas the hydrated and more soluble (*S*-PEA)(*S*-LA)·$H_2O$ was precipitated from 96% ethanol. This shows that the formation of the hydrated salt of (*S*-PEA)(*S*-LA) is very favourable in contrast to (*R*-PEA)(*S*-LA), which displays no tendency to form hydrates. In order to investigate the relative stability of (*S*-PEA)(*S*-LA)·$H_2O$ and (*S*-PEA)(*S*-LA), numerous unsuccessful attempts were carried out to prepare the unhydrated (*S*-PEA)(*S*-LA) to be able to determine $\Delta G^{\ominus}$ for the process

$$(S\text{-PEA})(S\text{-LA})\cdot\mathrm{H_2O(s)} \rightarrow (S\text{-PEA})(S\text{-LA})(\mathrm{s}) + \mathrm{H_2O(g)}$$

with

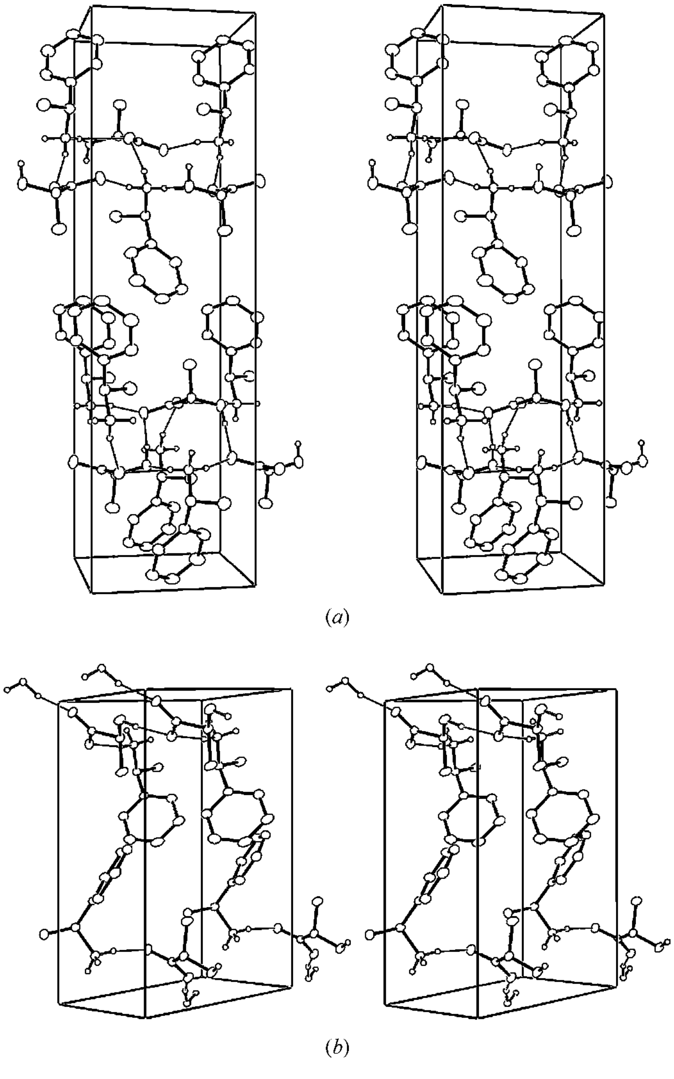
$$\Delta G^{\ominus} = -RT\ln[(p_{\mathrm{H_2O}})/(p^{\ominus})],$$

where $p_{\mathrm{H_2O}}$ is the equilibrium vapour pressure of water. Though we have been unable to obtain (*S*-PEA)(*S*-LA) in a pure form, the desiccator experiments unambiguously showed that the equilibrium pressure for the above reaction is less than the vapour pressure of water at room temperature. Using the vapour pressure of $H_2O$ at 293.15 K (17.535 mm Hg), it can be deduced that $\Delta G^{\ominus}$ is larger than 9 kJ mol$^{-1}$. The DSC traces in Fig. 1 show that (*S*-PEA)(*S*-LA)·$H_2O$ melts just as sharply as the unhydrated (*R*-PEA)(*S*-LA), and that the melting of (*S*-PEA)(*S*-LA)·$H_2O$ is not associated with a loss of water and subsequent melting of the unhydrated salt, which explains our difficulties of obtaining the unhydrated salt. This leads us to conclude that (*S*-PEA)(*S*-LA)·$H_2O$ is much more stable than the unhydrated (*S*-PEA)(*S*-LA) and the relative stability of the three salts is as follows:

$$(R\text{-PEA})(S\text{-LA}) > (S\text{-PEA})(S\text{-LA})\cdot\mathrm{H_2O} > (S\text{-PEA})(S\text{-LA}).$$

### 3.3. Significance of crystal water on the solubility of diastereomeric salts

The observation that the hydrated salt is the more soluble was not expected because, in a previous investigation of the diastereomeric mandelate salts of 2-hydroxy-1-phenylethylamine (Larsen *et al.*, 1994*b*), we found the hydrated form to be less soluble. Also, in this system the hydrated salt was the more densely packed, thus the solubility differences cannot be related to the difference in density. To examine these aspects further, a search was initiated for other diastereomeric salt pairs with known structures where only one of them is hydrated. The characteristics of the seven systems we extracted from the literature are listed in Table 6. Introducing water molecules into the structure results in a larger number


(*a*)

(*b*)

**Figure 4**
Stereo diagrams showing crystal packing in (*a*) (*R*-PEA)(*S*-LA) viewed along the *a* axis and (*b*) (*S*-PEA)(*S*-LA)·$H_2O$ viewed along the *ab* diagonal.

**Table 6**
Comparison of diastereomeric salts pairs (where one is hydrated).

| Compound | Solubility | $D_x$ (g cm$^{-3}$) |
|---|---|---|
| *R*-1-Phenylethylammonium *S*-lactate | Less | 1.213 |
| *S*-1-Phenylethylammonium *S*-lactate$\cdot H_2O$ | More | 1.251 |
| *R*-2-Hydroxy-1-phenylethylammonium *R*-mandelate$\cdot H_2O$† | Less | 1.356 |
| *S*-2-Hydroxy-1-phenylethylammonium *R*-mandelate† | More | 1.299 |
| D-Leucine *S*-(−)-1-phenylethanesulfonic acid$\cdot H_2O$‡ | Less | 1.285 |
| L-Leucine *S*-(−)-1-phenylethanesulfonic acid‡ | More | 1.313 |
| (1*R*,2*S*)-2-Amino-1,2-diphenylethanol *R*-2-phenylbutanoic acid$\cdot H_2O$§ | Less | 1.197 |
| (1*R*,2*S*)-2-Amino-1,2-diphenylethanol *S*-2-phenylbutanoic acid§ | More | 1.207 |
| (−)-Phosphorinane (−)-ephedrine¶ | Less | 1.29 |
| (−)-Phosphorinane (+)-ephedrine$\cdot H_2O$†† | More | 1.26 |
| BRINAM‡‡ | Less | 1.414 |
| BRINAP (incl. 2 $H_2O$)‡‡ | More | 1.388 |
| DICLINAM‡‡ | Less | 1.334 |
| DICLINAP (incl. $H_2O$)‡‡ | More | 1.354 |
| (1*R*,2*S*)-2-Amino-1,2-diphenylethanol *S*-2-(*p*-tolyl)butanoic acid$\cdot H_2O$§ | Comparable | 1.146 |
| (1*R*,2*S*)-2-Amino-1,2-diphenylethanol *R*-2-(*p*-tolyl)butanoic acid§ | Comparable | 1.182 |

† Larsen *et al.* (1994*b*). ‡ Yoshioka *et al.* (1998). § Kinbara *et al.* (1998). ¶ Garcia-Granda *et al.* (1988). †† Kok *et al.* (1988). ‡‡ Leusen *et al.* (1992).

of hydrogen bonds. However, as is apparent from Table 6, this does not necessarily lead to the more stable and less soluble diastereomeric salt; in fact, the hydrated salts fall almost evenly between the less and the more soluble salts.

### 3.4. Origins of the solubility differences between the two diastereomeric lactate salts

The solubility measurements for the two diastereomeric salts of 1-phenylethylamine and lactic acid showed that the solubility of (*R*-PEA)(*S*-LA) was about half that of (*S*-PEA)(*S*-LA)$\cdot H_2O$. This difference, which enables an efficient separation of the two diastereomeric salts, corresponds to a difference between the $\Delta G^\ominus$ values for the solubility process of the two salts that is less than 2 kJ mol$^{-1}$. It is noteworthy that the accuracy of most of the experimental and theoretical methods one would apply to investigate the physicochemical characteristics of the optical resolution process is of the same order of magnitude. With this in mind, we have investigated the two crystal structures to achieve at least a qualitative understanding of the factors responsible for the solubility differences. The difference in the $\Delta G^\ominus$ values must have its origin in the enthalpy and/or the entropy difference for the solubility process of the two salts.

The difference in enthalpy is related to differences in the energy of the entities forming the crystal and to differences in their interaction energy. The 1-phenylethylammonium ion is very similar in the two salts and can be assumed to be of similar energy. The conformation and geometry of the lactate ion is, however, different in the two salts. An inspection of the lactate ions in Fig. 3 suggests that the one in (*S*-PEA)(*S*-LA)$\cdot H_2O$, which is more eclipsed, has a higher energy. In order to obtain an estimate of this difference, Hartree–Fock theoretical calculations were conducted for the lactate ion as found in the two crystal structures. Using the energy of the geometry-optimized structure of the lactate ion where the O—H group points towards the carboxylate group to form an intramolecular hydrogen bond as a reference, the relative energies of the lactate ions are 83.86 kJ mol$^{-1}$ for (*R*-PEA)(*S*-LA) and 89.41 kJ mol$^{-1}$ for (*S*-PEA)(*S*-LA)$\cdot H_2O$. This confirms that the lactate ion in the less soluble salt has the lower energy, with an energy difference that could more than account for the difference in solubility. The less favourable conformation adopted by the lactate ion in (*S*-PEA)(*S*-LA)$\cdot H_2O$ is likely to be an effect of the hydrogen-bond interactions. All possible donor atoms are engaged in hydrogen bonds in both salts. From the length (strength) and number of hydrogen bonds we would predict that these interactions are stronger in the more soluble salt. This is supported by the fact that the melting enthalpy of (*S*-PEA)(*S*-LA)$\cdot H_2O$ is 10 kJ mol$^{-1}$ higher than that of (*R*-PEA)(*S*-LA). However, these measurements do not provide a numerical measure for the differences in the interaction energies.

The difference in entropy should not be neglected in the discussion of the factors that influence the solubility of the two salts. It is noteworthy that the entropy difference has the opposite effect of the enthalpy difference, *i.e.* the crystal with the higher entropy would be the less soluble. A comparison of the two salts shows that the less soluble is also the less dense. One would associate a less dense structure with a less ordered (higher entropy) one. Consistent with this, the average ratio between the non-hydrogen $U_{\rm eq}$ values of (*R*-PEA)(*S*-LA) and (*S*-PEA)(*S*-LA)$\cdot H_2O$ is 1.33 (14).

Based on the above analysis, we propose that the difference in solubility between the two diastereomeric lactate salts is related to packing effects, where the higher energy of the lactate ion in the more soluble (*S*-PEA)(*S*-LA)$\cdot H_2O$ salt dominates over the increased stability exerted by the water molecules in the structure, and to the higher entropy of the less dense and less soluble (*R*-PEA)(*S*-LA) salt.

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