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Effects of crystallization in the presence of the opposite enantiomer on the crystal properties of (SS)-(+)-pseudoephedrinium salicylate

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Abstract

Previous work (*Int. J. Pharm.*, 94 (1993) 171–179) with (RS)-(−)-ephedrinium 2-naphthalenesulfonate, which forms a racemic compound with its opposite enantiomer, has shown that crystallization of the homochiral crystal (host) from aqueous solution containing traces of the opposite enantiomer (guest) leads to uptake of the guest with significant changes in various thermodynamic properties, including an increase in the intrinsic dissolution rate (IDR), perhaps through lattice disruption. The present work tests this possibility with a different but related chiral drug, (SS)-(+)-pseudoephedrinium salicylate, which forms a racemic conglomerate, instead of a racemic compound, with its opposite enantiomer. Increasing concentrations of the guest in the aqueous crystallization solution led to its increasing incorporation into the host crystals, corresponding to a segregation coefficient of 0.24. With increasing mole fraction, x_2, of the guest in the crystals, the IDR of the compacts increased to a maximum (12% increase at $x_2 = 0.0076$) and then decreased. Meanwhile, with increasing x_2, the enthalpy of fusion, ΔH^f, entropy of fusion, ΔS^f, and enthalpy of solution, ΔH^s, decreased to minima (4–5% decreases at $x_2 = 0.0028$), suggesting disruption of the crystal lattice of the host and an increase in lattice strain, and then increased, suggesting a release of lattice strain. The water content (0.006 mole fraction) and melting point (405.2 ± 1.2 K) were not significantly affected. The change in the free energy of solution, estimated from the IDR, was approximately linearly related to the calorimetric ΔH^s, suggesting enthalpy-entropy compensation. ΔS^f and ΔS^s decreased linearly with increasing ideal entropy of mixing, corresponding to values of 24.7 and 21.4, respectively, for the 'disruption index' (*Int. J. Pharm.*, 25 (1985) 57–72, 28 (1986) 103–112). These relatively high values indicate significant disruption of the crystal lattice of the host, suggesting potentiation of crystal defects by the incorporated guest.

Keywords: Chiral; Enantiomeric impurity; Crystallization; Segregation coefficient; Enthalpy of fusion; Entropy of fusion; Enthalpy of solution; Entropy of solution; Disruption index; Intrinsic dissolution rate; (SS)-(+)-Pseudoephedrinium salicylate; Enthalpy-entropy compensation

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1. Introduction

Crystallization is still the main method for the resolution of racemic forms (Jacques et al., 1981) and the purification of enantiomers, while the opposite enantiomer is always present as an impurity in the crystallization medium. The enantiomeric impurity may first be adsorbed onto certain surface sites on specific faces of the crystals and may eventually become occluded in the crystal resulting in an anisotropic distribution of the impurity in the crystal (Addadi et al., 1986). This occlusion results in the formation of a solid solution and a decrease in the overall symmetry of the crystals (Weissbuch et al., 1983). Although the existence of continuous solid solutions in the crystals of chiral substances is well recognized (Jacques et al., 1981), the existence of terminal solid solutions is not yet completely understood (Duddu et al., 1993). The interactions between the opposite enantiomers in the solid state, which determine the crystalline nature of the racemic form (i.e. whether it is a racemic compound or a racemic conglomerate) may also influence the formation of terminal solid solutions, as well as the nature and extent of disorder produced by the enantiomeric impurity in a homochiral crystal.

The guidelines of the Food and Drug Administration (FDA) consider even the opposite enantiomer to be an impurity in a chiral drug, because the impurity may have significant pharmacological and toxicological effects (De Camp, 1989). Our previous study (Duddu et al., 1991) has demonstrated that (SS)-(+)-pseudoephedrine from various suppliers and, indeed, different lots from the same supplier, contain varying quantities of the enantiomeric impurity. Furthermore, the enantiomeric impurity, even when present at less than 0.0025 mole fraction, was found to significantly alter the physicochemical properties of homochiral (RS)-(−)-ephedrinium 2-naphthalenesulfonate, (−)-EN, which forms a crystalline racemic compound with its opposite enantiomer (Duddu et al., 1993).

The present study reports the effect of the opposite enantiomer on the crystal properties of (SS)-(+)-pseudoephedrinium salicylate, (+)-PS. The racemic species formed from the enantiomers of PS is a racemic conglomerate, i.e. a physical mixture of the crystals of the individual enantiomers (Duddu, 1993; Duddu and Grant, 1994). The crystal structure of (+)-PS (and therefore of (−)-PS) has been determined by single crystal X-ray diffraction (Duddu and Grant, 1994). On the other hand, the stable crystalline racemic species formed from the enantiomers of the previously reported system (EN, Duddu et al., 1993) is a racemic compound, which contains equal proportions of the two opposite enantiomers in the unit cell of the crystal. However, the crystal structures of the homochiral and racemic EN have not yet been determined. With this background, the objectives of the present study are: (1) to compare the effects produced by the opposite enantiomer on the properties of (+)-PS crystals, with those observed on the (−)-EN crystals, in an effort to explore and to understand the changes produced by the opposite enantiomers in homochiral crystal systems, and (2) to examine whether any changes produced in the physicochemical properties are related to the preference of an enantiomer to interact with itself or with the opposite enantiomer, a factor that is most likely to determine whether the racemic form exists as a conglomerate or as a racemic compound.

2. Materials and methods

2.1. Materials

(RR)-(−)- and (SS)-(+)-pseudoephedrine hydrochloride were obtained from Sigma Chemical Company (St. Louis, MO). Sodium salicylate was obtained from Aldrich Chemical Company (Milwaukee, WI). Each pseuoephedrinium salicylate enantiomer was prepared by mixing equimolar aqueous solutions of the corresponding hydrochloride salt and sodium salicylate. The product was purified by two successive crystallizations from HPLC grade water (J.T. Baker Inc., Phillipsburg, NJ) and was filtered and dried over anhydrous calcium sulfate (Drierite, W.A. Hammond Drierite Company, Xenia, OH) prior to the crystallization experiments. All solvents, including water, were of HPLC grade.

2.2. Methods

2.2.1. Batch crystallization of (+)-PS

Crystals of (+)-PS were obtained by cooling 150 ml of hot, supersaturated aqueous solutions (0.330 M) in a three-neck flask to which various concentrations (ranging from 0 to 16.5×10^{-3} M) of the opposite enantiomer, (−)-PS, had been added. The solution containing (+)-PS and the added enantiomeric impurity (guest) at 60°C was cooled to 40°C at a rate of 0.2°C/min while being stirred at a rate of 200 rev./min. The solution at this stage was clear and supersaturated with respect to (+)-PS. To the solution at 40°C, 5 mg of seed crystals (passing through 200 mesh, < 75 μm) of (+)-PS were added. The solution was then cooled at the same rate and at the same stirring speed to 25°C and maintained at that temperature for 30 min. The slurry was quickly filtered through a 0.25 μm filter under reduced pressure. The crystals were washed with water and spread on a glass Petri dish. Subsequently, the crystals were air-dried at 40°C overnight and then over anhydrous calcium sulfate at 22°C for 72 h before use.

2.2.2. Differential scanning calorimetry (DSC)

The enthalpy (heat) of fusion, melting point and the entropy of fusion of the samples were determined using a Du Pont 910 differential scanning calorimeter equipped with a data station (Thermal Analyst 2000, TA Instruments, New Castle, DE). The temperature axis and the cell constant were calibrated using indium (10 mg, 99.99%, peak maximum at 156.6°C and heat of fusion 28.4 J/g). Samples (3 ± 0.1 mg, 106–125 μm) in open aluminum pans were heated at a rate of 10°C/min.

2.2.3. Solution calorimetry (SC)

The enthalpy (heat) of solution of doped and undoped samples (200 mg) of (+)-PS in water was determined using a Parr solution calorimeter (Model 1451, Parr Instruments, Moline, IL) equipped with a dual pen strip chart recorder (model 4523, Houston Instruments, Austin, TX) with an operating range of 1 mV to 2 V. The instrument was calibrated using an exothermic reaction between tris-(hydroxymethyl)aminomethane (TRIS, Parr Instruments, Moline, IL) and 0.1 M HCl.

2.2.4. Karl Fischer titrimetry (KFT)

The water content in the crystals was determined by Karl Fischer Titrimetry using a Mitsubishi Moisture Meter (Model CA-05, Mitsubishi Chemical Industries Ltd., Tokyo, Japan).

2.2.5. Intrinsic dissolution rate (IDR)

The intrinsic dissolution rate (the dissolution rate per unit surface area) of compacted discs was determined using the apparatus described by Doherty and York (1987), based on that of Collet et al. (1972). The compacts, 1 cm in diameter and of area 0.7854 cm^2, were prepared by weighing 150 mg of the powder into the sample holder, followed by compression under a hydraulic press (Carver Laboratory Press, Model C, Menomonie WI) at 187.5 MPa pressure for 90 s. The sample holder containing the compact was screwed into the center of the cell base so that a single face of the compact was exposed to 600 ml of distilled water which had been outgassed and equilibrated at 25 ± 0.2°C. Directly above the compact, a three-paddle stirrer was rotated at 50 rev./min by a synchronous motor (Slo Syn, Superior Electric Co., Bristol, CT). The samples were analyzed spectrophotometrically by measuring the absorbance at 294 nm.

Plots of the amount of (+)-PS dissolved against time were found to be linear over the first 45 to 60 min corresponding to about 40–50% dissolution of the compact. The slope of each plot, determined by linear regression of the data during the first 30 min of dissolution, while the surface of the compacts remained essentially flat and coplanar with the die, was used to calculate the intrinsic dissolution rate (IDR equals the slope/surface area of the compact). The relative residual standard deviations for triplicate measurements were less than 5%.

2.2.6. Liquid chromatographic analysis of the enantiomeric impurity

The relative amounts of enantiomeric impurity, (−)-PS, adsorbed onto the surface of the crystals

or occluded inside the crystals of (+)-PS in solid solution, were determined by slowly dissolving 50 mg of crystals, grown in the presence of 0.00165 M of (−)-PS (the maximum concentration employed) and placed on a 0.25 μm filter in a glass column, in a stream of 2-propanol flowing downwards at 100 μl/min (Duddu et al., 1993; also cf. Go and Grant, 1987). At 5-min time intervals the effluent and 5-mg samples of the residual crystals were analyzed for (−)-PS by means of the chiral high performance liquid chromatographic (HPLC) method of Doyle et al. (1986), with (R)-*N*-(3,5-dinitrobenzoyl)- phenylglycine as the chiral stationary phase and hexane/2-propanol/acetonitrile 90:9:1 (v/v/v) as the mobile phase. This method provided baseline separation of the two enantiomers ($k' = 7.98$ for (−)-PS, $k' = 9.28$ for (+)-PS) at a chromatographic flow rate of 2 ml/min and at a detection wavelength of 254 nm.

Fig. 1 shows the time plot of the mole fraction of (−)-PS (moles of (−)-PS/[moles of (+)-PS + moles of (−)-PS]) in the effluent and in the residual crystals. The relatively high mole fraction of (−)-PS in the effluent corresponds to the (−)-PS adsorbed onto the surface of the crystals

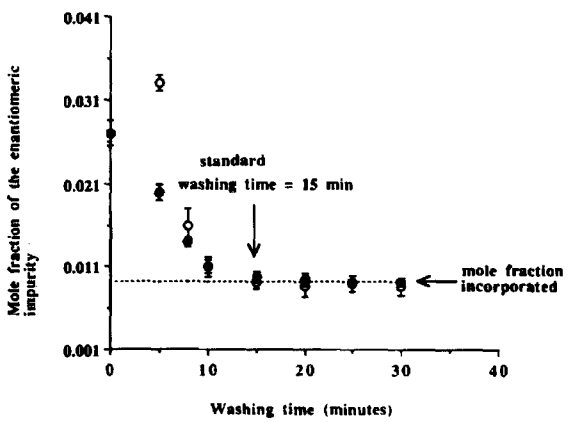

Fig. 1. Time plot of the enantiomeric impurity in the effluent (open circles) and in the doped crystals of (SS)-(+)-pseudoephedrinium salicylate during dissolution in 2-propanol. The doped crystals were obtained by crystallization from a solution containing the opposite enantiomer at a concentration of 16.5×10^{-3} M. The vertical bars represent standard errors of the respective means ($n = 3$).

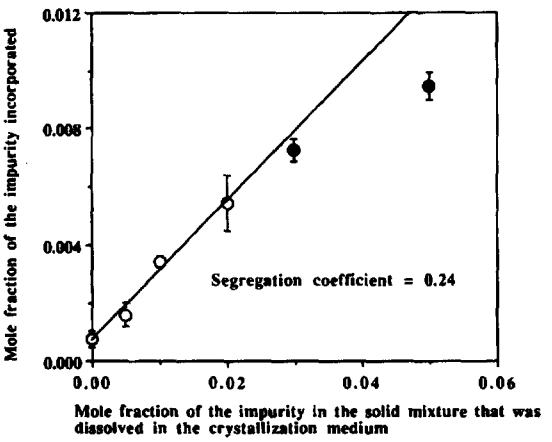

Fig. 2. Plot of the mole fraction of the opposite enantiomer incorporated into the crystals vs. the mole fraction of present in the solute mixture dissolved in the crystallization medium ($r = 0.991$). The vertical bars represent standard errors of the respective means ($n = 3$). The closed circles represent the data points exhibiting deviation from linearity.

(65–70%). The lower, constant mole fraction of (−)-PS in the effluent and in the crystals after 10 min (two-tailed t-test, $P > 0.05$) corresponds to that uniformly incorporated inside the crystals as a solid solution. Therefore, throughout this report (e.g. Figs. 2–6) the mole fraction of (−)-PS incorporated inside the (+)-PS crystals as a solid solution was determined by first washing the crystals with 2-propanol for 15 min to remove any (−)-PS that had been adsorbed onto the surface of the crystals during the crystallization, harvesting and/or the drying processes.

2.2.7. Statistical analysis

All data were analyzed by ANOVA ($\alpha = 0.05$). Individual means were compared by Bonferroni procedure ($\alpha = 0.05$) for multiple comparison in a completely randomized design.

3. Results and discussion

The plot of the mole fraction of the enantiomeric impurity (the guest) incorporated in solid solution versus the mole fraction present in the

mixture of solids dissolved in the crystallization medium (Fig. 2) shows that a significant mole fraction (approximately 10^{-3} to 10^{-2}) of the enantiomeric impurity (the guest) was progressively taken up into solid solution by the crystals of (+)-PS (the host) with increasing concentration of the guest in the crystallization medium. However, when the mole fraction of the impurity incorporated into the crystals exceeded about 0.005, Fig. 2 shows a deviation from linearity, suggesting an approach towards a solid solubility limit. The non-zero intercept value (0.0008 mole fraction) in Fig. 2 suggests that even the undoped crystals contained a trace quantity of the opposite enantiomer. This further emphasizes the fact that enantiomerically pure crystals are the exception rather than the rule and that homochiral crystals usually contain trace quantities of the opposite enantiomer as an impurity (Duddu et al., 1993). Further recrystallization did not completely eliminate this impurity from the crystals.

Although the plot in Fig. 2 appears slightly non-linear, we treat the first four data points as linear, corresponding to a limiting law. Linear regression of the first four data points in Fig. 2 affords a slope of 0.24, which gives the segregation coefficient, $k = 0.24$ (95% confidence interval 0.15–0.33). The mole fraction of water in the crystals was found to be 0.006 (0.04% w/w) independent of the concentration of the enantiomeric impurity, as observed with (−)-EN when doped with its opposite enantiomer (Duddu et al., 1993).

With increasing mole fraction of the enantiomeric guest in the crystals, the enthalpy of fusion, ΔH^f, of the crystals of (+)-PS decreased to a minimum indicating an increase in energy of the crystal lattice and an increase in the lattice strain (Fig. 3a). The melting point (T_m, 405.2 ± 1.2 K) was not significantly affected ($P > 0.05$). Thus, the resulting entropy of fusion ($\Delta S^f = \Delta H^f / T_m$) decreased to a minimum indicating an increase in crystal disorder (Fig. 3b). This increase in disorder and the corresponding increase in energy resulting from the increase in the uptake of the guest is probably a result of an increase in the concentration and the disruptive influence of crystal defects. The decreases in ΔH^f and ΔS^f from the values corresponding to those of the undoped samples (Fig. 3a and Fig. 3b) were statistically significant ($P < 0.05$) when $0.0014 \leq x_2 \leq 0.0028$, where x_2 is the mole fraction of the guest incorporated into the crystals of the host. Minimum values of ΔH^f and ΔS^f, corresponding to reductions of about 4.6%, were reached at $x_2 = 0.0028$. At higher concentrations of the guest in the crystals, the enthalpy and entropy of fusion increased, indicating a return of the crystal energy and entropy towards the undoped values and suggesting a relaxation of lattice strain. Similar behavior was observed when (−)-EN was doped with its opposite enantiomer (Duddu et al., 1993),

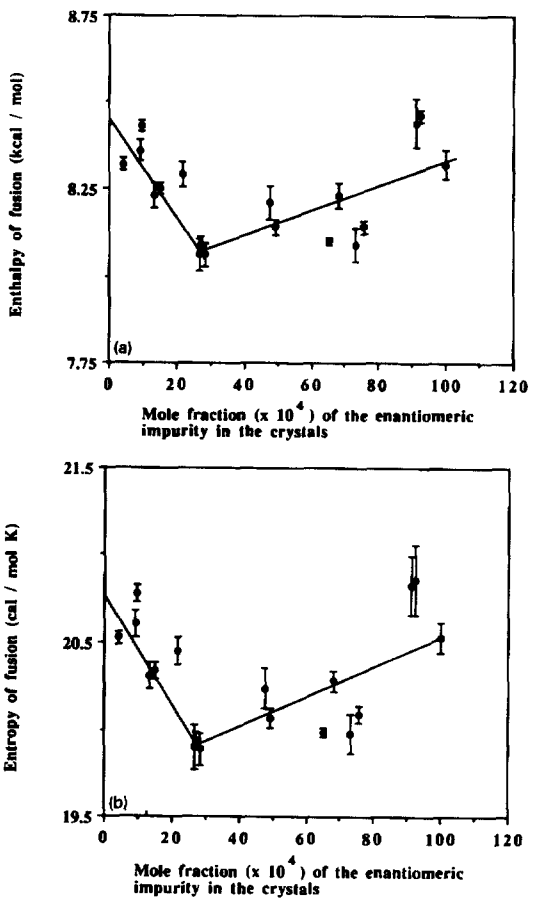

Fig. 3. Plot of (a) enthalpy of fusion and (b) entropy of fusion of (SS)-(+)-pseudoephedrinium salicylate vs. the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent the standard errors of the respective means ($n = 3$).

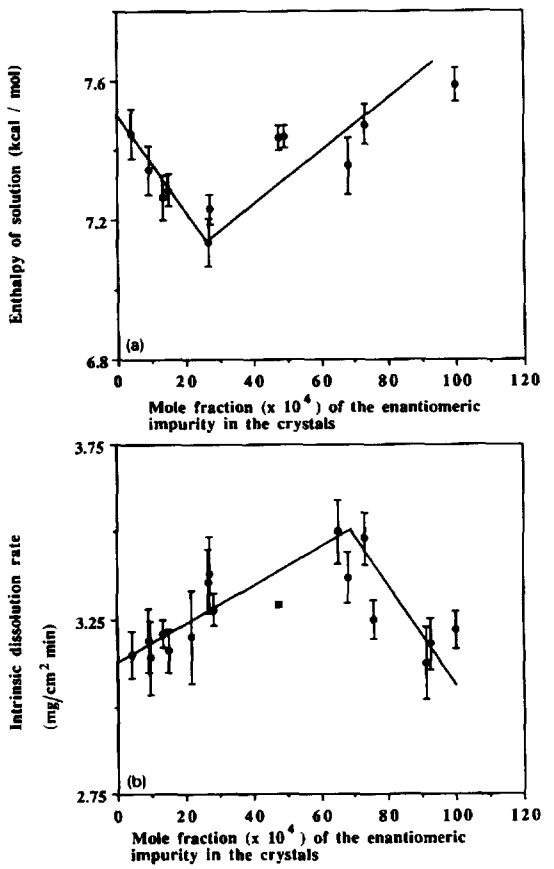

Fig. 4. Plot of (a) enthalpy of solution and (b) intrinsic dissolution rate of (SS)-(+)-pseudoephedrinium salicylate vs. the mole fraction of the enantiomeric impurity in the crystals. The vertical bars represent the standard errors of the respective means ($n = 3$).

and when adipic acid was doped with fatty acid impurities (Chow et al., 1984), for which analogous explanations have been offered.

With increasing uptake of the guest, the enthalpy of solution, ΔH^s, of the crystals (Fig. 4a) followed a pattern almost identical to that for ΔH^f (Fig. 3a), and so the explanation offered is the same as in the previous paragraph. The decreases in ΔH^s from the values corresponding to those of the undoped samples were statistically significant ($P < 0.05$), when $0.0014 \leq x_2 \leq 0.0028$. A minimum value of ΔH^s, corresponding to a reduction of about 5%, was reached at $x_2 = 0.0028$. At higher mole fractions of the enantiomeric impurity, the enthalpy of solution became more endothermic, suggesting a relaxation of the lattice strain. Although the exact reason for a relaxation of lattice strain at higher concentrations of the guest is unknown, the observation suggests a common underlying mechanism even in various structurally dissimilar systems (Grant and York, 1986; Duddu et al., 1993). The following possible mechanisms are proposed. (a) The guest molecules may be aggregating in certain regions of the crystal to produce inclusions, i.e. pockets, rich in the guest by a process akin to phase separation. (b) The guest molecules may be migrating to the surface by an analogous process. (c) The crystal defects arising from the guest molecules may reach a sufficiently high concentration so as to form a superlattice with reduced energy and entropy. In this situation the crystal defects will lock each other into definite positions in the crystal lattice and their motions will be mutually impeded. Each of the above mechanisms (a–c) will probably occur more rapidly by recrystallization in contact with the mother liquor before harvesting the crystals than by molecular processes in the dried crystals for which the activation energy will be much higher. By means of solid state nuclear magnetic resonance spectroscopy, including measurements of relaxation times, it is hoped to gain insight into the mechanism(s) involved.

An increase in x_2 from 0 to 0.0075 led to an increase in the intrinsic dissolution rate (IDR) of (+)-PS crystals (Fig. 4b). Although the IDR values at $x_2 \leq 0.0048$ were not statistically significantly different from those of the undoped samples, the differences were statistically significant at higher uptake of the guest ($0.0048 \leq x_2 \leq 0.0076$). The increase in IDR at these levels of doping may be attributed to an increase in the Gibbs free energy of the crystals arising from an increase in the concentration of crystal defects. A maximum value of IDR, corresponding to a 12% increase, was reached at $x_2 = 0.0076$. Further incorporation of the enantiomeric impurity led to a decrease in the IDR of (+)-PS. This decrease is in contrast to our previous study with the (−)-EN system for which the IDR increases to a plateau (Duddu et al., 1993). This difference sug-

gests that the distribution of the enantiomeric impurity within the crystal lattice may be different in the two types of chiral crystals, (+)-PS and (−)-EN.

A possible explanation for this difference in the distribution of guest can be offered by comparing the nature of the melting point phase diagrams of the respective enantiomers of the two types of chiral crystals. The thermodynamically stable crystalline racemic form from the EN enantiomers is a racemic compound, whereas that from the PS enantiomers it is a racemic conglomerate (Duddu, 1993; Duddu and Grant, 1994). These observations suggest that the interaction between the opposite enantiomers, and the formation of a centrosymmetric racemic structure involving both the enantiomers, are favored by EN, while the interaction between molecules of same chirality, and the formation of a homochiral crystal structure, are favored by PS.

As discussed above, Fig. 1 indicates that the enantiomeric guest, at lower concentrations, is incorporated primarily into the bulk of the lattice of (+)-PS leading to lattice disruption and to an increase in IDR. At higher concentrations, the impurity may exist as tiny crystallites trapped on the surface of the host crystals. Similarly, Matsuoka et al. (1990) reported the existence of tiny crystallites of the enantiomeric impurity trapped on enantiomerically pure crystals of L-threonine, which also forms a racemic conglomerate as the thermodynamically stable racemic species. In the present study, even the maximum concentration of the guest added to the crystallization medium (16.5×10^{-3} M) is well below its equilibrium solubility value (0.15 M in water at 25°C) and hence the guest is unlikely to crystallize along with the host crystals. However, after filtration and during drying for 72 h, slow evaporation of the solvent from the mother liquor adsorbed onto the crystals may lead to the crystallization of both enantiomers of PS. Since this process is expected to take place slowly over a longer time than that for the crystallization experiments (about 2 h), the crystals formed by slow solvent evaporation may have a higher enantiomeric purity, and hence may have a lower IDR, than the doped crystals of (+)-PS. This process may also explain why the IDR of (+)-PS exhibits a maximum and decreases at higher concentrations of the guest (Fig. 4b) and why the enthalpy of fusion (Fig. 3a), entropy of fusion (Fig. 3b), and enthalpy of solution (Fig. 4a) decrease to minima and then increase with increasing concentration of the incorporated guest. Since the stable racemic form in the case of our previously reported system, EN, is a racemic compound, the enantiomeric impurity at higher concentrations cannot exist as crystallites of the individual enantiomers and instead may exist as domains resembling the structure of the racemic compound. In the present system, it is interesting that the IDR increases, while ΔH^{f} and ΔH^{s} decrease. However, the maximum in the IDR (Fig. 4b) does not correspond to the minima in ΔH^{f} and ΔH^{s} (Fig. 3a and Fig. 4a).

The lines of best fit for the initial decrease and subsequent increase in the enthalpy of fusion (Fig. 3a), entropy of fusion (Fig. 3b), and enthalpy of solution (Fig. 4a), as the mole fraction of incorporated guest was increased, were drawn by simple regression analysis. An analogous procedure was employed to draw the lines of best fit for the initial increase and subsequent decrease in the IDR (Fig. 4b).

The changes in the thermodynamic properties of the host resulting from the incorporation of the guest can be quantified using the concept of 'disruption index' (York and Grant, 1985, Grant and York, 1986). The disruption index (d.i.), which is a measure of the rate of change of the difference between the entropy of the solid and that of the liquid, with respect to the ideal entropy of mixing of the host with the guest, can be evaluated from the enthalpy of fusion at the melting temperature (York and Grant, 1985) or from the enthalpy of solution and IDR data at room temperature (Grant and York, 1986). The negative slope of a plot of the entropy of fusion or the entropy of solution against the ideal entropy of mixing gives the 'disruption index' (d.i. $= b - c$) according to the following equations:

$$\Delta S^{f} = \Delta S^{fo} - (b - c)\Delta S^{id}_{mix} \quad (1)$$

$$\Delta S^{s} = \Delta S^{so} - (b - c)\Delta S^{id}_{mix} \quad (2)$$

The d.i. values obtained by these two methods will differ, when the process of heating the sample from 22°C to its melting temperature causes significant changes in the nature and concentration of the crystal defects. On the other hand, if the defects are much less sensitive to heating, the d.i. values will be similar.

Since fusion at the melting point is an equilibrium process, the free energy of fusion is zero. Therefore, the entropy of fusion is given by the heat of fusion divided by the melting temperature, all of which can be, and were, determined by DSC:

$$\Delta S^{f} = \Delta H^{f}/T_{m} \quad (3)$$

For mole fractions of the guest ≤ 0.0028, Fig. 5a shows that the disruption index estimated from the fusion data equals 24.7 (95% confidence interval 11.2–38.2), suggesting that the increase in disorder of the crystal lattice of the host is more than 20 times that expected for a random ideal solid solution of the guest in the host lattice.

The enthalpy of solution was measured at 295 K under non-equilibrium conditions (0 $\approx$ concentration $<$ solubility). Hence, the free energy for the solution process is not equal to zero. Therefore, calculation of the entropy of solution, ΔS^{s}, requires knowledge of both the free energy of solution and the enthalpy of solution according to Eq. (4).

$$\Delta S^{s} = \Delta H^{s}/T - \Delta G^{s}/T \quad (4)$$

While the enthalpy of solution, ΔH^{s}, was measured using a solution calorimeter, the standard free energy of solution, ΔG^{so}, can be obtained by measuring the metastable equilibrium solubility, C_s, of the solid phase. However, C_s of doped crystals is difficult to measure because the process of recrystallization during the equilibrium solubility measurement would lead to a reduction in ΔG^{so} towards that of the pure crystals. Grant and York (1986) suggested two possible approaches to measure the disruption index from the enthalpy of solution data.

The first approach involves an estimation of ΔG^{so} from the intrinsic dissolution rates, J, of the doped and undoped crystals. According to Noyes and Whitney (1897), under sink conditions,

$$J = kC_s \quad (5)$$

where k is the mass transfer coefficient for dissolution. Therefore,

$$\frac{J,\text{doped}}{J,\text{undoped}} = \frac{C_s,\text{doped}}{C_s,\text{undoped}} \quad (6)$$

From the measured J values of the doped and undoped crystals and from the equilibrium solubility value of the pure undoped crystals, the metastable equilibrium solubility value, C_s, of the doped crystals can be estimated from Eq. (6). Then, the standard free energy of solution is calculated from Eq. (7)

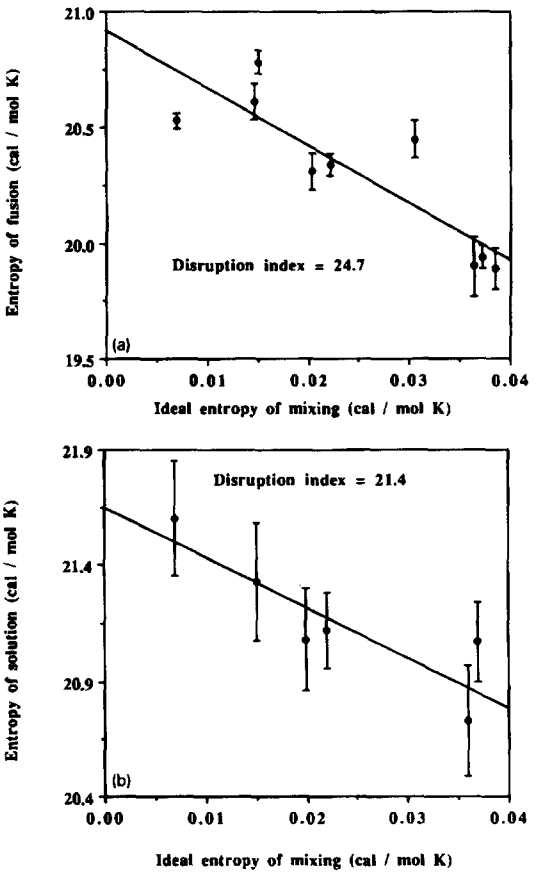

Fig. 5. Plot of (a) entropy of fusion and (b) entropy of solution of (SS)-(+)-pseudoephedrinium salicylate vs. the ideal entropy of mixing of (SS)-(+)-pseudoephedrinium salicylate with the enantiomeric impurity ($r = 0.862$ and $r = 0.872$, respectively). The vertical bars represent the standard errors of the respective means ($n = 3$).

$$\Delta G^{so} = -RT\ln C_s \quad (7)$$

The entropy of solution is calculated from the free energy of solution and the enthalpy of solution using Eq. (4).

The second approach suggested by Grant and York (1986) is to derive ΔS^s by assuming enthalpy-entropy compensation (Tomlinson, 1983; Vachon and Grant, 1987). If enthalpy-entropy compensation occurs, then

$$\delta(\Delta H^s) = \beta.\delta(\Delta S)^s \quad (8)$$

where β is a constant, termed the compensation temperature, which cannot usually be predicted. Since β is not necessarily the same as the temperature at which the ΔH^s is measured, Grant and York (1986) defined a pseudo-disruption index, p.d.i. $= b' - c'$, as follows:

$$T(b' - c') = \beta(b - c) \quad (9)$$

The p.d.i. can be calculated from the negative slope of a plot of $\Delta H^s/T$ vs. ideal entropy of mixing, according to Eq. (10):

$$\Delta H^s/T = \Delta H^{so}/T - (b' - c')\Delta S^{id_{mix}} \quad (10)$$

Eq. (9) implies that the value of p.d.i approximates d.i. when T approximates β. The p.d.i. equals d.i. when $T = \beta$. For a system obeying enthalpy-entropy compensation, a plot of ΔG against ΔH yields a straight line, the slope of which is $(1 - T/\beta)$ which affords the value of β (Vachon and Grant, 1987).

Enthalpy-entropy compensation in the present system was tested by plotting ΔG^{so}, determined according to Eq. (7), vs. ΔH^s (Fig. 6a). Although this plot is approximately linear (correlation coefficient, $r = 0.8$), the large deviations in the measurements yielded a wide 95% confidence interval (293–403) for the compensation temperature, $\beta = 342$ K. Since β (342 K) is larger than the T (295 K) by only 47 K, there is a significant enthalpy-entropy compensation at room temperature. However, the large confidence interval for β implies that any conclusions about enthalpy-entropy compensation can only be qualitative. Other pharmaceutical solid systems that obey enthalpy-entropy compensation have been reviewed by Tomlinson (1983), Vachon and Grant (1987) and Buckton (1990).

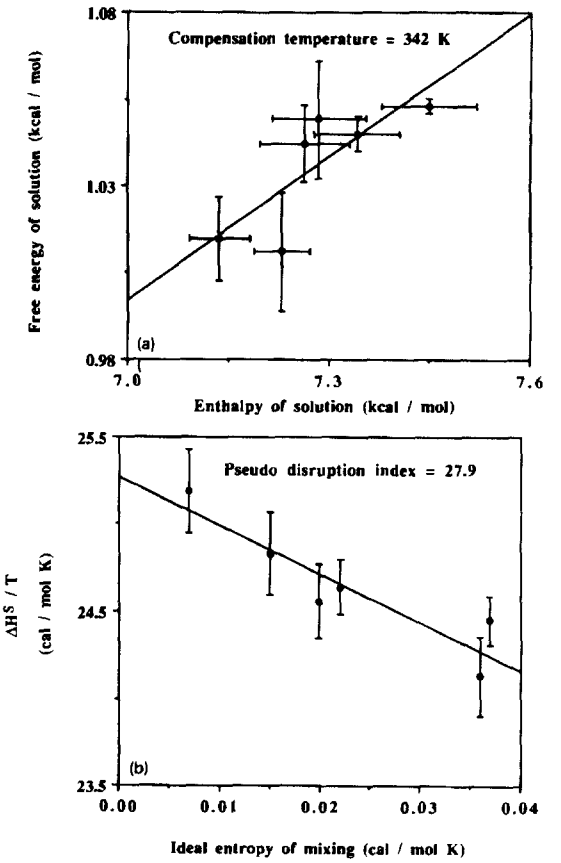

Fig. 6. Plot of (a) free energy of solution, ΔG^s, vs. enthalpy of solution, ΔH^s, of (SS)-(+)-pseudoephedrinium salicylate in water at 22°C ($r = 0.802$); (b) Plot of $\Delta H^s/T$ vs. the ideal entropy of mixing of (SS)-(+)-pseudoephedrinium salicylate with the enantiomeric impurity ($r = 0.918$). The vertical bars represent the standard errors of the respective means ($n = 3$).

Both the approaches described above were used to estimate values of the entropy of solution for the present system. Fig. 5b and Fig. 6b give the plots according to Eqs. (2) and (10) for the calculation of d.i. (21.4, 95% confidence interval 5.3–37.5) and p.d.i. (27.9, 95% confidence interval 11.2–44.6), respectively. Since the d.i. values obtained from ΔS^f (24.7) and ΔS^s (21.4 and 27.9) data are similar, the influence of the enantiomeric impurity on the nature and concentration of crystal defects is approximately the same at 298 K as at the melting point (405 K) and is therefore relatively insensitive to heating. A comparison of

the d.i. values calculated from ΔS^f and ΔS^s for a variety of systems (Grant and York, 1986) indicates that, although the d.i. value calculated from the ΔS^s data is usually larger than the d.i. value calculated from ΔS^f data, the values are comparable for adipic acid when doped with undecanoic acid. A more fundamental understanding of the actual nature of defects produced by various impurities is required before any further explanation can be offered for this behavior. The d.i. value (21.4) from the ΔS^s data and the p.d.i. value (27.9) from the ΔH^s data alone are found to be similar, further emphasizing that enantiomeric doping of (+)-PS is accompanied by enthalpy-entropy compensation.

Similar d.i. values of approximately 20 observed at lower levels of enantiomeric doping ($x_2 \leq 0.0028$) for both (−)-EN (Duddu et al., 1993) and (+)-PS (in the present work) suggest that the enantiomeric impurities, when present in trace proportions, produce significant and comparable lattice disruption of the homochiral crystals of the host. The enantiomeric impurity in the crystals also produces significant changes in the physicochemical properties of the host, such as enthalpy of fusion, entropy of fusion, enthalpy of solution and intrinsic dissolution rate.

4. Conclusions

(1) Growth of crystals of (+)-PS (the host) from aqueous solutions containing traces of the opposite enantiomer (the guest) led to uptake of the guest which was still present in washed crystals, indicating a solid solution of the guest in the host, and corresponding to a segregation coefficient, k, of 0.24.

(2) With increasing concentration of the opposite enantiomer in the crystallization medium, corresponding to mole fractions of enantiomeric impurity ≤ 0.0028 in the crystals, the enthalpy and the entropy of fusion of (+)-EN decreased to minima, indicating increases in lattice energy and disorder, corresponding to increases in lattice strain.

(3) Crystallization in the presence of higher mole fractions of the opposite enantiomer (> 0.0028) led to increases in the enthalpy of fusion and entropy of fusion of (+)-PS, suggesting decreases in lattice energy and disorder, corresponding to relaxation of the lattice strain.

(5) The intrinsic dissolution rate of (+)-PS increased with increasing concentration of the enantiomeric impurity in the crystals and reached a maximum value at mole fractions of enantiomeric impurity approximately equal to 0.0075. Further incorporation of the impurity led to a decrease in the IDR

(6) With increasing mole fraction of enantiomeric impurity ≤ 0.0028 in the crystals, the entropy of fusion and entropy of solution decreased linearly with increasing ideal entropy of mixing, corresponding to disruption index values of 24.7 and 21.4, respectively.

(7) A plot of the free energy of solution versus the enthalpy of solution was found to be approximately linear, qualitatively suggesting enthalpy-entropy compensation, from which the pseudo-disruption index was calculated to be 27.9.

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