Effects of Configuration Around the Chiral Carbon Atoms on the Crystal Properties of Ephedrinium and Pseudoephedrinium Salicylates

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Received January 3, 1994; accepted May 20, 1994

The physicochemical properties and crystal structures of the crystalline salts formed by the interaction of an achiral anion, salicylate, with homochiral and racemic ephedrinium and pseudoephedrinium cations were determined. The interaction of ephedrinium or pseudoephedrinium with salicylate in aqueous solution yielded crystalline salts with the notable exception of homochiral ephedrinium. Evaporation of the solvent from solutions of homochiral ephedrine and salicyclic acid in various organic solvents, as well as grinding together solid homochiral ephedrine and solid salicylic acid, yielded viscous semisolids suggesting that homochiral ephedrinium salicylate has a low melting point and/or a high aqueous solubility. Mixing of the two viscous solids, obtained by grinding each of the opposite enantiomers of ephedrine with equimolar salicylic acid, resulted in the formation of racemic ephedrine and subsequently, upon heating, in the formation of racemic ephedrinium salicylate. While racemic ephedrinium salicylate exists as a crystalline compound ($P2_1/n$ space group) with an equal number of opposite enantiomers in the unit cell, its diastereomer, racemic pseudoephedrinium salicylate, exists as a conglomerate, i.e. a physical mixture, of the homochiral crystals of the opposite enantiomers (each $P2_1$ space group). The inability of homochiral ephedrinium to exist as a crystalline salicylate salt at 20–25°C is attributed to its high energy conformation and/or to the poor packing of homochiral ephedrinium salicylate molecules in the crystal lattice.

KEY WORDS: ephedrine; pseudoephedrine; salicylate; chirality; salt formation; homochiral crystal; racemic compound; racemic conglomerate; crystal structure; conformation.

INTRODUCTION

The solid state properties of a drug, such as its melting point and solubility, can be modified by preparing a suitable salt (1, 2). The properties of a crystalline salt are influenced by the spatial orientation of various groups present in the cation and in the anion constituting the salt. Thus, the interaction of two diastereomers, which differ in the spatial orientation of their various groups, with the *same* achiral counter-ion may produce salts with significantly different crystal properties.

Of additional interest are the contrasting properties of the salts consisting of the racemate or the enantiomer with the *same* achiral counter-ion. Wallach (3), after comparing the measured densities of members of eight pairs of racemic and homochiral crystals, stated that molecules in a racemic crystal tend to pack more tightly than those in a crystal composed solely of homochiral molecules. Recently Pratt-Brock *et al.* (4), based on the crystallographic densities of 129 pairs of racemic and chiral crystals from the Cambridge Structural Database (CSD), showed that Wallach's rule applies only to those systems which contain resolvable enantiomers. Pratt-Brock *et al.* (4) also suggested that racemic crystals tend to be more stable and denser than their homochiral counterparts, presumably as a result of the more compact packing arrangements in centrosymmetric racemic space groups than in chiral space groups.

Jacques *et al.* (5) compared the phase diagrams of over 500 chiral salts, with those of the corresponding chiral acids and bases, and reported that the formation of a racemic *comglomerate*, or an equimolar physical mixture of the two enantiomers, which is spontaneously resolved into its constituent enantiomers during crystallization, is far more frequent among salts than among free acids or bases. Furthermore, Jacques *et al.* (5) reasoned that the geometry imposed on the structure by the relatively strong acid-base interaction, involved in the formation of a salt, may disfavor the formation of a centrosymmetric structure of the racemic compound. Therefore, the general rule discussed in the previous paragraph, that the racemates are usually denser and more stable than the corresponding enantiomers, appears to have notable exceptions among the salts of racemic acids or bases.

Apart from the pharmaceutically important physicochemical properties, such as solubility, of chiral acids and bases, the fundamental nature of a crystalline racemate can also be altered by salt formation. The latter aspect, however, has not been addressed in detail in the pharmaceutical literature and appears not to have been exploited. For example, if the thermodynamically stable crystalline racemate of a chiral acid or a base is a racemic compound, and that of its salt with an achiral counter-ion is a racemic comglomerate, then an enantiomerically pure salt of the drug can be prepared from its racemate on a large scale by simple crystallization (6,7). To exploit this concept in preparing enantiomerically pure drugs, it is essential to understand the changes in the nature of crystalline racemates of chiral acids and bases due to salt formation with various achiral counter-ions.

The present study investigates changes in the nature of crystalline racemates of ephedrine and pseudoephedrine due to the formation of a salt with a model achiral anion, salicylate. Ephedrine and pseudoephedrine, each having two chiral carbon atoms in its structure, are diastereomers differing in the configuration of the various groups attached to one of their two chiral carbon atoms (Figure 1). The thermodynamically stable crystalline racemates of ephedrine and pseudoephedrine bases are the racemic compounds (8). The aims of this study are (a) to investigate the effects of the configuration of the functional groups around the chiral carbon atoms on the crystal properties of the racemic and homochiral salicylate salts of ephedrine and pseudoephedrine and (b) to compare the crystal properties of the salicylate salts of homochiral ephedrinium and homochiral pseudoephedrinium with the corresponding racemates.

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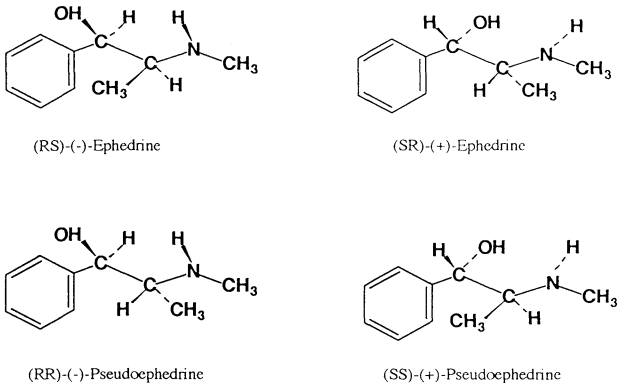


Figure 1. Molecular structures of ephedrine and pseudoephedrine stereoisomers.

MATERIALS AND METHODS

Materials

The free bases and hydrochloride salts of racemic, (RS)-(−)- and (SR)-(+)-ephedrine and of racemic, (RR)-(−)- and (SS)-(+)-pseudoephedrine were obtained from Sigma Chemical Company (St. Louis, MO). Sodium salicylate and salicylic acid were obtained from Aldrich Chemical Company (Milwaukee, WI). Before use, each compound was stored for 72 hours at 22°C and at 0% RH (over anhydrous calcium sulfate, Drierite, W. A. Hammond Drierite Company, Xenia, OH). All solvents used for recrystallizations were of ACS or HPLC grade.

Methods

Preparation of the Salts. Salicylate salts were prepared by mixing equimolar aqueous solutions of ephedrine hydrochloride or pseudoephedrine hydrochloride and sodium salicylate. Racemic (±)-ephedrinium salicylate [(±)-ES] crystallized from aqueous solution as prisms suitable for single crystal X-ray diffraction studies. However, (SS)-(+)-pseudoephedrinium salicylate [(+)-PS] and racemic pseudoephedrinium salicylate crystallized from aqueous solutions as very fine needles. Therefore, to obtain single crystals suitable for single crystal X-ray diffraction. (+)-PS was recrystallized from acetonitrile. Attempts to prepare (RS)-(−)- and (SR)-(+)-ephedrinium salicylate, by mixing equimolar aqueous solutions of the respective hydrochloride salt with sodium salicylate, were unsuccessful, even at the saturation concentrations of the reactants.

Grinding of equimolar quantities of (RS)-(−)-ephedrine or (SR)-(+)-ephedrine and salicylic acid in the solid state was carried out in an attempt to prepare (RS)-(−)-ephedrinium salicylate or (SR)-(+)-ephedrinium salicylate. Attempts were also made to crystallize (RS)-(−)-ephedrinium salicylate from solutions containing equimolar (RS)-(−)-ephedrine and salicylic acid in ethanol, methanol, isopropanol, acetonitrile, diethyl ether, dichloromethane, chloroform and carbon tetrachloride.

Construction of the Phase Diagram of the Pseudoephedrinium Salicylate Enantiomers. Thoroughly ground physical mixtures containing various mole fractions of the two enantiomers were weighed into open aluminum pans for differential scanning calorimetry (DSC). The heat of fusion and melting point of the mixtures were determined using a differential scanning calorimeter (DuPont 910) 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 mg) in open aluminum pans were heated at a rate of 10°C/min.

Physical mixtures, rather than fused mixtures, were used to construct the phase diagram because heating the mixtures above their melting point followed by cooling to room temperature resulted in a weight loss of the mixture, probably because of the volatility or the degradation of the molten liquid.

Crystal Structure Determination. A crystal of (±)-ES or (+)-PS of suitable size and form was mounted on a glass fiber. The conditions of data collection and the unit cell parameters are given in Table I. Each structure was solved by direct methods and the refinement parameters are given in Table I. The function minimized was $\Sigma\, w\,(|F_o| - |F_c|)^2$, where the weighting factor $w = 4F_o^2 / \sigma^2 (F_o)^2$, F_o is the observed structure factor and F_c is the calculated structure factor.

The unweighted agreement factor (R), the weighted agreement factor (R_w), and the standard deviation of an observed unit weight (S) were calculated as follows:

$$R = \frac{\Sigma||F_o| - |F_c||}{\Sigma|F_o|} \quad (1)$$

$$R_w = \frac{\Sigma w||F_o| - |F_c||^2}{\Sigma w|F_o|^2} \quad (2)$$

$$S = \frac{\Sigma w||F_o| - |F_c||^2}{(M - N)½} \quad (3)$$

where M is the number of observations and N is the number of variables. No unusual trends were shown by the plots of $\Sigma w\,(|F_o| - |F_c|)^2$ versus $|F_o|$, the reflection order in data collection [(sin Θ)/λ], and various classes of indices. Anomolous dispersion effects were included in F_c (10); the values of Δf and Δf′ were those of Cromer (11), where Δf and Δf′ are the real imaginary terms, respectively. All calculations were performed with TEXSAN software (Molecular Structure Corporation, Woodlands, TX).

Information from Cambridge Structural Database (CSD). Searches were made on the version 4.3, June 1990, of the CSD. Crystal structures and references were obtained by searching the database with the *compound name*. The structures and hydrogen bond patterns of the molecules were obtained from the original papers, where available, and also from the PLUTO and GSTAT programs included in the CSD package.

RESULTS AND DISCUSSION

Crystallization of the Solid Phases

Salicylate Salts of Ephedrine. Mixing of equimolar (0.5 M) aqueous solutions of racemic ephedrine hydrochloride and sodium salicylate resulted in the formation of prism-shaped crystals of racemic ephedrinium salicylate (m.p. 150°C, aqueous solubility 50 g/L at 25°C).

Table I. The Single Crystal Diffraction Data for Racemic (±)-Ephedrinium Salicylate[a] and (SS)-(+)-Pseudoephedrinium Salicylate[b]

Racemic (±)-Ephedrinium Salicylate		SS-(+)-Pseudoephedrinium Salicylate	
Crystal data		*Crystal data*	
$C_{17}H_{21}NO_4$	MoK_α	$C_{17}H_{21}NO_4$	MoK_α
M_w = 303.36	Cell parameters from 25 reflections	M_w = 303.36	Cell parameters from 25 reflections
Monoclinic		Monoclinic	
$P2_1/n$	θ = 10.00–18.00	$P2_1$	θ = 9.90–16.50
a = 15.996 (4) Å	T = 296.15 K	a = 7.689 (2) Å	T = 297.15 K
b = 6.393 (4) Å	Prism	b = 8.207 (2)	Prism
c = 16.641 (5) Å	0.5 × 0.35 × 0.25 mm	c = 13.152 Å	0.6 × 0.5 × 0.3 mm
β = 110.37°	Colorless	β = 103.97°	Colorless
z = 4	Crystal source: from water.	z = 2	Crystal source: from acetonitrile.
Data Collection			
CAD-4 diffractometer	ω-2θ scan, θ_{max} = 25.9°	CAD-4 diffractiometer	ω-2θ scan, θ_{max} = 27.9°
3309 measured reflections	Data corrected for absorption, Lorentz and polarization effects.	4142 measured reflections	Data corrected for absorption, Lorentz and polarization effects.
3309 independent reflections		2069 independent reflections	
2156 observed reflections		1541 observed reflections	
Refinement			
Refinement on F	$(\Delta/\sigma)_{max}$ = 0.01	Refinement on F	$(\Delta/\sigma)_{max}$ = 0.005
R = 0.051	$\Delta\rho_{max}$ = 0.30 $e^-/Å^3$	R = 0.035	$\Delta\rho_{max}$ = 0.17 $e^-/Å^3$
R_w = 0.062	$\Delta\rho_{min}$ = −0.30 $e^-Å^3$	R_w = 0.030	$\Delta\rho_{min}$ = −0.12 $e^-Å^3$
216 parameters	Weighting scheme included a factor, p = 0.05, to down-weight intense reflections	215 parameters	Weighting scheme included a factor, p = 0.05, to down-weight intense reflections
$w = 4F_o^2/\sigma^2(F_o)^2$		$w = 4F_o^2/\sigma^2(F_o)^2$	
H-atoms refined isotropically		H-atoms refined isotropically	
Non H-atoms refined anisotropically.	Neutral atom scattering factors from Cromer and Waber (9)	Non H-atoms refined anisotropically.	Neutral atom scattering factors from Cromer and Waber (9)

[a] (RS)-(−)-Ephedrinium salicylate and (SR)-(+)-ephedrinium salicylate could not be obtained as crystalline salts.
[b] Racemic (±)-pseudoephedrinium salicylate exists as a racemic conglomerate of the two homochiral crystals (Figure 2).

In contrast to racemic ephedrine hydrochloride, either (RS)-(−)- or (SR)-(+)-ephedrine hydrochloride in aqueous solution, when mixed with an equimolar aqueous solution of sodium salicylate did not result in the formation of a solid product, even at saturation concentrations of the reactants (≈1.25 M for ephedrine hydrochloride and ≈6 M for sodium salicylate). Attempts at crystallization from solutions containing equimolar salicylic acid and (RS)-(−)- or (SR)-(+)-ephedrine in ethanol, methanol, isopropanol, acetonitrile, diethyl ether, dichloromethane, chloroform or carbon tetrachloride, yielded a viscous and semi-solid mass. Grinding of (RS)-(−)- or (SR)-(+)-ephedrine with salicylic acid in the solid state also resulted in the formation of a viscous semi-solid. This semi-solid, when cooled to −40°C and heated to 160°C in a DSC, showed no thermal transitions such as melting or crystallization. One or both of the following explanations may be offered for the inability to obtain a crystalline homochiral ephedrinium salicylate.

1. The salicylate salt formed has such a low melting point that it exists as a liquid at room temperature, and/or has such a high aqueous solubility that it dissolves in the trace quantity of water present either in the solvents of crystallization or taken up from the atmosphere. Furthermore, ephedrine enantiomers are very hygroscopic and even at 0% RH each enantiomer contains 0.5% w/w of water which can serve as a solvent for the salt produced by grinding in the solid state.
2. (RS)-(−)- or (SR)-(+)-ephedrinium salicylate may not attain a suitable packing arrangement to form a homochiral crystal and hence form glasses for which the glass transition temperature is below room temperature, 22°C. Kitaigorodski (6, 12) suggested that molecules which cannot attain a packing coefficient of at least 0.6, as a consequence of their geometry, do not crystallize and form glasses upon cooling.

Thus, the formation of crystals of the racemic compound of ephedrinium salicylate from aqueous solutions appears more favorable than the formation of the individual enantiomers.

Equimolar quantities of the two semisolids obtained by grinding either (RS)-(−)-ephedrine or (SR)-(+)-ephedrine with salicylic acid were thoroughly mixed with a spatula and kept in a glass vial. After 24 hrs, long needles were observed to grow from the surface of the semisolid mass. Characterization of the needles using DSC revealed that the needles were crystals of racemic ephedrine base (m.p. 77°C), rather than racemic ephedrinium salicylate (m.p. 150°C).

Heating the entire semisolid mass, along with the nee-

dles, in a DSC and under a hot stage microscope showed a sequence of thermal events. The needle-shaped racemic ephedrine melted at 76°C followed by the subsequent crystallization of racemic ephedrinium salicylate at approximately 112°C. Finally, the racemic ephedrinium salicylate melted at 150°C. This finding shows that the formation of racemic ephedrine from the two enantiomers precedes formation of their salicylate salts. Evidently, in the solid state, the formation of racemic ephedrine from a physical mixture of the opposite enantiomers of ephedrine and salicylic acid is a more favorable reaction than the formation of ephedrinium salicylate, homochiral or racemic. As reported previously (13), the formation of racemic ephedrine from its individual enantiomers is a spontaneous reaction which is driven by a negative enthalpy change (≈ -2.28 kcal/mol) and occurs even via the vapor state. From the above discussion, the sequence of events in the formation of racemic ephedrinium salicylate by heating a physical mixture of ephedrine enantiomers and salicylic acid in the solid state may be represented as follows

$$(-)\text{-E} + 2\text{SA} + (+)\text{-E} \rightarrow 2(\pm)\text{-E} + 2\text{SA} \rightarrow 2(\pm)\text{-E-SA} \quad (4)$$

where (−)-E and (+)-E and (±)-E represent (RS)-(−)-, (SR)-(+)- and racemic ephedrine, respectively, and SA represents salicylic acid. Thus, the formation of the thermodynamically stable racemic ephedrinium salicylate in the solid state proceeds via the formation of racemic ephedrine.

Salicylate Salts of Pseudoephedrine. In contrast to the observations with ephedrine, the (RR)-(−)-, (SS)-(+)- and racemic pseudoephedrinium salicylate salts could each be obtained by mixing equimolar aqueous solutions (0.5 M) of the respective hydrochloride salt with sodium salicylate. This result suggests that the enantiomers of pseudoephedrine, unlike the enantiomers of its diastereomer, ephedrine, form higher melting and/or less water soluble salicylate salts (m.p. $\approx$ 132°C, aqueous solubility $\approx$49 g/L at 25°C).

The racemate of pseudoephedrinium salicylate was found to have a melting point (109°C) lower than that of the pure enantiomers ($\approx$132.5°C) suggesting that the racemate is a eutectic mixture or a lower melting racemic compound. To understand the nature of the crystalline racemate, the melting point phase diagram (Figure 2) of the pseudoephedrinium salicylate enantiomers was constructed. Figure 2 shows that the thermodynamically stable racemate of pseudoephedrinium salicylate is a *conglomerate*, i.e. a eutectic mixture of the two enantiomers. The experimentally determined melting points for the various mixtures of enantiomers are in close agreement with the values predicted from the following Schröder-Van Laar Equation (6)

$$\ln x = \frac{\Delta H_A^f}{R}\left(\frac{1}{T_A^f} - \frac{1}{T^f}\right) \quad (5)$$

where x ($0.5 \leq x \leq 1$) is the mole fraction of the enantiomer which is present in excess in a mixture whose terminal melting point is T^f, while ΔH_A^f and T_A^f are the heat of fusion and melting point, respectively, of the pure enantiomers.

The results discussed so far suggest that the stable crystalline racemate formed from the opposite enantiomers of ephedrinium salicylate is a *racemic compound,* and that

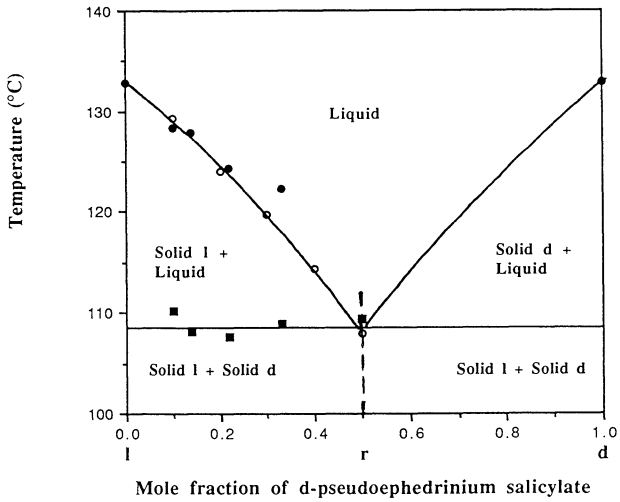


Figure 2. Phase equilibrium diagram of pseudoephedrinium salicylate enantiomers. 1, d and r refer to (RR)-(−)-, (SS)-(+)-, and racemic pseudoephedrinium salicylate, respectively. Closed circles (●) represent experimentally measured temperatures of complete melting, T^f, and closed squares (■) represent the experimentally measured temperatures of the initial melting, corresponding to the eutectic temperature. Open circles (○) are values predicted by the Schröder-van Laar equation (6; Equation 5).

from pseudoephedrinium salicylate enantiomers is a *conglomerate*. Thus, although the ephedrine and pseudoephedrine molecules process the same substituent groups, the configuration of these groups around the chiral centers, i.e. RS (or SR) for the ephedrine enantiomers but RR (or SS) for the pseudoephedrine enantiomers, strongly influences the existence and the physicochemical properties of the respective homochiral and racemic salicylate salts.

The crystal structures of racemic ephedrinium salicylate and (SS)-(+)-pseudoephedrinium salicylate were obtained by single crystal X-ray diffraction to gain further insight into the conformations of ephedrine and pseudoephedrine in the structures of their salicylate salts and possibly to provide reasons for not obtaining crystals of (RS)-(−)- or (SR)-(+)-ephedrinium salicylate.

Crystal Structures of Racemic Ephedrinium Salicylate (±ES) and (SS)-(+)-Pseudoephedrinium Salicylate (+PS)

As discussed in the previous section, crystals of (−)-ES or (+)-ES could not be obtained. Therefore, only the crystal structure of (±)-ES was determined. In the case of PS, the determination of the crystal structure of only one enantiomer, (+)-PS, was sufficient to reveal information about the crystallographic parameters of the opposite enantiomer, (−)-PS, and of the racemate. By symmetry, the crystals structure of (−)-PS is a mirror image of (+)-PS. Since the stable racemate of PS enantiomers is a conglomerate consisting of a physical mixture of the two enantiomers, the structure determined for any single crystal from the racemate would be identical to that of the pure enantiomer.

Crystal Structure of Racemic Ephedrinium Salicylate [(±)-ES]. The monoclinic unit cell ($P2_1/n$) of (±)-ES consists of 4 molecules (one molecule per asymmetric unit) as shown

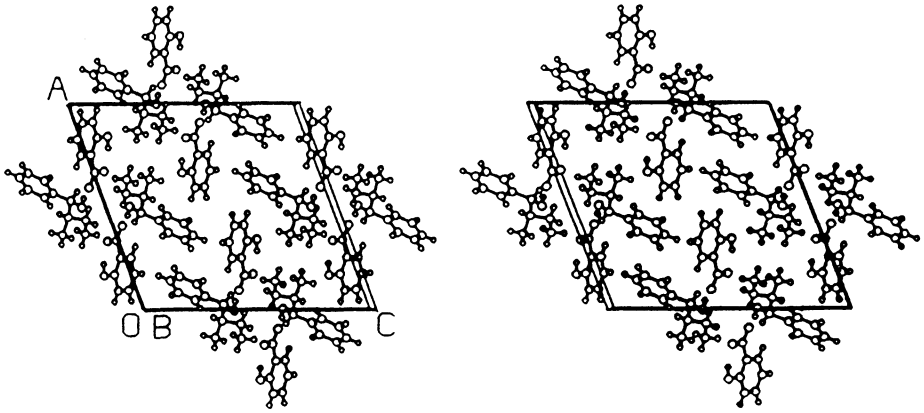


Figure 3. The stereographic packing diagram of racemic ephedrinium salicylate showing four molecules in the monoclinic $P2_1/n$ unit cell.

in Figure 3. Thus, each unit cell contains four salicylate anions and two cations of each of the two enantiomers of ephedrine. The ephedrinium cation has three hydrogen bond donors, comprising a protonated secondary amine, which can donate two protons, and a secondary alcohol. The salicylate anion has two oxygens on the carboxylate group, each of which can accept two protons, and a phenolic hydroxyl which can donate a proton. Hence, four hydrogen bond interactions per molecule are likely to occur in the crystal structure of (±)-ES. As expected, the single crystal X-ray diffraction data revealed a total of three intermolecular and one intramolecular hydrogen bond interactions, which lead to the formation of a centrosymmetric structure (Figure 4). The following four types of hydrogen bond interactions are discerned in the (±)-ES crystal structure (Figures 3 and 4).

1. The protonated secondary amine forms a hydrogen bond with the oxygen, O9A′, on the carboxylate group of the salicylate anion of a different asymmetric unit related by a translation along the y axis, viz., N11C-H11C---O9A′ interaction, H11C---O9A′ distance 1.84 Å.
2. The hydroxyl group on the ephedrinium cation forms a hydrogen bond with the oxygen, O8A, on the carboxylate group of the salicylate anion of the same asymmetric unit, viz., O8C-H8C---O8A interaction, H8C---O8A distance 1.90 Å.
3. The oxygen O8A, which participates in the second interaction above, also accepts a second proton on the protonated secondary amine of the ephedrinium cation of a different asymmetric unit related by a center of symmetry. This interaction between O8A and the proton, which is the equivalent of H′11C but present in a different asymmetric unit, is shown in Figure 4 as an incomplete hydrogen bond involving the atoms O8A and H′11C, and can be discerned more clearly from the stereographic packing diagram in Figure 3. Since ephedrinium salicylate is chiral, a molecule related to the other by a center of symmetry is the opposite enantiomer. Therefore, the interaction, by symmetry, is between the opposite enantiomers. The hydrogen bond length for this interaction was found to be 1.84 Å.
4. The oxygen O9A′, which participates in the first interaction above, also accepts a proton in the intramolecular hydrogen bonding interaction, O10A′-H10A′---O9A′, H10A′---O9A′ distance 1.71 Å. Thus, each oxygen on the carboxylate group of the salicylate anion acts as a hydrogen bond acceptor for two protons.

Crystal Structure of (SS)-(+)-Pseudoephedrinium Salicylate [(+)-PS]. The monoclinic unit cell ($P2_1$) of (+)-PS contains two molecules per unit cell (one molecule per asymmetric unit) as shown in Figure 5. As in the structure of racemic ephedrinium salicylate, a total of three intermolecular hydrogen bonds and one intramolecular hydrogen bond was observed in the crystal structure of (SS)-(+)-pseudoephedrinium salicylate, as shown in Figures 5 and 6. The following four hydrogen bonds are discerned in (+)-PS crystal structure.

1. The protonated secondary amine forms a hydrogen bond with the oxygen, O9A, on the carboxyl group of the salicylate anion in the same asymmetric unit, i.e. the N11C-H11C---O9A interaction, H11C---O9A distance 1.88 Å
2. The hydroxyl group of the pseudoephedrinium cation forms a hydrogen bond with the oxygen, O8A, on the carboxyl group of the salicylate anion in the same asymmetric unit, viz., the O8C-H8C---O8A interaction, H8C---O8A distance 1.91 Å.
3. The oxygen, O8A, on the carboxylate anion accepts the

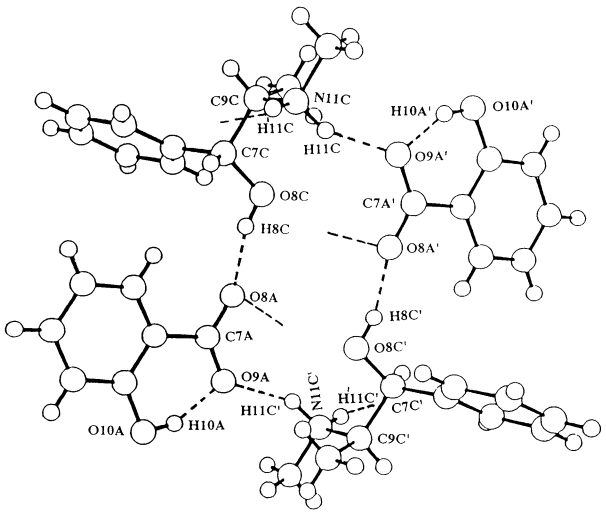


Figure 4. The spatial relationship and hydrogen bonding interactions in racemic ephedrinium salicylate.

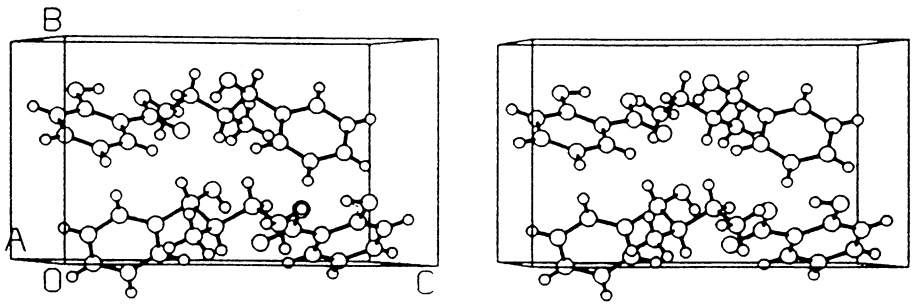


Figure 5. The stereographic packing diagram of (SS)-(+)-pseudoephedrinium salicylate showing two molecules in the monoclinic $P2_1$ unit cell.

second proton of the protonated secondary amine of a different asymmetric unit related by a screw axis along the y direction. This interaction between O8A and the proton, which is equivalent to H'11C but present in a different asymmetric unit, is shown in Figure 6 as an incomplete hydrogen bond involving the atoms O8A and H'11C, and can be discerned more clearly from the stereographic packing diagram in Figure 5. The hydrogen bond distance for this interaction was found to be 1.90 Å.

4. The oxygen O9A, which also participates in interaction 1 above, acts as a hydrogen bond acceptor in the intramolecular hydrogen bonding, viz., O10A-H10A---O9A, interaction, H10A---O9A distance 1.73 Å.

Thus, both oxygens, O8A and O9A, accept two protons each. In contrast to the structure of racemic ephedrinium salicylate, more than one hydrogen bond interaction can be discerned between the cation and the anion of the same asymmetric unit in the crystal structure of (SS)-(+)--pseudoephedrinium salicylate. These two interactions, 1 and 2 above, within the same asymmetric unit, result in the formation of a nine-membered ring, as shown in Figure 6.

Conformational Analysis of Ephedrine and Pseudoephedrine in the Crystal Structures

The conformations of ephedrine and pseudoephedrine molecules may be conveniently represented by four torsion angles, τ, ψ, ω and χ, which are defined as follows:

τ, which describes the conformation about the C_1-C_7 bond, is defined by the atoms C_2-C_1-C_7-O_1;

ω, which describes the conformation about the C_7-C_8 bond, is defined by the atoms O_1-C_7-C_8-N_1

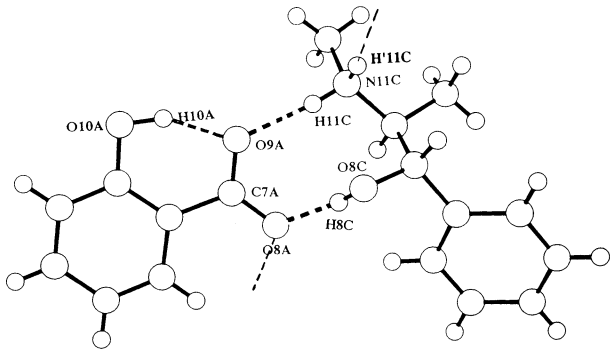
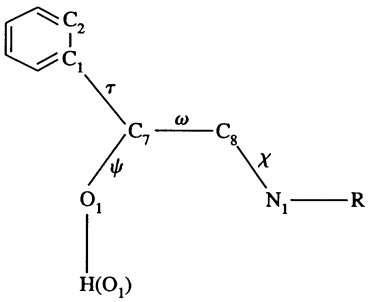


Figure 6. The spatial relationship and hydrogen bonding interactions in (SS)-(+)-pseudoephedrinium salicylate.

χ, which describes the conformation about the C_8-N_1 bond is defined by the sequence R-N_1-C_8-C_7; and

ψ, which describes the conformation about the O_1-C_7 bond, is defined by the atoms $H(O_1)$-O_1-C_7-C_{8-}.



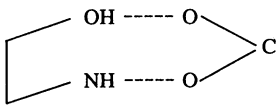
A comparison of the conformations of ephedrine and pseudoephedrine exhibited in their salicylate salts in the present work with the conformations of ephedrine and pseudoephedrine in their other salts reported in the literature is given in Table II. The magnitudes of τ and ω remain approximately constant for both the ephedrine and pseudoephedrine enantiomers in virtually all the structures (Table II). In this comparison, the signs of τ, ω, and ψ and χ are arbitrary, since they depend on the enantiomer chosen. The limited range of ω values, $46° < \omega < 73°$ suggests that, in all the structures, the amino group is situated *gauche* with respect to the hydroxyl group. This observation is consistent with studies on the conformation of these molecules in solution (20) and may also be deduced from molecular orbital calculations (21).

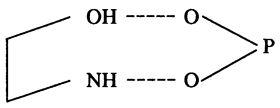
The torsion angle ψ is the angle that is most sensitive to structure (Table II). In six of the eleven structures, ψ is approximately 170°. However, in five structures, including that of (SS)-(+)-pseudoephedrinium salicylate, ψ is significantly different from 170° and ranged from 15° to 128°. This variation probably reflects the different hydrogen bonding patterns and the different packing patterns in the different crystal structures. In each of the five structures showing lower ψ values (15° – 128°), the ephedrine or pseudoephedrine molecule acts as a *bidentate hydrogen bond donor* so that the hydroxyl group and the secondary amino group are able to *clip* onto a *single carboxylate* or a *phosphate* as shown below (15)

Table II. The Torsion Angles of Ephedrine and Pseudoephedrine Molecules in Various Crystal Structures Previously Reported in the Literature and in the Present Work

Serial number and the reference	Compound name		τ	ω	χ	ψ
1. Bergin (14)	(RS)-(−)-Ephedrine hydrochloride		−21	−70	−170	175
2. Gorman *et al.* (15)	(RS)-(−)-Ephedrine-N-acetyl-L-valine		−18	−66	−159	168
3. Gais *et al.* (16)	(RS)-(−)-Ephedrine ent-2-methoxycarbonyl-cyclohex-4-ene-1-carboxylate		−14	−65	−174	165
4. Mathew and Palenik (17)	(SS)-(+)-Pseudoephedrine		44	52	−162	174
5. Mathew and Palenik (17)	(SS)-(+)-Pseudoephedrine hydrochloride		63	55	−171	162
6. Present work	Racemic Ephedrinium salicylate		23	−63	−170	163
7. Hearn and Bugg (18)	(RS)-(−)-Ephedrine dihydrogen phosphate		−21	−73	177	**128**[a]
8. Hearn *et al.* (19)	(RS)-(−)-Ephedrine monohydrogen phosphate monohydrate	A[b]	−36	−57	−168	**85**[a]
		B[b]	−11	−69	−169	**85**[a]
9. Gorman *et al.* (15)	(RS)-(−)-Ephedrine-N-benzyloxycarbonyl-L-leucine		−8	−66	**−53**[a]	**15**[a]
10. Present work	(SS)-(+)-Pseudoephedrinium salicylate		54	46	174	**49**[a]

[a] These angles are significantly different from the others in the same series.
[b] A and B are the two crystallographically independent cations in the structure.





Thus, ephedrinium and pseudoephedrinium cations have the ability to exist in a conformation which brings the secondary amine and the secondary alcohol groups close together during salt formation with a carboxylate or a phosphate.

The other torsion angle χ remained approximately constant at 170°, except in one crystal structure, (RS)-(−)-ephedrine-N-benzyloxycarbonyl-L-leucine, for which χ = −53°. Thus, in ten of the eleven structures, the side chain is fully extended. Interestingly, (RS)-(−)-ephedrine-N-benzyloxycarbonyl-L-leucine, the structure with an exceptionally low χ value, is the only crystal structure reported so far in which the ephedrine molecule acts as a bidentate hydrogen bond donor (hence a lower ψ value) and clips onto a single *carboxylate*. In the other four structures in which the molecules of ephedrine or pseudoephedrine act as bidentate donors, the change in ψ is not accompanied by a change in χ, suggesting that, in these four structures, the molecule can achieve a conformation capable of clipping a single carboxyl or phosphate merely by the movement of the *proton attached to the hydroxyl group*. However, in the structure of (RS)-(−)-ephedrine-N-benzyloxycarbonyl-L-leucine molecule, in which a lower ψ value (15°) is accompanied by a lower χ value (−53°), *the methyl group attached to the secondary amino group* and *the methyl group on* C_8 of ephedrine have to be forced into a *gauche* conformation for the molecule to clip onto the carboxylate (χ = −53°). Certain ephedrinium cations, even in this sterically unfavorable gauche conformation, may, however, yield homochiral crystals, provided the counter-ion imposes a geometry such that the molecules can attain a packing coefficient ≥ 0.6 in the crystal lattice. The compound (RS)-(−)-ephedrine-N-benzyloxycarbonyl-L-leucine is an example of this behavior. Therefore, by analogy with (RS)-(−)-ephedrine-N-benzyloxycarbonyl-L-leucine, (RS)-(−)- and (SR)-(+)-ephedrinium salicylate do not form crystalline solids because the energetically unfavorable gauche conformation of the cation is not compensated by a geometry imposed by the anion such that the molecules could attain a packing coefficient large enough to form a crystalline solid.

CONCLUSIONS

1. The addition of racemic, but not homochiral, ephedrine hydrochloride to an equimolar aqueous solution of sodium salicylate produces a crystalline salt. (RS)-(−)- and (SR)-(+)-ephedrinium salicylate do not exist as crystalline salts at room temperature (22°C) perhaps as a result of their low melting point or a high aqueous solubility.
2. The addition of racemic or homochiral pseudoephedrine hydrochloride to equimolar aqueous solutions of sodium salicylate produced crystalline salts.
3. The thermodynamically stable crystalline racemate of ephedrinium salicylate is a racemic compound, while that of pseudoephedrinium salicylate is a racemic conglomerate (a physical mixture of the two enantiomeric homochiral crystals). Thus, enantiomerically pure pseudoephedrinium salicylate can, in principle, be prepared from its racemate by simple crystallization.
4. The inability to obtain crystalline homochiral ephedrinium salicylate may be attributed to a high energy conformation and/or to the inability of the molecules to attain a packing coefficient large enough to form a crystalline solid.

ACKNOWLEDGMENTS

We thank Dr. Doyle Britton, X-ray Service Laboratory, Department of Chemistry, University of Minnesota, for determining the crystal structures of racemic ephedrinium salicylate and (SS)-(+)-pseudoephedrinium salicylate. We also thank Dr. Daniel A. Adsmond, the late Dr. Margaret C. Etter and Dr. Mark A. Whitener for valuable discussions.

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