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Optical Resolution Through Diastereomeric Salt Formation: the Crystal Structures of Cinchoninium (*R*)-Mandelate and Cinchoninium (*S*)-Mandelate at Low Temperature

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Abstract

The crystal structures of the diastereomeric salts formed between cinchonine and mandelic acid have been analysed. The more soluble of the two salts is cinchoninium (*S*)-mandelate, $C_{19}H_{23}N_2O^+.C_8H_7O_3^-$, $M_r = 446.55$, monoclinic, $P2_1$, $T = 110\,(1)$ K, $a = 11.2478\,(10)$, $b = 7.0880\,(6)$, $c = 14.684\,(2)$ Å, $\beta = 99.068\,(7)°$, $V = 1156.0\,(4)$ Å^3, $Z = 2$, $D_x = 1.283$ g cm^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, $\mu = 6.57$ cm^{-1}, $F(000) = 476$, $R = 0.029$ for 2338 observed reflections. The less soluble salt is cinchoninium (*R*)-mandelate, $C_{19}H_{23}N_2O^+.C_8H_7O_3^-$, $M_r = 446.55$, orthorhombic, $P2_12_12_1$, $T = 122.0\,(5)$ K, $a = 12.078\,(4)$, $b = 17.423\,(2)$, $c = 22.136\,(4)$ Å, $V = 4658\,(3)$ Å^3, $Z = 8$, $D_x = 1.273$ g cm^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, $\mu = 6.52$ cm^{-1}, $F(000) = 1904$, $R = 0.055$ for 4125 observed reflections. In the (*R*)-mandelate salt one of the two independent cinchoninium cations displays disorder of the $-CH{=}CH_2$ moiety. Apart from variations in the conformation of the vinyl group the cinchoninium cations are alike. The difference in conformation of the (*R*)- and (*S*)-mandelate ions can be related to differences in the hydrogen-bonding systems. Interionic interactions in the *S* salt stabilize it relative to the *R* salt. The differences in the melting enthalpies and entropies of the two diastereomeric salts are related to their structural differences.

Introduction

The separation of a racemic mixture into its enantiomers is often achieved by adding a suitable optically active compound. The difference in the solubilities of the diastereomeric compounds obtained may often be sufficient for a separation of the enantiomers. Though optical resolution through diastereomeric salt formation is a widely used method (Jacques, Collet & Wilen, 1981), it has not yet been possible to draw any general conclusions about the origin of the difference in solubilities. Careful analysis of the crystal structures of an equivalent pair of diastereomeric salts should provide information about their structural differences. If their differences can be related to differences in the physical properties of the compounds it should be possible to gain a deeper insight into the resolution process.

The naturally occurring alkaloids are frequently employed in the resolution of racemic acids (Jacques, Collet & Wilen, 1981). Racemic mandelic acid was first resolved by McKenzie (1899), who reacted it with cinchonine in water. He found that D-mandelic acid, which has an *S* configuration, forms a salt that is less soluble than the equivalent (*R*)-mandelate salt. We have prepared the diastereomeric salts of cinchonine and mandelic acid from ethyl acetate and have found, in contrast to McKenzie's (1899) results, that the less soluble salt is the (*R*)-mandelate salt. We report here a study of the crystal structures of these diastereomeric salts and follow that with a discussion of the relation between the crystal structures and their physico-chemical properties.

Experimental

The diastereomeric cinchoninium mandelates were prepared by dissolving 2.94 g (0.01 mol) cinchonine and 1.52 g (0.01 mol) optically pure [(*R*) or (*S*)] mandelic acid in 25 cm^3 warm methanol. After the solvent had evaporated a white microcrystalline residue was obtained in both cases. To get suitable crystals for the diffraction work, recrystallization from boiling ethyl acetate was performed. Both salts form colorless crystals. The crystals of the cinchoninium (*S*)-mandelate (the *S* salt) are needles elongated in the direction of the *b* axis, those of the cinchoninium (*R*)-mandelate (the *R* salt) are thin plates. The space groups and cell dimensions at room temperature were determined from Weissenberg photographs.

The melting points and enthalpy of fusion were determined by differential scanning calorimetry

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(DSC) in an argon atmosphere, on a DuPont 1090 calorimeter calibrated with indium and operated at a heating rate of 5 K min^{-1}, in the temperature range 293–473 K. The melting points (Table 1) of both salts differ from those given by McKenzie (1899). He reported melting points of 352–353 K and 438 K for the cinchoninium (*S*)-mandelate and cinchoninium (*R*)-mandelate, respectively.

The data collection was performed using an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å. The crystals were cooled during the data collection by an Enraf–Nonius gas-flow low-temperature device. The temperature, monitored with a thermocouple in the exhaust pipe, was constant to within 1 K. The different experimental conditions and results from the structure refinements are summarized in Table 1. Other crystallographic data are given in the *Abstract*. The orientation of the crystal was checked after every 300 reflections. The intensities of three standard reflections were recorded after every 10000 s. These measurements showed no systematic variations for the *S* salt. For the *R* salt a decrease in the intensities, linear in exposure time, to a total of 9% was observed. The data of the *R* salt were corrected for this decay by a rescale function that was linear in exposure time. Data reduction included corrections for Lp and background effects. Both structures were solved by direct methods using the program *SHELXS*86 (Sheldrick, 1990) and refined using the full-matrix least-squares method, minimizing $\sum w(|F_o| - |F_c|)^2$. Anisotropic displacement parameters were used for all non-H atoms. The positions of all the H atoms in the *S* salt were shown clearly in a $\Delta\rho$ map. Their positional parameters were refined and they were given a fixed isotropic temperature factor of 2.0 Å^2. The refinement of the *R* salt resulted in very large displacement parameters of the vinyl carbon atoms in the molecule labelled *B* and the $\Delta\rho$ map showed residual density close to these atoms, indicating some structural disorder. An attempt to describe this disorder with two partly populated positions for C(26*B*) and C(27*B*) resulted in a larger *R* value and in one position being much more populated than the other. In the final refinement the model with single sites for C(26*B*) and C(27*B*) was preferred, though this model results in large anisotropic displacement parameters and distances and angles for the C(26*B*)=C(27*B*) moiety, which do not agree with chemical reality but rather describe an average of different positions. Except for those in the disordered part the H atoms of the *R* salt were shown in a $\Delta\rho$ map. Those which have their positions fixed by the heavy-atom structure were introduced in idealized positions, the coordinates of those remaining were taken from the $\Delta\rho$ map. The coordinates of the H atoms in the *R* salt were not refined. They were given a fixed isotropic displacement parameter of 3 Å^2. In order to investigate the disorder in the *R* salt, a set of diffraction data was collected at room temperature. Apart from a change in the weighting the same procedure was used as for the low-temperature data set. Out of 5458 independent reflections, 2548 had $I/\sigma(I) > 1$ and were used in the refinement, which gave final residuals $R = 0.059$ and $wR = 0.057$. The structural results from the room-temperature study are given in the supplementary material. The final fractional coordinates for non-H atoms from low-temperature structure determinations are listed in Tables 2 and 3. All calculations except the structure determination were performed using the Enraf–Nonius structure determination package (*SDP*) program system (Enraf–Nonius, 1985). Scattering factors, including the contributions from anomalous dispersion were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV).*

Table 1. *Experimental data and a summary of data-collection and refinement results*

	S salt	*R* salt
Relative solubility	More	Less
Formula	$C_{27}H_{30}N_2O_4$	$C_{27}H_{30}N_2O_4$
Formula weight (g mol^{-1})	446.55	446.55
Melting point, T_m (K)	427 ± 1	462 ± 1
$\Delta H_{\rm fus}^{\ominus}$ at T_m (kJ mol^{-1})	41.5 ± 0.5	37.1 ± 0.4
$\Delta S_{\rm fus}^{\ominus}$ at T_m (J mol^{-1} K^{-1})	97 ± 1	80 ± 1
Temperature (K)	110 (1)	122.0 (5)
Space group	$P2_1$	$P2_12_12_1$
Z	2	8
D_x (g cm^{-3})	1.283	1.273
Reflections used in determination of cell parameters	18	22
θ range (°)	40.66–44.44	37.20–45.02
Crystal size (mm)	0.07 × 0.1 × 0.3	0.03 × 0.4 × 0.6
Scan type	ω–2θ	ω–2θ
Maximum $\sin\theta/\lambda$ (Å^{-1})	0.626	0.626
Standard reflections	110, $10\bar{3}$, 103	142, 011, 202
Range of h	−9–14	0–15
Range of k	0–8	0–21
Range of l	−18–18	0–27
$R_{\rm int}$	0.024	–
Number of measured reflections	3451	5345
Number of unique reflections	2571	5312
Observed reflections	$\|F\|^2 > 2\sigma(\|F\|^2)$	$\|F\|^2 > \sigma(\|F\|^2)$
Number of observed reflections, n	2338	4125
Number of variables, m	387	595
R	0.029	0.055
w^{-1}	$\sigma^2_{\rm cs}(F) + 0.0004F^2$	$\sigma^2_{\rm cs}(F) + 0.0009F^2$
wR	0.036	0.063
$S = [\sum w\Delta F^2/(n - m)]^{1/2}$	1.439	1.399
Maximum shift/e.s.d.	0.01	0.01
Maximum and minimum $\Delta\rho$ (e Å^{-3})	0.210, −0.185	0.443, −0.353

Discussion

Protonated cinchonine cations and mandelate ions are found in both diastereomeric salts. A description of the structural chemistry of these ions will be given

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55524 (111 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB0286]

Table 2. *Final fractional coordinates and equivalent isotropic thermal parameters for cinchoninium* (*S*)-*mandelate*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	U_{eq} (Å^2)
C(1)	0.5381 (1)	0.2776 (3)	−0.0160 (1)	0.0166 (4)
O(1)	0.5351 (1)	0.250	0.06792 (8)	0.0200 (3)
O(2)	0.4540 (1)	0.2338 (2)	−0.08014 (8)	0.0203 (3)
C(2)	0.6518 (1)	0.3680 (3)	−0.0434 (1)	0.0176 (4)
O(3)	0.7106 (1)	0.4875 (2)	0.02742 (8)	0.0195 (3)
C(3)	0.7419 (2)	0.2183 (3)	−0.0616 (1)	0.0174 (4)
C(4)	0.7199 (2)	0.0255 (3)	−0.0554 (1)	0.0237 (4)
C(5)	0.8079 (2)	−0.1053 (3)	−0.0676 (1)	0.0275 (4)
C(6)	0.9193 (2)	−0.0461 (3)	−0.0854 (1)	0.0267 (4)
C(7)	0.9416 (2)	0.1456 (3)	−0.0926 (1)	0.0284 (4)
C(8)	0.8538 (2)	0.2764 (3)	−0.0807 (1)	0.0252 (4)
C(9)	0.5177 (1)	0.5339 (3)	0.6680 (1)	0.0160 (4)
C(10)	0.6045 (1)	0.6730 (3)	0.6533 (1)	0.0175 (4)
C(11)	0.6299 (2)	0.8369 (3)	0.7092 (1)	0.0209 (4)
C(12)	0.7125 (2)	0.9675 (3)	0.6903 (1)	0.0250 (4)
C(13)	0.7734 (2)	0.9418 (3)	0.6138 (1)	0.0274 (5)
C(14)	0.7531 (2)	0.7846 (3)	0.5601 (1)	0.0250 (4)
C(15)	0.6694 (2)	0.6459 (3)	0.5787 (1)	0.0201 (4)
N(1)	0.6556 (1)	0.4889 (3)	0.5233 (1)	0.0231 (4)
C(16)	0.5780 (2)	0.3609 (3)	0.5419 (1)	0.0231 (4)
C(17)	0.5067 (2)	0.3777 (3)	0.6126 (1)	0.0195 (4)
C(18)	0.4380 (1)	0.5595 (3)	0.7417 (1)	0.0148 (4)
O(4)	0.3795 (1)	0.3882 (2)	0.75797 (8)	0.0182 (3)
C(19)	0.3440 (1)	0.7138 (3)	0.7096 (1)	0.0158 (4)
C(20)	0.2432 (2)	0.6530 (3)	0.6320 (1)	0.0185 (4)
C(21)	0.1265 (2)	0.7523 (3)	0.6458 (1)	0.0209 (4)
C(22)	0.1542 (2)	0.9616 (3)	0.6655 (1)	0.0245 (4)
C(23)	0.2329 (2)	0.9794 (3)	0.7613 (1)	0.0213 (4)
N(2)	0.2856 (1)	0.7884 (2)	0.78879 (9)	0.0158 (3)
C(24)	0.1866 (2)	0.6614 (3)	0.8102 (1)	0.0198 (4)
C(25)	0.0796 (2)	0.6682 (3)	0.7303 (1)	0.0222 (4)
C(26)	0.0237 (2)	0.4777 (4)	0.7117 (2)	0.0386 (5)
C(27)	−0.0929 (2)	0.4458 (4)	0.7130 (2)	0.0560 (6)

Table 3. *Final fractional coordinates and equivalent isotropic thermal parameters for cinchoninium* (*R*)-*mandelate at* 122 K

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	U_{eq} (Å^2)
O(1*A*)	0.6076 (2)	0.2266 (2)	0.9805 (1)	0.0352 (7)
O(2*A*)	0.7329 (2)	0.2098 (2)	0.9072 (1)	0.0299 (6)
C(1*A*)	0.6999 (3)	0.2386 (2)	0.9559 (2)	0.0270 (8)
C(2*A*)	0.7786 (3)	0.2929 (2)	0.9901 (2)	0.0290 (8)
O(3*A*)	0.7368 (3)	0.3057 (2)	1.0496 (1)	0.0370 (7)
C(3*A*)	0.7917 (3)	0.3693 (2)	0.9587 (2)	0.0295 (8)
C(4*A*)	0.8953 (3)	0.3934 (3)	0.9387 (2)	0.0320 (9)
C(5*A*)	0.9082 (4)	0.4657 (3)	0.9136 (2)	0.042 (1)
C(6*A*)	0.8180 (4)	0.5141 (3)	0.9067 (2)	0.049 (1)
C(7*A*)	0.7133 (4)	0.4895 (3)	0.9261 (3)	0.048 (1)
C(8*A*)	0.7010 (4)	0.4185 (3)	0.9528 (2)	0.039 (1)
O(1*B*)	0.9794 (3)	0.9984 (2)	0.9628 (2)	0.0474 (8)
O(2*B*)	0.8149 (2)	1.0049 (2)	0.9164 (1)	0.0414 (7)
C(1*B*)	0.8814 (4)	0.9780 (3)	0.9553 (2)	0.040 (1)
C(2*B*)	0.8383 (5)	0.9144 (3)	0.9984 (2)	0.054 (1)
O(3*B*)	0.9260 (4)	0.8909 (2)	1.0360 (2)	0.077 (1)
C(3*B*)	0.7901 (5)	0.8468 (3)	0.9647 (2)	0.052 (1)
C(4*B*)	0.6783 (5)	0.8328 (4)	0.9604 (3)	0.067 (1)
C(5*B*)	0.6358 (5)	0.7674 (4)	0.9310 (3)	0.063 (1)
C(6*B*)	0.7103 (5)	0.7161 (3)	0.9055 (3)	0.065 (1)
C(7*B*)	0.8213 (5)	0.7291 (3)	0.9076 (3)	0.058 (1)
C(8*B*)	0.8606 (5)	0.7944 (3)	0.9366 (2)	0.053 (1)
C(9*A*)	0.4177 (3)	0.2732 (2)	0.8030 (2)	0.0252 (8)
C(10*A*)	0.3640 (3)	0.3207 (2)	0.8471 (2)	0.0233 (8)
C(11*A*)	0.4002 (3)	0.3296 (2)	0.9066 (2)	0.0277 (8)
C(12*A*)	0.3421 (4)	0.3743 (2)	0.9467 (2)	0.0319 (9)
C(13*A*)	0.2436 (4)	0.4108 (2)	0.9284 (2)	0.0357 (9)
C(14*A*)	0.2084 (4)	0.4055 (2)	0.8704 (2)	0.0341 (9)
C(15*A*)	0.2678 (3)	0.3615 (2)	0.8283 (2)	0.0267 (8)
N(1*A*)	0.2300 (3)	0.3602 (2)	0.7696 (2)	0.0312 (8)
C(16*A*)	0.2850 (4)	0.3190 (3)	0.7301 (2)	0.0366 (9)
C(17*A*)	0.3780 (4)	0.2739 (2)	0.7453 (2)	0.0325 (9)
C(18*A*)	0.5167 (3)	0.2241 (2)	0.8195 (2)	0.0248 (8)
O(4*A*)	0.5737 (2)	0.1990 (2)	0.7673 (1)	0.0296 (6)
C(19*A*)	0.4783 (3)	0.1541 (2)	0.8557 (2)	0.0228 (8)
C(20*A*)	0.3931 (3)	0.1022 (2)	0.8254 (2)	0.0299 (8)
C(21*A*)	0.4131 (3)	0.0192 (2)	0.8453 (2)	0.036 (1)
C(22*A*)	0.4290 (4)	0.0179 (2)	0.9136 (2)	0.0357 (9)
C(23*A*)	0.5403 (4)	0.0576 (2)	0.9285 (2)	0.0304 (9)
N(2*A*)	0.5748 (3)	0.1040 (2)	0.8748 (1)	0.0233 (7)
C(24*A*)	0.6103 (3)	0.0498 (2)	0.8254 (2)	0.0284 (8)
C(25*A*)	0.5186 (3)	−0.0099 (2)	0.8142 (2)	0.0336 (9)
C(26*A*)	0.5020 (4)	−0.0291 (3)	0.7490 (2)	0.047 (1)
C(27*A*)	0.5373 (5)	0.0052 (3)	0.7011 (2)	0.060 (1)
C(9*B*)	0.1010 (3)	−0.0908 (2)	0.7879 (2)	0.0260 (8)
C(10*B*)	0.1696 (3)	−0.1212 (2)	0.8345 (2)	0.0251 (8)
C(11*B*)	0.1544 (3)	−0.1081 (2)	0.8966 (2)	0.0319 (9)
C(12*B*)	0.2225 (4)	−0.1411 (3)	0.9388 (2)	0.038 (1)
C(13*B*)	0.3091 (4)	−0.1902 (3)	0.9210 (2)	0.042 (1)
C(14*B*)	0.3282 (4)	−0.2037 (3)	0.8609 (2)	0.036 (1)
C(15*B*)	0.2600 (3)	−0.1694 (2)	0.8164 (2)	0.0272 (8)
N(1*B*)	0.2814 (3)	−0.1861 (2)	0.7574 (2)	0.0332 (8)
C(16*B*)	0.2170 (4)	−0.1551 (3)	0.7162 (2)	0.039 (1)
C(17*B*)	0.1254 (4)	−0.1083 (2)	0.7295 (2)	0.0336 (9)
C(18*B*)	0.0010 (3)	−0.0405 (2)	0.8022 (2)	0.0279 (8)
O(4*B*)	−0.0705 (2)	−0.0349 (2)	0.7517 (1)	0.0333 (7)
C(19*B*)	0.0407 (3)	0.0411 (2)	0.8183 (2)	0.0247 (8)
C(20*B*)	0.0955 (3)	0.0839 (2)	0.7658 (2)	0.0300 (9)
C(21*B*)	0.0621 (3)	0.1681 (2)	0.7673 (2)	0.0342 (9)
C(22*B*)	0.0766 (3)	0.1995 (2)	0.8315 (2)	0.038 (1)
C(23*B*)	−0.0029 (4)	0.1572 (2)	0.8742 (2)	0.0331 (9)
N(2*B*)	−0.0530 (3)	0.0907 (2)	0.8416 (2)	0.0258 (7)
C(24*B*)	−0.1269 (3)	0.1220 (2)	0.7922 (2)	0.0298 (9)
C(25B)	*−0.0612 (4)*	*0.1752 (3)*	*0.7500 (2)*	*0.045 (1)*
C(26*B*)	−0.0835 (5)	0.1620 (6)	0.6849 (3)	0.106 (2)
C(27*B*)	−0.1346 (9)	0.1329 (6)	0.6533 (4)	0.189 (2)

first and will be followed by a discussion of the intermolecular interactions in the diastereomeric salts and their relation to the physico-chemical properties of the salts.

Cinchoninium cations

The asymmetric unit of the *R* salt contains two formula units, so, as illustrated in Fig. 1, three independent observations are made of the cinchoninium cation. One of the cations in the *R* salt (labelled *B*) displays significant disorder of the —CH=CH$_2$ moiety in the crystal. In order to investigate if this disorder is of dynamic or static origin, a set of diffraction data was also collected at room temperature. Though the resolution at 293 K is limited, the refinement of the room-temperature data gave a structure that within experimental accuracy is identical to that obtained from the low-temperature data. An inspection of the anisotropic displacement parameters revealed, as expected, that those obtained from the room-temperature data are approximately three times as large as those from the low-temperature data except for C(26*B*) and C(27*B*). The ratios of displacement parameters determined at 293 and 110 K for these disordered atoms are significantly less, indicating that this part of the cation has a static disorder with positions so close that they cannot be resolved. Apart from this moiety, which also adopts different conformations in the three cations, the geometry of the remaining part of the molecule is virtually identical in the three cations, as shown by the bond lengths, bond angles and torsion angles listed in Tables 4 and 5. The molecular dimensions of the cinchoninium cations compare well with those found in the tetrachlorocadmate(II) salt (Oleksyn, Stadnicka & Hodorowicz, 1978). As noted

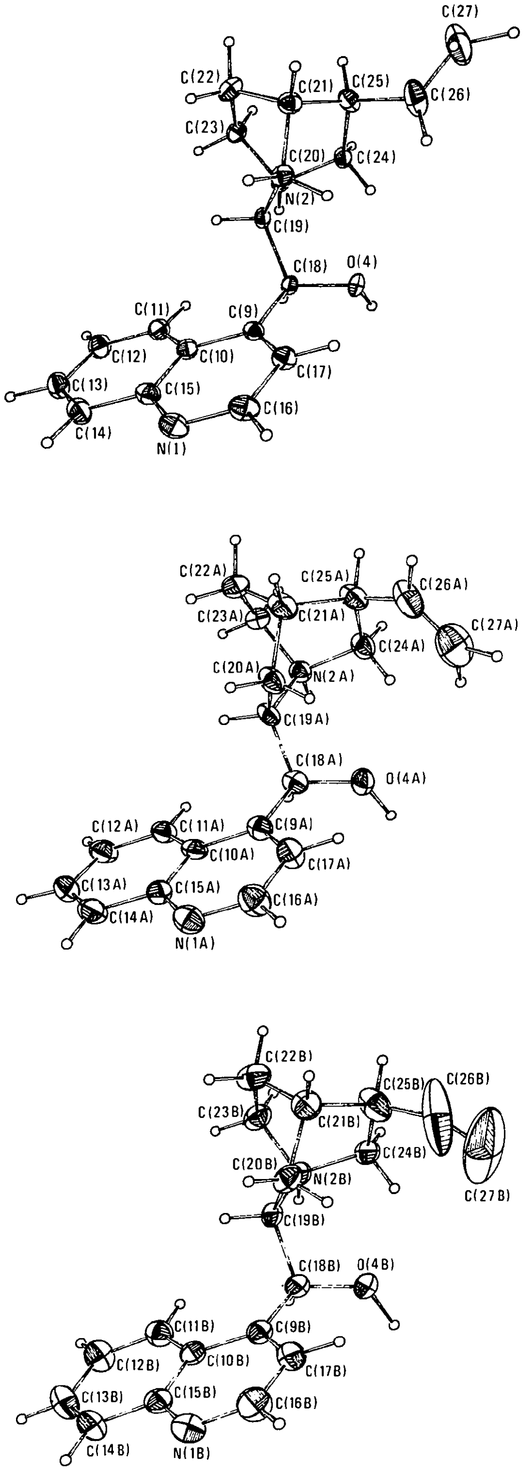

Fig. 1. *ORTEP*II drawings illustrating the atomic numbering scheme and the conformation of the cinchoninium cation in the two salts. The cation without letters in the labels is the one in the *S* salt. The two independent cations in the (*R*)-mandelate salt are distinguished by *A* or *B* in the atomic label. The thermal ellipsoids enclose 50% probability and the H atoms are drawn as spheres with a fixed radius.

Table 4. *Bond lengths* (Å) *and angles* (°) *in the cinchoninium cation found in cinchoninium* (*S*)-*mandelate and cinchonium* (*R*)-*mandelate*

		R salt	
	S salt	Molecule *A*	Molecule *B*
C(9)—C(10)	1.427 (2)	1.435 (5)	1.425 (5)
C(9)—C(17)	1.369 (2)	1.365 (6)	1.363 (6)
C(9)—C(18)	1.520 (2)	1.515 (5)	1.525 (5)
C(10)—C(11)	1.425 (2)	1.398 (6)	1.408 (6)
C(10)—C(15)	1.422 (2)	1.424 (5)	1.434 (5)
C(11)—C(12)	1.371 (2)	1.374 (6)	1.371 (6)
C(12)—C(13)	1.416 (2)	1.407 (6)	1.406 (7)
C(13)—C(14)	1.363 (3)	1.356 (7)	1.373 (7)
C(14)—C(15)	1.418 (2)	1.404 (6)	1.415 (6)
C(15)—N(1)	1.373 (2)	1.380 (5)	1.364 (5)
N(1)—C(16)	1.317 (2)	1.312 (6)	1.316 (6)
C(16)—C(17)	1.412 (2)	1.412 (6)	1.405 (7)
C(18)—O(4)	1.419 (2)	1.415 (5)	1.417 (5)
C(18)—C(19)	1.542 (2)	1.532 (5)	1.542 (5)
C(19)—C(20)	1.537 (2)	1.525 (5)	1.532 (6)
C(19)—N(2)	1.519 (2)	1.516 (5)	1.514 (5)
C(20)—C(21)	1.530 (2)	1.532 (6)	1.522 (6)
C(21)—C(22)	1.534 (2)	1.526 (7)	1.533 (7)
C(21)—C(25)	1.543 (2)	1.534 (6)	1.541 (6)
C(22)—C(23)	1.545 (2)	1.547 (6)	1.536 (6)
C(23)—N(2)	1.507 (2)	1.498 (5)	1.492 (5)
N(2)—C(24)	1.503 (2)	1.509 (5)	1.514 (5)
C(24)—C(25)	1.544 (2)	1.539 (5)	1.537 (6)
C(25)—C(26)	1.497 (3)	1.496 (7)	1.487 (8)
C(26)—C(27)	1.334 (3)	1.292 (8)	1.062 (12)
C(10)—C(9)—C(17)	117.97 (14)	118.4 (4)	118.6 (4)
C(10)—C(9)—C(18)	121.25 (14)	121.1 (3)	121.5 (3)
C(17)—C(9)—C(18)	120.77 (14)	120.5 (4)	119.8 (4)
C(9)—C(10)—C(11)	123.80 (14)	124.5 (3)	124.9 (4)
C(9)—C(10)—C(15)	118.0 (2)	117.2 (3)	117.2 (3)
C(11)—C(10)—C(15)	118.23 (14)	118.4 (3)	117.9 (4)
C(10)—C(11)—C(12)	121.0 (2)	120.9 (4)	121.3 (4)
C(11)—C(12)—C(13)	120.1 (2)	120.1 (4)	120.7 (4)
C(12)—C(13)—C(14)	120.4 (2)	120.4 (4)	120.0 (4)
C(13)—C(14)—C(15)	120.7 (2)	120.4 (4)	120.5 (4)
C(10)—C(15)—C(14)	119.5 (2)	119.7 (4)	119.6 (4)
C(10)—C(15)—N(1)	122.9 (2)	122.5 (4)	122.4 (4)
C(14)—C(15)—N(1)	117.61 (14)	117.9 (4)	117.9 (4)
C(15)—N(1)—C(16)	116.83 (13)	118.1 (4)	117.8 (4)
N(1)—C(16)—C(17)	124.5 (2)	123.2 (4)	123.9 (4)
C(9)—C(17)—C(16)	119.8 (2)	120.5 (4)	119.9 (4)
C(9)—C(18)—O(4)	111.04 (13)	111.1 (3)	110.9 (3)
C(9)—C(18)—C(19)	108.63 (12)	109.7 (3)	109.4 (3)
O(4)—C(18)—C(19)	110.13 (12)	109.2 (3)	107.9 (3)
C(18)—C(19)—C(20)	114.73 (13)	116.5 (3)	114.1 (3)
C(18)—C(19)—N(2)	111.79 (12)	111.8 (3)	111.9 (3)
C(20)—C(19)—N(2)	107.87 (11)	107.5 (3)	107.7 (3)
C(19)—C(20)—C(21)	108.75 (13)	109.1 (3)	109.7 (3)
C(20)—C(21)—C(22)	108.49 (14)	108.6 (3)	109.5 (4)
C(20)—C(21)—C(25)	109.76 (14)	108.3 (3)	109.2 (3)
C(22)—C(21)—C(25)	107.83 (14)	109.7 (3)	108.2 (4)
C(21)—C(22)—C(23)	108.73 (14)	108.4 (3)	109.1 (3)
C(22)—C(23)—N(2)	108.37 (14)	108.2 (3)	109.2 (4)
C(19)—N(2)—C(23)	107.88 (12)	108.6 (3)	107.8 (3)
C(19)—N(2)—C(24)	112.12 (12)	112.1 (3)	113.5 (3)
C(23)—N(2)—C(24)	108.74 (12)	108.6 (3)	108.1 (3)
N(2)—C(24)—C(25)	109.65 (13)	109.7 (3)	110.6 (3)
C(21)—C(25)—C(24)	107.40 (12)	107.5 (3)	107.4 (4)
C(21)—C(25)—C(26)	112.9 (2)	113.4 (4)	113.8 (4)
C(24)—C(25)—C(26)	111.4 (2)	113.8 (4)	113.8 (5)
C(25)—C(26)—C(27)	122.4 (2)	130.2 (5)	145.0 (9)

by Oleksyn, Lebioda & Ciechanowicz-Rutkowska (1979), in their study of the free base, the conformation of cinchonine does not change by protonation. Some of the torsion angles observed in the free base are included in Table 5 for comparison.

Mandelate anions

The molecular geometry of the mandelate anions as observed in the two cinchoninium salts is illustrated by the *ORTEP*II (Johnson, 1971) drawings in

Table 5. *Comparison of selected torsion angles in the cinchoninium cations of the S salt, the R salt and the free cinchonine base* (*Oleksyn et al.*, 1979)

		R salt		
	S salt	Molecule *A*	Molecule *B*	Free base
Around the C(9)—C(18) bond				
C(10)—C(9)—C(18)—O(4)	−166.70 (14)	−164.2 (3)	−163.9 (3)	−158.7
C(17)—C(9)—C(18)—O(4)	14.5 (2)	15.2 (5)	15.3 (5)	23.4
C(17)—C(9)—C(18)—C(19)	−106.8 (2)	−105.7 (4)	−103.7 (4)	−99.8
C(10)—C(9)—C(18)—C(19)	72.1 (2)	75.0 (4)	77.2 (4)	78.1
Around the C(18)—C(19) bond				
C(9)—C(18)—C(19)—N(2)	−163.31 (13)	−178.5 (3)	−171.8 (3)	−160.3
C(9)—C(18)—C(19)—C(20)	73.5 (2)	57.4 (4)	65.6 (4)	73.0
O(4)—C(18)—C(19)—C(20)	−48.4 (2)	−64.6 (4)	−55.2 (4)	−50.6
O(4)—C(18)—C(19)—N(2)	74.9 (2)	59.5 (4)	67.4 (4)	76.1
Around the line C(21)–N(2)				
C(25)—C(21)—N(2)—C(24)	10.40 (12)	8.7 (3)	5.3 (3)	9.1
C(25)—C(21)—N(2)—C(19)	133.73 (14)	131.8 (3)	130.1 (3)	132.0
C(25)—C(21)—N(2)—C(23)	−108.47 (13)	−109.9 (3)	−112.7 (3)	−110.0
C(20)—C(21)—N(2)—C(19)	12.49 (12)	12.6 (3)	10.1 (3)	11.0
C(20)—C(21)—N(2)—C(23)	130.29 (14)	131.0 (3)	127.4 (3)	129.0
C(20)—C(21)—N(2)—C(24)	−110.84 (14)	−110.5 (3)	−114.7 (3)	−111.9
C(22)—C(21)—N(2)—C(23)	10.29 (12)	10.7 (3)	6.0 (3)	9.1
C(22)—C(21)—N(2)—C(24)	129.16 (14)	129.3 (3)	123.9 (3)	128.2
C(22)—C(21)—N(2)—C(19)	−107.51 (13)	−107.7 (3)	−111.2 (3)	−108.9
C(24)—C(25)—C(26)—C27)	124.0 (2)	−13.7 (7)	9 (2)	

Fig. 2 and the bond lengths and angles listed in Table 6. Although the conformation of the mandelate ion differs in these structures, this is not reflected in the bond lengths and angles of the ions. As illustrated by the torsion angles in Table 6, the conformations of the two mandelate ions in the *R* salt differ by *ca* 15°. An analysis of 23 mandelate structures (Larsen & Lopez de Diego, 1993) showed that the most frequently observed value for the torsion angle C(1)—C(2)—C(3)—C(4) is around 100°. The two (*R*)-mandelate ions adopt this usual conformation, which was shown by empirical force-field calculations to have an energy *ca* 8 kJ mol^{-1} lower than the virtually planar arrangement of the C(1)—C(2)—C(3)—C(4) fragment found in the *S* salt (Larsen & Lopez de Diego, 1993). This almost planar arrangement has previously been observed only in the structure of (*S*)-2-hydroxy-1-phenylethylammonium (*S*)-mandelate monohydrate (Acs, Kozma & Larsen, 1992).

Analysis of the crystal packing

The cinchoninium ion contains two possible hydrogen-bond donors, a tertiary ammonium ion and a hydroxy group. It has two possible acceptors, the hydroxy group and the heterocyclic N atom. In the mandelate ion there is one possible donor group, O(3)—H, and three possible acceptor atoms, O(1), O(2) and O(3). Although all possible hydrogen-bond donors are involved in hydrogen bonding in the two diastereomeric salts, the hydrogen-bond patterns display great differences, as illustrated in Table 7 and the packing diagrams in Figs. 3 and 4. As the positions of the H atoms in the *R* salt were less well

Table 6. *Bond lengths* (Å), *bond angles and torsion angles* (°) *in the mandelate ion found in cinchoninium* (*S*)-*mandelate and cinchoninium* (*R*)-*mandelate*

		R salt	
	S salt	Molecule *A*	Molecule *B*
O(1)—C(1)	1.254 (2)	1.258 (5)	1.246 (6)
O(2)—C(1)	1.264 (2)	1.254 (5)	1.268 (6)
C(1)—C(2)	1.540 (2)	1.540 (6)	1.552 (7)
C(2)—O(3)	1.421 (2)	1.430 (5)	1.408 (7)
C(2)—C(3)	1.520 (2)	1.510 (6)	1.512 (7)
C(3)—C(4)	1.394 (2)	1.392 (6)	1.374 (8)
C(3)—C(8)	1.395 (2)	1.396 (6)	1.393 (8)
C(4)—C(5)	1.389 (3)	1.384 (6)	1.409 (9)
C(5)—C(6)	1.385 (3)	1.386 (7)	1.387 (9)
C(6)—C(7)	1.389 (3)	1.402 (7)	1.360 (9)
C(7)—C(8)	1.386 (3)	1.380 (6)	1.390 (8)
O(1)—C(1)—O(2)	124.14 (14)	125.9 (4)	125.9 (4)
O(1)—C(1)—C(2)	118.30 (13)	115.8 (3)	116.1 (4)
O(2)—C(1)—C(2)	117.56 (13)	118.2 (3)	118.1 (4)
C(1)—C(2)—O(3)	111.53 (12)	109.4 (3)	108.6 (4)
C(1)—C(2)—C(3)	111.05 (13)	112.3 (3)	112.4 (4)
O(3)—C(2)—C(3)	107.32 (12)	108.9 (3)	110.8 (4)
C(2)—C(3)—C(4)	122.87 (14)	120.5 (4)	123.4 (5)
C(2)—C(3)—C(8)	118.5 (2)	120.2 (4)	119.7 (5)
C(4)—C(3)—C(8)	118.5 (2)	119.2 (4)	116.9 (5)
C(3)—C(4)—C(5)	120.6 (2)	120.3 (4)	122.2 (6)
C(4)—C(5)—C(6)	120.5 (2)	120.6 (4)	118.3 (6)
C(5)—C(6)—C(7)	119.4 (2)	119.2 (4)	121.1 (5)
C(6)—C(7)—C(8)	120.2 (2)	120.1 (4)	119.3 (5)
C(3)—C(8)—C(7)	120.8 (2)	120.5 (4)	122.3 (5)
O(1)—C(1)—C(2)—O(3)	28.6 (2)	11.8 (5)	−2.8 (6)
O(1)—C(1)—C(2)—C(3)	91.1 (2)	−109.2 (4)	−125.8 (5)
C(1)—C(2)—C(3)—C(4)	1.3 (2)	−119.3 (4)	−105.3 (6)
O(3)—C(2)—C(3)—C(4)	123.4 (2)	119.4 (4)	133.0 (6)

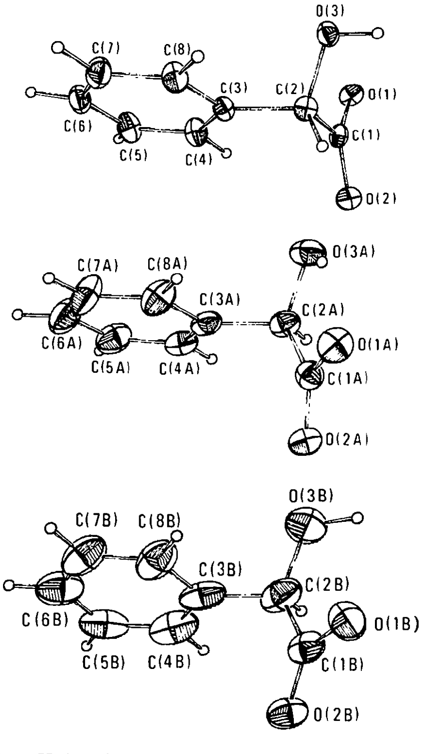

Fig. 2. *ORTEP*II drawings illustrating the atomic labelling and the conformation of the mandelate anion found in the two salts. The labelling follows the same lines as that in Fig. 1 for the cations. The thermal ellipsoids enclose 50% probability and the H atoms are drawn as spheres with a fixed radius.

Table 7. *Hydrogen-bond geometry* (Å, °)

D—H···*A*	*D*—*A*	*H*—*A*	∠*D*H*A*
S salt			
N(2)—H(N2)—O(1^{i})	2.689 (2)	1.73 (2)	166 (2)
O(4)—H(O4)—O(2^{ii})	2.631 (2)	1.73 (2)	167 (2)
O(3)—H(O3)—O(2^{iii})	2.743 (2)	1.86 (2)	176 (2)

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

D—H···*A*	*D*—*A*	*H*—*A*	∠*D*H*A*
R salt at 122 K			
N(2*A*—H(N2*A*)—O(2*A*)	2.748 (4)	1.81	168
N(2*B*)—H(N2*B*)—O(2*B*^{iv})	2.742 (4)	1.78	177
O(4*A*)—H(O4*A*)—N(1*B*)	2.714 (4)	1.68	157
O(4*B*)—H(O4*B*)—N(1*A*^{vi})	2.696 (4)	1.54	165
O(3*A*)—H(O3*A*)—O(1*A*)	2.585 (4)	1.81	136
O(3*B*)—H(O3*B*)—O(1*B*)	2.560 (5)	2.12	98

Symmetry code: (iv) $-1 + x, -1 + y, z$; (v) $1 - x, \frac{1}{2} + y, 1\frac{1}{2} - z$; (vi) $-x, -\frac{1}{2} + y, 1\frac{1}{2} - z$.

determined, most emphasis is made on donor–acceptor distances in this compound.

The strongest hydrogen bond would be predicted to be between the two oppositely charged groups and as expected hydrogen bonds are formed between the tertiary ammonium group in the cinchoninium ion and the carboxylate group of the mandelate ion in both salts. The N—O distance is slightly longer in the *R* salt than in the *S* salt [2.745 (4) compared to 2.689 (2) Å]. The hydroxy group of the cinchoninium ion donates its proton to the carboxylate group of a mandelate ion in the *S* salt. In the *R* salt the two independent cinchoninium hydroxy groups donate protons to a heterocyclic N atom of the cinchoninium cation. In the *S* salt intermolecular hydrogen bonds connect the hydroxy group of the mandelate ion and the carboxylate group of a mandelate ion generated by the symmetry of the twofold screw axis. In the *R* salt an intramolecular O(3)—H···O(1) hydrogen bond is present in the mandelate fragment in molecule *A*. The distances from both O(3) atoms to potential acceptor atoms in other molecules are larger than 3.0 Å. The O(3*B*)—O(1*B*) distance (2.560 Å) is slightly smaller than the equivalent distance in molecule *A*. This suggests that an intramolecular hydrogen bond is also formed in the mandelate fragment in molecule *B*. In both salts there are three hydrogen bonds per formula unit but in the *S* salt all the hydrogen bonds connect different ions while in the *R* salt only 2/3 of them are between different ions.

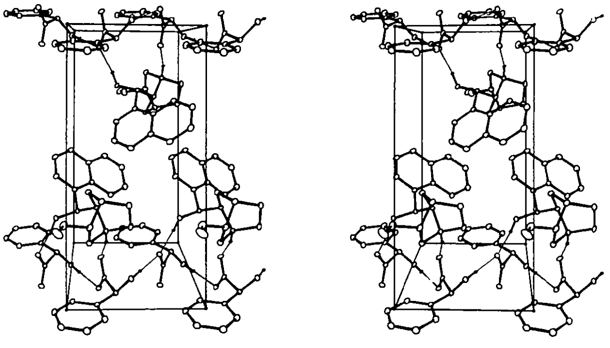

Fig. 3. Stereo drawing of the packing in cinchoninium (*S*)-mandelate seen in the direction of the crystallographic $\bar{a}$ axis with horizontal $\bar{b}$ axis and vertical $\bar{c}$ axis. Hydrogen bonds are indicated by thin lines.

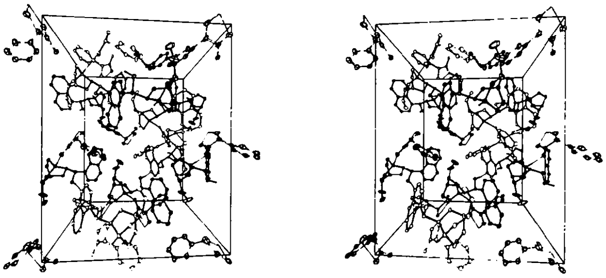

Fig. 4. Stereo drawing of the packing in cinchoninium (*R*)-mandelate seen in the direction of the crystallographic $\bar{a}$ axis with horizontal $\bar{b}$ axis and vertical $\bar{c}$ axis. Hydrogen bonds are indicated by thin lines. The *A* ions are drawn with open atoms and the atoms in the *B* ions are drawn as 'footballs'.

Relation between structure and thermodynamic properties

The DSC curves showed that no phase transitions occur in the two diastereomeric salts between 293 K and their melting points. As agreement was found between the Weissenberg photographs and the low-temperature crystal data, we conclude that the crystal structures do not change in the temperature range and that the crystal structure can be related to thermodynamic properties.

The diastereomeric salts isolated from ethyl acetate had different melting points than those reported earlier by McKenzie (1899), who performed the resolution in water. In order to make a comparison the cinchoninium mandelate salts were also recrystallized from water at room temperature. Thermogravimetric and DSC measurements were made for the four salts. They showed that a solvated cinchoninium (*R*)-mandelate salt containing one molecule of ethyl acetate could be obtained under certain circumstances. This salt looses the ethyl acetate at 373 K and is transformed to the cinchoninium (*R*)-mandelate salt described here. Identical unsolvated salts were obtained by recrystallization from ethyl acetate and water. They can be heated to 473 K without any decomposition. The DSC curves showed that cinchoninium (*S*)-mandelate melts at 427 K and that cinchoninium (*R*)-mandelate melts at a higher temperature with $T_{\text{fus}} = 462$ K. A resolution of racemic mandelic acid with cinchonine was performed. This demonstrated that the difference in the solubilities between the two salts is so large that cinchonine can be used to resolve mandelic acid and that the higher melting (*R*)-mandelate also is the less soluble of the two diastereomeric salts. A difference between the melting enthalpies would be due to a difference in the crystal enthalpies, if the resulting liquids had very similar thermodynamic properties. The DSC measurements showed that the more soluble (*S*)-mandelate salt has the larger heat of fusion indicating a smaller crystal enthalpy for this compound relative to the *R* salt. As the two diastereomeric salts have virtually identical densities this difference in the crystal enthalpies would correspond to an equivalent difference in the crystal energies. The *S* salt has more interionic interactions in terms of hydrogen bonds than the *R* salt, as described previously. On the other hand, the (*S*)-mandelate ion is found in a conformation with an energy that is *ca* 8 kJ mol^{-1} larger than the energy of the (*R*)-mandelate ion. This difference in conformational energy would be more than compensated for by the intermolecular hydrogen bonds in the *S* salt which consequently would have a lower energy and a larger energy of fusion, as found experimentally. The *R* salt has disorder in one of the cinchoninium ions and the displacement parameters are larger than those in the *S* salt. One would expect that these differences would be reflected in a smaller entropy of fusion for the *R* salt. The experimental data supports this, as $\Delta S^{\ominus}_{\rm fus}$(*S* salt) = 97 J K^{-1} mol^{-1} and $\Delta S^{\ominus}_{\rm fus}$(*R* salt) = 80 J K^{-1} mol^{-1} at their respective melting points. Assuming correspondence between the melting and solution processes for the two salts, the difference in the solubilities of the diastereomeric salts should be caused by differences in their melting enthalpies and entropies. If the difference in solubility was due solely to a difference in enthalpy the *S* salt should be the less soluble, but the difference in entropy more than compensates for the ΔH difference, making the *R* salt the less soluble salt. This leads one to the conclusion that the difference in the solubilities of the diastereomeric cinchoninium mandelates has its origin in the difference between the crystal entropies.

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β-Alkoxy Schiff Base–Oxazolidine Tautomerism: Solid-State Structure of *N*-Diphenylmethylene-L-threonine Methyl Ester

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Abstract

The benzophenone Schiff base of methyl L-threonate, $C_{18}H_{19}NO_3$, $M_r = 297.36$, crystallized as its cyclic methyl (4*S*,5*R*)-5-methyl-2,2-diphenyl-1,3-oxazolidine-4-carboxylate tautomer, orthorhombic, $P2_12_12_1$, $a = 8.455$ (2), $b = 12.648$ (2), $c = 14.650$ (3) Å, $V = 1566.6$ (5) Å^3, $Z = 4$, $D_x = 1.26$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.8$ cm^{-1}, $F(000) = 632$, $T = 296$ K. The structure was solved by direct methods; $R = 0.040$ and $wR = 0.045$ for 1113 observed reflections. H atoms were included in the refinement, but were constrained to their attached atoms. The amine hydrogen (HN) was located from a difference map and was refined with a fixed isotropic thermal parameter. The structure confirms the existence of

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† To whom questions concerning the preparation and reactivity of the Schiff bases should be addressed.

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