Structural Study of the Solid-State Ring-Closure Reaction of (2*R*,3*R*)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid

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Marthi, K., Larsen, S., Ács, M. and Fogassy, E., 1996. Structural Study of the Solid-State Ring-Closure Reaction of (2*R*,3*R*)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid. – Acta Chem. Scand. 50: 899–905. © Acta Chemica Scandinavica 1996.

The crystal structure of the (2*R*,3*R*)-(−)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid has been determined from single-crystal X-ray diffraction data in order to study the solid state ring closure reaction between the carboxylic acid and the amino substituent. This reaction occurs only in the optically active crystals, whereas the racemate reacts only in melt or solution. (2*R*, 3*R*)-(−)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid ($C_{16}H_{17}NO_4S$) crystallizes in the monoclinic space group $P2_1$ with $a = 14.240(2)$, $b = 5.3154(11)$, $c = 19.535(6)$ Å, $\beta = 91.93(2)°$, $V = 1477.8(6)$ Å^3, $Z = 4$, $D_x = 1.435$ g cm^{-3}, $\mu = 20.63$ cm^{-1}. The two independent molecules differ in their protonization: one is a cation and the other is an anion. A very short hydrogen bond [O⋯O = 2.480(6) Å] links the carboxylic acid and the carboxylate groups. The two molecules adopt different conformations: one has an extended structure whereas the other has the amino group close to the carboxylate group. The latter molecule requires only minor changes for the solid-state reaction to take place forming the seven-membered ring. From the analysis of the hydrogen-bonding pattern a reaction mechanism for the ring closure reaction is proposed.

It has long been recognised that the pure enantiomers have different physico-chemical properties (e.g. melting point, melting enthalpy, solubility) and reaction rates than their corresponding racemates.[1,2] Mixtures of enantiomers with compositions different from 1:1 tend to behave as mixtures of two different compounds, i.e. racemates and the enantiomer in excess.[3]

3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid (1) has been observed to form a racemic compound which has a melting point ca. 40 K higher than the pure enantiomer. In accordance with this the binary phase diagram has its eutectic composition with a mole fraction higher than 0.92.[4] This explains why the racemate precipitates from most mixtures of enantiomers upon recrystallization.[5] A ring closure reaction of the compound (Scheme 1) performed in xylene or melt had a reaction rate for the enantiomer that was twice the rate for the racemate.[4]

Besides the different behaviour of the racemate and enantiomer in solution it was observed that by heating the optically pure compound to 125 °C for 90 min the ring-closure reaction occurs in the solid state with a yield of 98%.[4] No reaction was detected for the racemate under the same conditions. This could indicate major structural differences between the racemate and enantiomer in the solid state.

The behaviour of racemic and optically pure 1 upon heating has been studied earlier.[4] Distinct differences in the infrared spectra of the enantiomers and racemate were observed.[4] These spectra show that the racemate contains a deprotonated carboxylic acid group, whereas the enantiomer contains both ionized and neutral carboxylic acid and amino groups.

Originally it was our aim to determine the crystal structures of both the racemic and the optically active crystals to investigate the intermolecular interactions. Unfortunately all attempts to prepare single crystals of the racemate were futile, which enabled us to study the racemate only by powder diffraction. Here we report the crystal structure of the optically active compound

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‡ The Centre for Crystallographic Studies is funded by the Danish National Research Foundation.
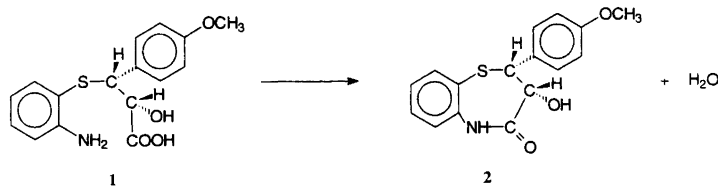
Scheme 1.

which enabled us to analyze the hydrogen bonding scheme and to suggest a mechanism for the ring closure reaction.

Experimental

Preparation. The racemic compound was prepared as described in Ref. 6. The resolution was carried out as described by Kojić-Prodić *et al.*[7] and Gizur *et al.*[8] to obtain the compound with a high optical purity ($[\alpha]_D = -335.3$, $c = 0.3$ ethanol).

Thermodynamic measurements. Melting points and heats of fusion for racemic and optically active 1 were measured by differential scanning calorimetry using a PL-DSC instrument calibrated with indium and tin. The measurements were carried out under a nitrogen atmosphere in open crucibles. Sampling was made every 1.25 s, and heating rates of 10, 5 and 2 K min^{-1} were used. The mass of the samples varied between 3.8 and 4.1 mg measured with a precision of 0.001 mg. The error of the melting point determination is ± 0.5 K. Thermogravimetric measurements on the samples showed slight (0.3%) decomposition in the investigated temperature range; therefore sealed crucibles were used for the reheating experiments.

Spectroscopic measurements. Optical rotations were measured at room temperature at 589 nm (Na$_D$) with a Perkin Elmer 241 polarimeter.

X-Ray powder diffraction patterns. A STOE Stadi P powder diffractometer was used to record the diagrams of racemic and optically pure 1. Cu Kα_1 radiation selected by a curved germanium monochromator was used for the experiment. The diffraction patterns from samples in a transmission mode were recorded with a position sensitive detector covering 7° in 2θ. The software[9] Visual X^{POW} provided with the instrument was used to analyze the diffraction pattern of (2R, 3R)-1 employing the results obtained from the single-crystal X-ray diffraction study.

Structure determination of (2R,3R)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid. Crystals for the single-crystal diffraction study were grown from a 5:1 chloroform/n-heptane mixture.

The data collection was performed with a CAD4 diffractometer. CuKα ($\lambda = 1.541\,78$ Å) radiation obtained

from a graphite monochromator was used. The crystal was cooled with an Enraf-Nonius gas-flow low-temperature device. The temperature, 122.0(5) K, was monitored with a thermocouple placed a few centimetres above the crystal in the exhaust pipe. During the experiment it remained constant within 1 K. The experimental conditions and a summary of the results of data reduction and structure refinement are presented in Table 1. An analysis of reflection profiles provided the basis for the selection of ω–2θ scan mode and scan width for the data

Table 1. Crystal data and summary of the data collection and structure refinement results.

Formula	$C_{16}H_{17}NO_4S$
Formula weight	319.37
Radiation	CuKα ($\lambda = 1.541\,78$ Å)
Temperature	122.0(5) K
Space group	$P2_1$
a/Å	14.240(2)
b/Å	5.3154(11)
c/Å	19.535(6)
β/°	91.93(2)
V/Å^3	1477.8(6)
Z	4
$F(000)$	672
Crystal size/mm	$0.02 \times 0.10 \times 0.20$
D_x/g cm^{-3}	1.435
μ(CuKα)/mm^{-1}	2.063
Refl. used in determination of cell parameters	18
θ-range/°	14.16 to 19.41
Scan type	ω–2θ
θ-range for data collection/°	2.26 to 75.05
Range of h	−17 to 17
Range of k	−6 to 6
Range of l	−24 to 24
R_{int}	0.1091
Transmission factor range	0.758 to 0.958
No. of measured reflections including standard reflections	13055
No. of independent reflections	5441
No. of observed reflections	
$[I > 2\sigma(I)]$	4816
Refinement	$\theta_{max} = 64.98$
No. of independent reflections	4597
No. of observed reflections	
$[I > 2\sigma(I)]$	4184
No. of variables	405
w^{-1} $[P = (F_0^2 + 2F_c^2)/3]$	$\sigma^2(F_0^2) + (0.0929P)^2 + 0.7617P$
R for $F > 4\sigma(F)$	0.0589
wR_2 for all F^2 data	0.1614
S for all F^2 data	1.106
Max. shift/e.s.d.	−0.001
Max. and min. $\Delta\rho$/e Å^{-3}	0.444 and −0.522

collection. The intensities of three standard reflections [(1 0 0), (0 0 7) and (0 1 1)] were measured after every 10^4 s. They showed a decay up to 17%. The orientation of the crystal was checked after every 300 reflections. Reflections measured only in prescan, i.e. with the highest possible scan speed and having intensities less than ten times their e.s.d., were omitted as they have been shown to suffer from systematic errors.[10] In the data reduction performed with the DREADD programs,[11] corrections were made for the degradation, Lorentz, polarization, background and absorption effects. Reflections related by the symmetry of the crystal class were averaged. The structure was solved by direct methods using SHELXS-86[12] and refined by full matrix least-squares with SHELXL-93[13] minimizing $\Sigma w(F_0^2 - F_c^2)^2$. Scattering factors were taken from Ref. 14 and used as contained in the program. The analysis of the reflection data showed that the crystal is weakly diffracting with a corresponding max. resolution of ca. 0.60 Å. The final least-squares cycles of the refinement were based on reflections with θ values less than 65° ($d \approx 0.60$ Å). After anisotropic displacement parameters were introduced for the non-hydrogen atoms, the difference Fourier map showed the positions of most of the hydrogen atoms. The hydrogen atoms bonded to carbon atoms were fixed in their idealized positions. A subsequent difference Fourier map showed the position of two hydrogen atoms bonded to the nitrogen atom in molecule A. The position of these atoms was included in the refinement. The remaining six hydrogen atoms bonded to oxygen and nitrogen atoms could not be located from difference Fourier maps and were not generated due to ambiguous possibilities. The final atomic coordinates are listed in Table 2. Polar axis restraints were applied according to the method of Flack and Schwarzenbach.[15] The absolute configuration was chosen to match the absolute configuration known from the synthesis of Diltiazem [(2S,3S)-3-acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one hydrochloride],[7] and this choice was supported by the value for the x absolute structure parameter,[16] −0.01(3). Anisotropic displacement parameters, parameters for the hydrogen atoms and lists of the observed and calculated structure factors can be obtained from the authors (S.L.).

Results and discussion

Description of the crystal structure. The crystals of (−)-1 contain two molecules in the asymmetric unit which differ in their protonation and conformation as illustrated by the bond lengths, angles and torsion angles in Table 3 and by Fig. 1. Both molecules have 2R,3R absolute configuration as predicted from the optical rotation of the compound using the known absolute configuration of Diltiazem.[7]

Molecule A adopts a conformation where the amino/ammonium group is close to the carboxylate group,

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (in Å²) in (2R,3R)-3-(2-amino-phenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid.

Atom	x	y	z	U_{eq}^a
S1A	0.40142(7)	0.2624(2)	0.59880(6)	0.0326(3)
N1A	0.5368(3)	0.4006(9)	0.7205(2)	0.0386(10)
O1A	0.3601(3)	−0.3211(7)	0.7363(2)	0.0438(9)
O12A	0.3878(3)	0.0625(8)	0.7757(2)	0.0683(14)
O2A	0.2411(2)	0.2551(7)	0.7010(2)	0.0412(8)
O4A	0.0487(2)	0.0127(7)	0.3891(2)	0.0402(8)
C1A	0.3468(3)	−0.0906(10)	0.7357(3)	0.0349(11)
C2A	0.2755(3)	0.0151(8)	0.6828(2)	0.0308(10)
C3A	0.3157(3)	0.0052(9)	0.6113(2)	0.0320(10)
C4A	−0.0226(3)	0.2017(10)	0.3852(3)	0.0399(12)
C11A	0.2424(3)	0.0111(9)	0.5539(2)	0.0305(10)
C12A	0.1742(3)	0.1963(10)	0.5492(3)	0.0400(12)
C13A	0.1082(3)	0.2046(9)	0.4953(3)	0.0367(11)
C14A	0.1106(3)	0.0249(9)	0.4446(2)	0.0318(10)
C15A	0.1790(3)	−0.1649(9)	0.4473(3)	0.0348(11)
C16A	0.2443(3)	−0.1672(9)	0.5015(3)	0.0328(10)
C21A	0.5098(3)	0.1173(9)	0.6218(2)	0.0322(10)
C22A	0.5644(3)	0.1961(9)	0.6790(3)	0.0361(11)
C23A	0.6488(3)	0.0759(12)	0.6950(3)	0.0457(12)
C24A	0.6798(4)	−0.1173(12)	0.6549(3)	0.0509(14)
C25A	0.6278(3)	−0.1940(11)	0.5972(3)	0.0460(13)
C26A	0.5430(3)	−0.0766(10)	0.5813(3)	0.0397(12)
S1B	0.71896(13)	−0.4141(3)	1.01667(8)	0.0592(4)
N1B	0.6589(3)	−0.0560(10)	1.1284(3)	0.0531(12)
O1B	0.5728(3)	0.2489(8)	0.8608(2)	0.0616(11)
O12B	0.4983(3)	−0.1156(9)	0.8637(2)	0.0650(12)
O2B	0.5449(3)	−0.0939(9)	1.0033(2)	0.0568(11)
O4B	0.9548(3)	−0.0408(9)	0.7480(2)	0.0544(10)
C1B	0.5576(3)	0.0478(10)	0.8873(3)	0.0405(12)
C2B	0.6097(3)	−0.0312(11)	0.9539(3)	0.0424(12)
C3B	0.6738(4)	−0.2538(10)	0.9386(2)	0.0415(11)
C4B	1.0146(4)	0.1777(14)	0.7541(4)	0.063(2)
C11B	0.7495(3)	−0.1865(9)	0.8894(3)	0.0374(11)
C12B	0.8051(3)	0.0314(9)	0.8959(3)	0.0388(11)
C13B	0.8737(3)	0.0843(11)	0.8502(3)	0.0410(11)
C14B	0.8886(3)	−0.0750(11)	0.7948(3)	0.0438(13)
C15B	0.8336(3)	−0.2911(10)	0.7882(3)	0.0444(13)
C16B	0.7655(4)	−0.3426(10)	0.8337(3)	0.0431(12)
C21B	0.7903(4)	−0.1840(10)	1.0588(3)	0.0411(12)
C22B	0.7536(4)	−0.0336(11)	1.1087(3)	0.0427(12)
C23B	0.8121(5)	0.1492(13)	1.1393(3)	0.061(2)
C24B	0.9028(5)	0.167(2)	1.1227(4)	0.083(3)
C25B	0.9409(5)	0.020(2)	1.0759(4)	0.095(4)
C26B	0.8846(5)	−0.161(2)	1.0435(4)	0.071(2)

$^a U_{eq}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

whereas this fragment in molecule **B** has an elongated conformation, predicted by MM2 calculations.[2]

From Fig. 1 and Table 2 it is apparent that the atoms of molecule **B** have much larger displacement parameters than the corresponding atoms in molecule **A**. This could be an indication of disorder in the crystal and could explain the poor quality of the diffraction data, which did not enable us to locate all the hydrogen atoms. Therefore it requires a detailed analysis to establish whether one molecule is a cation and the other is an anion, or one is a zwitter-ion and the other is neutral, or all four types of molecules are present in the crystal. However, as shown in the following paragraphs, there is

Table 3. Bond distances (in Å), bond and selected torsion angles (in °) in (2*R*,3*R*)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid.

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S1A–C21A	1.769(4)	S1B–C21B	1.775(6)
S1A–C3A	1.854(5)	S1B–C3B	1.844(5)
N1A–C22A	1.419(7)	N1B–C22B	1.419(7)
O1A–C1A	1.240(6)	O1B–C1B	1.210(7)
O12A–C1A	1.257(6)	O12B–C1B	1.286(6)
O2A–C2A	1.416(6)	O2B–C2B	1.398(6)
O4A–C14A	1.375(5)	O4B–C14B	1.349(6)
O4A–C4A	1.429(6)	O4B–C4B	1.442(8)
C1A–C2A	1.531(6)	C1B–C2B	1.534(8)
C2A–C3A	1.528(7)	C2B–C3B	1.531(7)
C3A–C11A	1.508(6)	C3B–C11B	1.511(7)
C11A–C12A	1.384(7)	C11B–C12B	1.406(7)
C11A–C16A	1.396(7)	C11B–C16B	1.393(7)
C12A–C13A	1.389(7)	C12B–C13B	1.376(7)
C13A–C14A	1.377(7)	C13B–C14B	1.395(8)
C14A–C15A	1.402(6)	C14B–C15B	1.394(8)
C15A–C16A	1.385(7)	C15B–C16B	1.365(8)
C21A–C22A	1.405(7)	C21B–C22B	1.377(8)
C21A–C26A	1.392(7)	C21B–C26B	1.390(8)
C22A–C23A	1.387(7)	C22B–C23B	1.402(8)
C23A–C24A	1.374(8)	C23B–C24B	1.344(9)
C24A–C25A	1.389(8)	C24B–C25B	1.329(13)
C25A–C26A	1.385(7)	C25B–C26B	1.393(13)
C21A–S1A–C3A	102.6(2)	C21B–S1B–C3B	104.1(2)
C14A–O4A–C4A	116.3(4)	C14B–O4B–C4B	118.4(5)
O1A–C1A–O12A	124.6(5)	O1B–C1B–O12B	124.6(5)
O1A–C1A–C2A	117.8(5)	O1B–C1B–C2B	121.1(5)
O12A–C1A–C2A	117.7(4)	O12B–C1B–C2B	114.3(5)
O2A–C2A–C3A	113.8(4)	O2B–C2B–C3B	111.3(5)
O2A–C2A–C1A	112.9(4)	O2B–C2B–C1B	109.9(4)
C3A–C2A–C1A	110.0(4)	C3B–C2B–C1B	108.7(4)
C11A–C3A–C2A	114.1(4)	C11B–C3B–C2B	112.6(4)
C11A–C3A–S1A	109.2(3)	C11B–C3B–S1B	113.5(3)
C2A–C3A–S1A	111.4(3)	C2B–C3B–S1B	112.9(3)
C12A–C11A–C16A	117.8(4)	C12B–C11B–C16B	117.1(5)
C12A–C11A–C3A	122.0(4)	C12B–C11B–C3B	123.3(5)
C16A–C11A–C3A	120.1(4)	C16B–C11B–C3B	119.6(5)
C11A–C12A–C13A	121.9(5)	C11B–C12B–C13B	121.3(5)
C12A–C13A–C14A	119.4(4)	C12B–C13B–C14B	120.6(5)
O4A–C14A–C13A	124.7(4)	O4B–C14B–C13B	124.9(5)
O4A–C14A–C15A	114.9(4)	O4B–C14B–C15B	116.8(5)
C13A–C14A–C15A	120.4(4)	C13B–C14B–C15B	118.3(5)
C14A–C15A–C16A	118.9(4)	C14B–C15B–C16B	120.9(5)
C11A–C16A–C15A	121.7(4)	C11B–C16B–C15B	121.9(5)
C22A–C21A–C26A	118.9(4)	C22B–C21B–C26B	119.6(6)
C22A–C21A–S1A	121.8(4)	C22B–C21B–S1B	120.2(4)
C26A–C21A–S1A	119.3(3)	C26B–C21B–S1B	120.2(5)
C21A–C22A–C23A	119.6(5)	C21B–C22B–C23B	118.0(5)
C21A–C22A–N1A	121.7(4)	C21B–C22B–N1B	122.0(5)
C23A–C22A–N1A	118.7(5)	C23B–C22B–N1B	119.9(5)
C22A–C23A–C24A	120.6(5)	C22B–C23B–C24B	120.4(7)
C23A–C24A–C25A	120.7(5)	C23B–C24B–C25B	122.9(7)
C24A–C25A–C26A	119.1(5)	C24B–C25B–C26B	118.4(6)
C21A–C26A–C25A	121.1(5)	C21B–C26B–C25B	120.5(7)
N1A–C22A–C21A–S1A	−1.7(7)	N1B–C22B–C21B–S1B	0.2(7)
C22A–C21A–S1A–C3A	−114.9(4)	C22B–C21B–S1B–C3B	94.4(5)
C21A–S1A–C3A–C2A	93.5(3)	C21B–S1B–C3B–C2B	−64.7(4)
S1A–C3A–C2A–C1A	−77.4(4)	S1B–C3B–C2B–C1B	−166.5(3)
C3A–C2A–C1A–O1A	−72.7(5)	C3B–C2B–C1B–O1B	−113.1(6)
C3A–C2A–C1A–O12A	107.5(5)	C3B–C2B–C1B–O12B	67.2(6)
O2A–C2A–C1A–O1A	158.9(4)	O2B–C2B–C1B–O1B	125.0(5)
O2A–C2A–C1A–O12A	−20.8(6)	O2B–C2B–C1B–O12B	−54.7(6)
S1A–C3A–C2A–O2A	50.4(4)	S1B–C3B–C2B–O2B	−45.4(5)
C26A–C21A–S1A–C3A	66.5(4)	C26B–C21B–S1B–C3B	−88.1(5)
C21A–S1A–C3A–C11A	−139.7(3)	C21B–S1B–C3B–C11B	65.0(4)
C1A–C2A–C3A–C11A	158.4(4)	C1B–C2B–C3B–C11B	63.3(5)
O2A–C2A–C3A–C11A	−73.8(5)	O2B–C2B–C3B–C11B	−175.6(4)
S1A–C3A–C11A–C12A	−72.3(5)	S1B–C3B–C11B–C12B	−83.0(6)
S1A–C3A–C11A–C16A	104.9(4)	S1B–C3B–C11B–C16B	98.1(5)
C2A–C3A–C11A–C12A	53.0(6)	C2B–C3B–C11B–C12B	46.9(6)
C2A–C3A–C11A–C16A	−129.8(4)	C2B–C3B–C11B–C16B	−132.1(5)
C13A–C14A–O4A–C4A	−0.3(7)	C13B–C14B–O4B–C4B	−1.0(7)
C15A–C14A–O4A–C4A	179.2(4)	C15B–C14B–O4B–C4B	−178.6(5)
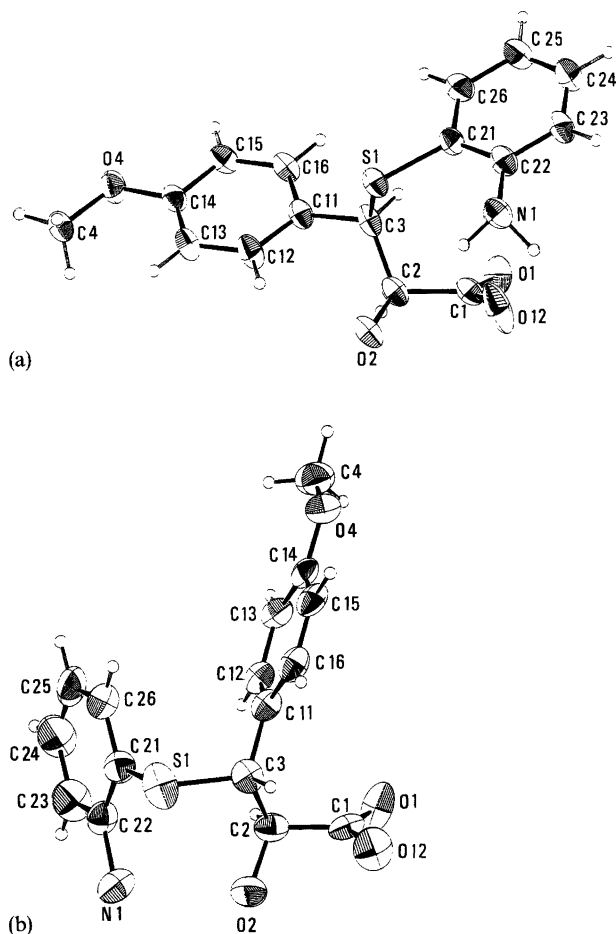
Fig. 1. ORTEPII[17] drawing showing the molecular geometry of (a) molecule **A** and (b) molecule **B**. The thermal ellipsoids are scaled to include 50% probability. The hydrogen atoms are drawn as spheres with a fixed radius.

tion/protonization. Because the bond lengths involving disordered atoms tend to be shorter, one could expect that the true N1B–C22B bond length is longer than observed, indicating that N1B might be positively charged.

All N···O, N···S, O···O and O···S distances shorter than the sum of the van der Waals radii[18] were examined. We were left with several short interatomic N···O and O···O distances of a magnitude that could correspond to hydrogen bonds after possible hydrogen bonds leading to five-membered rings were excluded. Although the positions of most of the hydrogen atoms involved in the hydrogen bonds were not established, we have been able to suggest a plausible hydrogen-bonding system where all hydrophilic hydrogen atoms take part in hydrogen bonds. The suggested hydrogen bonding pattern is listed in Table 4 and illustrated by the packing diagram in Fig. 2. These results are in agreement with the conclusion obtained from a previous analysis of the IR spectrum of (+)-1. It showed the presence of three different types of hydrogen-bonded hydroxy groups.[4] They can be identi-

Table 4. Short interatomic contact distances in (2R,3R)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid.

D–H···A	D···A/Å	D–H···A/°	H··· A/Å
N1A–H1NA···O1B	2.886(6)	161(5)	1.87(7)
N1A–H2NA···O1A[a]	2.944(6)	150(5)	2.06(7)
O12B–H···O12A	2.480(6)		
O2A–H···O1A[a]	2.888(5)		
N1B–H···O2B	2.895(7)		
N1B–H···O1A[b]	2.945(6)		
N1B–H···O12A[c]	2.855(7)		
O2B–H···O2B[c]	2.950(3)		

[a] x, $y+1$, z. [b] $1-x$, $y+0.5$, $2-z$. [c] $1-x$, $y-0.5$, $2-z$.

good evidence that molecule **A** is an anion and molecule **B** a cation.

Except for the carboxyl groups, the bond length and angles in the two molecules are similar. The difference of the carbon–sulfur bond length (S–C3 and S–C21) reflects to the sp^3 and sp^2 character of the two carbon atoms. The difference in the C1–O1 and C1–O12 bond lengths shows clearly that molecule **B** has a carboxylic acid group, whereas molecule **A** is a carboxylate. The carbon–nitrogen bond lengths are within experimental error identical in the two molecules. They fall between the expected values of bond distances for C(aromatic)– NH_3^+ and C(aromatic)–NH_2(N sp^3) (1.465 and 1.394 Å).[14]

Two protons bonded to the nitrogen atom in molecule **A** could be located from difference Fourier maps and refined to geometrically reasonable positions in terms of bond distances and angles to the nitrogen atom and the formation of hydrogen bonds. The large displacement parameters of the atoms in molecule **B** can reflect either large thermal vibrations or a static disorder corresponding to the average of molecules with different conforma-
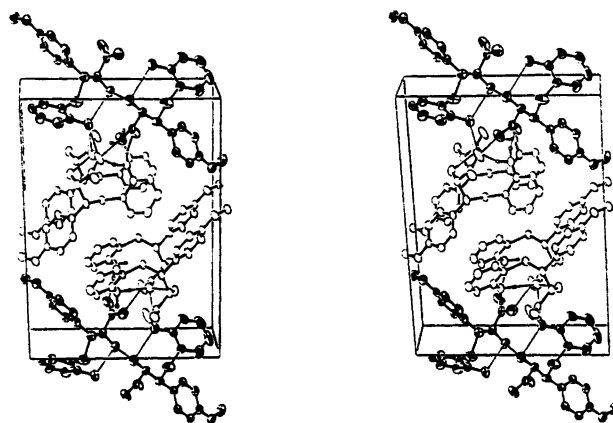

Fig. 2. Stereo pair[17] illustrating the packing in the crystal viewed along the b-axis. Only the outline of the thermal ellipsoids are shown for the atoms in molecule **A**. In molecule **B** the thermal ellipsoids are drawn with their principal directions shown. The hydrogen atoms are omitted for clarity except for the two hydrogen atoms bonded to N1 in molecule **A**. The short interatomic contact distances are shown as thin lines.

fied in the crystal structure with the hydroxy groups of atoms O12B, O2A and O2B, which provides additional evidence for the protonation of one of the amino groups.

The two molecules in the asymmetric unit are linked by a hydrogen bond between the carboxylic acid (from atom O12B) and carboxylate groups (atom O12A) with a very short hydrogen bond usually observed for acid salts of dicarboxylic acids.[19] The two molecules are also connected by a N1A–H1NA···O1B hydrogen bond. This makes molecule A adopt a conformation where the carboxylate and amino groups are close. H2NA is hydrogen bonded to O1A from a molecule related by translational symmetry along the *b*-axis. O1A is also acceptor for another hydrogen atom bonded to O2A of the same molecule.

The donor–acceptor distances in Table 4 imply that N1B donates three protons: one in a intramolecular hydrogen bond to O2B, and two to O1A and O12A. Molecules of type **B** are linked by the hydrogen bond between two O2B atoms to form chains parallel to the *b*-axis.

Based on the molecular geometry and the intermolecular interactions described above we find it likely that molecule **A** is an anion and molecule **B** is a cation linked by hydrogen bonds to form a pattern that is more complex than the one proposed earlier based only on thermochemical and spectroscopic data.[4]

The solid-state ring-closure reaction. Knowledge of the crystal structure has enabled us to make predictions on the structural changes that are associated with the solid-state reaction in Scheme 1. It is obvious that molecule **A** (anion) has a conformation where the atoms are virtually aligned to undergo the ring-closure reaction; therefore we would expect that the reaction takes place for the molecules in this conformation. In order to explain the 98% yield reported for the ring-closure reaction[4] we have to assume that the high displacement parameters of molecule **B** indicate that after or during the reaction of molecule **A**, molecule **B** adopts a conformation similar to that of molecule **A** and reacts similarily. Crystal structures of compounds containing the product[20] have shown that the seven-membered ring has a fairly rigid conformation with torsion angles C3–C2–C1 = O and O2–C2–C1 = O ca. 98 and 29° , respectively. Assuming that the product formed by the reaction has a similar conformation we would predict that O1A should be the leaving atom.

The reaction can be envisioned as a chain reaction occuring along the *b*-axis of the crystal. O1A is acceptor for three hydrogen bonds. Two of the donating hydrogen atoms, H2NA and one H bonded to N1B could move towards O1A to form a water molecule.

Similar results are obtained if one assumes that the first step in the reaction is the formation of an oxocarbenium intermediate, C1A=O12A$^+$.[21]

In most systems with very short O···O distances the O atoms are rarely seen to accept other protons than the

one involved in the short hydrogen bond.[22] This makes O12A unique because it accepts an additional proton besides the one in the very short hydrogen bond; therefore we find the formation of oxocarbenium intermediate less likely.

Only the optically active-1 makes the solid-state reaction shown in Scheme 1. This indicates that the reaction is hindered in the racemic-1.

Unfortunately it proved impossible to make single crystals of the racemate suitable for diffraction studies. Therefore powder diffraction measurements were used to characterize racemic and optically active-1. Content of racemate in samples of the optically active-1 could be easily detected in the powder diffraction pattern, where one weak line at 2θ = 5.1905° was not in agreement with the diffraction pattern calculated from the single crystal data. This 2θ-value corresponds to the strongest line in the diffraction pattern of the racemate.

The DSC measurements showed that the optically active compound melts at a slightly higher temperature (138.5 °C) than the melting point reported earlier.[4] It is noteworthy that the racemic content was not observed as an eutectic peak on the DSC curves nor did we detect the exothermic peak, assigned to the solid-state ring-closure reaction.[4] The powder diffraction pattern of the racemate is completely different from that of the enantiomer, indicating a very different crystal packing. This is not surprising, since the IR spectra showed that the racemate contains the molecules as zwitterions.[4] This excludes the formation of a short (carboxylic acid–carboxylate) hydrogen bond. This has lead us to conclude that this very strong intermolecular interaction found in the crystal structure of the optically active compound plays an important role for keeping the molecule in an unfavourable conformation ready for the solid-state reaction.

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