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Solid solution of two diastereomers of [3a(*R*,*S*),7a(*R*,*S*)]-3-[(1′*R*)-1-phenylethyl]perhydro-1,3-benzothiazol-2-iminium chloride

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A mixture of two diastereomers with the configurations (3a*S*,7a*S*,1′*R*) and (3a*R*,7a*R*,1′*R*) forms co-crystals in which there is one unique molecule in the asymmetric unit, but the molecule displays disorder which is a result of the presence of the two diastereomers at the same crystallographic site. Theoretical calculations carried out by the DFT method with the 6-311++G(2df,p) basis set allowed for the estimation of the energy difference between the two diastereomers both in the isolated and the solid state, while the natural bond orbital (NBO), Mulliken, natural population (NPA) and CHelpG analyses helped to establish the electronic structure of the thazolidin-2-imine fragment.

1. Introduction

Aziridines are excellent substrates for the addition of various nucleophiles. This reaction constitutes a general method for the synthesis of various 2-substituted amines (Hu, 2004). The reaction is highly *trans*-stereoselective and usually requires the use of either a Lewis acid or a Lewis base as a catalyst. Trimethylsilyl nucleophiles, such as trimethylsilylcyanide, trimethylsilylazide or trimethylsilylchloride, are commercially available alternatives for hydrogen nucleophiles (Gawroński *et al.*, 2008). Recently, we demonstrated that Me_3SiNCS reacts with *N*-substituted aziridines (1) and cyclohexene oxide without the action of any activator to give the ring-opening products (2) with good to high yields. Me_3SiNCS is an ambiphilic reagent, however, in these additions it behaved preferentially as a sulfur-centered nucleophile (Prusinowska & Gawroński, 2009). Bifunctional ring-opening products, such as (2), can be transformed to chiral thiazolidin-2-imines (3) (see Fig. 1). A wide interest in thiazolidin-2-imines and related heterocycles is due to their pharmacological and biological

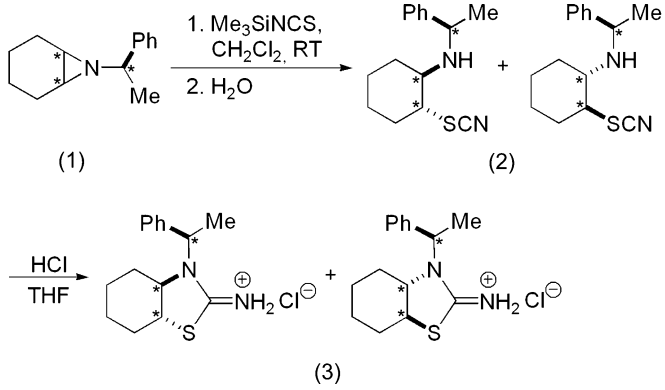

Figure 1
Synthesis of 3-[1-phenylethyl]hexahydro-1,3-benzathiazol-2(3*H*)-iminium chloride. Stereogenic centers are marked with asterisks.

activity such as local anesthetic, anti-seizure, anti-tubercular, anti-bacterial, anti-amoebic, anti-diabetic, anti-inflammatory, anti-oxidant and anti-fungal activity (Chaurasia, 1971; Eswaramoorthy *et al.*, 1991; Zimenkovsky *et al.*, 1999; Shankaran *et al.*, 2004; Heinelt *et al.*, 2004). Substituted 1,3-thiazolidines have also been explored as valuable starting materials for the preparation of more complex structures (Zask *et al.*, 1990; Hwu *et al.*, 1999; Jin & Kim, 2002). The most popular method to synthesize thiazolidines is the cyclization reaction of aziridines with heterocumulenes, such as phenyl isothiocyanate, in the presence of a catalyst [NaI; Campbell & Craig, 1980; Nadir & Basu, 1995; compounds of palladium(II); Baeg *et al.*, 1995; Butter *et al.*, 2000; or Bu_3P; Wu *et al.*, 2008]. Also, the thiocyanate ion was found to react with aziridines with Bu_4NHSO_4 as the catalyst to give a five-membered thiazoline structure (Weitzberg *et al.*, 1984). *p*-Toluenesulfonyl chloride (TsCl)/NaOH was introduced as a reagent combination for the synthesis of 2-amino-thiazolidines from *N*-(2-hydroxyethyl)-thioureas (Heinelt *et al.*, 2004). The treatment of amino thiocyanates with dry hydrogen chloride also provides access to thiazolidines (Kleist *et al.*, 1998).

In relation to our synthetic work on chiral 2-amino thiocyanates, we obtained a mixture of diastereomeric products (2) which were converted to a mixture of diastereomers of thiazolidin-2-imines as hydrochloride salts (3) by the last of the above-mentioned methods. These salts showed the unexpected property of preferentially crystallizing together, which prompted our interest in determining their structure. The presence of two diastereomers in one crystal is rare and unexpected as it violates the method of chiral resolution, discovered by Pasteur, which rests upon the combination of a racemate with an enantiomerically pure chiral resolving agent and subsequent separation of the mixture of diastereomeric salts by crystallization (Eliel *et al.*, 1994). Incorporation of diastereomers into the same crystal lattice can be carried out in two ways, *i.e.* either by multiplication of the asymmetric unit or by the formation of a substitutional solid solution. In the former case the two diastereomers are incorporated in a regular sequence and form co-crystals. As pointed out by Brock and co-workers (Lloyd *et al.*, 2007), the formation of co-crystals containing diastereomers is unlikely because of the difficulty of simultaneously optimizing the translational spacings for both isomers. On the other hand, in substitutional solid solutions the two diastereomers are inserted into the lattice randomly, and their ratio is not necessarily an integer. They occupy equivalent lattice sites and can substitute for one another at these sites. Obviously, this random distribution of stereoisomers can occur in cases when the shapes of the two stereoisomers are very similar and when they occupy the same volume, and when the parts that are disordered are engaged in only weak interactions. The formation of solid solutions of enantiomers is not common (see, for example, Chion *et al.*, 1978; Huang *et al.*, 2006; Zeller *et al.*, 2009), but is still more frequently encountered than the formation of solid solutions of two diastereomers (Jacques *et al.*, 1994). The rarity of two diastereomers appearing on the same crystallographic site will be discussed in more detail in §3.

Besides solid solutions of enantiomers and diastereomers, examples of solid solution behavior for molecular crystals are found in various other crystal systems including inorganic (Gopalan *et al.*, 1993) and organic salts (Pal *et al.*, 2002), mixtures of small molecules (Sridharan *et al.*, 2009), conformational rotamers (Lampe *et al.*, 1993), multicomponent organic alloys (Dabros *et al.*, 2007; Sada *et al.*, 2005) and metal complexes (Rychlewska *et al.*, 2007).

In this paper we report a rare example of the solid solution of two diastereomers, *i.e.* (3a*S*,7a*S*)-3-[(1′*R*)-1-phenylethyl]perhydro-1,3-benzothiazol-2-iminium chloride and (3a*R*,7a*R*)-3-[(1′*R*)-1-phenylethyl]perhydro-1,3-benzothiazol-2-iminium chloride (see Fig. 2) in a homochiral crystal (space group $P3_121$). The geometry and electronic structure of the 1,3-thiazolidin-2-iminium cation established from the X-ray experiment is compared with that obtained for an isolated cation by density functional theory (DFT) using the 6-311++G(2df,p) basis set. The quantum chemical calculations have also been applied to estimate the energetic difference between the *S*,*S*,*R* and *R*,*R*,*R* isomers in geometry extracted from the crystal and in fully optimized geometry in the isotated state.

2. Experimental

2.1. Synthesis and spectral characteristics

NMR spectra were recorded on a Varian Gemini 300 spectrometer with TMS as an internal standard. Mass spectra were recorded with an AMD 402 mass spectrometer. Melting points were determined on a Büchi B-450 apparatus and were uncorrected. Optical rotations were measured with a Perkin–Elmer 243 B polarimeter.

(1*R*,2*S*,1′*R*)-*N*-[(*R*)-α-Phenyl]cyclohexene aziridine (1) was obtained according to a literature procedure (Praceju *et al.*, 1987; Watson & Yudin, 2003).

2.1.1. Mixture of diastereomers (2). Trimethylsilylisocyanate (0.24 ml, 223 mg, 1.7 mmol, 1.4 equiv.) was added to a stirred solution of aziridine (1) (240 mg, 1.2 mmol) in 8 ml of dry CH_2Cl_2 at room temperature. The solution was stirred for

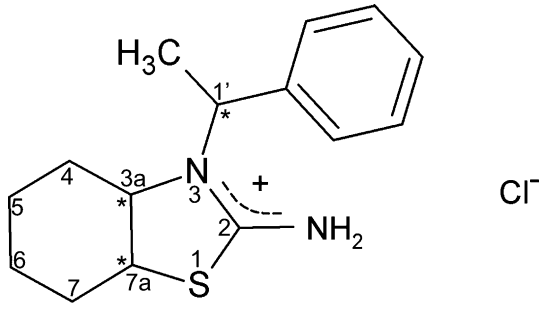

Figure 2
Chemical formula and charge distribution in the investigated solid solution of (3a*R*,*S*,7a*R*,*S*)-3-[(1′*R*)-1-phenylethyl]hexahydro-1,3-benzathiazol-2(3*H*)-iminium chloride (3). Stereogenic centers are marked with asterisks. Presented here, the IUPAC numbering scheme differs from that used in the X-ray structure analysis.

Table 1
Selected crystal data, data collection and refinement parameters for the investigated crystal.

Crystal data	
Chemical formula	$C_{15}H_{21}N_2S{\cdot}Cl$
M_r	296.85
Crystal system, space group	Trigonal, $P3_121$
Temperature (K)	130
a, c (Å)	9.0538 (1), 32.4921 (4)
V (Å^3)	2306.59 (5)
Z	6
Radiation type	Cu $K\alpha$
μ (mm^{-1})	3.36
Crystal size (mm)	0.4 × 0.2 × 0.1
Data collection	
Diffractometer	SuperNova, detector: Atlas
Absorption correction	Multi-scan
T_{min}, T_{max}	0.295, 0.715
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10 612, 3132, 3105
R_{int}	0.024
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.028, 0.072, 1.07
No. of reflections	3132
No. of parameters	284
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.36, −0.37
Absolute structure	Flack (1983)
Flack parameter	−0.009 (13)

Computer programs used: *SHELXS*97, *SHELXL*97 (Sheldrick, 2008).

24 h, and then the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic fraction was dried over $MgSO_4$ and evaporated, and the product was purified by column chromatography on silica gel (eluent dichloromethane and its mixtures with AcOEt). Oil, yield: 173 mg (56%). ^{1}H NMR ($CDCl_3$): δ 1.00–1.50 (m, 6H), 1.67 (d, J = 7.1 Hz, 3H), 1.71 (d, J = 7.4 Hz, 3H), 1.73–2.07 (m, 2H), 3.08–3.17 (dt, J = 11.3, 3.3 Hz, 1H), 3.22–3.39 (dt, J = 11.5, 3.3 Hz, 1H), 5.73–5.79 (q, J = 6.8 Hz, 1H), 7.27–7.40 (m, 5H). LR-MS 261(M+1), 157, 104. IR (KBr): 2936, 2859, 2051, 1585, 1577, 1447, 1213, 741, 699, $[\alpha]_D^{20}$ +179.7 (c = 1.15, $CHCl_3$).

2.1.2. Mixture of diastereomers (3). Dry hydrogen chloride was bubbled through a solution of (2) (127 mg, 0.5 mmol) in dry THF (10 ml) for 30 min. The precipitated salts (3) were filtered off and washed with THF. Yield 127 mg (90%). The product was crystallized from water to give colorless crystals, m.p. 526–537 K, ^{1}H NMR (CD_3OD): δ 1.08–1.71 (m, 6 H), 1.79 (d, J = 7.1 Hz, Me), 1.81 (d, J = 7.1 Hz, Me), 2.05–2.20 (m, 2 H), 3.50–3.59 (dt, J = 12.0, 3.3 Hz, 1 H), 3.57–3.60 (dt, J = 11.9, 3.4 Hz, 1 H), 3.71–3.78 (dt, J = 11.9, 3.4 Hz, 1 H), 3.83–3.88 (dt, J = 12.0, 3.3 Hz, 1 H), 5.45 (q, J = 6.9 Hz, 1 H), 7.33–7.50 (m, 5 H), $[\alpha]_D^{20}$ +112.5 (c = 0.91, MeOH).

2.2. X-ray diffraction

A colorless trigonal-pyramidal crystal of (3) was used to measure the intensity data with a SuperNova diffractometer equipped with a 135 mm Atlas detector. The temperature of the sample was kept at 130 K with an Oxford Instruments Cryojet Controller device and a nitrogen atmosphere. Data reduction and analysis for this structure were carried out with the *CrysAlisPro* program (Oxford Diffraction, 2009). The structure was solved by direct methods using *SHELXS*97 (Sheldrick, 2008), and refined by the full-matrix least-squares techniques with *SHELXL*97 (Sheldrick, 2008). The intensity data were corrected for Lorentz and polarization effects. A multi-scan correction for absorption was also applied (*SCALE*3 *ABSPACK*; Oxford Diffraction, 2006). All heavy atoms (C, N, O, S) were refined anisotropically. For the phenyl rings, rigid-group constraints (AFIX 66) were used. H atoms bound to C atoms were placed in their idealized positions and were refined as riding on their parent atoms, with C—H distances of 0.96 (methyl), 0.97 (methylene), 0.98 (methine) and 0.93 Å for aromatic groups, and their U_{iso} values were $1.2U_{eq}$(C). H atoms attached to the N atom were located reliably on difference Fourier maps and their positions and isotropic displacement parameters were refined. Owing to the disorder of the cation, which resulted from the presence of two diasteroisomers at the same crystallographic site, the occupancy factors for each diastereomer were first refined freely with their sum constrained to unity, while the displacement parameters of the corresponding components of disorder were kept equivalent. For the molecule possessing the *S*,*S* configuration at C2*A* and C7*A*, the site occupation factor refined to 0.54 (1). Hence, for the isomer with an *R*,*R* configuration at C2*B* and C7*B* this value was 0.46 (1). These values were kept fixed at the final stages of the refinement allowing the individual displacement parameters of the disorder components to vary. The correct absolute structure was assumed from the known absolute configuration of (1) used in the synthesis. Moreover, the absolute structure of the crystals was verified on the basis of the Flack parameter (Flack, 1983), which is provided in Table 1, together with the relevant crystal data collection and refinement parameters. *Jmol* (*Jmol*, 2010), *ORTEP*3 (Farrugia, 1997) and *Mercury* (Taylor & Macrae, 2001; Bruno *et al.*, 2002) programs were used to prepare the drawings. The puckering parameters of five- and six-membered rings were calculated using *PLATON* (Spek, 1990, 1998).

2.3. Quantum chemical calculation

The structures of both diastereoisomers observed in the crystal were used as starting points for DFT full-geometry optimization. The structures were optimized using the hybrid functional-B3LYP (Lee *et al.*, 1988; Parr & Yang, 1989; Becke, 1993) at the split-valence triple ζ 6-311++G(2df,p) basis set (Ditchfield *et al.*, 1971; Hehre *et al.*, 1972; Hariharan & Pople, 1973, 1974; Gordon, 1980; Clark *et al.*, 1983; Frisch *et al.*, 1984). The molecular geometry obtained is compared with the X-ray results in Table 2. Also, the single-point energies were calculated at the same level of theory for the 3a*S*,7a*S*,1′*R* and 3a*R*,7a*R*,1′*R* stereoisomers in the geometry extracted directly from the crystal structure. The electronic properties were

Table 2
Selected bond lengths (Å), valence angles (°) and torsion angles (°) obtained from X-ray and DFT calculations.

	X-ray	DFT
S1—C1	1.748 (2)	1.747
C1—N1	1.335 (2)	1.325
C1—N2	1.309 (2)	1.332
N1—C2*A*	1.514 (9)	1.499
C2*A*—C7*A*	1.496 (12)	1.524
S1—C7*A*	1.822 (4)	1.844
N1—C8*A*	1.555 (17)	1.495
N1—C2*B*	1.385 (13)	1.497
C2*B*—C7*B*	1.541(11)	1.524
S1—C7*B*	1.832 (5)	1.844
N1—C8*B*	1.420 (2)	1.499
C1—N1—C2*A*	112.4 (4)	111.87
N1—C2*A*—C7*A*	107.1 (7)	104.96
C2*A*—C7*A*—S1	105.0 (4)	103.51
C7*A*—S1— C1	91.12 (13)	89.06
S1—C1—N1	114.08 (13)	115.45
C1—N1—C2*B*	115.2 (5)	115.16
N1—C2*B*—C7*B*	107.7 (8)	107.74
C2*B*—C7*B*—S1	104.2 (5)	104.21
C7*B*—S1—C1	89.25 (16)	89.25
S1—C1—N1—C2*A*	7.7 (3)	10.1
C1—N1—C2*A*—C7*A*	−27.4 (5)	−33.2
N1—C2*A*—C7*A*—S1	33.0 (5)	39.5
C2*A*—C7*A*—S1—C1	−25.5 (3)	−30.1
C7*A*—S1—C1—N1	11.0 (2)	12.7
S1—C1—N1—C2*B*	−8.6 (4)	−8.6
C1—N1—C2*B*—C7*B*	27.2 (7)	27.2
N1—C2*B*—C7*B*—S1	−32.0 (7)	−32.0
C2*B*—C7*B*—S1—C1	23.3 (5)	23.3
C7*B*—S1—C1—N1	−10.3 (2)	−10.3
C2*A*—C3*A*—C4*A*—C5*A*	−52.4 (10)	−55.1
C3*A*—C4*A*—C5*A*—C6*A*	48.9 (13)	53.1
C4*A*—C5*A*—C6*A*—C7*A*	−49.6 (14)	−53.1
C5*A*—C6*A*—C7*A*—C2*A*	56.7 (10)	59.9
C6*A*—C7*A*—C2*A*—C3*A*	−67.5 (7)	−65.2
C7*A*—C2*A*—C3*A*—C4*A*	63.6 (8)	59.6
C2*B*—C3*B*—C4*B*—C5*B*	56.4 (18)	56.4
C3*B*—C4*B*—C5*B*—C6*B*	−53.2 (19)	−53.2
C4*B*—C5*B*—C6*B*—C7*B*	52.2 (13)	52.2
C5*B*—C6*B*—C7*B*—C2*B*	−62.3 (11)	−62.3
C7*B*—C2*B*—C3*B*—C4*B*	−55.5 (11)	−55.5
C6*B*—C7*B*—C2*B*—C3*B*	64.0 (11)	64.0

analyzed by means of the natural (NPA; Foster & Weinhold, 1980; Reed & Weinhold, 1983*a*,*b*; Reed *et al.*, 1985, 1988; Carpenter & Weinhold, 1988), Mulliken (Mulliken, 1955) and CHelpG (Breneman & Wiberg, 1990) population analyses. Using these analyses, the atomic charge distribution was calculated. The results for the 1,3-thiazolidine-2-iminium fragment are listed in Table 3. Also the Wiberg indices (Wiberg, 1968) were calculated in order to analyze bond orders and hence the degree of electron delocalization in the 1,3-thiazolidine-2-imine moiety. All calculations were carried out with the *GAUSSIAN*03 (Frisch *et al.*, 2003) program at the Poznan Supercomputing and Networking Center.

3. Results and discussion

(1*R*,2*S*,1′*R*)-*N*-[(*R*)-α-Phenyl]cyclohexene aziridine (1) was prepared in a two-step reaction from cyclohexene oxide by ring opening with (*R*)-α-phenylethylamine (Praceju *et al.*, 1987), followed by the Mitsunobu reaction to close the ring

Table 3
Partial charges on atoms in the *S*,*S*,*R* isomer (e).

Atoms	Mulliken	NPA	ChelpG
S1	−0.623	0.349	−0.105
C1	0.629	0.381	0.284
N1	0.539	−0.451	0.047
N2	−0.466	−0.683	−0.711
H1N	0.315	0.398	0.396
H2N	0.361	0.384	0.435
C2*A*	−0.969	0.039	−0.249
H2*A*	0.227	0.171	0.069
C3*A*	−0.105	−0.348	0.222
H3*A*	0.190	0.189	−0.049
H3*B*	0.186	0.195	−0.058
C4*A*	−0.485	−0.317	0.072
H4*A*	0.148	0.175	−0.001
H4*B*	0.189	0.194	0.001
C5*A*	−0.464	−0.336	−0.019
H5*A*	0.198	0.195	0.019
H5*B*	0.143	0.178	−0.003
C6*A*	−0.444	−0.332	0.142
H6*A*	0.181	0.199	0.027
H6*B*	0.161	0.186	−0.035
C7*A*	0.853	−0.276	0.215
H7*A*	0.248	0.180	−0.005
C8*A*	−0.724	0.041	0.112
H8*A*	0.113	0.171	0.044
C9*A*	−0.530	−0.532	−0.082
H9*A*	0.164	0.190	0.083
H9*B*	0.196	0.209	0.048
H9*C*	0.187	0.197	0.026
C10*A*	1.109	−0.052	0.017
C11*A*	−0.388	−0.176	−0.118
H11*A*	0.143	0.164	0.072
C12*A*	−0.312	−0.132	−0.062
H12*A*	0.195	0.172	0.110
C13*A*	−0.311	−0.134	−0.092
H13*A*	0.193	0.173	0.123
C14*A*	−0.385	−0.129	−0.097
H14*A*	0.194	0.173	0.124
C15*A*	−0.042	−0.173	−0.105
H15*A*	0.190	0.169	0.101

(Watson & Yudin, 2003). Ring opening of aziridine (1) in the uncatalyzed reaction with Me_3SiNCS (1.4 equiv.) led to a mixture of diastereomers (2). Finally, diastereomers of thiazolidine-2-iminium chloride (3) were obtained from (2) in the reaction with dry hydrogen chloride (Fig. 1).

The isolated products (2) and (3) were identified by the ^{1}H NMR spectra, and the diastereomers could be readily distinguished by the position of the diagnostic signals of protons attached to the heteroatom-substituted C atoms of the cyclohexane skeleton. In the case of (2) detailed analysis showed integration of the diagnostic signals C*H*N and C*H*S in the ratio 1.4:1. In the ^{1}H NMR spectrum of (3) the two methine ring protons were observed as four overlapping doublets of triplets in the interval 3.5–3.95 p.p.m., which were due to diastereomers of (3) (Fig. 3).

The diastereomers could not be separated readily and, as subsequently revealed by the crystal structure determination, crystallization yielded single crystals in which both diastereomers were incorporated, rather than crystals of a single diastereomer.

Crystals of (3) subjected to X-ray analysis were obtained by crystallization from water. The asymmetric part of the unit cell

comprises a thiazolidinum cation and a chloride anion. The cation includes the bicyclic ring system consisting of the 1,3-thiazolidine-2-iminium moiety *trans*-fused with a cyclohexane ring, and the ethylphenyl moiety attached to an endocyclic N atom. The cation molecule displays disorder, except for S1, C1, N1 and N2 (see an enhanced Fig. 4, and Fig. 5). It contains three stereogenic centers, namely at C2, C7 and C8. The disorder is due to the presence of two diastereomers, at the same crystallographic site, differing in their configuration at C2 and C7 (*S*,*S* and *R*,*R* for molecules *A* and *B*). For both isomers, the stereogenic center at C8 is the same and has been

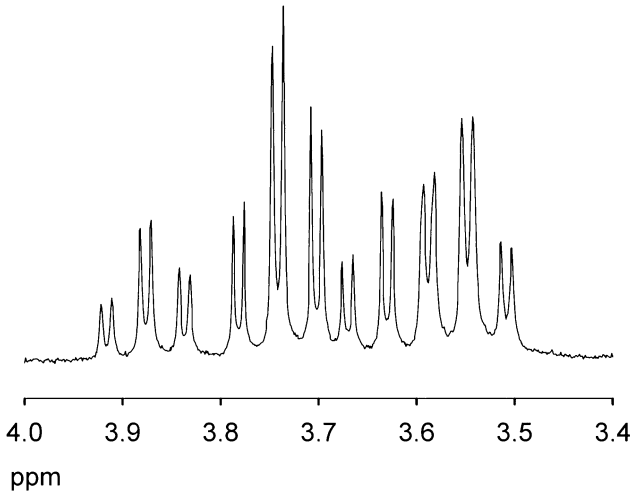

Figure 3
Diagnostic signals of protons C*H*N and C*H*S in diastereomers (3).

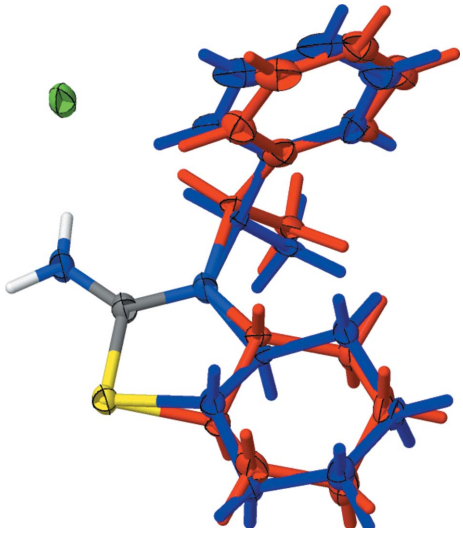

Figure 4
Overlay of two diastereomers occupying the same crystallographic site (red and blue), highlighting the changes in the molecular orientation and stereochemistry. See Fig. 5 for the full atom-numbering scheme. The interactive figure can be viewed online at http://submission.iucr.org/jtkt/edit/z/s/hoj166XChRsasQrX/zz0000/640/512.

determined as *R* on the basis of the Flack parameter (Flack, 1983), and in accordance with the absolute configuration of (1). Owing to this disorder, the standard IUPAC numbering cannot be fully implemented for (3). The numbering scheme used in the X-ray analysis, together with the atomic displacement ellipsoid plot, is shown in Fig. 5.

A search of the Cambridge Structural Database (Version 5.31, November 2009 + three updates; Allen, 2002) using *ConQuest* Version 1.12 (Bruno *et al.*, 2002) reveals 12 275 entries that contain stereomers, but not enantiomers, in their crystal lattice. This sub-base was used to search for disordered structures, among which we expected to identify the solid solutions of diastereomers. Identification of such structures has been performed by individually examining each of the 1152 structures. Moreover, independent searches have been performed for the phrases 'diastereomer' and 'diastereoisomer'. The resulting entries were also individually examined. A combination of the three searches provided 29 instances of the presence of both diastereomers at the same crystallographic site (multiple appearances not counted), to which we have added a case recently reported from our laboratory (Rychlewska *et al.*, 2010) but not yet incorporated into the CSD. The list of these structures is provided in the supplementary material[1] (Table 1S). The performed search illustrates that the solid solution of diastereomers is very rarely encountered, being reported only in 29 out of 12 275 cases, which makes $\sim 0.24\%$ of all deposited structures that have diastereomers in their crystal lattice. Except for one case (Rychlewska *et al.*, 2010), the molecules that possess the ability to form solid solutions of diastereomers are built of aliphatic or aromatic rings, and a significant percentage of them (11 out of 29, *i.e.* 38%) contain a metal atom as one of the stereogenic centers. In 41% of cases the diastereomers form homochiral crystals. A somewhat analogous situation to that described in this paper is observed in the crystal structure of RAQLEB (Yeori *et al.*, 2005), where the overlapping diastereomers feature the opposite chirality at the diaminocyclohexane fragment but the same chirality at the metal atom, and thus form homochiral crystals. Examination of the CSD provides some idea of when to expect that a single crystal of the solid solution could be made from a solution of diastereomers. The ability of two diastereomers to appear at the same crystallographic site seems to be analogous to the ability of a molecule in a crystal to display an orientational disorder. Obviously both orientations must be easily accommodated in the available space and in this part of the crystal the molecules should be only very weakly bound. In the parts of the crystal where the molecules are strongly bound both diastereomers should be involved in the same type of intermolecular interactions.

A random distribution of diastereomers in the crystal suggests that the shape and the volume occupied by the diastereomeric molecules is very similar. Indeed, the two

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: ZB5015). Services for accessing these data are described at the back of the journal.

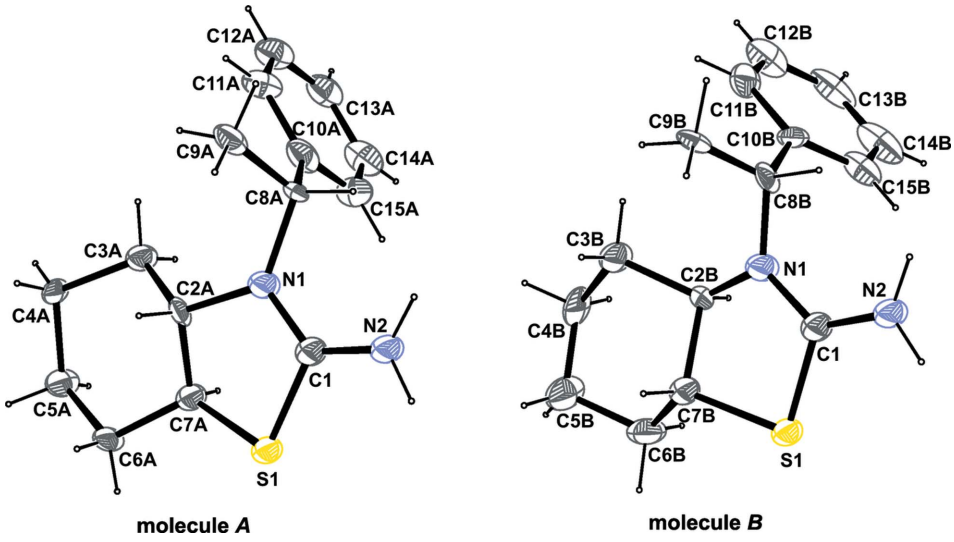

Figure 5
ORTEP-style representation of two diastereomeric cations occupying the same site in the crystal showing the atom-labelling for the molecules *A* and *B* of the *S*,*S*,*R* and *R*,*R*,*R* configurations. The displacement ellipsoids for the non-H atoms are drawn at the 40% probability level.

diastereomeric cations display similar, albeit complementary, conformations and orientations. The five-membered rings in both stereoisomers adopt a half-chair conformation with the pseudo-C_2 axis passing through the C1 atom and the midpoint of the opposite C2—C7 bonds. In the *S*,*S*,*R* isomer atoms C2*A* and C7*A* are disposed −0.187 (8) and 0.347 (7) Å out of the plane defined by S1, C1 and N1 atoms, while in the *R*,*R*,*R* isomer C2*B* and C7*B* atoms deviate from this plane by 0.188 (9) and −0.328 Å, *i.e.* by the same amount but in the opposite direction. The asymmetry parameters for the two heterocycles are: $\Delta C_2^{2A-7A} = 2.69°$ and $\Delta C_2^{2B-7B} = 3.01°$ (Duax & Norton, 1975). The Cremer and Pople puckering parameters (Cremer & Pople, 1975) for the atom ring sequences S1/C1/N1/C2*A*/C7*A* are Q = 0.331 (6) Å, φ = 134.7 (4)°, and indicate a distortion intermediate between an envelope and a half-chair form. For the ring sequences S1/C1/N1/C2*B*/C7*B* these parameters are Q = 0.316 (7) Å, φ = −45.1 (6)° and indicate a similar type of distortion but in the opposite direction. The six-membered ring composed of atoms labelled with '*A*' adopts a nearly perfect inverted-chair conformation, as indicated by the puckering parameters: Q = 0.589 (9) Å, φ = 173 (5)° and θ = 169 (1)°. In contrast to that, the other cyclohexane ring (C2*B*–C7*B*) adopts a chair conformation for which the corresponding puckering parameters amount to Q = 0.582 (11) Å, φ = −29 (7)° and θ = 9 (1)°.

Selected bond lengths, valence angles and torsion angles are listed in Table 2 and compared with the geometry obtained during energy minimalization. The endocyclic C1—N1 bond [1.335 (2) Å] is slightly longer than the exocyclic N2—C1 bond [1.309 (2) Å], and simultaneously these bonds are shorter than typical single Csp^2—Nsp^2 bonds. For comparison, the mean values of the single endo- and exocyclic Csp^2—Nsp^2 bonds, listed in the *International Tables for Crystallography* (2004), amount to 1.372 (16) and 1.336 (17) Å, whereas for double endo- and exocyclic Csp^2—Nsp^2 bonds these values are 1.313 (11) and 1.279 (8) Å. The C1—S1 bond length is 1.748 (2) Å and is comparable with the value of 1.741 (11) Å which is typical of the ring Csp^2—S bond length. Similarly, the S1—C7*A* and S1—C7*B* bond distances which are 1.822 (2) and 1.832 (5) Å agree well with the value of 1.827 (18) Å for Csp^3—S ring bonds.

The Wiberg bond indices of C1—N1 and C1—N2, calculated using the NBO analysis (Foster & Weinhold, 1980) at the B3LYP/6-311++G(2df,p) level, are 1.366 and 1.305 Å. The fact that these bond orders are significantly different from the ideal values for a single (1.0) or a double bond (2.0) suggests delocalization of electrons within the N2—C1—N1 fragment. Furthermore, a detailed analysis of the NBO results shows that the electrons from the lone pairs of N1 and N2 are delocalized to C1—N1 and C1—N2 bonds, leading to partially double bonds. The geometrical consequence of such a redistribution of electrons is a shortening of the C1—N1 and C1—N2 bonds compared with formally single C—N bonds. Indeed, the calculated C—N bond lengths range from 1.325 to 1.332 Å and their values are in between the formally single and double C—N bonds (*International Tables for Crystallography*, 2004). Other bond orders are very close to the expected values (see Fig. 6) and they agree with the bond character obtained from the X-ray analysis. Delocalization of positive charge between exo- and endocyclic N atoms in the 1,3-thiazolidine-2-amine

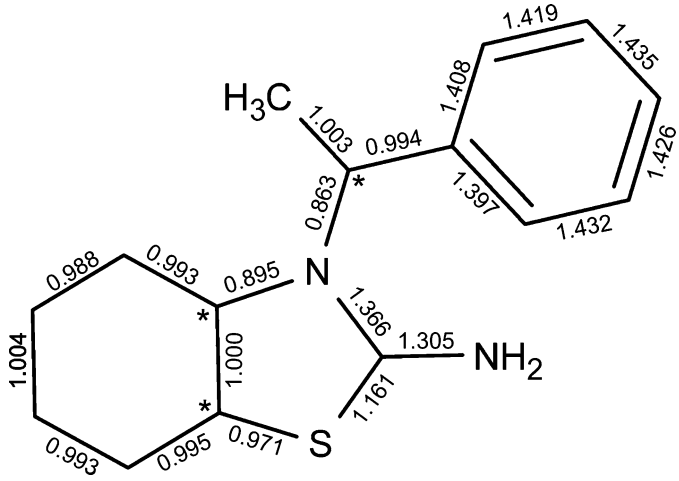

Figure 6
Wiberg indices calculated for an isolated cation using NBO analysis.

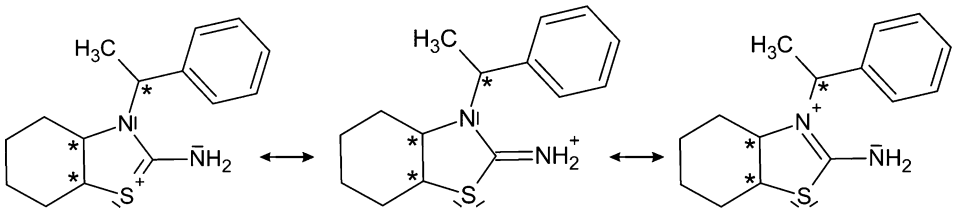

Figure 7
Possible resonance structures of the cation assigned from Mulliken, NPA and CHelpG analyses.

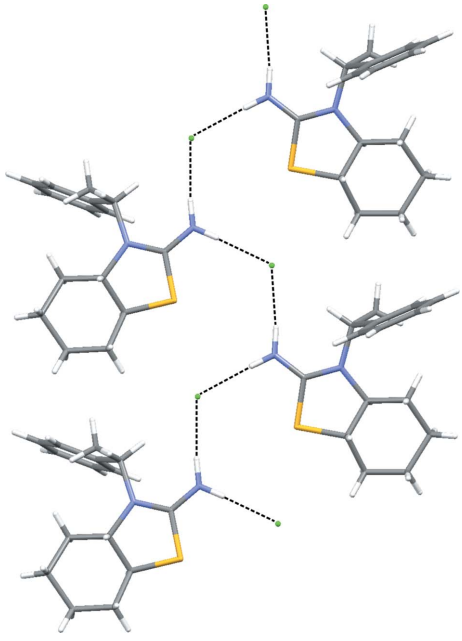

Figure 8
N—H···Cl^- hydrogen-bond chains – the supramolecular motif unaffected by changes of chirality.

ring has been reported previously (see for example the recent publication by Glidewell *et al.*, 2004).

Secondly, we investigated the Mulliken, NPA and ChelpG point charge values of each atom to examine the charge distribution in the cation, particularly in the 1,3-thiazolidine-2-imine moiety. These results are given in Table 3. Inspection of this table reveals dramatic differences in the calculated atomic charges depending on the actual population analysis performed. Point charges obtained from Mulliken population analysis exhibit large variations upon going from one atom to its neighbour. The results indicate that the positive charge of the cation can be located at either the C1 or the N1 atom, the point charges on these atoms being 0.629 and 0.536 e. Meanwhile, the values of NPA charges show that C1 and S1 are the atoms that have the highest (and comparable) partial positive charges (0.381 and 0.349 e). The diversity in charge distribution obtained from ChelpG analysis is not as dramatic as from Mulliken or NPA analysis. A slightly positive charge is located on C1 as well as on the whole NH_2 group. Their values amount to 0.284 and 0.120 e. It is worth noting that N2 is negatively charged in each of the population analyses applied (−0.466 e in MPA, −0.683 e in NPA and −0.711 e in ChelpG), and in all cases the whole NH_2 group has a positive charge (0.210, 0.099 and 0.120 e). Distribution of partial atomic charges derived from Mulliken, NPA and ChelpG analyses seems to indicate that the molecule is a hybrid of three resonance structures shown in Fig. 7.

With regard to the molecular geometry in the crystal, there are significant differences in the Csp^3—Nsp^2 bond lengths for the two diastereomers. The differences exceed several times their standard uncertainty [0.129 (16) and 0.135 (17) Å]. The values of both Csp^3—Nsp^2 bond lengths are smaller in *R*,*R*,*R* than in the *S*,*S*,*R* diastereomer, the larger values being closer to those obtained during full geometry optimization.

In order to check the energetic preferences of the two diastereomers present in the crystal we performed single-point energy calculations at the B3LYP/6-311++G(2df,p) level for both diastereomeric molecular cations with geometries directly extracted from the crystal. The resulting calculated energies predicted the *S*,*S*,*R* isomer to be significantly more energetically favourable than the *R*,*R*,*R* one. The energy difference between the two diastereomers is as high as 72.1 kJ mol^{-1} and might result from the substantial difference in Csp^3—Nsp^2 bond lengths. The relative energies calculated for both stereoisomers in the gas phase indicate that the *R*,*R*,*R* isomer is energetically more favourable, but, as expected, the energy difference is only 1.3 kJ mol^{-1}.

The supramolecular aggregation in the solid state is dominated by strong charge-assisted N—H···Cl hydrogen bonds involving the iminium group of the cation as a double hydrogen-bond donor and the chloride anion as a hydrogen-bond acceptor. The interactions present link alternating cations and anions into zigzag chains (see Fig. 8). The chains located at approximately 0, 1/3 and 2/3 *z* levels propagate along the [110], [100] and [010] lattice directions. The hydrogen-bond parameters are listed in Table 4. An identical type of hydrogen bond has been observed in a large number of crystal structures deposited in the CSD (Allen, 2002; 445 hits), for which the mean H···Cl^- distance amounts to 2.52 (1) Å. However, such short H···Cl^- distances as we obtained [2.21 (3) and 2.23 (3) Å] were only present in 19 non-disordered structures.

4. Conclusions

Unlike enantiomers which, when crystallized from racemic mixtures, predominantly form achiral racemic crystals, diastereomers crystallized from mixtures usually produce single crystals containing only one of the possible diastereomeric components. Nevertheless, from a mixture of two diastereomers of the hydrochloride salts of thiazolidin-2-imines we have obtained a solid solution in which the two

Table 4
Intermolecular hydrogen-bond parameters (Å, °).

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
N2—H1N···Cl1	0.95 (3)	2.21 (3)	3.145 (2)	170 (2)
N2—H2N···Cl1^{i}	0.89 (3)	2.23 (3)	3.107 (2)	171 (2)

Symmetry code: (i) $x-y+1, -y+1, -z+\frac{2}{3}$.

diastereomers are disordered over the same crystallographic site and randomly distributed throughout the crystal. Their ability to form a molecular solid solution can be attributed to the similarity of their molecular shapes resulting from the inversion of the cyclohexane ring and the simultaneous inversion of configuration at two of the three stereogenic centers. Furthermore, the impossibility to resolve (3) into diastereomers by crystallization might arise from the formation of strong, charge-assisted hydrogen bonds, unaffected by the changes of chirality at some of the stereogenic centers.

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