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Structural diversity in imidazolidinone organocatalysts: a synchrotron and computational study

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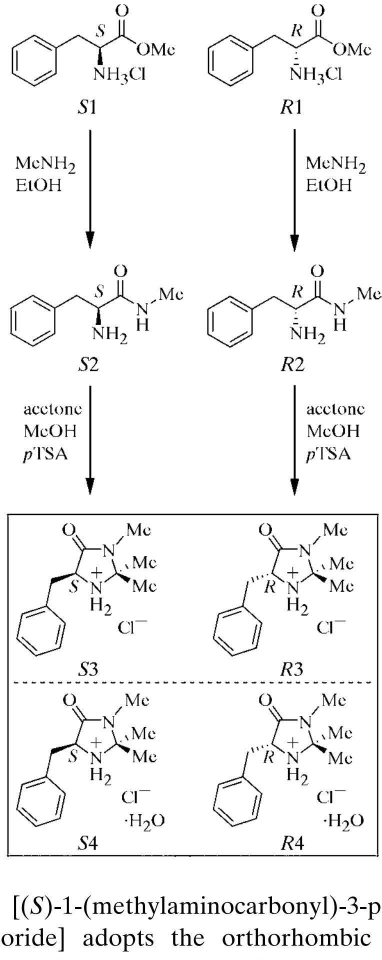
(*S*)-1-(Methylaminocarbonyl)-3-phenylpropanaminium chloride (*S*2·HCl), $C_{10}H_{15}N_2O^+\cdot Cl^-$, crystallizes in the orthorhombic space group $P2_12_12_1$ with a single formula unit per asymmetric unit. (5*R*/*S*)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride (*R*3 and *S*3), $C_{13}H_{19}N_2O^+\cdot Cl^-$, crystallize in the same space group as *S*2·HCl but contain three symmetry-independent formula units. (*R*/*S*)-5-Benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride monohydrate (*R*4 and *S*4), $C_{13}H_{19}N_2O^+\cdot Cl^-\cdot H_2O$, crystallize in the space group $P2_1$ with a single formula unit per asymmetric unit. Calculations at the B3LYP/6–31G(*d*,*p*) and B3LYP/6–311G(*d*,*p*) levels of the conformational energies of the cation in *R*3, *S*3, *R*4 and *S*4 indicate that the ideal gas-phase global energy minimum conformation is not observed in the solid state. Rather, the effects of hydrogen-bonding and van der Waals interactions in the crystal structure cause the molecules to adopt higher-energy conformations, which correspond to local minima in the molecular potential energy surface.

Comment

A number of research groups have reported on the utility of chiral imidazolidinone catalysts for a range of enantioselective organic reactions (Ahrendt *et al.*, 2000; Wilson *et al.*, 2005; Paras & MacMillan, 2001; Jen *et al.*, 2000; Marigo *et al.*, 2005; Kunz & MacMillan, 2005; Beeson & MacMillan, 2005; Brochu *et al.*, 2004). Several reviews of the field of organocatalysis exist (Almaşi *et al.*, 2007; Bolm *et al.*, 2005; Gaunt *et al.*, 2007; Tsogoeva, 2007; List, 2006). Enantiomeric excesses greater than 90% are regularly achieved in relatively high yielding reactions that are difficult to accomplish by other means. However, there are to date very few structural studies of these materials, and no reports of their stability to storage or recrystallization. Both of these factors are expected to be highly relevant to possible use of the materials in both industrial and laboratory settings.

The catalyst studied in the current work is a typical example of the class (Ahrendt *et al.*, 2000), is commercially available, and has been described as 'an inexpensive, bench-stable solid that is readily handled by experimentalists or automated systems' (Beeson & MacMillan, 2005). We therefore selected this compound for a full structural characterization, which is of interest both to confirm the reported molecular structure of this material, and with a view to rationalizing its solid-state properties, including particle morphology and flow, solubility, stability, *etc*. Synchrotron radiation was employed in order to gain the best quality structural information from these weakly scattering materials and to ensure that our study was not biased in favour of solid forms which readily form single crystals. A simplified reaction scheme is given below.



*S*2·HCl [(*S*)-1-(methylaminocarbonyl)-3-phenylpropanaminium chloride] adopts the orthorhombic space group $P2_12_12_1$ with a single formula unit per asymmetric unit (Fig. 1*a*). All chemically intuitive hydrogen-bonding opportunities are satisfied in the solid state (Fig. 2*a*). Sheets of hydrogen bonds are formed, which lie parallel to the *ab* plane. The chloride ion is hydrogen bonded by three protonated amine groups [N16···Cl1 = 3.094 (2), 3.149 (2) and 3.166 (2) Å], and the carbonyl group of the amide unit is hydrogen bonded to the amide H atom on an adjacent molecule [N11···O10 = 3.018 (3) Å]. The hydrophobic (phenyl)

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and hydrophilic (amide) fragments of the molecule form layers, which are segregated along the *c* axis. Solid-state packing forces appear to have a slight influence on the molecular conformation; comparison of the observed molecular conformation with one computed using a gas-phase molecular mechanics model shows no unusual features, the two conformations being broadly similar. The primary differences arise because of a change in the C6—C7—C8—C9 torsion angle from 98.15° in the gas phase (calculated as described in the *Experimental*) to 54.65° in the solid-state, which is presumably driven by a combination of crystal packing (optimal space filling) requirements and intermolecular hydrogen bonding of the amide group.

*R*3 and *S*3 [(5*R*/*S*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride] both crystallize in the orthorhombic space group $P2_12_12_1$ with three formula units per asymmetric unit (*S*3 is shown in Fig. 1*b*). The three organic molecules adopt different but related conformations, which differ primarily as a result of changes in the orientation of the imidazolidinone fragment with respect to the phenyl ring *via* C—C bond rotation. These differences in conformation do not affect the hydrogen-bonding topology, with all three organic cations forming two N—H···Cl hydrogen bonds from the protonated N atom to the free chloride ion (Fig. 2*b*). Neither the carbonyl group nor the N atom of the amide group are involved in classical hydrogen bonding for any of the three distinct molecules, which is in contrast to the extensive hydrogen bonding observed for the precursor *S*2·HCl. Two of the three independent formula units are linked to one another by hydrogen bonding through atoms Cl1 and Cl2 *via* N—H···Cl interactions and thereby form a chain of hydrogen bonds which runs parallel to the *a* axis. The third symmetry-independent formula unit again forms N—H···Cl hydrogen bonds to create a chain that runs parallel to both the *a* axis and the other hydrogen-bonding chain, but in this case the chain comprises only a single symmetry-independent molecule and a single symmetry-independent chloride ion (Cl1). The hydrophilic sections of the structure (Cl^- ions and the polar parts of the organic cation) are layered in the *ac* plane and are separated by the hydrophobic phenyl rings. As expected, no significant differences exist between the crystal packing of the *R* and *S* isomers.

The presence of three formula units with different molecular conformations in the asymmetric unit is curious, and could result from either different minima on the molecular energy surface or distortions away from the same minimum caused by differences in packing forces experienced by the three independent molecules in the unit cell. To distinguish between these possibilities, we have performed calculations designed to elucidate the gas-phase conformers and their relative energies. *R*3 and *S*3 have two torsional degrees of freedom, which we label φ (torsion angle C6—C7—C8—C9) and θ (torsion angle C5—C6—C7—C8). Initial low-level calculations (using the molecular mechanics model Tripos 5.2) indicate that three distinct conformational energy minima exist in the gas phase (Fig. 3). The three minima were then re-optimized at higher levels of theory for more reliable relative energies, revealing large energy differences between the conformations: the relative energies are 0, +10.67 [+11.29] and +32.57 [+33.95] kJ mol^{-1} for conformations i, ii and iii, respectively, at the B3LYP/6–31G(*d*,*p*) [B3LYP/6–311G(*d*,*p*)] levels. The good quantitative agreement between the two methods indicates that the effect of basis set superposition error on the relative conformational energies is small, while the stability of the most folded conformation i might even be underestimated owing to the known poor treatment of nonbonded interactions in density functional theory calculations (van Mourik *et al.*, 2006). As typical energy differences between polymorphs are of the order of 1–10 kJ mol^{-1} (Bernstein, 2002), we might only expect the lowest energy conformation to be observed in the crystal structure. However, it is clear from Fig. 3 that two molecules (*A* and *C*) adopt conformations related to the intermediate-energy calculated conformation ii, while molecule *B* is within the

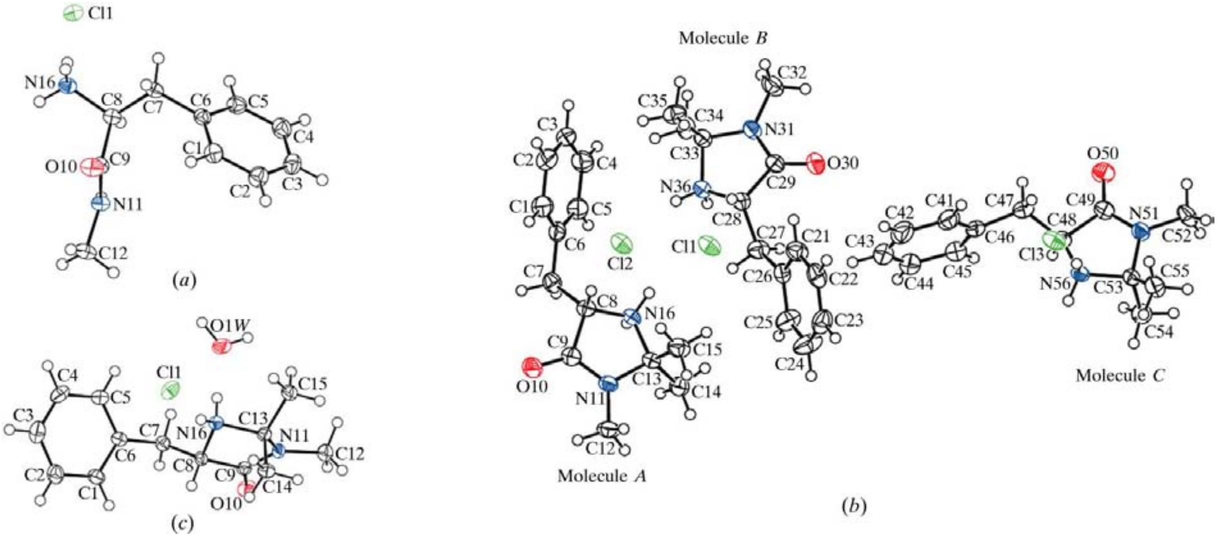

Figure 1

The asymmetric units of (*a*) *S*2·HCl, (*b*) *S*3 and (*c*) *S*4. Displacement ellipsoids are shown at the 50% probability level.

potential energy well of the highest-energy calculated conformation iii, although significantly distorted away from the minimum. It therefore appears that in order to optimize the lattice energy, the three molecules avoid the lowest-energy folded gas-phase conformation in favour of the two open conformations. The conformational energy penalty of at least 18 kJ mol^{-1} (2 × 11 kJ mol^{-1} for *A* and C, 33 kJ mol^{-1} for *B*) is presumably compensated by the formation of hydrogen bonds and van der Waals interactions in the crystal structure.

Both *R*4 and *S*4 [(*R*/*S*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride monohydrate] crystallize in the noncentrosymmetric monoclinic space group $P2_1$ with a single formula unit per asymmetric unit (*S*4 is shown in Fig. 1*c*). The conformation of the cation (θ = 109.3° and φ = 173.4°) corresponds most closely with minimum ii (Fig. 3), and it therefore appears that, as with *R*3 and *S*3, intermolecular factors including hydrogen-bonding and van der Waals interactions outweigh intramolecular ones in determining the conformation of the cation in the solid state. Overall, the hydrogen bonding leads to the formation of tapes which run parallel to the *b* axis (Fig. 2*c*). Again, the hydrophobic and hydrophilic parts of the structure are segregated into chains which follow the hydrogen-bonding topology. Again, no unexpected differences exist between the crystal packing of the *R* and *S* isomers.

In conclusion, computational and experimental studies indicate that intermolecular rather than intramolecular forces are primarily responsible for the molecular conformations observed in the solid state for this class of compounds.

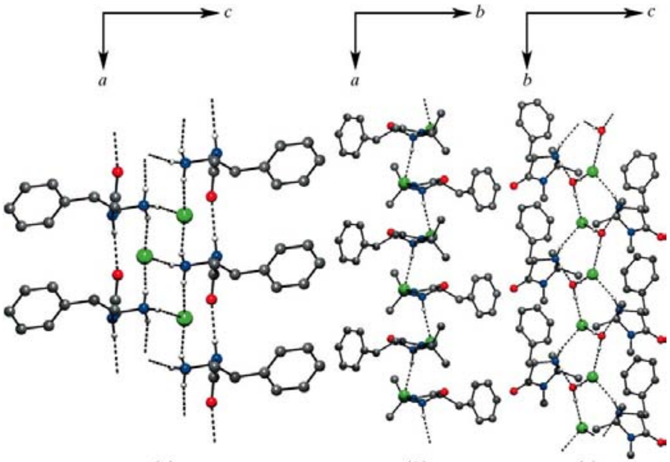

Figure 2
Hydrogen-bonding patterns observed in (*a*) *S*2·HCl (the hydrogen-bonded sheet is viewed side-on for clarity), (*b*) *S*3 (only one of the three chains is shown for clarity) and (*c*) *S*4. (Colour key for the electronic version of the paper: carbon grey, hydrogen white, nitrogen blue, oxygen red and chlorine green.)

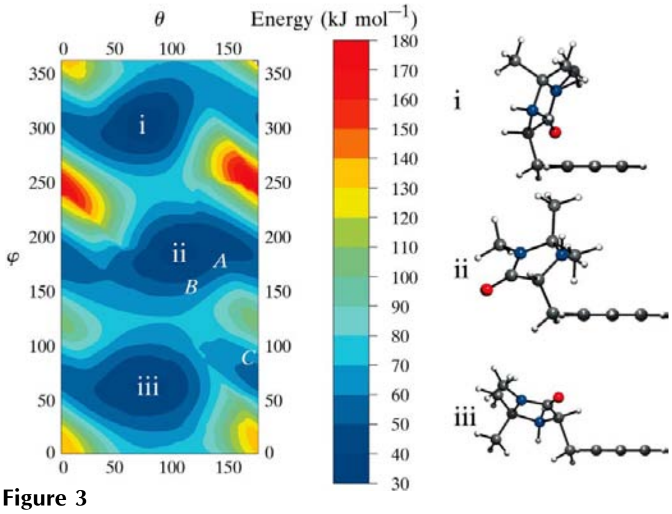

Figure 3
Calculated (Tripos 5.2) conformational energy landscape for the (*S*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium cation, and energy-minimized calculated conformations. Numbers refer to calculated conformations, letters to those observed experimentally. See *Comment* and Fig. 1 for further details.

Experimental

(5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one was synthesized from commercially available (*S*)-phenylalanine methyl ester hydrochloride according to the literature method described by Ahrendt *et al.* (2000). Treatment of (*S*)-phenylalanine methyl ester hydrochloride with ethanolic methylamine furnished the intermediate (*S*)-phenylalanine *N*-methylamide hydrochloride, which was not isolated, but heated to reflux in MeOH and acetone with catalytic *p*-toluenesulfonic acid (*p*-TSA). The cyclized (*S*)-imidazolidinone product was precipitated as the HCl salt and recrystallized from 2-propanol to yield a microcrystalline white needle-like material, which was identical to that previously characterized. The *R* enantiomer was prepared in an identical manner starting from commercially available (*R*)-phenylalanine methylamide hydrochloride. This material displayed identical ^{1}H and ^{13}C NMR spectra to the *S* enantiomer, and had an equal but opposite optical rotation value, as expected. A simplified reaction scheme is shown in the *Comment* section.

Initial attempts to grow large crystals by slow evaporation (several months, 277 K) from $CHCl_3$ were successful in this aim, but crystallographic characterization indicated that ring opening of the imidazolidinone had occurred to yield (*R*/*S*)-phenylalanine methylamide hydrochloride. As the crystal structure of this material had not been reported, a full data set was collected on the *S* isomer and is reported here. Crystals of (5*R*/*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride were grown by rapid evaporation (*ca* 2 d, ambient temperature) from $CHCl_3$. Samples of (5*R*/*S*)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride monohydrate were crystallized from 2-propanol as a microcrystalline powder and correspond to the 'raw' reagent described in the synthesis; these were subjected to standard benchtop storage conditions for several months after crystallization.

Single crystals were selected, mounted at the end of two-stage glass fibres and studied at 150 K on station 9.8 or station 16.2 SMX of the UK Synchrotron Radiation Source, Daresbury. Routine data collection involved three series of ω scans. Data were corrected for beam decay and absorption using a method based on equivalents. Further details can be found in the relevant section of the CIF that accompanies this paper.

Computational studies were performed to investigate the conformational energy landscape of the molecular cations. Both for protonated (*R*/*S*)-phenylalanine methylamide and for the imidazolidinium cation, initial calculations were performed using a simple molecular mechanics model (Tripos 5.2), as implemented in *Ghemical* (Hassinen & Peräkylä, 2001). For the imidazolidinium cation, for which the potential energy landscape was relatively complex, the three local minima located in the initial molecular mechanics search were investigated at a higher level of theory. The three molecular mechanics energy minima were energy minimized using both B3LYP/6–31G(*d*,*p*) and B3LYP/6–311G(*d*,*p*) levels of theory, giving refined gas-phase molecular structures and their relative energies. All density functional theory calculations were performed using the program *CADPAC* (Amos, 1995).

Compound *S*2·HCl

Crystal data

$C_{10}H_{15}N_2O^+\cdot Cl^-$
$M_r = 214.69$
Orthorhombic, $P2_12_12_1$
$a = 4.9758$ (7) Å
$b = 8.6213$ (13) Å
$c = 25.521$ (4) Å
$V = 1094.8$ (3) Å^3
$Z = 4$
Synchrotron radiation
$\lambda = 0.69040$ Å
$\mu = 0.32$ mm^{-1}
$T = 150$ (2) K
0.15 × 0.07 × 0.07 mm

Data collection

Bruker D8 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.953$, $T_{max} = 0.978$
12758 measured reflections
3619 independent reflections
2971 reflections with $I > 2\sigma(I)$
$R_{int} = 0.091$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.058$
$wR(F^2) = 0.157$
$S = 1.00$
3619 reflections
141 parameters
4 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.58$ e Å^{-3}
$\Delta\rho_{min} = -0.57$ e Å^{-3}
Absolute structure: Flack (1983), 1447 Friedel pairs
Flack parameter: −0.01 (9)

Compound *R*3

Crystal data

$C_{13}H_{19}N_2O^+\cdot Cl^-$
$M_r = 254.75$
Orthorhombic, $P2_12_12_1$
$a = 7.1167$ (14) Å
$b = 19.237$ (4) Å
$c = 30.370$ (6) Å
$V = 4157.7$ (14) Å^3
$Z = 12$
Synchrotron radiation
$\lambda = 0.69040$ Å
$\mu = 0.26$ mm^{-1}
$T = 150$ (2) K
0.1 × 0.08 × 0.04 mm

Data collection

Bruker D8 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.974$, $T_{max} = 0.990$
24370 measured reflections
9772 independent reflections
7354 reflections with $I > 2\sigma(I)$
$R_{int} = 0.071$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.131$
$S = 0.99$
9772 reflections
488 parameters
6 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.28$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}
Absolute structure: Flack (1983), 4169 Friedel pairs
Flack parameter: 0.00 (6)

Compound *S*3

Crystal data

$C_{13}H_{19}N_2O^+\cdot Cl^-$
$M_r = 254.75$
Orthorhombic, $P2_12_12_1$
$a = 7.123$ (1) Å
$b = 19.232$ (3) Å
$c = 30.384$ (4) Å
$V = 4162.3$ (10) Å^3
$Z = 12$
Synchrotron radiation
$\lambda = 0.69040$ Å
$\mu = 0.26$ mm^{-1}
$T = 150$ (2) K
0.2 × 0.06 × 0.04 mm

Data collection

Bruker D8 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.949$, $T_{max} = 0.990$
48955 measured reflections
13171 independent reflections
8896 reflections with $I > 2\sigma(I)$
$R_{int} = 0.126$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.071$
$wR(F^2) = 0.171$
$S = 1.03$
13171 reflections
488 parameters
6 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.46$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}
Absolute structure: Flack (1983), 5804 Friedel pairs
Flack parameter: 0.09 (6)

Compound *R*4

Crystal data

$C_{13}H_{19}N_2O^+\cdot Cl^-\cdot H_2O$
$M_r = 272.77$
Monoclinic, $P2_1$
$a = 9.6320$ (19) Å
$b = 7.0446$ (14) Å
$c = 11.093$ (2) Å
$\beta = 105.82$ (3)°
$V = 724.2$ (3) Å^3
$Z = 2$
Synchrotron radiation
$\lambda = 0.79770$ Å
$\mu = 0.26$ mm^{-1}
$T = 150$ (2) K
0.08 × 0.03 × 0.01 mm

Data collection

Bruker D8 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.979$, $T_{max} = 1.000$ (expected range = 0.978–0.999)
6282 measured reflections
3480 independent reflections
2485 reflections with $I > 2\sigma(I)$
$R_{int} = 0.049$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.130$
$S = 0.96$
3480 reflections
182 parameters
5 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.39$ e Å^{-3}
Absolute structure: Flack (1983), 1560 Friedel pairs
Flack parameter: −0.15 (9)

Compound *S*4

Crystal data

$C_{13}H_{19}N_2O^+\cdot Cl^-\cdot H_2O$
$M_r = 272.77$
Monoclinic, $P2_1$
$a = 9.6425$ (14) Å
$b = 7.0517$ (10) Å
$c = 11.0895$ (16) Å
$\beta = 105.796$ (2)°
$V = 725.57$ (18) Å^3
$Z = 2$
Synchrotron radiation
$\lambda = 0.79770$ Å
$\mu = 0.26$ mm^{-1}
$T = 150$ (2) K
0.04 × 0.04 × 0.01 mm

Data collection

Bruker D8 diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.987$, $T_{max} = 0.990$
6377 measured reflections
3330 independent reflections
2438 reflections with $I > 2\sigma(I)$
$R_{int} = 0.052$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.122$
$S = 0.98$
3330 reflections
181 parameters
5 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.38$ e Å^{-3}
Absolute structure: Flack (1983), 1395 Friedel pairs
Flack parameter: −0.01 (9)

For all compounds, data collection: *APEX2* (Bruker, 2004); cell refinement: *APEX2*; data reduction: *APEX2*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *WinGX* (Version 1.64; Farrugia, 1999); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3055). Services for accessing these data are described at the back of the journal.

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