Isopropylidene glycerol hydrogen phthalate as a resolving agent: a study of its diastereomeric salts with (*S*)- and (*R*)-1-phenylethylamine

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Abstract

An insight into the mechanism of the highly efficient resolution of 1-phenylethylamine with enantiomerically pure isopropylideneglycerol hydrogen phthalate is provided by comparison of physicochemical and X-ray crystallographic data of the two diastereomeric salts formed by the amine with the *S* acid. In the nearly identical structures of these salts, the different disposition of the isopropylidene glycerol moiety stands out drawing attention to the critical role played by the chiral part of the acid in the discrimination between the amine enantiomers. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have described a new acidic resolving agent, the hydrogen phthalate of isopropylidene glycerol **1**, which has resolved various 1-arylalkylamines with high resolution efficiencies and the same stereochemical outcome, its *S* enantiomer always giving the less soluble diastereomeric salt with the *S* amines.[1,2]

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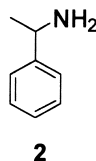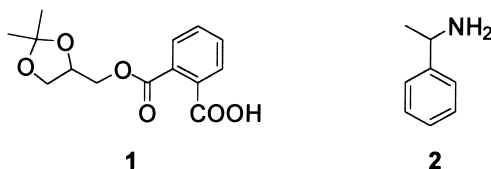
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On the basis of such an invariable behaviour and of the presence of the same framework, i.e. the 1-phenylethylamine substructure, in all the resolved amines, it seemed likely that a common recognition mechanism was involved in the stereoselective precipitation of these salts. In this context, a rationale accounting for the different solubilities of a diastereomeric salt pair generated by one of the tested amines with (*S*)-**1** would have wider significance.

Therefore we decided to investigate the crystal structure and the physicochemical properties of the two diastereomeric salts of 1-phenylethylamine **2** with (*S*)-**1**, hoping to find some explanation of the resolution results. The choice of the amine was made considering that **2** was the lead substrate and its resolution one of the most efficient.

2. Results

The physicochemical and the X-ray crystallographic data of the two diastereomeric salts (*S*)-**1**·(*S*)-**2** and (*S*)-**1**·(*R*)-**2** are listed in Table 1. (*S*)-**1**·(*S*)-**2** has a slightly more compact structure and is more stable than (*S*)-**1**·(*R*)-**2**, as proved by the higher density and mp, respectively. These features are associated with lower solubility, consistent with what some authors have observed examining a large variety of resolvable diastereomeric salt pairs.[3]

Table 1
Physicochemical and crystal data

	(*S*)-**1**· (*S*)-**2**	(*S*)-**1**· (*R*)-**2**
Formulae	$C_{22}H_{27}NO_6$	$C_{22}H_{27}NO_6$
M_w	401.45	401.45
M. p. (°C)	139.6	129.2
Heat of fusion (kJ mol^{-1})	69.4	42.7
Solubility (20°C, g per 100 ml solvent)		
in water	1.4	4
in methanol	4.4	20
in ethanol 96%	1.3	5.9
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$ (Nr. 4)	$P2_1$ (Nr. 4)
a (Å)	13.770(2)	13.950(3)
b (Å)	6.122(1)	6.101(2)
c (Å)	14.367(2)	14.068(3)
β (°)	117.80(1)	116.06(1)
Volume (Å^3)	1071.3(3)	1075.6(5)
Z	2	2
Density (calculated) (Mg/m^3)	1.244	1.240

A drawing of the molecular structures of both diastereomeric ion pairs with atom labelling is shown in Fig. 1. The main bond distances and angles are listed in Table 2.

Notwithstanding the opposite configurations, similar conformations of the phenylethylammonium cation can be observed in both salts, the hydrogen H(16), bonded to C(16), approximately lying
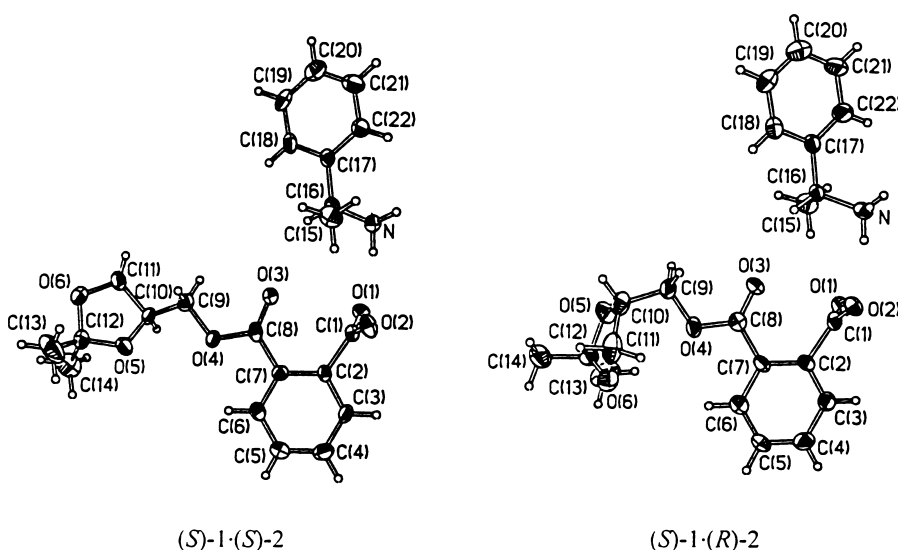
(S)-1·(S)-2   (S)-1·(R)-2

Figure 1. Molecular structures of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2**. Thermal ellipsoids are at 30% probability

in the phenyl plane. Methyl and ammonium groups are placed on opposite sides with respect to this plane, the former with a wider torsion angle (about 69.5°). Analogous dispositions are generally found in phenylethylammonium salt structures.[4–7]

In the monoesterified phthalate anion of the two diastereomeric salts, the torsion angles of the planes of the carboxylate and of the esterified carboxyl with respect to the phenyl plane are remarkably different. This is consistent with the fact that such a difference, frequently shown by derivatives of phthalic acid, increases when one of the two carboxyl groups is negatively charged. The carboxylate plane makes angles of 75.5° and 78.3° with the plane of the phenyl ring in (S)-**1**·(S)-**2** and in (S)-**1**·(R)-**2**, respectively, while the corresponding values are 12.5° and 17.2° for the esterified carboxyl group. Similar values have been observed in the known structures of (−)-strychninium (+)-neopentyl phthalate chloroform solvate[8] and of (R)-1-methylbenzylammonium (2S,3R)-3-methyl-4-phenylsulfanylbutan-2-yl phthalate.[7]

As can be seen in Fig. 1, the isopropylideneglycerol moieties of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2** are similar in the dioxolane conformation, but the torsion angles O(4) C(9) C(10) C(11) are quite different in the two cases: it is equal to 178.4° and the oxygen O(4) points to the opposite side with respect to the dioxolane ring in (S)-**1**·(S)-**2**, while the same angle is equal to 41.1° in (S)-**1**·(R)-**2**, whose oxygen O(4) points to the same side as the dioxolane ring. Such different situations are schematically represented in Fig. 2, where two Newman-like projections of these moieties are shown. In the more soluble (S)-**1**·(R)-**2** salt, C(11), O(4) and O(5) exhibit a crowded *gauche* disposition resulting in a folded conformation of the isopropylideneglycerol moiety, while only O(5) is in a *gauche* disposition with respect to O(4) in the less soluble (S)-**1**·(S)-**2** salt, C(11) having an *anti* arrangement. A lot of crystal structures containing a polysubstituted dioxolane or a dioxolane fused in a polycyclic framework have been determined.[9] To the best of our knowledge, however, the only known structure containing the unsubstituted isopropylideneglycerol moiety is that of di(4-oxyphenyl-2′,2′-dimethyl-1′,3′-dioxacyclopentyl-4′-methyl)ethanedione-1,2, which has been studied either in the *meso* or in the (S,S) form.[10] In the structure of these two stereoisomers of the above compound, the torsion angles equivalent to our O(4) C(9) C(10) C(11) (2° and 2° in the *meso* and 11° and 3° in the (S,S) form) are very similar to that found in (S)-**1**·(S)-**2**.

Table 2
Main bond distances [Å] and angles [°]

	(S)-**1**·(S)-**2**	(S)-**1**·(R)-**2**		(S)-**1**·(S)-**2**	(S)-**1**·(R)-**2**
O(1)–C(1)	1.263(8)	1.240(8)	C(10)–C(11)	1.53(1)	1.52(1)
O(2)–C(1)	1.25(1)	1.281(7)	O(5)–C(12)	1.41(1)	1.429(7)
C(1)–C(2)	1.516(9)	1.527(8)	C(11)–O(6)	1.381(8)	1.433(8)
C(2)–C(3)	1.384(9)	1.384(8)	O(6)–C(12)	1.419(9)	1.394(7)
C(2)–C(7)	1.40(1)	1.392(9)	C(12)–C(14)	1.50(1)	1.50(1)
C(3)–C(4)	1.39(1)	1.394(9)	C(12)–C(13)	1.52(1)	1.49(1)
C(4)–C(5)	1.37(1)	1.37(1)	N–C(16)	1.508(8)	1.494(6)
C(5)–C(6)	1.39(1)	1.372(8)	C(15)–C(16)	1.51(1)	1.524(9)
C(6)–C(7)	1.408(9)	1.400(8)	C(16)–C(17)	1.516(9)	1.502(8)
C(7)–C(8)	1.49(1)	1.472(8)	C(17)–C(18)	1.37(1)	1.390(9)
C(8)–O(3)	1.204(8)	1.206(6)	C(17)–C(22)	1.39(1)	1.375(9)
C(8)–O(4)	1.347(8)	1.335(7)	C(18)–C(19)	1.39(1)	1.387(8)
O(4)–C(9)	1.442(8)	1.425(7)	C(19)–C(20)	1.378(12)	1.37(1)
C(9)–C(10)	1.47(1)	1.52(1)	C(20)–C(21)	1.35(1)	1.35(1)
C(10)–O(5)	1.432(8)	1.433(8)	C(21)–C(22)	1.40(1)	1.388(9)
O(2)–C(1)–O(1)	125.4(8)	125.1(6)	C(12)–O(5)–C(10)	107.4(6)	108.6(5)
O(2)–C(1)–C(2)	116.1(8)	116.3(6)	O(6)–C(11)–C(10)	106.2(6)	103.3(7)
O(1)–C(1)–C(2)	118.1(8)	118.2(6)	C(11)–O(6)–C(12)	109.5(7)	106.2(6)
C(3)–C(2)–C(7)	118.1(7)	120.1(5)	O(5)–C(12)–O(6)	106.0(7)	105.6(5)
C(3)–C(2)–C(1)	117.6(7)	115.7(6)	O(5)–C(12)–C(14)	112.2(7)	109.2(5)
C(7)–C(2)–C(1)	124.2(7)	124.2(5)	O(6)–C(12)–C(14)	108.8(9)	112.9(7)
C(2)–C(3)–C(4)	121.6(8)	120.1(7)	O(5)–C(12)–C(13)	108.6(10)	107.4(7)
C(5)–C(4)–C(3)	120.2(8)	119.7(6)	O(6)–C(12)–C(13)	109.4(8)	108.0(6)
C(4)–C(5)–C(6)	120.1(8)	120.5(6)	C(14)–C(12)–C(13)	111.7(9)	113.3(6)
C(5)–C(6)–C(7)	119.1(8)	120.5(7)	N–C(16)–C(15)	109.4(7)	108.1(5)
C(2)–C(7)–C(6)	120.9(7)	118.9(6)	N–C(16)–C(17)	111.4(5)	112.1(4)
C(2)–C(7)–C(8)	120.3(7)	121.0(5)	C(15)–C(16)–C(17)	112.3(7)	112.9(5)
C(6)–C(7)–C(8)	118.7(8)	120.0(6)	C(18)–C(17)–C(22)	119.3(8)	118.6(6)
O(3)–C(8)–O(4)	121.7(8)	122.6(5)	C(18)–C(17)–C(16)	119.3(8)	119.3(6)
O(3)–C(8)–C(7)	126.4(8)	124.7(6)	C(22)–C(17)–C(16)	121.2(8)	122.0(6)
O(4)–C(8)–C(7)	111.9(7)	112.6(5)	C(17)–C(18)–C(19)	121.4(9)	120.5(7)
C(8)–O(4)–C(9)	118.2(6)	115.7(4)	C(20)–C(19)–C(18)	119.0(10)	119.7(7)
O(4)–C(9)–C(10)	108.1(6)	108.1(5)	C(21)–C(20)–C(19)	119.8(10)	120.2(7)
O(5)–C(10)–C(9)	110.2(7)	109.2(7)	C(20)–C(21)–C(22)	122.1(11)	120.6(8)
O(5)–C(10)–C(11)	103.4(6)	104.0(6)	C(17)–C(22)–C(21)	118.4(9)	120.3(7)
C(9)–C(10)–C(11)	113.8(7)	115.5(6)			

In spite of the outlined differences in conformation, the crystal structures of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2** are only slightly dissimilar. This may be related to the fact that the conformational differences concern a portion of the two molecules which is relatively small and far from the charged ends exerting the main stabilising forces in the lattice. In both the crystals, the packing is stabilised by the presence of chains of hydrogen bonded ions. The chains grow along *b* direction and are
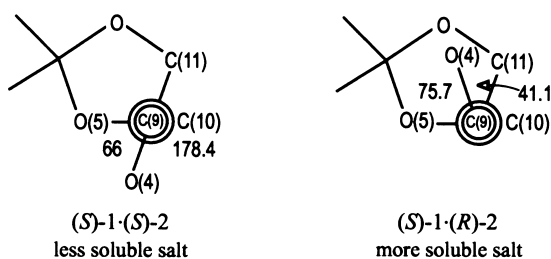
Figure 2. Newman-like projections of the isopropylideneglycerol moieties in the two solid diastereoisomers (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2**

characterised by the presence of a 2_1 screw helix. Fig. 3 shows a fragment of these chains in the two compounds. Each $-NH_3^+$ group is involved as a donor in three hydrogen bonds with three different carboxylate groups (N⋯O distances 2.75–2.85 Å). In the crystal structure of (S)-**1**·(S)-**2**, each carboxylate accepts one hydrogen bond from a $-NH_3^+$ group by the oxygen O(2) and two others from two different $-NH_3^+$ groups by the oxygen O(1). In (S)-**1**·(R)-**2**, the situation is similar, but the involved oxygens are exchanged: one hydrogen bond is accepted by O(1) and two others by O(2). The presence of these stable chains aligned with b makes the crystal growth in this direction easier. Both the crystals of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2** are prismatic and elongated with b.
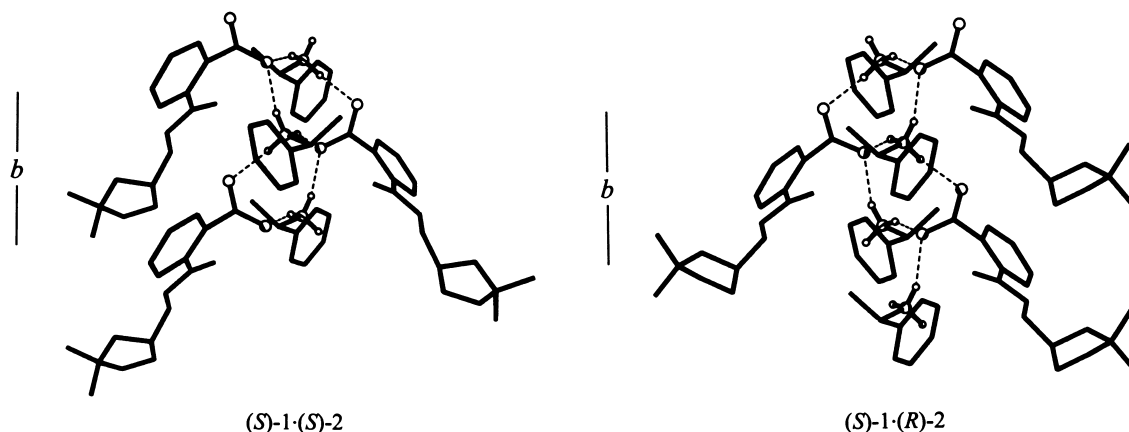

Figure 3. Ion columns present in the crystal structure of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2**. The first drawing is projected along a, the second down c. Only O, N and H atoms involved in hydrogen bonding (dashed lines) have been represented by open circles

3. Discussion

The present physicochemical and crystal data support the hypothesis, already framed by some authors,[11,12] that the solubility and thermal behaviour differences between diastereomeric salts cannot be explained on the basis of differences in the strong interactions. In fact, the hydrogen

bonds are similarly situated between the counter ions in (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2** forming the same helical columns in both cases.

The success of the resolution is rather determined by the presence of weak second-order interactions. These are responsible for the only significant difference found between the two structures, i.e. the different orientation of the dioxolane ring of (S)-**1**.

A plausible resolution mechanism might involve the following steps. Initially, the resolving agent recognises the two amine enantiomers approaching them by Coulombic attraction. Hence, it tries to accommodate to the R- and S-base isomers. This process requires a favourable position of the isopropylideneglycerol framework, which can be assumed only in two different conformations. We believe that slight and not disfavoured conformational changes of the iso-propylideneglycerol residue would be necessary for the most favourable binding to (S)-**2**. On the other hand, the incorporation of the R amine molecules in the cavities formed by (S)-**1** molecules would involve the transformation of the latter into a less favoured rotamer around the C(10)–C(9) bond. All this would result in the preferred crystallisation of the (S,S) salt or, in other words, in the lower solubility of the same.

Finally, it should be emphasised that the main conformational difference between the two diastereoisomers was observed in the chiral portion of the acid molecule. In particular, such a difference is due to the rotation around the bond linking the asymmetric carbon of the dioxolane ring to the exocyclic C(9). In light of this, it should not be surprising that **1** exhibits resolving ability though its stereogenic centre is remote from the carboxyl. In fact, the asymmetric carbon is directly involved in those different conformational changes of **1**, which take place on forming the two diastereomeric crystals and likely determine the resolution outcome.

4. Conclusion

Woodward has proposed that resolutions via selective crystallisation of diastereomeric salts are more likely to succeed when the acidic and basic functional groups responsible for salt formation are proximal in space 'to those factors which render each asymmetric'.[13] On the basis of the results provided by the structural analysis of the two salts of (S)-**1** with (S)- and (R)-**2**, we believe that the high resolving capability showed by **1** is not substantially discordant with that widely proved empirical guideline. In the case of acid **1**, in fact, the stereogenic carbon is remote from the carboxyl, yes, but two factors would contribute to undo the otherwise negative implications of such a distance and to make the asymmetry of the molecule nevertheless effective on the resolution. The former is the relative rigidity of the phthalic substructure. Significantly, we observed that isopropylideneglycerol hydrogen succinate resolves **2** with much lower efficiency. The latter is the inclusion of the asymmetric carbon in the dioxolane ring, which limits the rotation possibilities around two of the bonds afferent to the same carbon. The resultant decreased flexibility restricts the number of conformations of the chiral part of **1** fitting the two enantiomers of **2** and accentuates their dissimilarity. Consistently with this hypothesis, the absence of such a conformational restriction might be one of the reasons why the deketalised derivative of (S)-**1** was found to produce, upon reaction with (S)- and (R)-**2**, unresolvable amorphous salts.

In summary, the analysis of the present diastereomeric salts provides some explanation of the ability of isopropylideneglycerol hydrogen phthalate to resolve 1-phenylethylamine. The extension of these results to the other 1-arylalkylamines[1,2] resolved by the same acid seems reasonable, though not presently supported by analytical data on the corresponding diastereomeric salt pairs with **1**.

5. Experimental

Thermal data were recorded using a Mettler DSC 20 instrument and TC 10A-TA processor. HPLC analyses were performed on a Chiralcel OD-R column (250×4.6 mm I.D.).

5.1. Preparation of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2**

(S)-**1**·(S)-**2** was obtained by selective crystallisation from an equimolar methanolic solution of racemic **2** and (S)-**1** as previously reported.[1] The mother liquor was concentrated to dryness and the residual salt decomposed by treatment with 10% HCl and CH_2Cl_2. The aqueous phase was separated, made alkaline with 1N NaOH, and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave an oil, which was distilled under vacuum yielding R-enriched **2** with 69.1% e.e. [determined by HPLC analysis of the precipitated salt and of the corresponding liberated amine on a Chiralcel OD-R column, using a mixture of 1.5 M $NaClO_4$ and CH_3CN (85:15) as a mobile phase (flow rate 0.4 ml/min)] and in 89.0% yield (44.5% of the starting **2**).

The resolution was completed by crystallisation of the neutral sulphate of (R)-**2** from 95% ethanol, subsequent decomposition of the precipitated salt and final distillation of the free amine according to a literature procedure[14] to give enantiomerically pure (R)-**2** in 42.6% yield (21.3% of the starting **2**). Finally, (S)-**1**·(R)-**2** was obtained as a white precipitate from a methanolic solution containing equimolar amounts of (R)-**2** and (S)-**1**. ^{1}H NMR spectra (200 MHz) of (S)-**1**·(R)-**2** and of an equimolar mixture of (S)-**1**·(R)-**2** and (S)-**1**·(S)-**2** were identical to that previously reported[1] of (S)-**1**·(S)-**2**.

5.2. X-Ray investigations

Colourless prismatic crystals of (S)-**1**·(S)-**2** and (S)-**1**·(R)-**2** were grown from water and samples of both compounds were glued at the end of glass fibres, working under air. The measurements were done at room temperature (293(2) K) on a Siemens P4 diffractometer, equipped with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The intensity data were collected on a redundant set of reflections for estimating, on merging the equivalent reflections, the internal consistency of the measurement. The stability of the specimens were checked by the measurement of three standard reflections collected every 97 measurements. The intensity data were corrected for the Lorentz and polarisation effects, but not for absorption owing to the very low absorption coefficients of the samples. The data reductions were done by means of SHELXTL programme.[15] Structure solution and structure refinement were performed by full-matrix least-squares methods based on F^2, by means of SHELX-97 programme.[16]

5.3. The crystal of (S)-**1**·(S)-**2**

(S)-**1**·(S)-**2** showed the lattice parameters listed in the second column of Table 1. The systematic absences and the request of a noncentric space group indicated the $P2_1$ as the unique possible choice. The structure solution was obtained by standard direct methods and the hydrogen atoms were in part located by the difference Fourier map and in part introduced in calculated positions. The reliability indexes obtained in the last refinement cycles were $S = 1.025$, $R_1 = 0.0589$, $wR_2 = 0.1101$, refining 262 parameters on 1124 independent intensity data having $I > 2\sigma$ (I)

$(S = [\sum[w(F_o^2 - F_c^2)^2]/(N-P)]^{\frac{1}{2}}$, where N, P are the numbers of observations and parameters, respectively, $R_1 = \sum ||F_o|-|F_c||/ \sum |F_o|$; $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/ \sum[w(F_o^2)^2]]^{\frac{1}{2}}$; $w = 1/[\sigma^2(F_o^2)+(AQ)^2+BQ]$ where $Q = [MAX(F_o^2, 0)+2F_c^2]/3)$. The residual peaks and holes in the last difference Fourier map were comprised between 0.199 and –0.169 e·Å^{-3}.

5.4. The crystal of (S)-**1**·(R)-**2**

(S)-**1**·(R)-**2** showed the lattice parameters listed in the third column of Table 1. As in the case of (S)-**1**·(S)-**2** the space group appeared to be $P2_1$. The structure solution was obtained by the automatic direct method procedure (TREF) contained in SHELX-97 programme and the molecule was completed by finding the missing atoms on the difference Fourier map. Some of the hydrogen atoms was introduced in calculated positions. In the final refinement cycle, with anisotropic thermal factors for all the heavy atoms, 265 parameters were refined on 1371 independent intensity data having $I > 2\sigma(I)$. The final reliability factors were $S = 1.029$, $R_1 = 0.0556$ and $wR_2 = 0.1259$, where the symbols have the same meaning as before. The greater peaks and holes in the last difference Fourier were 0.170 and –0.271 e·Å^{-3}.

Further details of structure determinations, such as lists of atomic coordinates, thermal factors and detailed lists of atomic distances and angles in the form of CIF files have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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