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Synthesis, Structure, and Discrimination of Chiral Bimolecular Crystals by Using Diphenylacetic Acid and Aza Aromatic Compounds

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Although diphenylacetic acid (**1**) and aza aromatic compounds such as phenanthridine (**2**) and acridine (**3**) are achiral molecules, chiral bimolecular crystals **1·2** and **1·3** were obtained by recrystallization from the solutions. A 1:1 hydrogen bonding between **1** and **2** or **3** is formed in the crystal lattice. Spontaneous crystallization gave two enantiomorphous crystals of *M*- and *P*-form. The absolute configuration of *P*-**1·2** could be determined by the Bijvoet method using anomalous dispersion of an oxygen atom during X-ray analysis. The chirality in the crystalline state is generated from the propeller-like chiral conformation of two phenyl planes and a carboxyl plane of the diphenylacetic acid molecule. The two enantiomorphous *M*- and *P*-crystals of **1·2** and **1·3** could be easily discriminated by the solid-state CD spectra by using Nujol.

Introduction

One of the topics in organic solid state chemistry is an absolute asymmetric synthesis by the reaction of a chiral crystal formed from an achiral molecule.[1,2] We have also described an absolute asymmetric synthesis by the photoreaction of a chiral bimolecular crystal formed from diphenylacetic acid and acridine.[3] Most of such examples previously reported have been attributed to accidental successes. It is most essential to synthesize new chiral bimolecular crystals utilizing achiral organic compounds and elucidate the chirality generation mechanism not only for the design of absolute asymmetric syntheses[3−5] but also for the development of new materials of crystal optics.[6] Furthermore, this type of chiral crystallization is relevant to the prebiotic origin of chirality.[7] In the case of one-component crystal, chiral crystallization of achiral molecules has been described,[8,9] and the hydrogen bonding network and molecular structure have been discussed as the factors for inducing crystal chirality.[10] However, chiral bimolecular crystals of achiral molecules are scarcely known.[3−5,11]

The chirality of the bimolecular crystal of diphenylacetic acid and acridine can be generated by virtue of the propeller-like conformation of two phenyl planes and a carboxyl plane of the diphenylacetic acid molecule in the crystal lattice.[3] Here we report the synthesis of a series of two-component crystals in which diphenylacetic acid is combined with aza aromatic compounds to result in a new finding that another chiral bimolecular crystal is formed with phenanthridine. Further we report that solid-state circular dichroism (CD) spectrometry[12] is applicable for the chiral discrimination of two enantiomorphous crystals.

Results and Discussion

The bimolecular crystals incorporate diphenylacetic acid (**1**) as a torsional molecule and five aza aromatic compounds, phenanthridine (**2**), acridine (**3**), benzo[*f*]quinoline (**4**), quinoline (**5**), and phenazine (**6**) as hydrogen bonding connectors (Scheme 1). Recrystallization from the solutions of each two components by evaporation or cooling gave five bimolecular crystals. The melting points, IR spectra, and elemental analyses are described in the Experimental Section. The bimolecular crystals were submitted to X-ray crystallographic analysis[18] to confirm the chiral nature of **1·2** and **1·3**[3] crystals whose space groups are $P2_1$ and $P2_12_12_1$, respectively. The other crystals **1·4**, **1·5** and **1·6** were achiral whose space groups are $P2_1/a$, $P2_1/c$, and $P2_1/n$, respectively. In all the crystals, O−H···N hydrogen bonding is formed between the hydroxyl group of **1** and the N atom of aza aromatic compond in a 1:1 ratio for **1·2**, **1·3**, **1·4**, and **1·5**, and 2:1 for **1·6**. The distances and angles are summerized in Table 1.

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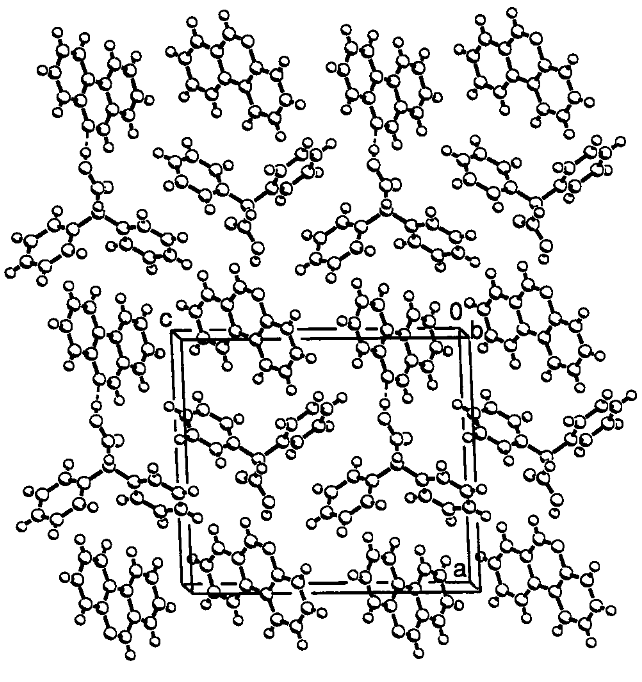

Figure 1. Packing drawing of *P*-**1·2** viewed along the *b* axis.

Scheme 1

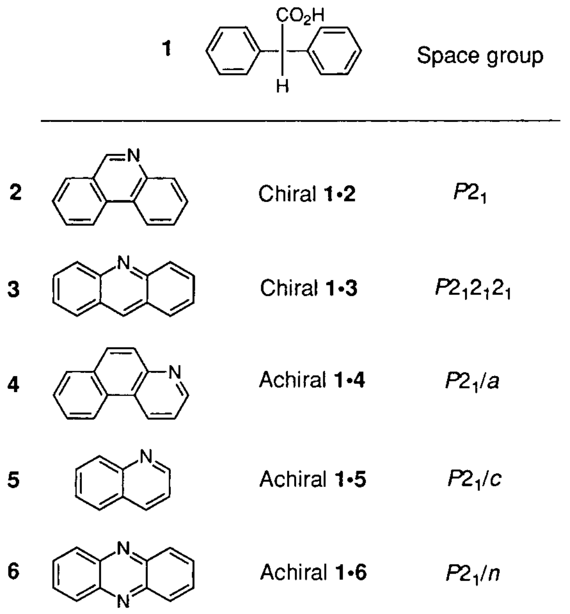

Table 1. Distance and Angle Data of the Hydrogen Bonding Pairs

	M-**1·2**	*P*-**1·2**	*M*-**1·3**	*P*-**1·3**	**1·4**	**1·5**	**1·6**
H-Bonding (O−H···N)							
H···N distance(Å)	1.92	1.92	1.79	1.79	1.76	1.67	1.82
O···N distance (Å)	2.72	2.72	2.71	2.71	2.70	2.63	2.77
O−H···N angle (deg)	148	148	172	172	172	171	172
Dihedral Angle of H-Bonding Pair (deg)							
NAr/COO	35.5	35.5	59.3	59.3	143.6	10.8	149.5

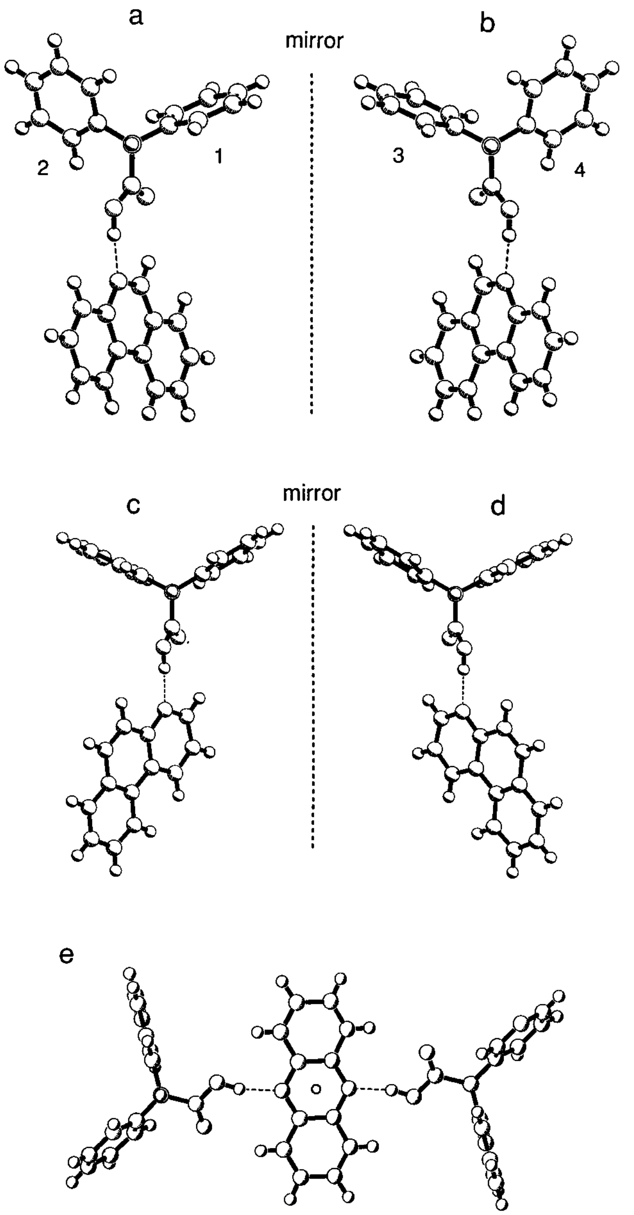

Figure 2. Molecular pairs self-assembed in the crystals. a and b exist separately in *M*-**1·2** and *P*-**1·2**, respectively. c and d coexist in achiral **1·4**. is a 2:1 pair packed in the achiral **1·6**.

Left- and right-handed crystals of **1·2** could be obtained by spontaneous crystallization from the methanol solutions. A single crystal of **1·2** was cut into two pieces. One half was subjected to solid-state CD spectroscopy (curve b in Figure 3). The second half was polished into a spherical form and subjected to X-ray structure analysis followed by absolute configuration determination and was identified as *P*-**1·2** with a high degree of certainty[13] by using the Bijvoet method based on X-ray anomalous dispersion of the oxygen atom with Cu Kα radiation. Figure 1 shows the packing arrangement of *P*-**1·2** of which the absolute configuration is correct. In the hydrogen bonding pair, two phenyl planes and the carboxyl plane of a diphenylacetic acid molecule form a propeller-like conformation as shown in Figure 2b. The torsion angles around the C−C bond to the methine group are −13.0° (Ph-3), −50.3° (Ph-4), and −33.9° (COO) (Table 2). The helicity[14] around the C−H bond of the methine group is generated in a clockwise (plus) manner, termed as *P*-**1·2**. An important feature of *P*-**1·2** is that only the hydrogen bonding pairs of a single absolute configuration shown in Figure 2b are packed in the crystal lattice, inducing chirality in the crystal. On the other hand, only the molecular pairs with opposite torsion

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Table 2. Torsion Angles in the Bimolecular Crystals

torsion angle[a] (deg)	*M*-**1·2**	*P*-**1·2**	*M*-**1·3**	*P*-**1·3**	**1·4**	**1·5**	**1·6**
Ph-1	13.0		52.3		8.1	26.1	3.8
Ph-2	50.3		16.2		1.3	36.1	0.5
COO	33.9		30.3		17.4	31.8	58.3
Ph-3		−13.0		−52.3	−8.1	−26.1	−3.8
Ph-4		−50.3		−16.2	−1.3	−36.1	−0.5
COO		−33.9		−30.3	−17.4	−31.8	−58.3

[a] Plane numbers are shown in Figure 2.

angles of 13.0° (Ph-1), 50.3° (Ph-2), and 33.9° (COO) are packed in the crystal *M*-**1·2** (Figure 2a). The two kinds of molecular pairs (a and b) are in a mirror image relationship to each other. Such a mechanism of chirality generation is similar to that for the chiral crystals *M*-**1·3** and *P*-**1·3** of **1** and acridine **3** as we previously reported.[3]

Here it is understandable that the diphenylacetic acid molecule is achiral in the solution phase due to the free-rotation of planes but chiral in the crystals **1·2** and **1·3** due to freezing into the most stable conformation. Namely, this type of chiral crystallization is like a spontaneous resolution of racemic compounds. Thus, the flexible planes of the diphenylacetic acid molecule play an essential role. However, the crystal of diphenylacetic acid alone is achiral (space group $P2_1/n$) due to the formation of an achiral carboxyl dimer of the antipodal molecules in the crystal lattice.[3] We have been aware that a chiral crystal of benzophenone[15] (space group $P2_12_12_1$) is in a similar situation. The two phenyl planes of benzophenone molecule have some torsions in the crystal. Although two torsional conformations with a mirror image relationship are possible, only the molecules of a single absolute configuration are packed in a crystal.

However, such a chiral conformation cannot necessarily induce chiral crystallization. The crystal **1·4** of **1** and benzo[*f*]quinoline **4** crystallizes in an achiral space group ($P2_1/a$, $Z = 4$). The feature of the achiral **1·4** is that two molecular pairs of the left-handed conformation and two of the right-handed one coexist in a unit cell (Figure 2c,d). Therefore, the chirality is nullified in the crystal to give the achiral crystal. The crystal **1·5** ($P2_1/c$) of **1** and quinoline **5** is achiral due to the same reason as for the crystal **1·5**. In the case of achiral crystal **1·6** ($P2_1/n$), two antipodal molecules of **1** connect to two N atoms of a phenazine molecule to form a 2:1 hydrogen bonding pair, in which an inversion center exists in the center of the phenazine plane, resulting in the offset of crystal chirality (Figure 2e). The prediction whether the molecular pairs are self-assembled in only one handed conformation or in both handed conformations in spontaneous crystallization remains difficult, depending on a small difference among the molecular structures of the aza aromatic compounds. We reached, however, a principal guideline that the torsional conformation such as a phenyl plane is effective for the induction of chirality in the formation of two-component crystals.

This type of chiral crystal has inherent optical activity as a crystal. We succeeded to measure the solid-state CD spectra of the chiral crystals **1·2** and **1·3** by the Nujol mull method[12] (Figure 3). The plus and minus ellipticities of *M*-**1·3** and *P*-**1·3** are accordant with those of *M*-**1·2** and *P*-**1·2**, respectively, reflecting the similarity between the spatial arrangements of the molecular pairs in the two crystals. Reasonably, such CD spectra were not observed in solution state. Since irradiation of *M*-**1·3** and *P*-**1·3** caused decarboxylating condensation to give the corresponding chiral products with minus (α^{20}_D −30) and plus (α^{20}_D +30) optical rotation, respectively, as the main products,[3] the handedness can be differentiated from the optical rotation signal of the obtained chiral product. However, such a method could not be applied for **1·2** because the photodecarboxylating condensation of **1·2** is accompanied with subsequent dehydrogenation to lead to the formation of an achiral product. Therefore, solid-state CD spectrometry can be powerful for the discrimination of chirality. Furthermore, this methodology can be utilized for discriminating whether a given crystal is chiral or not without X-ray crystallographic analysis. In the future, the determination of absolute configuration

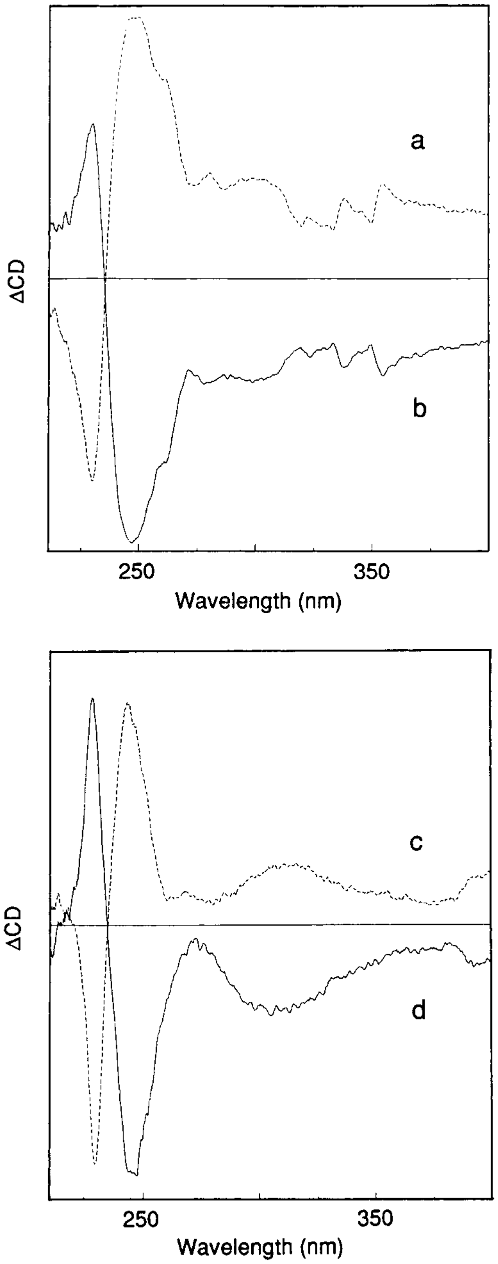

Figure 3. CD spectra of the enantiomeric cryatals of (a) *M*-**1·2**, (b) *P*-**1·2**, (c) *M*-**1·3** and (d) *P*-**1·3** measured by the Nujol mull method. A mixture of 2 mg of the crystal and 10 mg of liquid paraffin was well ground and placed between two NaCl plates into a thin layer. The peak intensities were reasonably reproduced under these conditions.

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of a chiral crystal by the CD spectrum pattern will become possible by the accumulation of a large number of experimental data, and the theoretical considerations. In addition, the optical rotations of *M*-**1·3** and *P*-**1·3** by HAUP (high-accuracy universal polarimeter)[16] using a single crystal will be described elsewhere.

Which handed crystal, *P* or *M*, can spontaneously crystallize from the solution without any external perturbation is an interesting subject. A 1:1 methanol solution of **1** and **2** prepared in a flask was divided into six small glass vessels and allowed to stand without stirring on separate laboratory benches at room temperature to give the fine crystals of **1·2** due to the sudden crystallization from the supersaturated solutions. All the crystals obtained in the each vessel were ground, and the CD spectra were measured to result in the curve of *P*-**1·2** (Figure 3b) for the three vessels and that of *M*-**1·2** (Figure 3a) for the other three, showing a single or at least predominant handedness in the each vessel. However, the result does not necessarily mean that the probability of spontaneous crystallization of *M*-**1·2** and *P*-**1·2** without stirring is 1:1 in general due to an insufficient number of trials. Kondepudi et al. reported that crystallization of $NaClO_3$ from the aqueous solution resulted in the statistically equal numbers of L- and D-crystals without stirring, and either L or D alone with stirring.[17] The accordance of the latter result obtained under stirring with our result obtained without stirring suggests that the microcrystals which were firstly formed could act as the seed crystals in both cases.

Experimental Section

Preparation of Bimolecular Crystals. Five bimolecular crystals **1·2**−**1·6** were prepared by recrystallization from 1:1 solutions of **1** and **2**−**5**, and 2:1 of **1** and **6**. The crystals were characterized by IR, DSC, and elemental analysis.

1·2: colorless plate crystals; mp 116 °C (from MeOH); IR (KBr) 3056−2499, 1878 (broad), 1710 cm^{-1}. Anal. Calcd for $C_{27}H_{21}NO_2$ (1:1): C, 82.95; H, 5.62; N, 3.56. Found: C, 82.84; H, 5.41, N, 3.58.

1·3:[3] yellow rod crystals; mp 101 °C (from MeCN); IR (KBr) 3085−2490, 1705 cm^{-1}. Anal. Calcd for $C_{27}H_{21}NO_2$ (1:1): C, 82.95; H, 5.62; N, 3.56. Found: C, 83.26; H, 5.64; N, 3.57. This crystal **1·3** corresponds to the crystal (−)-**1·a** or (+)-**1·a** in reference 3.

1·4: colorless rod crystals; mp 122 °C (from MeOH); IR (KBr) 3028−2466, 1912 (broad), 1703 cm^{-1}. Anal. Calcd for $C_{27}H_{21}NO_2$ (1:1): C, 82.95; H, 5.62; N, 3.56. Found: C, 82.84, H, 5.41; N, 3.58.

1·5: colorless rod crystals; mp 89 °C (from MeOH); IR (KBr) 2403 (broad), 1715 cm^{-1}. Anal. Calcd for $C_{23}H_{19}NO_2$ (1:1): C, 80.99; H, 5.83; N, 4.08. Found: C, 80.92, H, 5.61; N, 4.10.

1·6: yellow needle crystals; mp 137 °C (from MeOH); IR (KBr) 3060−2560, 1963 (broad), 1704 cm^{-1}. Anal. Calcd for $C_{34}H_{32}N_2O_4$ (2:1): C, 79.44; H, 5.34; N, 4.63. Found: C, 79.50, H, 5.54; N, 4.57.

X-ray Crystallographic Analysis of the Bimolecular Crystals. Data collections were performed on a Rigaku AFC7R automatic four-circle X-ray diffractometer equipped with a graphite monochromated Mo Kα ($\lambda = 0.71069$ Å) or Cu Kα ($\lambda = 1.54178$ Å) radiation and a rotating anode. Absorption correction was applied. No degradation of the crystal by X-ray was ascertained in all cases by repeated monitoring of the three representative reflections every 150 reflections. These structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Atomic parameters were refined by the full matrix least-squares method at the final stage. All the calculations were carried out on teXsan crystallographic software package, Molecular Structure Corporation.

P-**1·2**: monoclinic; $P2_1$; $a = 12.837(4)$ Å, $b = 5.478(2)$ Å, $c = 14.592(2)$ Å, $\beta = 92.80(2)°$; $V = 1024.9(5)$ Å^3; $Z = 2$; $D_{calc} = 1.268$ g cm^{-3}; GOF = 3.23. The structure was solved by direct method (SHELXS86) and refined by the full-matrix least squares procedure to $R = 0.026$ and $R_w = 0.025$ for 2932 independent observed reflections [$I > 3.00\sigma(I)$] of total 3604 reflections (Bijvoet method) with $2\theta \leq 120.1°$ (Cu Kα).

The absolute configuration of *P*-**1·2** was determined very carefully by the Bijvoet method using anomalous despersion during X-ray crystallographic analysis. Although oxygen is a light atom ($\Delta f'' = 0.032$ for Cu Kα radiation), its use as an anomalous scatterer was preferred, because even slight modification of *P*-**1·2** by induction of heavier elements such as sulfur and chlorine may cause changes in the initial crystal structure. A single crystal was cut into two pieces. The spherical crystal (0.3-mm diameter) of the half was submitted to X-ray structure analysis followed by absolute configuration determination by the Bijvoet method based on anomalous dispersion of the oxygen atom with Cu Kα radiation. Further, the diffraction intensities of 25 reflections $\{0.88 > |\Delta Fc|/\sigma(Fo) > 0.31\}$ of the Bijvoet pairs which were selected in order of larger absolute value $\{0.88 > |\Delta Fc|/\sigma(Fo) > 0.31\}$ were carefully measured manually at a low speed to give opposite plus and minus signs of the 23 reflections.[13] Therefore, *x*, *y*, and *z* axes were converted; the packing diagram in Figure 1 show the correct absolute configuration of *P*-**1·2**. The CD spectrum of the second half has a minus Cotton effect at around 250 nm (Figure 3b).

M-**1·3**:[3] monoclinic; $P2_12_12_1$; $a = 14.908(4)$ Å, $b = 25.367(6)$ Å, $c = 5.457(3)$ Å; $V = 2063(1)$ Å^3; $Z = 4$; $D_{calc} = 1.260$ g cm^{-3}; GOF = 1.84. The structure was solved by direct method (SIR88) and refined by the full-matrix least squares procedure to $R = 0.043$ and $R_w = 0.058$ for 1501 independent observed reflections [$I > 3.00\sigma(I)$] of total 10378 reflections with $2\theta \leq 110.0°$ (Cu Kα). Absolute configuration of *M*-**1·3** was also determined in a high degree of certainty as previously reported;[3] *M*-**1·3** corresponds to (−)-**1·a** in ref 3.

1·4: monoclinic; $P2_1/a$; $a = 16.456(3)$ Å, $b = 6.106(4)$ Å, $c = 21.569(2)$ Å, $\beta = 108.490(9)°$; $V = 2055(1)$ Å^3; $Z = 4$; $D_{calc} = 1.265$ g cm^{-3}; GOF = 1.96. The structure was solved by direct method (SHELXS86) and refined by the full-matrix least squares procedure to $R = 0.046$ and $R_w = 0.076$ for 2636 independent observed reflections [$I > 3.00\sigma(I)$] of total 4142 reflections with $2\theta \leq 50.0°$ (Mo Kα).

1·5: monoclinic; $P2_1/c$; $a = 11.044(6)$ Å, $b = 19.484(2)$ Å, $c = 9.238(3)$ Å, $\beta = 110.94(3)°$; $V = 1856(1)$ Å^3; $Z = 4$; $D_{calc} = 1.221$ g cm^{-3}; GOF = 1.47. The structure was solved by direct method (SHELXS86) and refined by the full-matrix least squares procedure to $R = 0.045$ and $R_w = 0.076$ for 2083 independent observed reflections [$I > 3.00\sigma(I)$] of total 3558 reflections with $2\theta \leq 50.0°$ (Mo Kα).

1·6: monoclinic; $P2_1/n$; $a = 5.824(1)$ Å, $b = 18.128(1)$ Å, $c = 15.194(2)$ Å, $\beta = 97.99(2)°$; $V = 1588.4(4)$ Å3; $Z = 2$; $D_{calc} = 1.264$ g cm^{-3}; GOF = 1.79. The structure was solved by direct method (SHELXS86) and refined by the full-matrix least squares procedure to $R = 0.057$ and $R_w = 0.088$ for 2022 independent observed reflections [$I > 3.00\sigma(I)$] of total 2737 reflections with $2\theta \leq 120.1°$ (Cu Kα).

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(18) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.