A Curious Case of Partial Spontaneous Resolution on Crystallization of a Racemate. The Crystal and Molecular Structures of N-Acetyl-DL-alanine Methylester and N-Acetyl-L-alanine Methylester

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In memoriam Jan Kroon

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Chirality, Racemate, Amino Acids

N-Acetyl-L-alanine methylester crystallizes in the orthorhombic space group $P 2_1 2_1 2_1$ with one molecule in the asymmetric unit ($a = 7.768(1)$, $b = 9.606(1)$, $c = 10.215(2)$ Å, $Z = 4$). The individual molecules are linked into infinite strands by intermolecular hydrogen bonds between the amide hydrogen atom as donor and the acetyl oxygen atom as acceptor. The strands run parallel to the crystallographic $b$ axis. The respective racemate, N-acetyl-DL-alanine methylester, crystallizes in the monoclinic space group $P 2_1/n$ with three molecules in the asymmetric unit ($a = 14.442(3)$, $b = 8.467(2)$, $c = 19.336(5)$ Å, $\beta = 93.68(1)^\circ$, $Z = 12$). Again, the individual molecules are linked into infinite strands by N-H...O=\text{acetyl} hydrogen bonds which run along the crystallographic $a$ axis. The individual strands are made up of molecules of opposite chirality in a $2:1$ ratio. More specifically, one set of strands consists of molecules in the sequence [0, $d$, 1]$_\infty$ while a second set has the sequence [1, $l$, 0]$_\infty$ as imposed by the centrosymmetry of the space group. Thus, although crystals of N-acetyl-DL-alanine methylester contain equal amounts of the molecules of opposite chirality, the strand formation through intermolecular hydrogen bonds leads to an incomplete resolution of the racemic mixture of molecules within one strand. The reason for the preference of the observed structure of N-acetyl-DL-alanine methylester over spontaneous resolution is seen in the optimization of hydrogen bonding within one strand versus the overall crystal packing energy. Some principles of the crystallization of achiral molecules, chiral molecules, and racemates are briefly reviewed, as is the phenomenon of spontaneous resolution.

Introduction

Suitably substituted amino acids and peptides have been used frequently in conformational studies. In particular, molecules with reduced capability to form hydrogen bonds have attracted interest because they allow the investigation of the influence of specific hydrogen bonds on the molecular conformation.

N-Acetyl-L-alanine methylester (I) can only form (strong) hydrogen bonds with its N-H bond (as hydrogen bond donor) and its amide and ester carbonyl oxygen atoms (as hydrogen bond acceptors).

IR spectroscopy of N-acetyl-L-alanine methyl-ester in dilute CCl$_4$ and CHCl$_3$ solutions has been used to exclude the formation of intramolecular hydrogen bonds [1]. Variable-concentration $^1$H and $^{13}$C NMR spectra in CDCl$_3$ indicated the formation of dimers (II) by intermolecular hydrogen bonds between the amide N-H function and the ester carbonyl oxygen atom [2].

It should also be noted that the acidity and basicity of N-acetyl-L-alanine methylester has been determined experimentally in the gas phase [3], while the influence of alkali and alkaline earth metal ions...
on its conformation has been studied computationally [4].

We were now able to determine the crystal and molecular structures of N-acetyl-L-alanine methyl-ester (m.p.: room temperature [5]) and N-acetyl-DL-alanine methylester (m.p.: 45 - 47 °C [6]). In the crystal both the pure enantiomer as well as the racemate show a hydrogen bond pattern which is distinctly different from the one proposed for the solution. More importantly, the crystal structure of N-acetyl-DL-alanine methylester shows what may be termed “partial spontaneous resolution”. Due to the importance of these findings for the spontaneous resolution of racemates, some principles of the crystallization of achiral molecules, chiral molecules with rapidly interconverting enantiomers in solution, chiral molecules with resolvable enantiomers, and racemates are briefly reviewed, as is the phenomenon of spontaneous resolution.

A preliminary report of this work has appeared [7].

Review of the Crystallization of Achiral Molecules, Chiral Molecules, and Racemates

Enantiomerically pure chiral compounds can only crystallize in non-centrosymmetric space groups lacking symmetry operations of the second kind, as, e.g., improper rotations [8]. These space groups belong to the 11 non-centrosymmetric point groups containing only proper rotations (symmetry operations of the first kind) [9, 10]. As these space groups do not contain symmetry elements which interconvert enantiomers, they are also called enantiomorphic space groups [11]. Achiral molecules, chiral molecules with rapidly interconverting enantiomers in solution, and racemates (equimolar mixtures of a pair of enantiomers) can crystallize in any of the 230 space groups [12, 13].

Particularly interesting cases are achiral molecules, rapidly interconverting chiral molecules, and racemates when crystallizing in an enantiomorphic space group [14]. This amounts to the formation of a chiral object (an enantiomorphic crystal) from an achiral system (achiral molecules, rapidly interconverting chiral molecules, or racemates in solution) under achiral conditions. For racemates this process is called spontaneous resolution. Spontaneous resolution results in the formation of a racemic conglomerate, an equimolar mechanical mixture of crystals, each one of which contains only one of the enantiomers present in solution [15, 16]. As was first demonstrated by Pasteur with sodium ammonium tartrate [17], under favorable circumstances pure enantiomers can by obtained from a racemic conglomerate by manual sorting [18, 19]. An inventory of older examples of organic conglomerates is given by Jacques et al. [14]. For achiral and rapidly interconverting chiral molecules the formation of enantiomorphic crystals is also well documented. Prominent inorganic examples are crystals of sodium chlorate (space group $P2_13$) [20] and quartz ($\alpha$-quartz: space groups $P3_121 / P321$ (enantiororphic pair); $\beta$-quartz: space groups $P6_222 / P6_422$) [21], the constituents of which are achiral. Hydrogen peroxide and dibenzoyl peroxide are typical examples of chiral molecules with rapidly interconverting enantiomers in solution which form enantiomorphic crystals [22]. In a single crystal these molecules adopt identical chiral conformations. As in these examples the molecules/ions are achiral or chiral but rapidly interconverting in solution, each of these molecules or ion pairs can form any of the enantiomorphic lattices. Hence there is no need that on complete crystallization equal amounts of enantiomorphic crystals of opposite chirality must be formed [23]. A spectacular case of such a chiral symmetry breaking by crystallization from stirred solutions has been found for sodium chlorate [24].

The factors leading to spontaneous resolution of a racemate or to the formation of enantiomorphic crystals from achiral and rapidly interconverting chiral substances are only poorly understood, and predictions are hardly possible at present. In essence, for spontaneous resolution of a racemate to occur the free energy change for the process

\[
1 \text{ mol DL (racemic) crystal} \rightarrow \frac{1}{2} \text{ mol D crystal} + \frac{1}{2} \text{ mol L crystal}
\]

has to be negative [25]. Some of the difficulties in assessing the free energy changes for such processes are as follows. In cases of spontaneous resolution the DL (racemic) crystals are markedly less stable than the conglomerate, which means that they are usually unobtainable [26]. In cases where no spontaneous resolution occurs, i.e., where the DL (racemic) crystal is more stable, the endergonic free energy change for the above process is only of the order of a few kcal/mol [27]. That means that small changes in the enthalpic contribution to $\Delta G^o$ may
Crystals colorless needles colorless needles
Crystal size [mm³] 0.12×0.12×0.45 0.10×0.10×0.48
Formula C₆H₁₁NO₃ C₆H₁₁NO₃
M₉ [g/Mol] 145.16 145.16
Crystal sytem orthorhombic monoclinic
Space group P₂₁₂₁₂ (No. 19) P₂₁/n (No. 14)
a [Å] 7.768(1) 14.442(3)
b [Å] 9.606(1) 8.467(2)
c [Å] 10.215(2) 19.336(5)
β [deg.] 90.0 93.68(1)
V [Å³] 762.2(2) 2360(1)
Z 4 12
ρealed [g/cm³] 1.265 1.226
μ(Mo-Kα) [cm⁻¹] 1.01 0.98
F(000) [e] 312 936
Scan type θ/2θ θ/2θ
Δω [deg.] 1.0 + 0.35 tan θ 1.0 + 0.35 tan θ
(sin θ/λ)max [Å⁻¹] 0.648 0.606
hkl Range ±10, ±12, ±13 ±17, +10, ±23
Reflexions measured 6840 8778
Independent reflexions 1018 4391
Rint 0.035 0.060
Reflexions with I > 2 σ(I) 953 2378
Ref. parameters/restraints 98/0 292/0
(shift/error)max 0.00 0.00
R(F)/wR(F²); all data⁴ 0.027/0.070 0.047/0.137
GoF (F²) 1.13 0.98
Δρ(fin) (max./min.) [e/Å³] 0.12/−0.18 0.22/−0.25

be decisive [28, 29]. The magnitudes of these contributions cannot be measured directly. Although they can be derived from the enthalpies and entropies [30] of fusion, from melting points and heat capacities, only a few cases have been dealt with in detail [14, 28]. Clearly, what would be most desirable is the systematic computation of packing energies from intermolecular potentials, and thus the prediction of preferred packing modes. Despite considerable effort and progress over the past years, the reliable computation of intermolecular energies in molecular crystals is still in its infancy, however [31].

Results

<table>
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<td>colorless needles</td>
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<tr>
<td>M₉ [g/Mol] 145.16</td>
<td>145.16</td>
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<td>F(000) [e] 312</td>
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<tr>
<td>(sin θ/λ)max [Å⁻¹] 0.648</td>
<td>0.606</td>
</tr>
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<td>hkl Range ±10, ±12, ±13</td>
<td>±17, +10, ±23</td>
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<tr>
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<td>R(F)/wR(F²); all data⁴ 0.027/0.070</td>
<td>0.047/0.137</td>
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<tr>
<td>GoF (F²) 1.13</td>
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</tr>
<tr>
<td>Δρ(fin) (max./min.) [e/Å³] 0.12/−0.18</td>
<td>0.22/−0.25</td>
</tr>
</tbody>
</table>

Table 1. Crystal structure data for N-acetyl-L-alanine methylester (1) and N-acetyl-DL-alanine methylester (2).

The dimensions of the hydrogen bond are given in Table 3.

Fig. 1. Molecular structure of N-acetyl-L-alanine methylester in the crystal and atomic numbering scheme adopted. (ORTEP-III. Displacement ellipsoids at the 50% probability level; H atoms as spheres with arbitrary radius).
The respective racemate, N-acetyl-DL-alanine methylester, crystallizes in the monoclinic space group $P2_1/n$ with three molecules in the asymmetric unit ($Z = 12$; Table 1) [32, 33]. Each of the three crystallographically independent molecules occur in the D and the L form in the crystal as imposed by the space group symmetry. The geometric parameters of the individual molecules are summarized in Table 2 together with those of N-acetyl-L-alanine methylester. Again, the individual molecules are linked to infinite strands by N-H–O = C acetyl hydrogen bonds (Table 3) which run along the crystallographic $a$ axis (Fig. 3). The repeating units of the individual strands are the three crystallographically independent molecules. However, within one single strand these three molecules are of opposite chirality in a 2:1 ratio. More specifically, one set of
Table 3. Hydrogen bond dimensions (Å; deg.) for \textit{N}-acetyl-L-alanine methylester and \textit{N}-acetyl-DL-alanine methylester with estimated standard deviations in parentheses.

\begin{tabular}{cccc}
\hline
                      & \textit{N}-Acetyl-L-alanine methylester & \textit{N}-Acetyl-DL-alanine methylester & \\
                      & N1-H11 \cdots O1' N1\cdots O1' N1-H11 \cdots O1' & N1-H11 \cdots O4 N1\cdots O4 N1-H11 \cdots O4 & \\
                      & 0.88(2) 2.07(2) 2.941(1) 174(2) & 0.85(3) 2.02(3) 2.862(2) 171(2) & \\
Symmetry code O1': 1 - x, 0.5 + y, 1.5 - z & & & \\
\hline
\end{tabular}

Fig. 3. Hydrogen-bonded strands of the three crystallographically independent molecules of \textit{N}-acetyl-DL-alanine methylester in the crystal and atomic numbering scheme adopted (ORTEP-III). H33 forms a hydrogen bond to a neighboring O1' (1 + x, y, z); O1 to a neighboring H33' (−1 + x, y, z) whereby the infinite-strand formation results.

strands consists of molecules in the sequence [D, D, L]\text{\infty} while a second set has the sequence [L, L, D]\text{\infty}. The [D, D, L]\text{\infty} strand is depicted in Fig. 3. Thus, although crystals of \textit{N}-acetyl-DL-alanine methylester contain equal amounts of the molecules of opposite chirality, the strand formation through intermolecular hydrogen bonds leads to a situation which may be considered as an incomplete resolution of the racemic mixture of molecules within one strand. This aspect of the crystal structure of \textit{N}-acetyl-DL-alanine methylester is discussed further below. It should be noted that the hydrogen bond pattern in the solid state is markedly different from that in solution where dimer formation through N-H \cdots O=C_{\text{ester}} hydrogen bonds (formula \textit{II}) has been made plausible by NMR spectroscopy [2].

Discussion

The crystal structures of \textit{N}-acetyl-L-alanine methylester and the racemate \textit{N}-acetyl-DL-alanine methylester provide the unique opportunity to compare the structural parameters of altogether four independent molecules in two crystal structures, one in the L form, three others each in the D and the L form in one crystal. Each of the latter three enantiomeric pairs of molecules have identical structural parameters with the exception of the torsion angles which are identical in value but opposite in sign for each pair [34]. As Table 2 clearly shows, with one single exception [35] the bond lengths and angles in the four independent molecules are identical within three standard deviations. This is not only a remarkable check on the internal consistency of the structure determinations but also shows that packing forces can only exert little influence on bond distances and angles of strongly bound atoms, as is the case for the C, N, and O atoms in amino acids. As expected, the torsion angles (Table 2) show a larger spread of their values. It is particularly remarkable, however, that major differences are between the enantiomorphic crystals (\textit{N}-Acetyl-L-alanine methylester) and the racemic \textit{N}-acetyl-DL-alanine methylester, while the differences between the torsion angles of the three independent molecules in the latter are far smaller (Table 2). In any case, the torsion angles \(\varphi\) and \(\psi\) (Table 2) are in the range typical for \(\beta\)-sheet formation [36] where the amino acid residues are also held together by N-H \cdots O=C_{\text{acetyl}} hydrogen bonds.

As described above, the hydrogen-bonded strands in \textit{N}-acetyl-L-alanine methylester and in the racemic structure of \textit{N}-acetyl-DL-alanine methylester are different in that the first ones are homochiral while the second ones are made up of the enantiomers in a 2:1 ratio. The racemic \textit{N}-acetyl-DL-alanine methylester, when crystallizing from its melt, does not show spontaneous resolution but the unequal amount of molecules of opposite chirality in one strand may be considered as a partial resolution of the racemate within one strand. We believe that the melting points and the densities of the enantiomerically pure substance and the racemate provide an answer for this behavior.
Table 4. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for N-acetyl-L-alanine methylester. (U(eq) is defined as one third of the trace of the orthogonalized Uij tensor).

<table>
<thead>
<tr>
<th>Atom</th>
<th>x/a</th>
<th>y/b</th>
<th>z/c</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
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<td>O1</td>
<td>0.5220(1)</td>
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</table>

N-Acetyl-L-alanine methylester (m.p.: room temperature [5]) melts slightly lower than N-acetyl-DL-alanine methylester (m.p.: 45 - 47 °C [6]). Despite the rather vague indication of the exact value, the lower melting point of the enantiomerically pure crystals is a strong indication of their lower thermodynamic stability [37]. Therefore, it is not surprising that no spontaneous resolution is observed on crystallization of the racemate.

Despite their higher thermodynamic stability, the racemic crystals of N-acetyl-DL-alanine methylester have a lower density, however, than those of N-acetyl-L-alanine methylester (Table 1), the difference Δ(%) being -3.13% [38]. Close packing, i.e., the minimization of the free volume, which goes along with a maximization of the van der Waals interaction and the density, is considered to be most important for the stability of molecular crystals as long as stronger interactions are absent [31q, r]. Hydrogen bonds are much stronger than van der Waals forces, and are thus considered to be structure determining [31g, 39]. Their strong directionality favors more open structures.

When comparing the hydrogen bonds in N-acetyl-L-alanine methylester with those in N-acetyl-DL-alanine methylester (Table 3), those in the racemic crystal are significantly shorter. Apparently, the better interstrand hydrogen bonding is made possible by the strand formation of molecules of opposite chirality in a 2:1 ratio, and concomitant small changes in the most sensitive torsion angles (Table 2). Furthermore, the stronger hydrogen bonds offset the loss in packing energy resulting from a less efficient packing of the strands in the racemic crystals as is evident from their lower density.

We therefore conclude that in our compounds homochiral strands are less favorable due to less efficient hydrogen bonding although they may be packed better in an enantiomorphic crystal. Racemic crystals are preferred due to better interstrand hydrogen bonding when the strand-forming molecules are of opposite chirality in a 2:1 ratio. This renders the racemic crystals more stable despite a less efficient packing of the strands. Spontaneous resolution is thus precluded as the racemate

<table>
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<tr>
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<td>0.1351(3)</td>
<td>0.7192(1)</td>
<td>0.0461(7)</td>
</tr>
<tr>
<td>O7a</td>
<td>1.1030(2)</td>
<td>0.6407(2)</td>
<td>0.6026(9)</td>
<td>0.0392(5)</td>
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<tr>
<td>O8a</td>
<td>1.2266(2)</td>
<td>0.9078(2)</td>
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<tr>
<td>O9a</td>
<td>1.1327(2)</td>
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<td>0.6592(9)</td>
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<tr>
<td>N3a</td>
<td>1.2446(1)</td>
<td>0.7413(2)</td>
<td>0.5922(1)</td>
<td>0.0270(6)</td>
</tr>
<tr>
<td>C13a</td>
<td>1.2304(2)</td>
<td>0.4598(3)</td>
<td>0.6051(2)</td>
<td>0.0360(8)</td>
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<tr>
<td>C14a</td>
<td>1.1874(1)</td>
<td>0.6199(3)</td>
<td>0.6007(1)</td>
<td>0.0261(6)</td>
</tr>
<tr>
<td>C15a</td>
<td>1.2114(2)</td>
<td>0.9021(3)</td>
<td>0.5900(1)</td>
<td>0.0297(6)</td>
</tr>
<tr>
<td>C16a</td>
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<td>1.0080(3)</td>
<td>0.5569(2)</td>
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<tr>
<td>C17a</td>
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<td>0.9597(3)</td>
<td>0.6624(1)</td>
<td>0.0268(6)</td>
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<tr>
<td>C18a</td>
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<td>1.1440(3)</td>
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<tr>
<td>H11</td>
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<td>0.566(3)</td>
<td>0.593(1)</td>
<td>0.027(6)</td>
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<tr>
<td>H22</td>
<td>0.972(2)</td>
<td>0.558(3)</td>
<td>0.595(1)</td>
<td>0.040(7)</td>
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<tr>
<td>H33a</td>
<td>1.297(2)</td>
<td>0.727(3)</td>
<td>0.597(1)</td>
<td>0.025(7)</td>
</tr>
</tbody>
</table>

The atomic coordinates of Mol. 3 in N-acetyl-DL-alanine methylester were deliberately chosen to lie outside the unit cell because in this way the molecule is directly part of the strand as shown in Fig. 3.
N-acetyl-DL-alanine methylester crystallizes as the 2:1/1:2 assembly. Apparently, both the packing of homochiral strands in a way that individual strands have opposite chirality [40] as well as the formation and packing of strands consisting of equal amounts of the enantiomers is less favorable for N-acetyl-DL-alanine methylester.

Experimental

N-Acetyl-L-alanine methylester was obtained commercially (Senn). N-Acetyl-DL-alanine methylester was synthesized from DL-alanine (Riedel de Haen) as described [6]. Suitable single crystals of both substances were obtained by slowly cooling the molten substances below their melting points under a polarizing microscope. They were mounted under nitrogen on glass fibers in an inert oil drop at 153(2) K [41]. The crystals were examined directly on the four-circle diffractometer (Enraf-Nonius CAD4) with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å). The crystal systems indicated by preliminary search and indexing procedures were checked for higher metrical symmetry by reduced-cell calculations (DELOS [42], LePage [43]). Exact cell dimensions were determined by refinement of the Bragg angles of 25 selected high-angle reflexions from various parts of reciprocal space carefully centered on the diffractometer. Lp corrections were applied. Crystal decay (N-acetyl-L-alanine methylester: -9.7%; N-acetyl-DL-alanine methylester: -5.0%; N-acetyl-DL-alanine methylester: -9.7%) was corrected for linearly. For N-acetyl-L-alanine methylester absorption was corrected for empirically on the basis of ψ scans around the diffraction vectors of 9 reflexions near χ = 90° which served to evaluate the transmission curves (T_min: 0.93, T_max: 1.00). For N-acetyl-DL-alanine methylester absorption was corrected for using DIFABS [44]. The structures were solved by direct methods (SHELXS-97 [45]). All H atoms of both crystal structures could be located in difference syntheses. Refinements were done with anisotropic displacement parameters for the non-H atoms. The hydrogen bond H atoms in both structures were refined freely with isotropic displacement parameters. All others were treated as rigid groups with their U(iso) tied to U(eq) of the corresponding carbon atoms (SHELXL-97 [46]). For the first refinement of N-acetyl-L-alanine methylester all unique reflexions including Friedel opposites were used. As the Flack parameter [15, 47] did not allow to distinguish between the absolute structure and its inverse (x = 0.1(9)), the final refinement was done on a data set with merged Friedel pairs, and the absolute structure was assigned according to the known configuration of L-alanine. Refinements were done on F^2 of all reflexions. Other programs used included ORTEP-III [48] (structure drawings) and PLATON [49] (molecular geometry).

Crystal data and numbers pertinent to data collection and structure refinement are summarized in Table 1. Tables 2 and 3 contain the bond distances, angles and torsion angles, Tables 4 and 5 the atomic coordinates.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-164574 (N-acetyl-L-alanine methylester), -164575 (N-acetyl-DL-alanine methylester). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgement

We are grateful to Professor Gautam Desiraju, Hyderabad, for valuable suggestions. The Fonds der Chemischen Industrie, Frankfurt (Main), is thanked for financial support.

[5] For N-acetyl-L-alanine methylester it was stated: “The product melted too close to room temperature for the m. p. to be determined in a conventional apparatus. The crystals ... melted on standing at room temperature”; J. P. Wolf, C. Niemann, Biochemistry 2, 493 (1963).
[8] Improper rotations are rotoinversions or rotoreflections. Rotoinversions and rotoreflections are equivalent in pairs making it sufficient to adopt only one kind to represent these symmetry operations. The notation most often adopted by chemists for the description of molecular symmetry uses rotoreflections as is done in the Schoenflies notation. Crystallographers, on the other hand, prefer the use of rotoinversions (International or Hermann-Mauguin notation). It should be noted that inversions and reflections may be regarded as special cases either of rotoinversions or of rotoreflections.
[9] Point groups: 1, 2, 222, 4, 422, 3, 32, 6, 622, 23, 432.
[10] Symmetry operations of the first kind are concerned with congruent parts of an object. They relate chiral objects to each other without changing their chirality. In addition to proper rotations, simple translations or screw axes are symmetry operations of the first kind. Symmetry operations of the second kind invert the chirality of an object. They convert a chiral object into its mirror image (enantiomer). In addition to improper rotations, glide planes are symmetry operations of the second kind.
[11] The term “chiral” has also been used for these space groups but the term “enantiomorphic” seems to be more apt. Apparently, the terms “enantiomorphic” and “enantiomorphous” are often used synonymously in the literature.
[12] The 230 space groups are conveniently subdivided into 65 non-centrosymmetric space groups without improper rotations [9], 73 non-centrosymmetric space groups containing improper rotations (point groups: m, mm2, 4, 4mm, 42m, 3m, 6, 6mm, 6m2, 43m), and 92 centrosymmetric space groups (point groups: 1, 2/m, m, 2/m, 4/m, 4/mmm, 3, 3m, 3/m, 6/m, 6/mmm, m3, m3m).
[16] The special cases of racemic (inversion) twinning and the crystallization of pairs of enantiomers in enantiomorphic space groups, which are also encountered in the crystallization of racemates, shall not be discussed here. For details see the following leading references. Racemic twinning: Ref. 15 and: A. Karrer, J. D. Dunitz, Acta Crystallogr. A43, 430 (1987); B. S. Green, M. Knossow, Science, 14, 795 (1981). Pairs of enantiomers in enantiomorphic space groups: Ref. 14.
[19] The spontaneous resolution of a racemate has even been used to produce pure enantiomers on an industrial scale. For this a saturated solution of the racemate is seeded with crystals of one of the pure enantiomers whereupon only crystals of the seeded enantiomer form (preferential crystallization; resolution by entrainment). See ref’s 14 and 18.
[23] This is in contrast to the spontaneous resolution of a racemate where on complete crystallization equal amounts of the constituent enantiomorph crystals of the conglomerate must be formed.
[25] The crystals on the right side of the equation constitute the racemic conglomerate.
[26] In a number of cases the crystallization of racemic solutions of chiral compounds yields crystals of the enantiomers (spontaneous resolution) or of racemic crystals, depending on the conditions. Examples are Pasteur’s sodium ammonium tartrate, which crystallizes only below 28 °C as conglomerate, and glutamic acid (α-L-glutamic acid: M. S. Lehmann, A. C. Nunes, Acta Crystallogr. B36, 1621 (1980); β-L-glutamic acid: M. S. Lehmann, T. F. Koetzle, W. C. Hamilton, J. Cryst. Mol. Struct. 2, 225 (1972); DL-glutamic acid: J. D. Dunitz, W. B. Schweizer, Acta Crystallogr. C51, 1377 (1995); DL-glutamic acid monohydrate: Z. Ciunik, T. Glowiak, Acta Crystallogr. C39, 1271 (1983)). Other cases are given in ref. 18. In some cases even mixtures of several forms are obtained simultaneously (M. S. Dunn, M. P. Stoddard, J. Biol. Chem. 121, 521 (1937)). This suggests that apart from thermodynamic factors (crystallization temperature), also kinetic factors may be operative. Not the least, even tiny amounts of impurities may be decisive for the outcome of the crystallization of racemates.
[27] In one thoroughly investigated case the difference in packing potential energy between the racemic crystal and the enantiomorphic crystal was estimated computationally to +7 kcal/mol: A. Uchida, J. D. Dunitz, Acta Crystallogr. B46, 45 (1990).
The low quality of the structure determinations as well as disorder in the racemic crystals make it desirable to refer to the structural parameters of the three crystallographically independent molecules in N-acetyl-DL-alanine methylester (Table 2) including the methyl group conformations (Fig. 3) prompted us to search carefully for overlooked higher crystal symmetry. Apart from the usual checks for higher metrical symmetry as described in the Experimental Section, the intermolecular contacts of the independent molecules were examined and found to be different. For example C2 (Mol. 1) - C4 (Mol. 2; 1 - x, 1 - y, 1 - z) 3.572(3) Å. No such distance < 4 Å is found for C8 (C2 in Mol. 2). Atom C14 (C2 in Mol. 3) - C10 (C4 in Mol. 2; 0.5 + x, 0.5 - y, 0.5 + z) 3.900(4) Å.

Table 2 contains the molecular parameters as based on the refined coordinates. They belong to two molecules in the L-configuration (Mol.'s 1, 2) and one in the D-configuration (Mol. 3) as they are shown in Fig. 3.

The angle C2-N1-C3 in N-acetyl-L-alanine methylester (120.1(1)°) differs from that in Mol. 3 of the racemate (121.5(2)°) by 0.5° if the sum of the respective 3 esd’s is subtracted from the difference.


This is especially so, because the enantiomorphic (enantiomerically pure) crystals of N-acetyl-L-alanine methylester are in equilibrium with a one-component liquid while the racemic crystals of N-acetyl-DL-alanine methylester are in equilibrium with an entropically favored two-component liquid at their respective melting points [30]. In other words, enantiomorphic crystals may have a higher melting point than their racemic counterparts even if they are thermodynamically less stable. In our case, they have a lower one, however. See Fig. 6 in ref. 28 for an illustration of these facts.

\[ \Delta(\%) = 100 \left( \rho_R - \rho_L \right) / 0.5(\rho_R + \rho_L) \], where \( \rho_R \) is the density of the racemate, \( \rho_L \) that of the enantiomer.


It should be noted that N-acetyl-DL-alanine-N'-methylamide (space group P2_1/a) and N-acetyl-L-alanine-N'-methylamide (space group P2_12_1) also form strams in which pairs of molecules are held together by two N-H-O=C\_acetyl hydrogen bonds. While the individual strands in N-acetyl-L-alanine-N'-methylamide are necessarily homochiral, those in the racemic crystals also seem to be so. In the latter case the crystals must be made up of homochiral strands of opposite chirality in a 1:1 ratio. The low quality of the structure determinations as well as disorder in the racemic crystals make it desirable to...