Hydrophobic 'lock and key' recognition of N-4-nitrobenzoylamino acid by strychnine

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During racemic resolution of N-4-nitrobenzoyl-DL-amino acids (alanine, serine and aspartic acid) by a fractional crystallization of strychninium salts, crystals of both diastereomeric salts were grown, and the crystal structures of strychninium N-4-nitrobenzoyl-L-alaninate methanol disolvate (1a), strychninium N-4-nitrobenzoyl-D-alaninate dihydrate (1b), strychninium N-4-nitrobenzoyl-D-serinate dihydrate (2a), strychninium N-4-nitrobenzoyl-L-serinate methanol solvate hydrate (2b), strychninium hydrogen N-4-nitrobenzoyl-L-aspartate 3.75 hydrate (3a) and strychninium hydrogen N-4-nitrobenzoyl-D-aspartate 2.25 hydrate (3b) were determined. The strychninium cations form corrugated layers, which are separated by hydrogen-bonded anions and solvent molecules. Common features of the corrugated layers are deep hydrophobic grooves at their surfaces, which are occupied by the 4-nitrobenzoyl groups of suitable anions. The hydrophobic 'lock and key' recognition of 4-nitrobenzoyl groups of amino acid derivatives in deep grooves of the strychnine self-assembly causes the resulting surface to have more hydrophilic properties, which are more appropriate for interactions in the hydrophilic environments from which strychninium salts were crystallized. In the crystal structure of (2a) and (3a), such hydrophobic 'lock and key' recognition is responsible for the lack of $N-H^+\cdots O^-$ hydrogen bonds that are usually formed between the protonated tertiary amine N atom of the strychninium cation and the deprotonated carboxyl group of the resolved acid. In the crystal structure of (2a) and (3a), the protonated amine N atom is a donor of hydrogen bonds, while the hydroxyl group of the serine derivative and water molecules are their acceptors. In light of the hydrophobic recognition, chiral discrimination depends on the nature of the hydrogen-bond networks, which involve anions, solvent molecules and the protonated amine N atom of strychninium cations.

1. Introduction

Molecular recognition, defined by the energy and the steric information involved in the selection and binding of substrate(s) by a given receptor, is revealed in its efficiency and selectivity (Lehn, 1995). This broad conception has been rapidly expanding at the frontiers of chemical science with physical and biological phenomena. Pasteur's (1853) resolution of racemic compounds *via* fractional crystallization of diastereomeric salts of chiral resolving agents reveals molecular recognition at a high level of efficiency and selectivity. Brucine is one of the most frequently used resolving agents for

the separation of racemic acids (Jacques *et al.*, 1991). Therefore, it seems peculiar that only one pair of crystal structures of brucinium salts, as a result of racemic resolution, is known (Kuwata *et al.*, 1993). Again, as far as we were able to ascertain, we know of no similar case of crystal structures for strychnine, which is stereochemically related to brucine.

When one enantiomer of a racemic mixture is recognized by a resolving agent, giving rise to crystals of a diastereomeric salt, the other enantiomer, remaining in solution, is recognized by the resolving agent more slowly or not at all. It is interesting that both brucine and strychnine seem to be highly selective for a given enantiomer, yet they reveal a low selectivity for a variety of other compounds. Both these features allow the use of brucine and strychnine to separate a wide spectrum of racemic acids.

Although the diastereomeric salt method remains the most important method for the preparation of enantiopure compounds, up to now, the mechanism of chiral discrimination prevalent during crystallization of the diastereomers has not been clarified fully owing to the high complexity of the process (Kinbara *et al.*, 1998, 2000, 2001; Kozsda-Kovacs *et al.*, 2000; Kano, 1997; Kato *et al.*, 2003; Grandeury *et al.*, 2004). In a recent paper, we concluded that in molecular recognition the donor/acceptor properties of a resolved compound can determine the self-assembly of the resolving agent, and the donor/acceptor capabilities of its surface correspond to the donor/acceptor properties of the resolved compound (Białońska & Ciunik, 2004). Depending on the kind of brucine and strychnine self-assembly, one or the other enantiomer of *N*-benzoyl- or *N*-phthaloylalanine was recognized at the surfaces of the self-assemblies. This result shows the importance of resolving agent self-assemblies, which provide particular donor/acceptor properties, and the specific shape of their surfaces for recognition of resolved compounds.
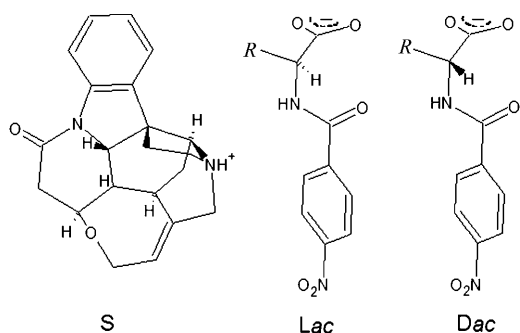
(1a)	**S·Lac·2CH₃OH;**	*R* = CH₃
(1b)	**S·Dac·2H₂O;**	*R* = CH₃
(2a)	**S·Dac·2H₂O;**	*R* = CH₂OH
(2b)	**S·Lac·CH₃OH·H₂O;**	*R* = CH₂OH
(3a)	**S·Lac·3.75H₂O;**	*R* = CH₂COOH
(3b)	**S·Dac·2.25H₂O;**	*R* = CH₂COOH

A set of crystal structures of both diastereomeric salts, one including D and other including L enantiomers of a resolved compound, can provide more detailed information about chiral discrimination and, generally, about molecular recognition. Therefore we attempted to obtain crystal structures of both diastereomeric salts. Resolution of *N*-4-nitrobenzoyl-DL-amino acids by cocrystallization with strychnine allowed us to obtain the crystals of three diastereomeric salts pairs: strychninium *N*-4-nitrobenzoyl-L-alaninate methanol disolvate (1a) and strychninium *N*-4-nitrobenzoyl-D-alaninate dihydrate (1b), strychninium *N*-4-nitrobenzoyl-D-serinate dihydrate (2a) and strychninium *N*-4-nitrobenzoyl-L-serinate methanol solvate hydrate (2b), and strychninium hydrogen *N*-4-nitrobenzoyl-L-aspartate 3.75 hydrate (3a) and strychninium hydrogen *N*-4-nitrobenzoyl-D-aspartate 2.25 hydrate (3b).

2. Experimental

The *N*-4-nitrobenzoyl-DL-amino acids (alanine, serine and aspartic acid) were synthesized according to the method described previously (Wróbel, 1983). Crystals of the diastereomeric salts were obtained from methanol solutions containing the racemic amino acid derivative and strychnine (commercially available) at room temperature. Crystals of (1a) appeared as the first fraction in the racemic resolution of *N*-4-nitrobenzoyl-DL-alanine. Crystals of (1b) were crystallized from the solution after removal of the first crystalline fraction. In the same way, crystals of (2a) and (2b) and crystals of (3a) and (3b) were obtained during racemic resolution of *N*-4-nitrobenzoyl-DL-serine and *N*-4-nitrobenzoyl-DL-aspartic acid, respectively.

X-ray data were collected at 100 K using an Oxford Cryosystem device on a Kuma KM-4 CCD κ-axis diffractometer with graphite-monochromated Mo *K*α radiation (λ = 0.71073 Å). Data reduction and analysis were carried out with the *CrysAlis RED* program (Oxford Diffraction, 2001). The space groups were determined using the *XPREP* program. Other details of cell data, data collection and refinement are summarized in Table 1.[1] Structures were solved by direct methods using *SHELXS97* (Sheldrick, 1990) and refined using all F^2 data, as implemented by *SHELXL97* (Sheldrick, 1997). Non-H atoms were refined with anisotropic displacement parameters. Non-H atoms with values of occupancy factors lower than 0.5 were refined with isotropic displacement parameters. All the occupancy factors for the disordered water molecules [O2*W*, O3*W* and O4*W* (0.75), as well as O5*W* and O6*W* (0.25)] in the crystal structure of (3a) and for all the water molecules [O1*W*, O2*W* and O3*W* (0.5), as well as O4*W*, O5*W* and O6*W* (0.25)] in the crystal structure of (3b) were refined and their occupancy parameters fixed at suitable values. H atoms bonded to C atoms were included in their idealized positions and treated as riding in the subsequent refinement, with C—H distances in the range 0.95–1.00 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. The remaining H atoms were located in difference density maps and refined with isotropic

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Table 1
Experimental details.

|	(1a)	(1b)	(2a)	(2b)	(3a)	(3b)
Crystal data						
Chemical formula	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{10}H_9N_2O_5^-\cdot$ $2CH_4O$	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{10}H_9N_2O_5^-\cdot2H_2O$	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{10}H_9N_2O_6^-\cdot2H_2O$	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{10}H_9N_2O_6^-\cdot$ $CH_4O\cdot H_2O$	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{11}H_9N_2O_7^-\cdot$ $3.75H_2O$	$C_{21}H_{23}N_2O_2^+\cdot$ $C_{11}H^9N_2O_7^-\cdot$ $2.25H_2O$
M_r	636.69	608.64	624.64	638.66	684.18	657.15
Cell setting, space group	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$
Temperature (K)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)	100 (2)
a, b, c (Å)	7.478 (2), 18.007 (2), 11.416 (2)	7.868 (2), 10.757 (2), 34.038 (3)	8.131 (2), 10.648 (2), 33.057 (3)	7.483 (2), 11.500 (2), 34.436 (3)	7.536 (2), 11.092 (2), 19.540 (2)	8.197 (2), 9.967 (2), 36.351 (4)
β (°)	98.58 (3)	90.00	90.00	90.00	98.55 (3)	90.00
V (Å³)	1520.0 (5)	2880.8 (9)	2862.0 (9)	2963.4 (10)	1615.2 (5)	2969.9 (10)
Z	2	4	4	4	2	4
D_x (Mg m⁻³)	1.391	1.403	1.450	1.432	1.407	1.470
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm⁻¹)	0.10	0.10	0.11	0.11	0.11	0.11
Crystal form, colour	Block, colourless	Block, colourless	Block, colourless	Needle, pale yellow	Block, colourless	Needle, colourless
Crystal size (mm)	0.40 × 0.40 × 0.40	0.30 × 0.20 × 0.20	0.20 × 0.15 × 0.15	0.40 × 0.07 × 0.07	0.25 × 0.20 × 0.20	0.20 × 0.10 × 0.06
Data collection						
Diffractometer	Kuma KM-4 CCD	Kuma KM-4 CCD	Kuma KM-4 CCD	Kuma KM-4 CCD	Kuma KM-4 CCD	Kuma KM-4 CCD
Data collection method	ω scan	ω scan	ω scan	ω scan	ω scan	ω scan
Absorption correction	None	None	None	None	None	None
No. of measured, independent and observed reflections	8622, 3543, 3316	19 741, 3743, 2691	19 397, 3681, 2532	22 121, 3660, 2458	10 626, 3859, 3247	16 682, 2925, 1944
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.031	0.099	0.125	0.100	0.051	0.114
θ_{max} (°)	27.5	27.5	27.5	27.0	27.5	25.0
Refinement						
Refinement on	F^2	F^2	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.034, 0.083, 1.04	0.064, 0.116, 1.04	0.094, 0.281, 1.06	0.055, 0.082, 0.99	0.049, 0.126, 1.06	0.115, 0.327, 1.08
No. of reflections	3543	3743	3681	3660	3859	2925
No. of parameters	415	397	406	415	450	446
H-atom treatment	Constrained to parent site	Constrained to parent site	Constrained to parent site	Constrained to parent site	Constrained to parent site	Constrained to parent site
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0569P)^2 + 0.0323P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0492P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.1708P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.028P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0741P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.2105P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001	<0.0001	0.001	<0.0001	0.001	0.002
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å⁻³)	0.21, −0.23	0.23, −0.24	0.38, −0.26	0.21, −0.32	0.33, −0.36	0.36, −0.36
Absolute structure	From known structure (Robertson & Beevers, 1951)	From known structure (Robertson & Beevers, 1951)	From known structure (Robertson & Beevers, 1951)	From known structure (Robertson & Beevers, 1951)	From known structure (Robertson & Beevers, 1951)	From known structure (Robertson & Beevers, 1951)

Computer programs used: *CrysAlis CCD* (Oxford Diffraction, 2001), *CrysAlis RED* (Oxford Diffraction, 2001), *SHELXS97* (Sheldrick, 1990), *SHELXL97* (Sheldrick, 1997), *SHELXTL-NT* (Bruker, 1999).

displacement parameters; in the final cycle of refinement, they were allowed to ride on their parent atoms. Friedel pairs were merged before the final refinement. The absolute configurations of all the strychninium salts under investigation were chosen on the basis of the known absolute configuration of strychnine (Robertson & Beevers, 1951).

3. Results and discussion

Views of the crystal structures of (1a), (1b), (2a), (2b), (3a) and (3b), together with atom-numbering schemes employed,

are presented in Fig. 1. In all the crystals under investigation, strychninium cations form corrugated layers, which are separated by hydrogen-bonded anions of the amino acid derivatives and solvent molecules (Figs. 2–8). The cationic species, together with the anionic/solvent layers, are linked by ionic hydrogen bonds in which the protonated amine N2 atom of the strychninium cation is the donor. As presented in Fig. 1, in the crystal structures of (1a), (1b) and (2b), the carboxyl O3 atom of the amino acid derivative is an acceptor of an interlayer N—H$^+$···O$^-$ hydrogen bond. In the crystal structure of (3b), both carboxyl atoms O3 and O4 of the hydrogen N-4-

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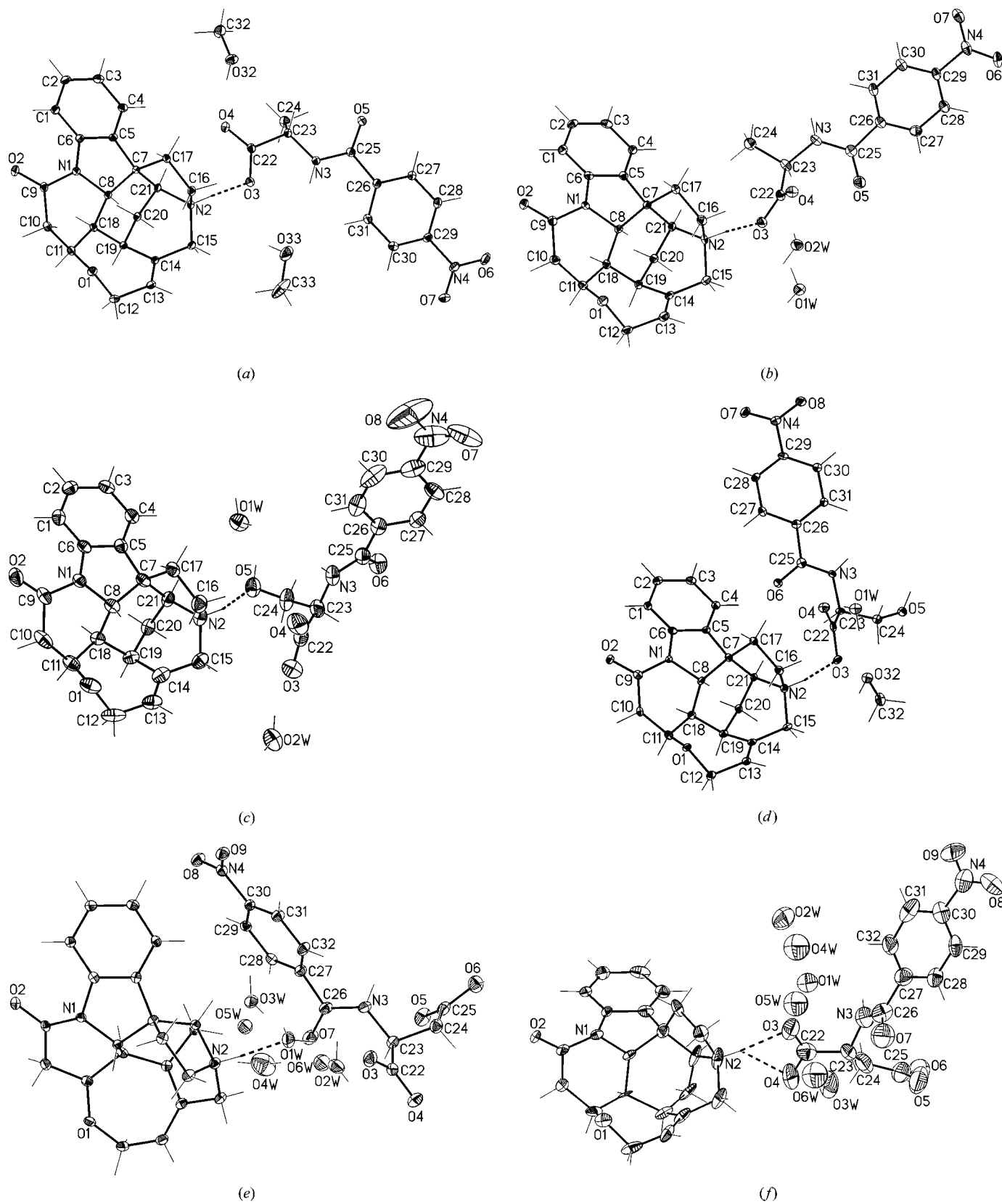
Figure 1
The components of (a) (1a), (b) (1b), (c) (2a), (d) (2b), (e) (3a) and (f) (3b), and the atom-labelling schemes. Displacement ellipsoids are drawn at the 30% probability level. The inter-layer N—H$^+$···O$^-$ and N—H$^+$···O hydrogen bonds are marked by dashed lines.

Table 2
Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
(1a)				
N2—H22···O3	0.93	1.64	2.572 (2)	175
O32—H32···O4	0.86	1.83	2.671 (2)	167
O33—H33···O32[i]	0.87	1.98	2.813 (3)	160
C31—H31···O33	0.95	2.38	3.270 (3)	155
C15—H15B···O2[ii]	0.99	2.41	3.397 (2)	178
(1b)				
N2—H22···O3	0.93	1.70	2.619 (4)	168
N3—H37···O1W[i]	0.88	2.11	2.936 (5)	155
O1W—H11W···O3	0.86	1.98	2.830 (4)	169
O1W—H12W···O2W[ii]	0.86	1.96	2.800 (4)	164
O2W—H21W···O4	0.86	1.95	2.766 (4)	158
O2W—H22W···O4[ii]	0.86	2.00	2.827 (4)	160
C24—H24A···O5[iii]	0.98	2.41	3.370 (5)	166
(2a)				
N2—H22···O5	0.93	1.85	2.720 (8)	155
O5—H57···O1W	0.84	1.84	2.619 (8)	153
O1W—H11W···O6[i]	0.86	1.97	2.779 (8)	156
O1W—H12W···O2W[ii]	0.86	1.91	2.743 (8)	162
O2W—H21W···O3	0.86	1.77	2.594 (10)	159
O2W—H22W···O4[iii]	0.86	1.95	2.768 (8)	159
(2b)				
N2—H22···O3	0.93	1.73	2.643 (4)	168
O5—H57···O3[i]	0.84	1.87	2.711 (4)	180
N3—H37···O5[i]	0.88	2.17	2.931 (4)	145
O32—H32···O1W[ii]	0.88	1.80	2.676 (4)	173
O1W—H11W···O32	0.86	1.90	2.757 (4)	177
O1W—H12W···O4	0.86	1.91	2.767 (4)	171
(3a)				
N2—H22···O1W	0.93	1.74	2.665 (4)	177
O6—H67···O3[i]	0.88	1.73	2.562 (4)	156
N3—H37···O2W[ii]	0.88	2.00	2.875 (5)	174
N3—H37···O6W[ii]	0.88	2.18	3.010 (17)	157
O1W—H11W···O3	0.86	1.89	2.735 (4)	168
O1W—H12W···O3W	0.86	1.85	2.645 (5)	154
O2W—H21W···O5[iii]	0.86	2.12	2.937 (5)	158
O2W—H22W···O4[iv]	0.86	1.91	2.759 (5)	172
O3W—H31W···O7[iv]	0.86	1.86	2.713 (5)	170
O3W—H32W···O4W	0.86	1.84	2.544 (8)	138
O4W—H41W···O2W	0.90	2.32	3.209 (8)	166
O4W—H42W···O3[v]	0.91	2.58	3.205 (8)	126
(3b)				
N2—H22···O3	0.91	2.00	2.885 (15)	164
N2—H22···O4	0.91	2.28	2.985 (15)	134
O6—H6A···O2W[i]	0.82	1.69	2.50 (4)	166
O6—H6A···O4W[i]	0.82	1.88	2.61 (8)	148
N3—H37···O4[ii]	0.86	2.17	2.97 (2)	154

Symmetry codes: (1a): (i) $-1+x, y, z$; (ii) $1-x, -\frac{1}{2}+y, 1-z$. (1b): (i) $x+1, y, z$; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $x+\frac{1}{2}, -y-\frac{1}{2}, -z+1$. (2a): (i) $x-\frac{1}{2}, -y+\frac{5}{2}, -z+1$; (ii) $x-1, y, z$; (iii) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$. (2b): (i) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+2$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+2$. (3a): (i) $-x+1, y+\frac{1}{2}, -z$; (ii) $-x+2, y+\frac{1}{2}, -z$; (iii) $-x+1, y-\frac{1}{2}, -z$; (iv) $x+1, y, z$; (iv) $-x+2, y-\frac{1}{2}, -z$. (3b): (i) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

nitrobenzoyl-D-aspartate anion are acceptors of an inter-layer bifurcated N—H⁺···O⁻ hydrogen bond. Conversely, in the crystal structures of (2a) and (3a), the hydroxyl O5 atom of the N-4-nitrobenzoyl-D-serinate anion and the water molecule O1W participate in inter-layer N—H⁺···O hydrogen bonds, respectively.

3.1. Hydrogen-bond networks of anion/solvent layers

As mentioned above, in all the crystals under investigation the anions and solvent molecules are linked by hydrogen bonds (Figs. 3–8 and Table 2).

As presented in Fig. 3, in the crystal structure of (1a), the N-4-nitrobenzoyl-L-alaninate anions and methanol molecules form chains, which extend along the [100] direction, stabilized by O—H···O and C—H···O hydrogen bonds. Amide atoms N3 and O5 participate in intramolecular hydrogen bonds. The methyl group of the N-4-nitrobenoyl-L-alaninate anion is a donor of C—H···π hydrogen bonds, and the arene ring of the strychninium cation is the acceptor.

In the crystal structure of (1b), the methyl group of the N-4-nitrobenzoyl-D-alaninate anion is the donor of a weak C—H···O hydrogen bond in which the amide O5($x+\frac{1}{2}, -y-\frac{1}{2}, -z + 1$) atom is the acceptor. The amide N3 atom is the donor of a hydrogen bond in which the O1W water molecule is the acceptor. The carboxyl O3 and O4 atoms of the anion and the O1W and O2W water molecules form a hydrogen-bonded tape, $T6(2)$, extending along the [100] direction (Fig. 4).

In the crystal structure of (2a), the amide N3 atom and carboxyl O4 atom of the N-4-nitrobenzoyl-D-serinate anion are linked by an intramolecular hydrogen bond. The O1W water molecule is the donor of hydrogen bonds in which the amide O6($x - \frac{1}{2}, -y + \frac{5}{2}, -z + 1$) atom of the anion and the O2W($x - 1, y, z$) water molecule are the acceptors (Fig. 5). The O1W water molecule also participates as the acceptor in a hydrogen bond in which the hydroxyl O5 atom of the anion is the donor. The carboxyl O3 and O4 atoms of the anion and the O2W water molecule form a hydrogen-bonded chain, $C4$, extending along the [100] direction.

In the crystal structure of (2b), the methanol and water molecules, linked by O—H···O hydrogen bonds, form a $C4$ chain extending along the [100] direction (Fig. 6). The $C4$ chain is linked with the anions by hydrogen bonds in which the O1W water molecule and carboxyl O4 atom of the N-4-nitrobenzoyl-L-serinate anions are the donor and the acceptor, respectively. Two neighbouring N-4-nitrobenzoyl-L-serinate anions are linked by hydrogen bonds involving the carboxyl O3 atom, the hydroxyl O5 atom and the amide N3 atom. The amide O6 atom of the anion is involved in an intramolecular C—H···O hydrogen bond.

In the crystal structures of (3a) and (3b), the water molecules are disordered. In (3a), the hydrogen N-4-nitrobenzoyl-L-aspartate anions and disordered water molecules form two alternative hydrogen-bond networks. In (3b) the hydrogen-bond network reveals an even greater disorder of the water molecules. It seems that in both (3a) and (3b), the hydrogen-bond networks involve all potential donors and acceptors of strong O—H···O and N—H···O hydrogen bonds (see Figs. 7 and 8).

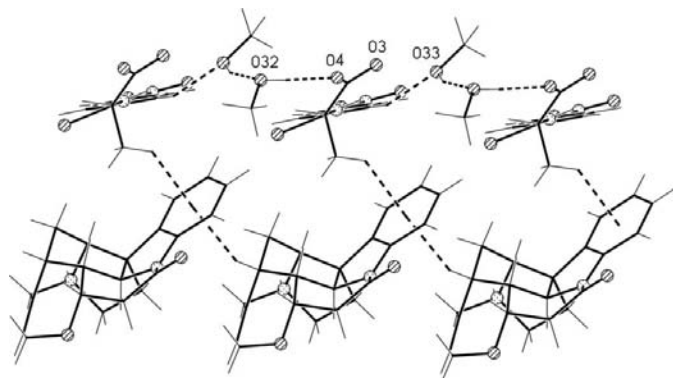## 3.2. Hydrogen bonds stabilizing strychninium self-assemblies

In all the crystal structures under investigation, the hydrogen-bonded anions of the amino acid derivatives and solvent molecules occupy the space between corrugated layers
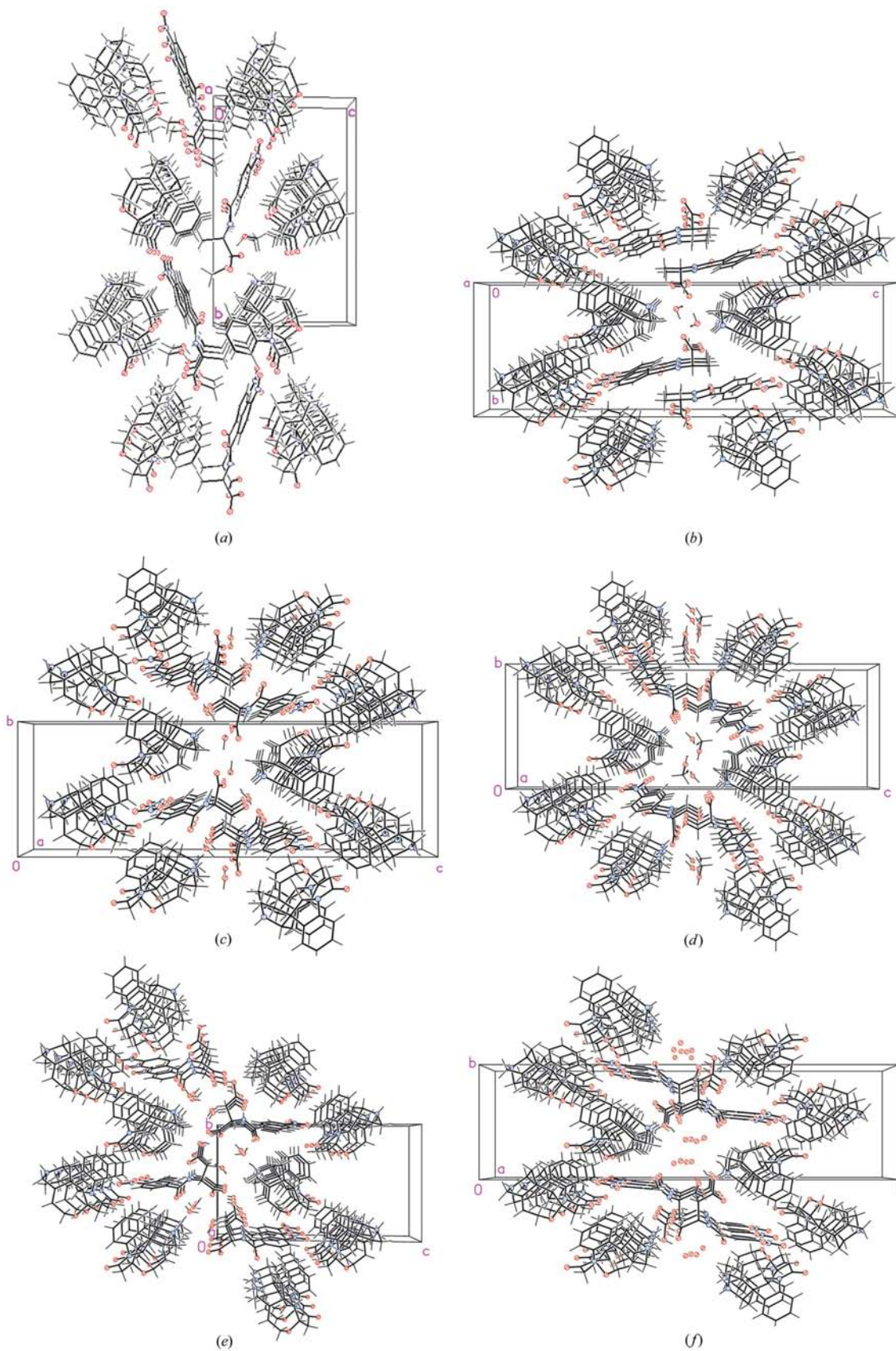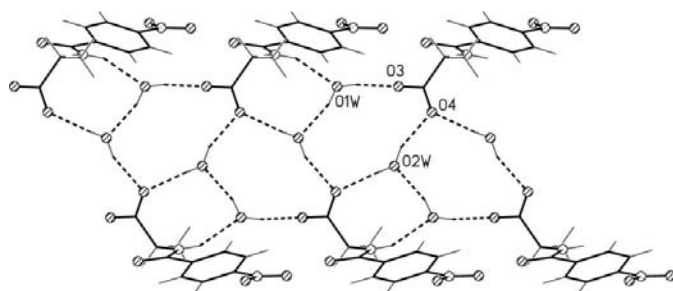
Figure 2
The packing of (a) (1a), (b) (1b), (c) (2a), (d) (2b), (e) (3a) and (f) (3b). Strychninium cations form layers, separated by anions and solvent molecules.

of strychninium cations (see Fig. 2). All the crystals belong to the monoclinic or orthorhombic systems, and individual components are related by translation vectors and twofold screw axes of symmetry. The translation vector or twofold screw axis of symmetry, which generate acceptor (A) atoms of the C—H$\cdots A$ hydrogen bonds, are distinguished by ($\uparrow$) and (2_1) following the A symbol, respectively. Generated by the translation vector ($\uparrow$), strychninium cations, linked by the C19—H19$\cdots\pi$ ($\uparrow$) hydrogen bond, form pillars extending along the [100] direction. Except for the crystal structure of (1a), neighbouring pillars are linked by C10—H10$\cdots\pi(2_1)$ hydrogen bonds resulting in the strychninium corrugated layer

self-assembly. In the crystal of (1a), neighbouring pillars are linked by weak C15—H15$\cdots$O2(2_1) hydrogen bonds; furthermore, as mentioned above, the arene ring of the

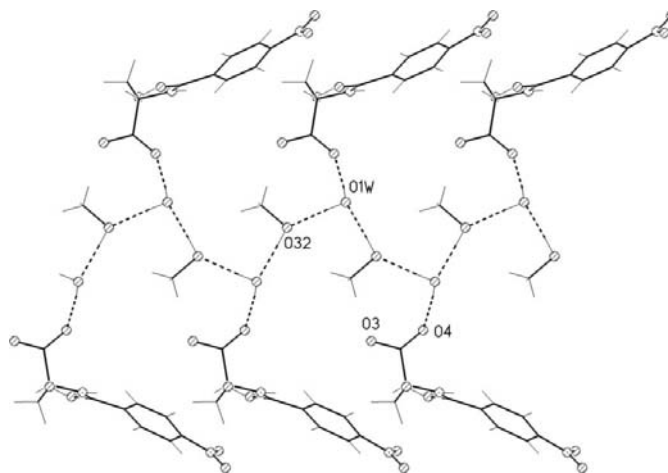**Figure 3**
Hydrogen-bond pattern in the crystals of (1a).

Figure 4
Hydrogen-bond pattern in the crystals of (1b). The carboxyl groups of anions and the water molecules form a $T6(2)$ tape extended along the [100] direction.
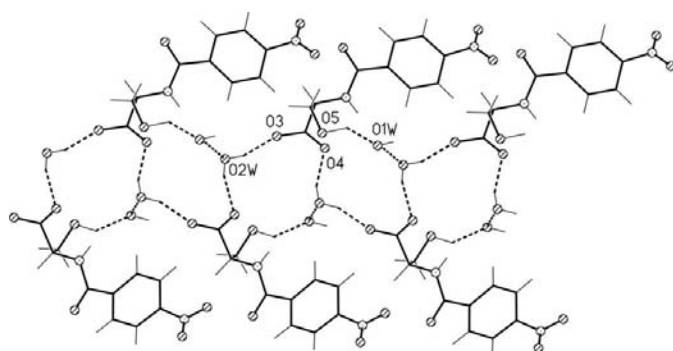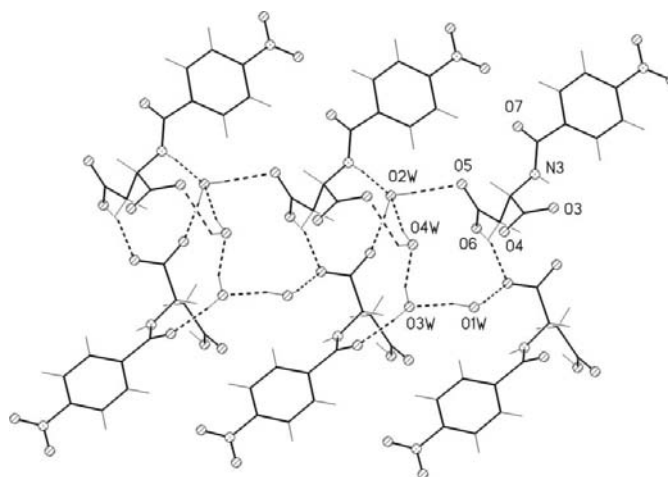

Figure 5
Hydrogen-bond pattern in the crystals of (2a). The carboxyl groups of anions and the water molecules form a $C4$ chain.
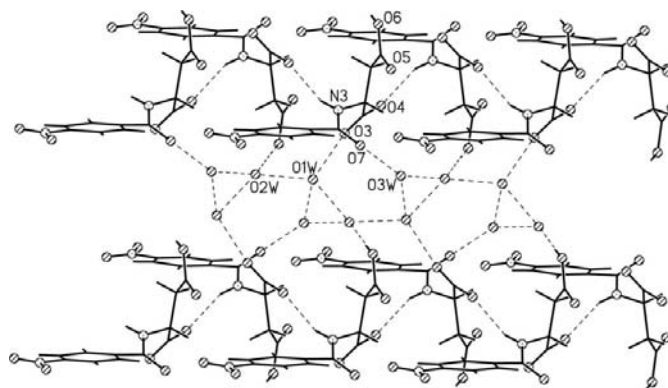

Figure 6
Hydrogen-bond pattern in the crystals of (2b). A $C4$ chain is formed by the methanol and water molecules.

Figure 7
Two alternative hydrogen-bond networks in the crystals of (3a).

Figure 8
Hydrogen-bond network in the crystals of (3b). The water molecules that have occupancy factors less than 0.5 have been omitted.

strychninium cation participates in a C—H⋯π hydrogen bond in which the L-alanine derivative is the donor.

3.3. Molecular recognition

3.3.1. Donor/acceptor fitting. Similar strychninium corrugated layers in the crystal structures of strychninium diastereomeric salts, one containing the D and the other containing the L enantiomer of N-4-nitrobenzoylamino acid, are evidence of the donor/acceptor fitting of the resolved compound and of the surface of a resolving agent self-assembly. The D and L enantiomers of N-4-nitrobenzoylamino acid, which have similar donor/acceptor properties, determine similar self-assemblies, as presented above (see also Fig. 2).

3.3.2. Hydrophobic 'lock and key' recognition. The self-assembly of strychninium cations supplies corrugated surfaces containing specific deep grooves for interactions with cocrystallizing guests. In the crystals under investigation [except for the crystal of (1a)], the deep grooves at the surfaces of the strychninium self-assemblies are occupied by the 4-nitrobenzoyl groups of N-4-nitrobenzoyl-D- or N-4-nitrobenzoyl-L-amino acid anions (Figs. 2 and 9, and supplementary materials). The carbonyl O2 atom of the strychninium cations, located at the bottom of the hole, is an acceptor of a C—H⋯O hydrogen bond, in which the C atom of the 4-nitrobenzoyl group of the amino acid derivative is the donor. The nitro group of N-4-nitrobenzoyl-D- or N-4-nitrobenzoyl-L-amino acid, directed towards the groove, participates in C—H⋯O hydrogen bonds in which strychninium cations are the donors.
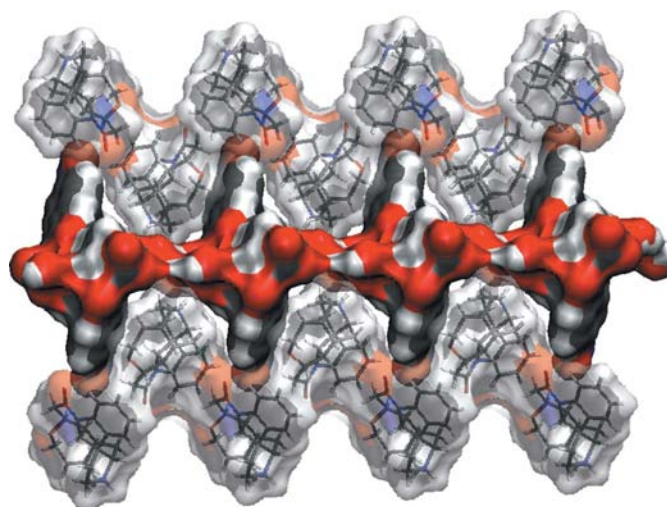
The deep grooves at the surfaces of the strychninium self-assemblies are the only sites that recognize the same part of the N-4-nitrobenzoyl-D- and N-4-nitrobenzoyl-L-amino acids in the crystals under investigation. Therefore, independently of the type of amino acid and its D or L enantiomer, only the 4-nitrobenzoyl group of the amino acid derivative is recognized by the same site at the surface of the strychninium self-assembly. The deep groove at the surface of the strychninium corrugated sheet is like Fisher's (1894) lock, and the 4-nitrobenzoyl group of the amino acid derivative is the fitting key in the molecular recognition.

For the above 'lock and key' recognition of the 4-nitrobenzoyl group of the amino acid derivative at the surface of the strychninium corrugated layer, the layer has to be formed first. Here, it is worthy of note that, in all the crystals under investigation, the C19—H19⋯π(↑) hydrogen bonds, formed between strychninium cations, are present. The C19—H19⋯π(↑) hydrogen bonds also exist in most of the other known crystals of strychninium salts (Bokhoven et al., 1951; Robertson & Beevers, 1951; Gould & Walkinshaw, 1984; Gould et al., 1985, 1987; Mostad, 1985; Bottcher & Buchkremer-Hermanns, 1987; Ghosh et al., 1989; Costante et al., 1996; Yuan et al., 1994; Białońska & Ciunik, 2004, 2005a,b; see supplementary material). Additionally, in most of the known crystals of strychninium salts, C10—H10⋯A(2_1) [A = O2 or π(arene) of the strychninium cation] hydrogen bonds are formed (Bokhoven et al., 1951; Robertson & Beevers, 1951;

Bottcher & Buchkremer-Hermanns, 1987; Ghosh et al., 1989; Yuan et al., 1994; Białońska & Ciunik, 2004, 2005a,b). Moreover, the C10—H10⋯A(2_1) (A = O2 or π) hydrogen bonds are usually responsible for the corrugation of the resulting layer. Namely, when the arene ring is an acceptor of the C10—H10⋯A(2_1) hydrogen bond, then strychninium cations form the corrugated layers as in the crystals of (1b)–(3b). On the other hand, when the carbonyl O2 atom is an acceptor of the C10—H10⋯A(2_1) hydrogen bond, then strychninium cations form another common self-assembly, almost flat bilayer sheets. Again, the C10—H10⋯A(2_1) (A = O2 or π) hydrogen bonds are responsible for the donor/acceptor capabilities of the surfaces of the resulting layers. While the surface of the strychninium corrugated layer, stabilized by the C10—H10⋯π(2_1) bonds, has an opportunity to participate, as an acceptor, in hydrogen bonds with cocrystallizing guests, the surface of the bilayer sheet reveals only donor capabilities. In this light, the layers present in the crystal structure of (1a) seem to reveal similar features to the layers stabilized by the C10—H10⋯π(2_1) hydrogen bonds. In both cases, one acceptor, atom O2 or the arene ring of the strychninium cation, is involved in hydrogen bonds stabilizing the strychninium self-assembly. Simultaneously, another acceptor, the arene ring or atom O2, respectively, of the strychninium cation participates in a hydrogen bond in which the anion of the cocrystallizing guest is the donor (see also Białońska & Ciunik, 2006).

This discussion clearly shows that, for the formation and stabilization of strychninium self-assemblies, weak hydrogen bonds between strychninim cations play an important role.

Returning to the corrugated layers, from the above description, there appears to be a mechanism of molecular recognition in which strychinium cations recognize each other,

Figure 9
The strychninium corrugated layer, possessing deep hydrophobic grooves at the surface (transparent), recognizes the 4-nitrobenzoyl groups of the anion. Such hydrophobic 'lock and key' recognition causes the resulting surface to have more hydrophilic properties (opaque surface); H white, C silver, N blue, O red (Humphrey et al., 1996).

resulting in strychninium self-assembly. The self-assembly provides hydrophobic grooves at its surface, which recognizes the 4-nitrobenzoyl group of the amino acid derivative. When one takes into account the hydrophilic nature of the environments from which the strychninium salts were crystallized, such a mechanism should be expected. Strychnine molecules reveal rather hydrophobic properties. A hydrophobic nature is also revealed by the 4-nitrobenzoyl group of the N-4-nitrobenzoylamino acid. Self-recognition of strychnine units reduces the area of the hydrophobic surfaces in hydrophilic solution; however, the surface of the strychnine self-assembly remains hydrophobic. In fact, recognition of the 4-nitrobenzoyl groups of amino acid derivatives in deep grooves of the strychnine self-assembly causes the resulting surface to have more hydrophilic properties (see Fig. 9, supplementary materials). On the basis of the results obtained with the abovementioned crystals, it seems that in these systems there are no other groups that could penetrate the deep groove as efficiently as the 4-nitrobenzoyl group.

3.3.3. The inter-layer ionic hydrogen bonds. In all the above-mentioned cases, a proton, originally located at the carboxyl group of the resolved acid, is transferred at the tertiary amine N2 atom of the resolving agent. The N2 atom is the donor of a strong ionic hydrogen bond. It could be expected that the deprotonated α-carboxyl group of the amino acid derivative should be its acceptor. Indeed, in the crystal structures of (1a), (1b), (2b) and (3b), the deprotonated carboxyl groups are the acceptors of ionic $N-H^{+} \cdots O^{-}$ hydrogen bonds. In most of the known crystals of strychninium salts, the carboxyl group of the cocrystallized guest is the acceptor of an $N-H^{+} \cdots O^{-}$ hydrogen bond (Gould & Walkinshaw, 1984; Gould $et\ al.$, 1985, 1987; Sato & Yano, 1989; Costante $et\ al.$, 1996; Yuan $et\ al.$, 1994; Białońska & Ciunik, 2004). However, as mentioned above, the hydroxyl group in the crystal structure of (2a), and the water molecules in (3a) and in the previously described crystals of strychninium [1,3-diamino-2-(pentanyloxy)propane-N,N,N',N'-tetraacetato]cobalt(II) hexahydrate (Yano $et\ al.$, 1994) are acceptors of interlayer hydrogen bonds. In the latter case, the strychninium cations also form corrugated layers, similar to the layers observed in the crystals under investigation. In the previously described crystal structures of strychninium chlorate(VII) hydrate and strychninium hydrogen sulfate(VI) dehydrate (Białońska & Ciunik, 2005a), amine N2 atom is a donor of bifurcated hydrogen bonds. Water molecules, or chlorate(VII) or hydrogen sulfate(VI) anions, respectively, are the acceptors of the bifurcated hydrogen bonds. In these latter cases, the strychninium cations form bilayer sheets, and the anions are located in flat holes at the surfaces. In all cases, the anion, or part of it, occupies some specific site (a deep groove or flat hole) at the surface of the strychninium self-assembly. Base–acid pairing by $N-H^{+} \cdots O^{-}$ hydrogen-bond formation depends on whether the guest occupying the specific site gives, or does not give, an opportunity to its deprotonated group to be in close proximity to the protonated amine N2 atom of the strychninium cations. One way or another, both the N2 atom and the deprotonated group of a guest anion have an opportunity to participate in strong hydrogen bonds, for example, with solvent molecules.

In all crystals under investigation, the anions and solvent molecules form closed hydrogen-bond networks. However, the way that closed hydrogen-bond networks are formed is different in each of these cases. Thus, if recognition of the resolved compound occurs as mentioned above, at specific sites on the surface of strychninium self-assemblies, chiral discrimination and crystallization of a sequence of diastereomeric salts occur that depend on the hydrogen-bond network involving the resolved compound, solvent molecules and tertiary amine N2 atom. However, as far as we can see, we have not found any relationships between the sequence of the strychninium diastereomeric salt crystallization and the nature of the hydrogen-bond networks.

4. Conclusions

During racemic resolution of N-4-nitrobenzoyl-DL-amino acids (alanine, serine and aspartic acid) by a fractional crystallization of strychninium salts, crystals of both diastereomeric salts were grown, and their structures were determined. The crystal structures contain layers of strychninium cations separated by suitably hydrogen-bonded anions and solvent molecules. The cationic and anionic/solvent layers are linked by $N-H^{+} \cdots A$ hydrogen bonds. In the $N-H^{+} \cdots A$ hydrogen bond, the protonated amine N2 atom of the strychninium cation is the donor and the deprotonated carboxyl [in (1a), (1b), (2b) and (3b)] or hydroxyl group of the anion [in (2a)], or a water molecule [in (3a)], are the acceptor (A). Conversely, deep hydrophobic grooves at the surfaces of the corrugated strychninium layers are recognized in all cases by the 4-nitrobenzoyl group of anions. Such hydrophobic 'lock and key' recognition causes the resulting surface to have more hydrophilic properties, which are more appropriate for interactions in the hydrophilic environments from which the strychninium salts were crystallized. Chiral discrimination and the crystalline sequence of diastereomeric salts are dependent on the hydrogen-bond networks involving the resolved compound, solvent molecules and N2 atom of the strychninium cation.

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