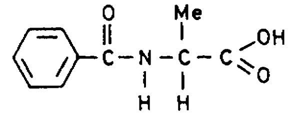
# Asymmetric Resolution and Molecular Recognition. Part 1. The Crystal Structure of *N*-Benzoyl-L-alanyl–Strychninium Dihydrate

**Robert O. Gould, Rosemary Kelly, and Malcolm D. Walkinshaw***
*Department of Chemistry, University of Edinburgh, Edinburgh EH9 3JJ*

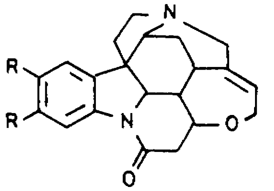
The crystal structure of the 1 : 1 complex of strychnine + *N*-benzoyl-L-alanine·$2H_2O$ ($a$ = 10.751, $b$ = 30.366, $c$ = 8.608 Å, space group $P2_12_12_1$) provides an insight into the mechanism of Pasteur's method for resolving racemic mixtures. Strychnine molecules pack in bilayers separated by impenetrable hydrogen-bonded sheets. A charge–charge interaction between the amino group on strychnine and a carboxy oxygen atom of the benzoyl-L-alanine provides the strongest intermolecular interaction, though specific van der Waals interactions involving the phenyl, amide, and indole π-electrons also play an important role in molecular recognition.

Pasteur's classical method for resolving a racemic acid (base) is by forming an insoluble diastereoisomeric salt of one enantiomer with an optically active base (acid). The technique has been particularly useful in resolving amino acids that are normally first converted into *N*-acetyl, *N*-benzoyl, or *N*-formyl derivatives.[1] These *N*-protected peptides may then form salts with an optically active base, normally a naturally occurring alkaloid such as strychnine, brucine, quinine, or morphine. Despite the widespread use of this technique, almost no prediction can be made as to whether a particular base will preferentially crystallise with the L- or D-isomer of a given acid. Small chemical changes in the base can also have profound effects on the preferred resolution. Thus, in Fischer's original work[2] it was found that for racemic mixtures of *N*-benzoyl-D,L-alanine (**1**), the *N*-benzoyl-L-alanine co-crystallises with strychnine while the *N*-benzoyl-D-alanine co-crystallises with brucine. The only difference between brucine and strychnine (**2**) is the presence of two methoxy groups on the aromatic ring of brucine. In an attempt to explain such recognition, binding, and co-crystallisation phenomena, a series of crystal-structure determinations of related alkaloid–peptide complexes has been undertaken.[3]

Most of the naturally occurring alkaloids used in resolutions are pharmacologically very active and the source of their activity lies in their ability to recognise and bind to specific protein receptor sites in the neurochemical pathway. Isolation and crystallisation of such membrane-bound receptor proteins is not yet possible, and there is only some low-resolution diffraction evidence and some indirect pharmacological studies on the molecular nature of the drug–receptor binding mechanism. The alkaloid–peptide complexes provide excellent high resolution models for just such interactions.



(1)



(2)

R = H, strychnine

R = OMe, brucine

## Experimental

The crystal complex of 1:1 strychnine–*N*-benzoyl-L-alanine was prepared in essentially the same way as described in Fischer's original paper. Equimolar amounts of strychnine and benzoyl-L-alanine were ground together and dissolved in boiling water. Slow cooling gave large colourless crystal plates.

Crystal data: $C_{21}H_{23}N_2O_2{\cdot}C_{10}H_{10}NO_3{\cdot}2H_2O$, $M$ = 563.5, space group $P2_12_12_1$, $a$ = 10.751(2), $b$ = 30.366(7), $c$ = 8.608(6) Å, $U$ = 2 810.2 Å$^3$, $Z$ = 4, $D_x$ = 1.33 g cm$^{-3}$, Mo-$K_\alpha$ radiation, $\lambda$ = 0.710 69 Å, $\mu$ = 0.89 cm$^{-1}$, $F(000)$ = 1 200, $T$ = 20 °C, $R$ = 0.051, calculated from 2 135 unique observed reflections.

A crystal was cut to give a fragment of dimensions 0.35 × 0.35 × 0.4 mm which was mounted on a glass fibre. Data were collected to $\theta = 25°$ ($h_{\text{max.}} = 12$, $k_{\text{max.}} = 36$, $l_{\text{max.}} = 10$) on a Nonius CAD4 diffractometer using Mo-$K_\alpha$, graphite-monochromated radiation. Of the 2 821 unique reflections measured, 2 135 were classed or observed with $I > 2.5\,\sigma(I)$. No absorption correction was applied and no crystal decay was apparent from monitoring two standard reflections.

The structure was solved, with some difficulty, using direct methods. No automatic solution was obtained from MULTAN;[4] however, the starting set of phases defined by the MULTAN routine CONVERGE were used as a starting point for the direct methods routine in SHELX-76.[5] This starting set was eventually increased to include eight hand-picked reflections with restricted phases and two with general phases. The resulting map provided a recognisable fragment of 40 atoms which gave an initial $R$-factor of 0.4.

Isotropic refinement of all non-hydrogen atoms gave $R$ = 0.11. All hydrogen atoms, including those on the two water molecules, were identified in Fourier difference maps. The six carbon atoms and five hydrogen atoms of the phenyl group were constrained to have an ideal geometry with C–C bond lengths of 1.395 Å, C–H bond lengths of 1.08 Å, and all bond angles of 120°. All non-hydrogen atoms were refined anisotropically and positional and isotropic thermal parameters were refined for all hydrogen atoms. The weighting scheme that gave the best analysis of variance in ranges of θ and $|F|$ was $1/w = \sigma^2(F) + 0.0034F^2$. In the final cycles of blocked matrix least-squares refinement, the average shift over error was less than 0.01 and the largest peak on a final difference Fourier map was 0.3 e Å$^{-3}$. The final $R$ and $R'$ were 0.051 and 0.085, respectively.

**Table** 1. Fractional co-ordinates of atoms with standard deviations

| Atom | *x* | *y* | *z* | $U_{eq.}$ |
|---|---|---|---|---|
| C(1) | 0.221 4(4) | 0.315 35(17) | 0.101 7(6) | 0.0327 |
| C(2) | 0.137 7(5) | 0.304 86(21) | 0.217 0(6) | 0.0416 |
| C(3) | 0.091 0(5) | 0.338 75(24) | 0.305 9(7) | 0.0478 |
| C(4) | 0.131 2(5) | 0.382 17(23) | 0.285 0(7) | 0.0479 |
| C(5) | 0.217 9(6) | 0.391 87(21) | 0.171 6(7) | 0.0441 |
| C(6) | 0.263 9(4) | 0.357 94(17) | 0.079 3(6) | 0.0326 |
| C(7) | 0.364 7(4) | 0.359 56(15) | −0.043 1(6) | 0.0316 |
| C(8) | 0.353 5(4) | 0.313 01(16) | −0.120 5(6) | 0.0311 |
| C(9) | 0.358 2(5) | 0.397 45(17) | −0.157 7(7) | 0.0380 |
| C(10) | 0.574 9(5) | 0.378 16(20) | −0.109 1(8) | 0.0460 |
| C(11) | 0.493 9(5) | 0.366 23(18) | 0.030 4(7) | 0.0386 |
| C(12) | 0.272 9(6) | 0.391 33(20) | −0.296 2(7) | 0.0415 |
| C(13) | 0.314 5(5) | 0.350 30(18) | −0.382 3(7) | 0.0389 |
| C(14) | 0.284 0(5) | 0.310 81(17) | −0.275 5(6) | 0.0336 |
| C(15) | 0.512 6(7) | 0.395 96(20) | −0.381 6(8) | 0.0509 |
| C(16) | 0.450 1(5) | 0.353 22(17) | −0.426 7(7) | 0.0377 |
| C(17) | 0.509 4(6) | 0.321 96(21) | −0.502 4(7) | 0.0490 |
| C(18) | 0.447 7(7) | 0.279 05(21) | −0.543 4(8) | 0.0489 |
| C(19) | 0.296 6(5) | 0.264 37(19) | −0.339 8(7) | 0.0415 |
| C(20) | 0.281 5(6) | 0.230 58(19) | −0.209 1(8) | 0.0492 |
| C(21) | 0.225 0(5) | 0.247 95(17) | −0.059 2(7) | 0.0423 |
| N(1) | 0.277 8(4) | 0.286 23(14) | −0.008 7(5) | 0.0329 |
| N(2) | 0.492 8(4) | 0.404 75(16) | −0.212 6(6) | 0.0450 |
| O(1) | 0.142 7(4) | 0.229 26(14) | 0.009 5(6) | 0.0643 |
| O(2) | 0.415 9(4) | 0.254 46(12) | −0.407 4(5) | 0.0443 |
| C(30) | 0.410 2(5) | 0.009 78(17) | 0.764 6(6) | 0.0415 |
| C(31) | 0.328 7(5) | 0.049 62(16) | 0.732 2(5) | 0.0364 |
| C(32) | 0.192 0(6) | 0.038 55(23) | 0.759 5(9) | 0.0590 |
| C(33) | 0.331 3(4) | 0.107 52(15) | 0.532 8(5) | 0.0325 |
| C(34) | 0.369 7(3) | 0.119 60(10) | 0.371 0(3) | 0.0358 |
| C(35) | 0.367 2(3) | 0.164 14(10) | 0.331 4(3) | 0.0483 |
| C(36) | 0.400 7(3) | 0.177 41(10) | 0.182 0(3) | 0.0594 |
| C(37) | 0.436 7(3) | 0.146 14(10) | 0.072 1(3) | 0.0569 |
| C(38) | 0.439 2(3) | 0.101 60(10) | 0.111 7(3) | 0.0557 |
| C(39) | 0.405 7(3) | 0.088 33(10) | 0.261 1(3) | 0.0479 |
| N(3) | 0.350 1(4) | 0.065 54(14) | 0.575 9(5) | 0.0370 |
| O(3) | 0.286 8(4) | 0.134 48(11) | 0.621 5(4) | 0.0477 |
| O(5) | 0.448 3(4) | −0.011 85(12) | 0.647 4(4) | 0.0512 |
| O(4) | 0.430 7(5) | 0.000 27(17) | 0.900 8(5) | 0.0739 |
| O(91) | 0.130 0(6) | 0.499 21(21) | −0.412 8(6) | 0.0812 |
| O(92) | 0.351 1(6) | 0.493 1(3) | −0.580 0(8) | 0.1094 |
| H(2) | 0.113(6) | 0.274 0(23) | 0.239(8) | 0.0548 |
| H(3) | 0.033(6) | 0.329 7(19) | 0.391(8) | 0.0491 |
| H(4) | 0.093(7) | 0.405 6(24) | 0.344(9) | 0.0674 |
| H(5) | 0.246(4) | 0.420 6(15) | 0.165(4) | 0.0097 |
| H(8) | 0.440(3) | 0.294 3(12) | −0.136(4) | 0.0011 |
| H(9) | 0.342(5) | 0.429 6(19) | −0.099(6) | 0.1414 |
| H(101) | 0.589(5) | 0.351 9(20) | −0.163(7) | 0.0370 |
| H(102) | 0.651(6) | 0.391 3(20) | −0.083(7) | 0.0484 |
| H(111) | 0.483(7) | 0.398 2(25) | 0.093(8) | 0.0701 |
| H(112) | 0.526(6) | 0.335 8(20) | 0.087(7) | 0.0489 |
| H(121) | 0.186(5) | 0.385 1(17) | −0.247(6) | 0.0279 |
| H(122) | 0.279(5) | 0.411 3(20) | −0.365(7) | 0.0320 |
| H(13) | 0.267(6) | 0.349 3(21) | −0.480(7) | 0.0439 |
| H(14) | 0.198(7) | 0.307 3(24) | −0.253(8) | 0.0592 |
| H(151) | 0.610(8) | 0.401 4(24) | −0.401(9) | 0.0768 |
| H(152) | 0.475(5) | 0.418 5(20) | −0.438(7) | 0.0385 |
| H(17) | 0.594(7) | 0.325 4(20) | −0.545(8) | 0.0553 |
| H(181) | 0.376(6) | 0.279 7(20) | −0.603(7) | 0.0476 |
| H(182) | 0.507(6) | 0.262 5(19) | −0.606(7) | 0.0430 |
| H(19) | 0.240(6) | 0.258 8(22) | −0.420(8) | 0.0501 |
| H(201) | 0.363(6) | 0.219 0(21) | −0.177(7) | 0.0490 |
| H(202) | 0.229(6) | 0.199 6(22) | −0.245(8) | 0.0569 |
| H(23) | 0.523(7) | 0.444(3) | −0.184(8) | 0.0824 |
| H(35) | 0.339 3(3) | 0.188 35(10) | 0.416 5(3) | 0.1202 |
| H(36) | 0.398 7(3) | 0.211 90(10) | 0.151 4(3) | 0.1514 |
| H(37) | 0.462 6(3) | 0.156 42(10) | −0.043 5(3) | 0.0674 |
| H(38) | 0.4671(3) | 0.077 40(10) | 0.026 6(3) | 0.1621 |
| H(39) | 0.4077(3) | 0.053 85(10) | 0.291 7(3) | 0.0926 |
| H(911) | 0.202(6) | 0.503 3(23) | −0.465(8) | 0.0582 |
| H(912) | 0.050(9) | 0.509(3) | −0.484(9) | 0.0937 |
| H(921) | 0.420(7) | 0.498 9(21) | −0.538(7) | 0.0483 |
| H(922) | 0.363(7) | 0.491(3) | −0.674(9) | 0.0665 |
| H(31) | 0.346(5) | 0.075 7(18) | 0.810(5) | 0.0356 |
| H(323) | 0.165(6) | 0.009 1(22) | 0.700(7) | 0.0580 |
| H(322) | 0.182(5) | 0.023 0(18) | 0.879(7) | 0.0457 |
| H(321) | 0.137(6) | 0.066 9(24) | 0.757(8) | 0.0748 |
| H(93) | 0.391(6) | 0.046 7(23) | 0.526(7) | 0.0603 |

Fractional co-ordinates are given in Table 1. Bond lengths, angles, and torsion angles are given in Table 2. Anisotropic thermal parameters and tables of observed and calculated structure factors have been deposited.*

## Discussion

*A. Strychnine Geometry* [*Figure* 1(*a*)].—A number of *X*-ray crystal-structure determinations involving strychnine have been carried out including those for the $NO_3^-$, $Cl^-$, $Br^-$, and $I^-$ salts.[6] The fact that, in this structure, strychnine is complexed with a much larger anion does not affect its geometry. Bond lengths are within the expected ranges and do not differ by more than $2\sigma$ from the corresponding average bond lengths found in the simple salts. One feature common to all structures is the long C(9)–N(2) bond length of 1.538 Å, which can be compared with the chemically similar but consistently shorter C(10)–N(2) and C(15)–N(2) bond lengths of 1.491 and 1.494 Å. All bond angles are also consistent ($\pm 1°$) with other strychnine determinations. All notable narrow angles are in the spiro five-membered rings [C(6)–C(7)–C(8) = 102.2°, C(9)–C(7)–C(11) = 102.2°] while the widest angle at an $sp^3$-hybridised atom is in the seven-membered ring: (C13)–C(14)–C(19) = 118.9°.

Molecular conformation is well conserved between the various crystal forms as would be expected for such a rigid molecule. Only the amide group shows any conformational freedom, and in this structure the torsion angle C(8)–N(1)–C(21)–C(20) = 17.4(7)° shows the largest deviation yet observed from the expected planar amide conformation. Similarly N(1)–C(21)–C(20)–C(19) = −47.9(7)° is significantly twisted from the average value of −42.9° found in the other structures. Co-ordination about the amide nitrogen is significantly different from the expected planar arrangement with the three subtended angles summing to 351.7°. The protonated tertiary amine nitrogen shows a more tetrahedral co-ordination with the three subtended angles summing to 334.8°.

*B.* N-*Benzoyl*-L-*alanine Geometry* [*Figure* 1(*b*)].—Bond lengths and angles are within $3\sigma$ of the equivalent parameters in the closely related structures: alanylalanine,[7] L-alanylalanine hydrochloride,[8] glycyl-L-alanine,[9] and glycyl-D,L-alanine.[10] The conformational angle N(3)–C(31)–C(30)–O(4) = −23° is in the middle of the range (−7° to −36°) found in other alanine structures. The angle ω, C(34)–C(33)–N(3)–C(3) = 174.2, is again consistent with other alanine structures and is significantly twisted from the idealised planar conformation. The conformation of *N*-benzoyl-D-alanine in the brucine

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* *Supplementary data available* (No. SUP56219, 3 pp.): anisotropic thermal parameters and observed and calculated structure factors. See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2* section 4.0 (January issue). Structure factors available from the editorial office on request.

**Table 2.** Bond lengths (Å), angles (°), and torsion angles (°)

Bond lengths (Å)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(1)–C(2) | 1.377(8) | C(10)–C(11) | 1.528(8) | C(18)–O(2) | 1.431(8) | C(32)–H(321) | 1.05(7) |
| C(1)–C(6) | 1.385(7) | C(10)–N(2) | 1.491(8) | C(18)–H(181) | 0.93(6) | C(33)–C(34) | 1.498(5) |
| C(1)–N(1) | 1.433(7) | C(10)–H(101) | 0.93(6) | C(18)–H(182) | 0.98(6) | C(33)–N(3) | 1.343(6) |
| C(2)–C(3) | 1.377(8) | C(10)–H(102) | 0.94(6) | C(19)–C(20) | 1.531(9) | C(33)–O(3) | 1.217(6) |
| C(2)–H(2) | 0.99(7) | C(11)–H(111) | 1.11(7) | C(19)–O(2) | 1.440(7) | C(34)–C(35) | 1.395(4) |
| C(3)–C(4) | 1.399(9) | C(11)–H(112) | 1.10(6) | C(19)–H(19) | 0.94(7) | C(34)–C(39) | 1.395(4) |
| C(3)–H(3) | 1.00(6) | C(12)–C(3) | 1.517(8) | C(20)–C(21) | 1.520(9) | C(35)–C(36) | 1.395(4) |
| C(4)–C(5) | 1.381(9) | C(12)–H(121) | 1.04(5) | C(20)–H(201) | 0.98(6) | C(35)–H(35) | 1.080(4) |
| C(4)–H(4) | 0.97(7) | C(12)–H(122) | 0.85(6) | C(20)–H(202) | 1.14(7) | C(36)–C(37) | 1.395(4) |
| C(5)–C(6) | 1.392(8) | C(13)–C(14) | 1.546(8) | C(21)–N(1) | 1.365(7) | C(36)–H(36) | 1.080(4) |
| C(5)–H(5) | 0.92(4) | C(13)–C(16) | 1.510(8) | C(21)–O(1) | 1.207(7) | C(37)–C(38) | 1.395(4) |
| C(6)–C(7) | 1.512(7) | C(13)–H(13) | 0.99(6) | N(2)–H(23) | 1.26(8) | C(37)–H(37) | 1.080(4) |
| C(7)–C(8) | 1.567(7) | C(14)–C(19) | 1.521(8) | C(30)–C(31) | 1.520(7) | C(38)–C(39) | 1.395(4) |
| C(7)–C(9) | 1.517(7) | C(14)–H(14) | 0.95(7) | C(30)–O(5) | 1.272(6) | C(38)–H(38) | 1.080(4) |
| C(7)–C(11) | 1.539(7) | C(15)–C(16) | 1.512(9) | C(30)–O(4) | 1.227(7) | C(39)–H(39) | 1.080(4) |
| C(8)–C(14) | 1.531(7) | C(15)–N(12) | 1.494(8) | C(31)–C(32) | 1.526(8) | N(3)–H(93) | 0.84(7) |
| C(8)–N(1) | 1.500(6) | C(15)–H(151) | 1.07(8) | C(31)–N(3) | 1.448(6) | O(91)–H(911) | 0.90(7) |
| C(8)–H(8) | 1.09(4) | C(15)–H(152) | 0.93(6) | C(31)–H(31) | 1.05(5) | O(91)–H(912) | 1.10(8) |
| C(9)–C(12) | 1.516(8) | C(16)–C(17) | 1.316(8) | C(32)–H(323) | 1.07(6) | O(92)–H(921) | 0.85(7) |
| C(9)–N(2) | 1.538(7) | C(17)–C(18) | 1.504(9) | C(32)–H(322) | 1.14(6) | O(92)–H(922) | 0.83(8) |
| C(9)–H(9) | 1.11(6) | C(17)–H(17) | 0.98(7) | | | | |

Bond angles (°)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(2)–C(1)–C(6) | 122.1(5) | C(14)–C(8)–N(1) | 105.7(4) | C(16)–C(17)–C(18) | 121.8(6) | C(31)–C(30)–O(4) | 117.8(5) |
| C(2)–C(1)–N(1) | 127.7(5) | C(7)–C(9)–C(12) | 116.5(5) | C(17)–C(18)–O(2) | 111.4(5) | O(5)–C(30)–O(4) | 125.4(5) |
| C(6)–C(1)–N(1) | 110.1(4) | C(7)–C(9)–N(2) | 105.4(4) | C(14)–C(19)–C(20) | 110.1(5) | C(30)–C(31)–C(32) | 110.6(4) |
| C(1)–C(2)–C(3) | 117.8(5) | C(12)–C(9)–N(2) | 110.2(4) | C(14)–C(19)–O(2) | 114.8(5) | C(30)–C(31)–N(3) | 110.2(4) |
| C(2)–C(3)–C(4) | 121.3(6) | C(11)–C(10)–N(2) | 105.1(5) | C(20)–C(19)–O(2) | 104.6(5) | C(32)–C(31)–N(3) | 111.7(4) |
| C(3)–C(4)–C(5) | 120.0(6) | C(7)–C(11)–C(10) | 102.9(4) | C(19)–C(20)–C(21) | 115.7(5) | C(34)–C(33)–N(3) | 116.6(4) |
| C(4)–C(5)–C(6) | 119.0(6) | C(9)–C(12)–C(13) | 107.8(5) | C(20)–C(21)–N(1) | 113.6(5) | C(34)–C(33)–O(3) | 121.8(4) |
| C(1)–C(6)–C(5) | 119.6(5) | C(12)–C(13)–C(14) | 106.5(4) | C(20)–C(21)–O(1) | 123.1(5) | N(3)–C(33)–O(3) | 121.6(4) |
| C(1)–C(6)–C(7) | 111.3(4) | C(12)–C(13)–C(16) | 111.1(5) | N(1)–C(21)–O(1) | 123.3(5) | C(33)–C(34)–C(35) | 117.3(3) |
| C(5)–C(6)–C(7) | 128.9(5) | C(14)–C(13)–C(16) | 113.6(4) | C(1)–N(1)–C(8) | 108.7(4) | C(33)–C(34)–C(39) | 122.7(3) |
| C(6)–C(7)–C(8) | 102.2(4) | C(8)–C(14)–C(13) | 112.4(4) | C(1)–N(1)–C(21) | 124.1(4) | C(35)–C(34)–C(39) | 120.0(3) |
| C(6)–C(7)–C(9) | 116.4(4) | C(8)–C(14)–C(19) | 108.3(4) | C(8)–N(1)–C(21) | 118.9(4) | C(34)–C(35)–C(36) | 120.0(3) |
| C(6)–C(7)–C(11) | 111.4(4) | C(13)–C(14)–C(19) | 118.9(4) | C(9)–N(2)–C(10) | 107.2(4) | C(35)–C(36)–C(37) | 120.0(3) |
| C(8)–C(7)–C(9) | 113.8(4) | C(16)–C(15)–N(2) | 109.9(5) | C(9)–N(2)–C(15) | 114.0(5) | C(36)–C(37)–C(38) | 120.0(3) |
| C(8)–C(7)–C(11) | 111.3(4) | C(13)–C(16)–C(15) | 114.5(5) | C(10)–N(2)–C(15) | 113.6(5) | C(37)–C(38)–C(39) | 120.0(3) |
| C(9)–C(7)–C(11) | 102.0(4) | C(13)–C(16)–C(17) | 123.4(5) | C(18)–O(2)–C(19) | 115.8(4) | C(34)–C(39)–C(38) | 120.0(3) |
| C(7)–C(8)–C(14) | 116.6(4) | C(15)–C(16)–C(17) | 122.1(5) | C(31)–C(30)–O(5) | 116.8(4) | C(31)–N(3)–C(33) | 123.3(4) |
| C(7)–C(8)–N(1) | 105.0(4) | | | | | | |

Torsion angles (°)

| | | | | | |
|---|---|---|---|---|---|
| C(6)–C(1)–C(2)–C(3) | 3.6(8) | C(8)–C(7)–C(11)–C(10) | 80.0(5) | C(13)–C(14)–C(19)–O(2) | 53.7(7) |
| N(1)–C(1)–C(2)–C(3) | −177.1(5) | C(9)–C(7)–C(11)–C(10) | −41.7(5) | N(2)–C(15)–C(16)–C(13) | 53.0(7) |
| C(2)–C(1)–C(6)–C(5) | −2.5(8) | C(7)–C(8)–C(14)–C(13) | 40.0(6) | N(2)–C(15)–C(16)–C(17) | −128.8(6) |
| C(2)–C(1)–C(6)–C(7) | 174.0(5) | C(7)–C(8)–C(14)–C(19) | 173.4(4) | C(16)–C(15)–N(2)–C(9) | −45.6(6) |
| N(1)–C(1)–C(6)–C(5) | 178.1(5) | N(1)–C(8)–C(14)–C(13) | 156.1(4) | C(16)–C(15)–N(2)–C(10) | 77.7(6) |
| N(1)–C(1)–C(6)–C(7) | −5.4(6) | N(1)–C(8)–C(14)–C(19) | −70.4(5) | C(13)–C(16)–C(17)–C(18) | −3.6(9) |
| C(2)–C(1)–N(1)–C(8) | 174.9(5) | C(7)–C(8)–N(1)–C(1) | 13.8(5) | C(15)–C(16)–C(17)–C(18) | 178.4(6) |
| C(2)–C(1)–N(1)–C(21) | 27.2(8) | C(7)–C(8)–N(1)–C(21) | 163.5(4) | C(16)–C(17)–C(18)–O(2) | −64.7(8) |
| C(6)–C(1)–N(1)–C(8) | −5.7(6) | C(14)–C(8)–N(1)–C(1) | −110.0(4) | C(17)–C(18)–O(2)–C(19) | 87.1(6) |
| C(6)–C(1)–N(1)–C(21) | −153.4(5) | C(14)–C(8)–N(1)–C(21) | 39.7(6) | C(14)–C(19)–C(20)–C(21) | 15.5(7) |
| C(1)–C(2)–C(3)–C(4) | −2.9(9) | C(7)–C(9)–C(12)–C(13) | −57.7(6) | O(2)–C(19)–C(20)–C(21) | 139.4(5) |
| C(2)–C(3)–C(4)–C(5) | 1.1(10) | N(2)–C(9)–C(12)–C(13) | 62.3(6) | C(14)–C(19)–O(2)–C(18) | −64.9(6) |
| C(3)–C(4)–C(5)–C(6) | 0.1(9) | C(7)–C(9)–N(2)–C(10) | 10.9(5) | C(20)–C(19)–O(2)–C(18) | 174.3(5) |
| C(4)–C(5)–C(6)–C(1) | 0.6(8) | C(7)–C(9)–N(2)–C(15) | 115.8(5) | C(19)–C(20)–C(21)–N(1) | −47.9(7) |
| C(4)–C(5)–C(6)–C(7) | −175.2(5) | C(12)–C(9)–N(2)–C(10) | −137.4(5) | C(19)–C(20)–C(21)–O(1) | 133.2(6) |
| C(1)–C(6)–C(7)–C(8) | 13.5(5) | C(33)–C(34)–C(39)–C(38) | 179.3(3) | C(20)–C(21)–N(1)–C(1) | 162.0(5) |
| C(1)–C(6)–C(7)–C(9) | 138.1(5) | C(12)–C(9)–N(2)–C(15) | −10.7(6) | C(20)–C(21)–N(1)–C(8) | 17.3(7) |
| C(1)–C(6)–C(7)–C(11) | −105.5(5) | N(2)–C(10)–C(11)–C(7) | 35.5(5) | O(1)–C(21)–N(1)–C(1) | −19.0(9) |
| C(5)–C(6)–C(7)–C(8) | −170.5(5) | C(11)–C(10)–N(2)–C(9) | −15.4(6) | O(1)–C(21)–N(1)–C(8) | −163.7(5) |
| C(5)–C(6)–C(7)–C(9) | −45.8(8) | C(11)–C(10)–N(2)–C(15) | −142.3(5) | O(5)–C(30)–C(31)–C(32) | 101.1(6) |
| C(5)–C(6)–C(7)–C(11) | 70.6(7) | C(9)–C(12)–C(13)–C(14) | 68.7(6) | O(5)–C(30)–C(31)–N(3) | −22.9(6) |
| C(6)–C(7)–C(8)–C(14) | 100.7(5) | C(9)–C(12)–C(13)–C(16) | −55.5(6) | O(4)–C(30)–C(31)–C(32) | −76.7(6) |
| C(6)–C(7)–C(8)–N(1) | −15.9(5) | C(12)–C(13)–C(14)–C(8) | −61.3(6) | O(4)–C(30)–C(31)–N(3) | 159.3(5) |
| C(9)–C(7)–C(8)–C(14) | −25.7(6) | C(12)–C(13)–C(14)–C(19) | 170.7(5) | C(30)–C(31)–N(3)–C(33) | −153.8(4) |
| C(9)–C(7)–C(8)–N(1) | −142.3(4) | C(16)–C(13)–C(14)–C(8) | 61.4(6) | C(32)–C(31)–N(3)–C(33) | 82.8(6) |
| C(11)–C(7)–C(8)–C(14) | −140.4(4) | C(16)–C(13)–C(14)–C(19) | −66.7(6) | N(3)–C(33)–C(34)–C(35) | −171.2(4) |
| C(11)–C(7)–C(8)–N(1) | 103.1(4) | C(12)–C(13)–C(16)–C(15) | −1.8(7) | N(3)–C(33)–C(34)–C(39) | 9.5(6) |

**Table 2** (*continued*)

Torsion angles (°)

| | | | | | |
|---|---|---|---|---|---|
| C(6)–C(7)–C(9)–C(12) | −83.7(6) | C(12)–C(13)–C(16)–C(17) | 180.0(6) | O(3)–C(33)–C(34)–C(35) | 7.7(6) |
| C(6)–C(7)–C(9)–N(2) | 153.8(4) | C(14)–C(13)–C(16)–C(15) | 121.9(5) | O(3)–C(33)–C(34)–C(39) | −171.6(4) |
| C(8)–C(7)–C(9)–C(12) | 34.9(6) | C(14)–C(13)–C(16)–C(17) | 59.9(7) | C(34)–C(33)–N(3)–C(31) | 174.2(4) |
| C(8)–C(7)–C(9)–N(12) | −87.7(5) | C(8)–C(14)–C(19)–C(20) | 1.5(6) | O(3)–C(33)–N(3)–C(31) | −4.8(7) |
| C(11)–C(7)–C(9)–C(12) | 154.9(5) | C(8)–C(14)–C(19)–O(2) | −76.2(5) | C(33)–C(34)–C(35)–C(36) | −179.3(3) |
| C(11)–C(7)–C(9)–N(2) | 32.3(5) | C(13)–C(14)–C(19)–C(20) | 171.4(5) | C(39)–C(34)–C(35)–C(36) | 0.0(5) |
| C(6)–C(7)–C(11)–C(10) | −166.6(4) | | | | |

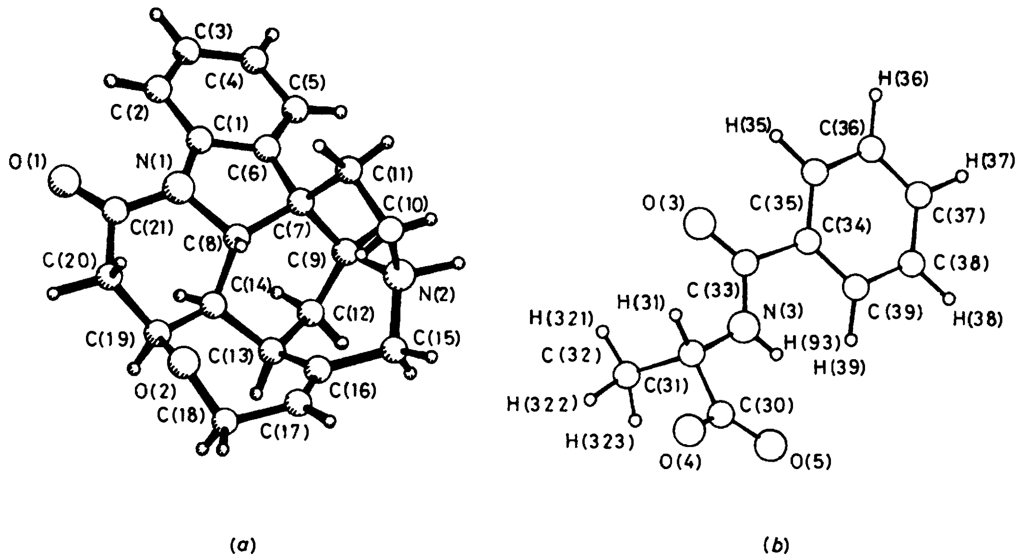

**Figure 1.** (*a*) The structure of strychnine, also showing the labelling scheme. (*b*) The structure of benzoyl-L-alanine

complex[11] is an almost exact mirror image of this L-isomer. The only significant (>2°) difference in torsion angles is the orientation of the phenyl ring: N(3)–C(33)–C(34)–C(35) = −171.2 and +173° in L(+)-strychnine and D(+)-brucine structures, respectively.

*C. Hydrogen Bonding*.—The structure is composed of bilayers of strychnine molecules separated by infinite hydrogen-bonded ribbons that tie together the two water molecules, the carboxy oxygen atoms from the benzoylalanine, and the protonated nitrogen atom on strychnine (Figure 2). The four water hydrogen atoms, two water oxygen atoms, and two carboxy oxygen atoms all have fractional co-ordinates of $y = 0(\pm 0.03$ Å). Both independent water molecules show a planar trigonal co-ordination, each being involved in three hydrogen bonds (Figure 3). Carboxy oxygen O(5) acts as an acceptor for two hydrogen bonds, O(5) ··· N(3) = 2.649 Å and O(5) ··· O(91) = 2.836 Å. The other carboxy oxygen O(4) is involved in only one hydrogen bond, O(4) ··· O(92) = 2.817 Å. Oxygen O(1), the carbonyl oxygen atom on strychnine, points in towards the centre of the hydrophobic bilayer and is not involved in hydrogen bonding. Hydrogen-bonded distances are given in Table 3.

*D. Environment of Benzoyl-L-alanine*.—An analysis of the intermolecular interactions in this structure should hold the key to explaining why the co-crystallisation of benzoylalanine with strychnine is so specific for one isomer. Apart from the obvious and important hydrogen bonds, there are other more subtle van der Waals interactions between atoms or groups of atoms that provide a complementary surface for molecular recognition and binding. There are no surprisingly short van der Waals contacts, but the packing arrangement in the crystal does, however, show some interesting patterns in the way that groups of atoms arrange themselves relative to each other. Table 4 shows all short intermolecular contacts.

*The phenyl group*. In *N*-benzoyl-L-alanine the phenyl group makes contacts with five different strychnine molecules and two benzoylalanine molecules. Its environment can be explained in terms of two general principles.

(*i*) The non-bonded interaction between two aromatic groups is such that the electron-deficient edge of one π-system will point into the electron-rich π-cloud lying above and below the plane of the second ring. (*ii*) Electronegative oxygen atoms will tend to lie round the edge of an aromatic ring. The phenyl–indole contacts are C(35) ··· H(3) = 2.99 Å, C(33) ··· H(3) = 2.96 Å, H(37) ··· C(2) = 2.67 Å, and H(37) ··· C(3) = 2.65 Å. These contacts provide a zigzag interaction through the crystal along the *c* axis. H(37) from the phenyl group points into the π-surface of the indole ring, while H(3) of the indole ring unit cell that is up points into the π-cloud of the phenyl ring. The interplanar angle between the phenyl group and the indole group is 56°. The phenyl–oxygen contacts are H(35) ··· O(2) = 2.65 Å and H(38) ··· O(4) = 2.61 Å; both of these oxygen atoms are approximately coplanar with the phenyl ring. A similar interaction between strychnine molecules is observed between O(2) and the indole atom H(2). The remaining two noteworthy contacts involving atoms on the phenyl group are both H ·· H contacts with aliphatic hydrogen atoms on two

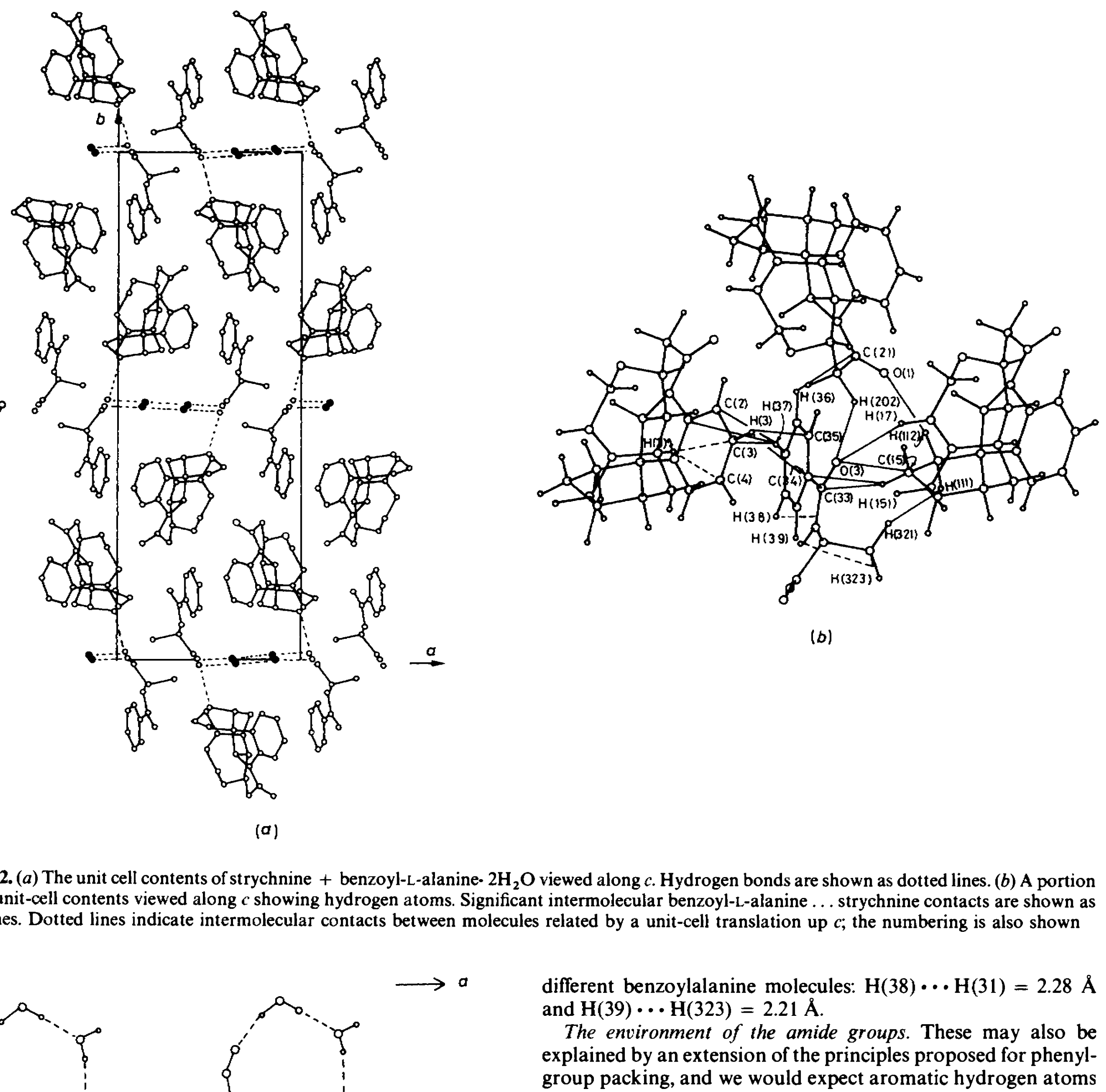

**Figure 2.** (*a*) The unit cell contents of strychnine + benzoyl-L-alanine$\cdot$ $2H_2O$ viewed along *c*. Hydrogen bonds are shown as dotted lines. (*b*) A portion of the unit-cell contents viewed along *c* showing hydrogen atoms. Significant intermolecular benzoyl-L-alanine ... strychnine contacts are shown as thin lines. Dotted lines indicate intermolecular contacts between molecules related by a unit-cell translation up *c*; the numbering is also shown

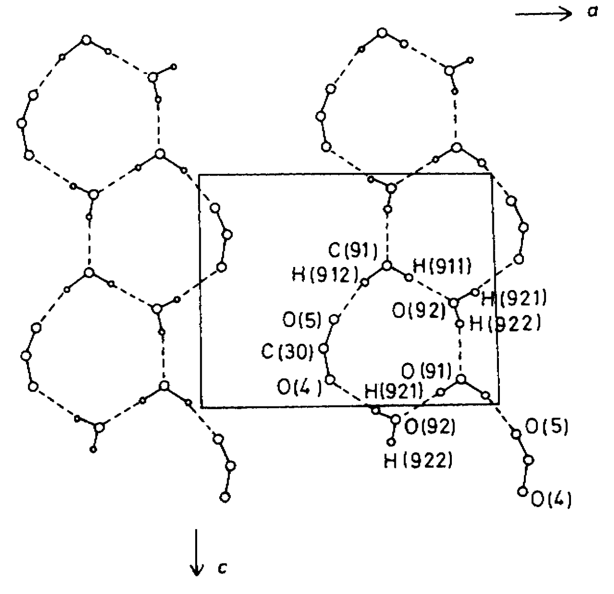

**Figure 3.** A view along *b* ($y = -0.1$ to 0.1) showing the hydrogen bonds (dotted lines) between water molecules [O(91) and O(92)] and the carboxy group of the benzoylalanine; the numbering is also shown

different benzoylalanine molecules: H(38) $\cdots$ H(31) = 2.28 Å and H(39) $\cdots$ H(323) = 2.21 Å.

*The environment of the amide groups.* These may also be explained by an extension of the principles proposed for phenyl-group packing, and we would expect aromatic hydrogen atoms to point into the cloud of the planar amide group. Such interactions are found in the contact H(36) $\cdots$ C(21) = 2.82 Å between the phenyl group and the amide group of the strychnine, and in the contacts H(3) $\cdots$ C(33) = 2.96 Å, H(3) $\cdots$ O(3) = 2.86 Å, and H(4) $\cdots$ N(3) = 2.84 Å between the indole hydrogen atoms and the amide group of the benzoylalanine. H(151) is two bonds away from the positively charged N(2) and is therefore expected to carry a slight positive charge. This may explain the short contacts to the amide carbon atoms: C(33) $\cdots$ H(151) = 2.66 Å and C(34) $\cdots$ H(151) = 2.88 Å. The amide oxygen, O(3), lies close to the plane of the vinyl system C(16)–C(17)–H(17) and is only 2.49 Å from H (17). It is probable that the vinyl group provides a slightly electropositive edge similar to those postulated for the aromatic systems. It is particularly interesting to note that neither O(3) nor H(93) (conventionally the amide group hydrogen-bond acceptor and donor) are involved in hydrogen bonding.

The few strychnine–strychnine and benzoylalanine–benzoylalanine contacts are caused mainly by stacking of like molecules along the short 8.6 Å cell edge. With strychnine this results in the 2.66 and 2.68 Å contacts between H(13) to C(3) and C(4). In

**Table 3.** Hydrogen bonds

| Atom 1 | Atom 2 | Symmetry operation applied to atom 2 | Distance (Å) |
|---|---|---|---|
| N(2) | O(5) | $(1 - x, \frac{1}{2} + y, \frac{1}{2} - z)$ | 2.670 |
| H(23) | O(5) | $(1 - x, \frac{1}{2} + y, \frac{1}{2} - z)$ | 1.411 |
| O(91) | O(92) | $(x, y, z)$ | 2.785 |
| H(911) | O(92) | $(x, y, z)$ | 1.914 |
| O(4) | O(92) | $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$ | 2.817 |
| O(4) | H(921) | $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$ | 1.991 |
| O(5) | O(91) | $(\frac{1}{2} + x, \frac{1}{2} - y, -z)$ | 2.836 |
| O(5) | H(912) | $(\frac{1}{2} + x, \frac{1}{2} - y, -z)$ | 1.787 |
| O(91) | O(92) | $(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$ | 2.881 |
| O(91) | H(922) | $(\frac{1}{2} - x, 1 - y, \frac{1}{2} + z)$ | 2.079 |

**Table 4.** Intermolecular van der Waals contacts (excluding the hydrogen bonds shown in Figure 3)

| C····H | contacts | <3.0 Å |
|---|---|---|
| C(30) | H(23) | 2.23 |
| C(3) | H(37) | 2.65[a] |
| C(33) | H(151) | 2.66[a] |
| C(3) | H(13) | 2.66[a] |
| C(2) | H(37) | 2.68[a] |
| C(4) | H(13) | 2.68[a] |
| C(21) | H(36) | 2.82[a] |
| C(34) | H(151) | 2.88[a] |
| C(30) | H(912) | 2.91 |
| C(1) | H(37) | 2.95[a] |
| C(33) | H(3) | 2.96[a] |
| C(35) | H(3) | 2.99[a] |

| C····O | contacts | <3.5 Å |
|---|---|---|
| C(15) | O(3) | 3.23[a] |
| C(20) | O(3) | 3.26 |
| C(11) | O(1) | 3.33 |
| C(10) | O(5) | 3.37 |
| C(2) | O(2) | 3.41 |
| C(17) | O(3) | 3.42 |
| C(3) | O(3) | 3.43 |

| C····C | contacts | <3.6 Å |
|---|---|---|
| C(3) | C(33) | 3.519 |
| C(21) | C(36) | 3.531 |

| H····H | contacts | <2.4 Å |
|---|---|---|
| H(39) | H(323) | 2.21[a] |
| H(38) | H(31) | 2.28[a] |
| H(111) | H(321) | 2.35[a] |
| H(23) | H(912) | 2.37 |
| H(9) | H(911) | 2.39 |

| O····H | contacts | <2.7 Å |
|---|---|---|
| H(202) | O(3) | 2.37[a] |
| H(112) | O(1) | 2.48[a] |
| H(17) | O(3) | 2.49[a] |
| H(8) | O(1) | 2.54 |
| H(23) | O(4) | 2.58 |
| H(38) | O(4) | 2.61 |
| H(35) | O(2) | 2.65 |
| H(152) | O(4) | 2.67 |
| H(2) | O(2) | 2.70 |

| N····H | contacts | <3.0 Å |
|---|---|---|
| H(4) | N(3) | 2.84 |
| H(36) | N(1) | 2.95 |

[a] Indicates bonds shown in Figure 2(*b*).

benzoylalanine, the stacking causes close contacts of 2.72 Å between two methyl hydrogen atoms on the α-carbon and both carboxy oxygen atoms O(4) and O(5).

## Conclusion

Selective co-crystallisation must depend on the ability of the two molecular species to aggregate in such a way that the charges distributed on their interacting surfaces are complementary. The salt bridge between the carboxy group of benzoylalanine and the charged nitrogen on strychnine is the single strongest intermolecular interaction in the structure. A standard value for such an interaction is estimated at *ca.* 22 kJ $\text{mol}^{-1}$.[12] The four unique hydrogen bonds involving the two water molecules and the carboxy oxygen atoms provide the next most important contributions to lattice stability, with each hydrogen bond contributing *ca.* 18 kJ $\text{mol}^{-1}$. The hydrogen-bonding pattern would, however, be equally available to the D-isomer and the specific recognition process must involve some further binding/recognition site. All non-bonded contacts given in Table 3 can be regarded as contributing to the van der Waals dispersion force, which can provide between 0.1 and 5 kJ $\text{mol}^{-1}$ for different types of interatomic contacts. The interactions found in this alkaloid–peptide complex, around aromatic and amide groups, which use their electron-rich faces and electron-deficient edges to provide electrostatically complementary surfaces, suggests that the role of such specific van der Waals interactions may be a crucial factor in molecular recognition.

Further strychnine–peptide complexes are currently under investigation in this laboratory. Such a series of crystal structures should highlight the relative importance of those conserved interactions.

## References

1 L. Pasteur, *C.R. Acad. Sci.*, 1853, **37**, 162.

2 E. Fischer, *Chem. Ber.*, 1899, **32**, 2451.

3 R. O. Gould and M. D. Walkinshaw, *J. Am. Chem. Soc.*, 1984, **106**, 7840.

4 P. Main, L. Lessinger, M. M. Woolfson, G. Germain and J. P. Declerq, MULTAN-77, University of York, 1977.

5 G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determinations, University of Cambridge, 1976.

6 (*a*) A. Cleasby, R. O. Gould, N. Moulden, and M. D. Walkinshaw, *Acta Crystallogr.*, 1981, **A37**, C72; (*b*) A. Cleasby, S. S. B. Glover, R. O. Gould, and M. D. Walkinshaw, *Acta Crystallogr.*, in the press.

7 R. J. Fletterick, C. Tsai, and R. E. Hughes, *J. Phys. Chem.*, 1971, **75**, 918.

8 Y. Tomuka, T. Ashida, and M. Kakudo, *Acta Crystallogr.*, 1969, **B25**, 1367.

9 A. H.-J. Wang and I. C. Paul, *Cryst. Struct. Commun.*, 1979, **8**, 269.

10 W. F. Paton and I. C. Paul, *Cryst. Struct. Commun.*, 1979, **8**, 275.

11 P. T. Beurskens, R. O. Gould, and M. D. Walkinshaw, submitted for publication in *Acta Crystallogr.*

12 G. E. Schulz and R. H. Schirmer, 'Principles of Protein Structure,' Springer-Verlag, New York, 1979, p. 28.

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