CRYSTAL STRUCTURE STUDIES

ON SOME DEHYDROPEPTIDES

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CONTENTS

Abstract

The aim of the project was the preparation and structural determination of dehydro-peptides.

To provide a benchmark for the dehydro-peptide structures two N-acetyl dipeptide structures were studied, N-Ac-L-Ala-L-Ser-OEt (Space group C2, a = 15.283 Å, b = 9.822 Å, c = 9.710 Å, β = 112.94°) which was solved in a straight forward manner and N-Ac-L-Ala-L-Ala-OEt (Space group C2, a = 14.6557 Å, b = 9.9312 Å, c = 9.631 Å, β = 112.501°) which was eventually solved using a starting set selected by a technique based on negative quartets.

Then N-acetyl dehydro-amino acids were investigated and the structures of N-Ac-ΔAla-OH (Space group $P2_1/n$, a = 3.9414 Å, b = 10.1558 Å, c = 14.8975 Å, β = 91.64°) and N-Ac-ΔPhe-OH (Space group $P2_1/a$, a = 18.2815, b = 6.0807, c = 11.4019, β = 105.94°) resolved.

Next N-acetyl dehydro-peptides were considered. Various methods of preparation were attempted:

Carbodiimide coupling. This was in the main unsuccessful, though interestingly when the coupling of N-Ac-ΔPhe-OH with an amino acid ester was attempted using D.C.C.I./HOBT the unsaturated oxazolone was formed in good yield.

β elimination. The tosyl derivatives of dipeptides containing serine were prepared. The products were non-crystalline.

Bergmann synthesis. A wide range of N-acetyl dehydro-peptides were synthesised using this technique. Although in the main crystalline, the crystals were usually unsuitable for structural determination. However, one compound, N-Ac-ΔPhe-L-Pro-OH (Space group C2, a = 18.516 Å, b = 9.515 Å, c = 10.538 Å, β = 120.102°) was found to form suitable crystals.

ABBREVIATIONS

Bessel function of argument Z and order m[1]	- $I_m(Z)$
Σf_j^n	- σ_n
$2\sigma_3\sigma_2^{-3/2}\lvert E_h E_{h-h'} E_{h'}\rvert$	- $\kappa_{hh'}$
$2\sigma_4\sigma_2^{-2}\lvert E_h E_k E_\ell E_{-h-k-\ell}\rvert$	- B
Probability distribution of Ω with fixed A	- $P(\Omega\lvert A)$
Expection value of Ω with fixed A	- $E(\Omega\lvert A)$
Average value of F	- $\langle F_h \rangle_h$
Ungerade	- u
Gerade	- g
A determinant	- Δ^*
$\lvert\lvert F_0\rvert - \lvert F_c\rvert\rvert$	- Δ^*
The torsion angle $\theta(C_{i-1}, N_i, C_i^\alpha, C_i)$[2]	- Φ_i^*
The torsion angle $\theta(N_i, C_i^\alpha, C_i, N_{i+1})$[2]	- Ψ_i^*
The torsion angle $\theta(C_i^\alpha, C_i, N_{i+1}, C_{i+1}^\alpha)$[2]	- ω_i^*
Di-isopropyl ethylamine	- D.I.E.A.
Dicyclohexylcarbodimide	- D.C.C.I.
Dicyclohexylamine	- D.C.H.A.
Dicyclohexylurea	- D.C.U.
Diazabicyclo [5.4.0] undec-5-ene	- D.B.U.
Phenyl	- Φ^*
Acetic anhydride	- Ac_2O
Toluene sulphonyl(tosyl)	- Ts
Benzyloxycarbonyl	- Z

1-hydroxybenzotriazole	- HOBT
Tertiary butyl hypochlorite	- tert-BHC

Standard contractions are used for amino acids. The dehydro-(Δ*) prefix signifies an α,β double bond.

*If an abbreviation has more than one meaning, it will be used only where the context makes the intended meaning clear.

CHAPTER ONE

A SUMMARY OF THE THEORY OF X-RAY STRUCTURE DETERMINATION

1.1 Diffraction Theory

It can be shown from diffraction theory[3] that the amplitude of X-ray scattering, in a direction represented by hkℓ, from a three dimensional regularly repeating motif is

$$1.1.1 \quad F_{hk\ell} = V\iiint \rho(x,y,z)e^{2\pi i \underline{r}^*\underline{r}}\,dx\,dy\,dz$$

$\rho(x,y,z)$ - electron density at (x,y,z)

$\underline{r} = x\underline{a} + y\underline{b} + z\underline{c}$

$\underline{a},\underline{b},\underline{c}$ - the vectors defining the unit cell

$\underline{r}^* = h\underline{a}^* + k\underline{b}^* + \ell\underline{c}^*$

$\underline{a}^* = \underline{b} \times \underline{c} \,/\, \underline{a}\cdot\underline{b} \times \underline{c}$ with similar definitions for $\underline{b}^*$ $\underline{c}^*$, the three vectors defining the reciprocal lattice (r.l.) cell.

It is computationally more convenient to write 1.1.1 as

$$1.1.2 \quad F_{hk\ell} = \sum_{j}^{N} f_j e^{2\pi i(hx_j+ky_j+\ell z_j)}$$

(x_j,y_j,z_j) are the coordinates of the j^{th} atoms centre

f_j is an atomic scattering factor, representing the scattering ability of the j^{th} atom, being, because of finite atomic size, only the same as the atomic number Z when $\sin\theta/\lambda = 0$.

As 1.1.1 is the Fourier transformation of $\rho(x,y,z)$, the desired electron density function

$$1.1.3 \quad \rho(x,y,z) = 1/V \sum_{h}\sum_{k}\sum_{\ell} F_{hk\ell} e^{-2\pi i(hx+ky+\ell z)}$$

A comparison of 1.1.3 with a three dimensional Fourier series[4] reveals it to be just a Fourier series with Fourier coefficients $F_{hk\ell}/V$. Representing $F_{hk\ell}$ on an Argand diagram reveals the difficulty in calculating 1.1.3 (Figure 1.1.1)

$F_{hk\ell} = A + iB$ (Generally, but for centrosymmetric structures B=0)

$F_{hk\ell} = |F_{hk\ell}|\, e^{2\pi i \alpha_{hk\ell}}$ with $\alpha_{hk\ell} = \mathrm{Tan}^{-1}B/A$

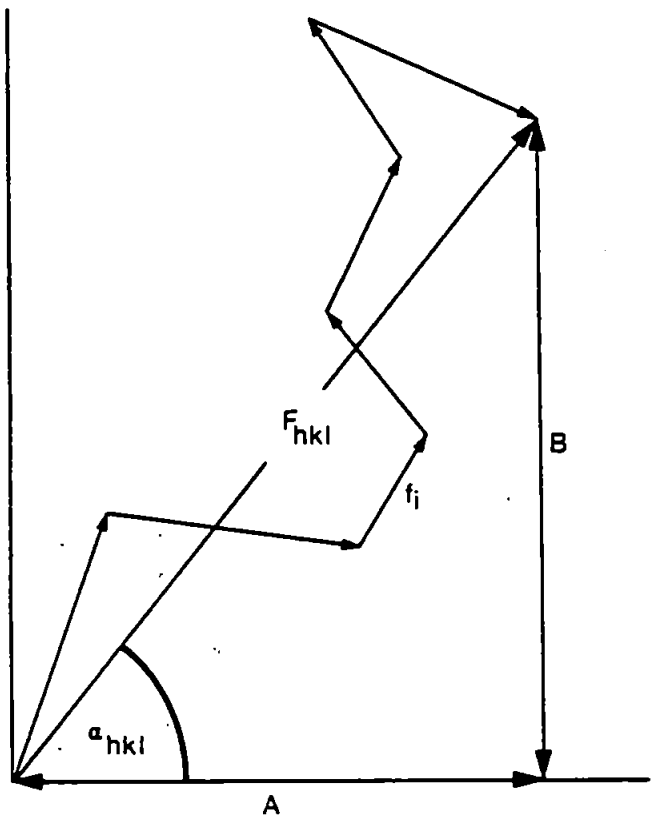

Figure 1.1.1. An Argand diagram showing the structure factor F_{hkl} and its relationship to the atomic scattering factor f_i.

The parameter actually measured in X-ray diffraction is effectively $|F_{hk\ell}|$ so rewriting in terms of $|F_{hk\ell}|$ and $\alpha_{hk\ell}$, the phase angle,

$$1.1.4 \quad \rho(x,y,z) = 1/V \; \Sigma \; \Sigma \; \Sigma \; |F_{hk\ell}| e^{-2\pi i(hx+ky+\ell z-\alpha_{hk\ell})}$$

a form that lays bare the central problem in structure determination, the phase problem.

The exponent of 1.1.4 has the form of a plane, so that each term is a function having constant electron density on the plane (hkℓ), the electron density varying sinusoidally along the normal to the plane, with a maximum magnitude $|F_{hk\ell}|/V$ (electrons per unit volume) at a distance $\alpha_{hk\ell}$ from the origin.

As $\alpha_{hk\ell}$ is experimentally unknown so is the position of the maximum, though in the case of centrosymmetric structures with α as 0 or π, the problem reduces to whether the maximum or minimum is at the origin.

The Reciprocal Lattice

A very convenient way of visualising the diffraction conditions is by means of the Ewald sphere (Figure 1.1.2).

The sphere is of unit radius and diffraction only occurs when a point (of the reciprocal lattice) is on the surface of the sphere.

$$d^* = 2 \sin\theta$$

From comparison with the Bragg equation, $n\lambda = 2d \sin\theta$ one sees that

$$n\lambda/d_{hk\ell} = d^*_{hk\ell}$$

'n' being the diffraction order so

$$d^*_{hk\ell} = d^*_{nh\ nk\ n\ell}/n$$

To clarify the relationship between the real and reciprocal lattice (r.l.) consider the set of real planes (hkℓ), with the usual meaning that the plane intercepts a, b, c at (1/h, 1/k, 1/ℓ) (h,k,ℓ being relatively prime). All the planes so defined (real/rational planes) contain lattice points, and conversely, no lattice points are

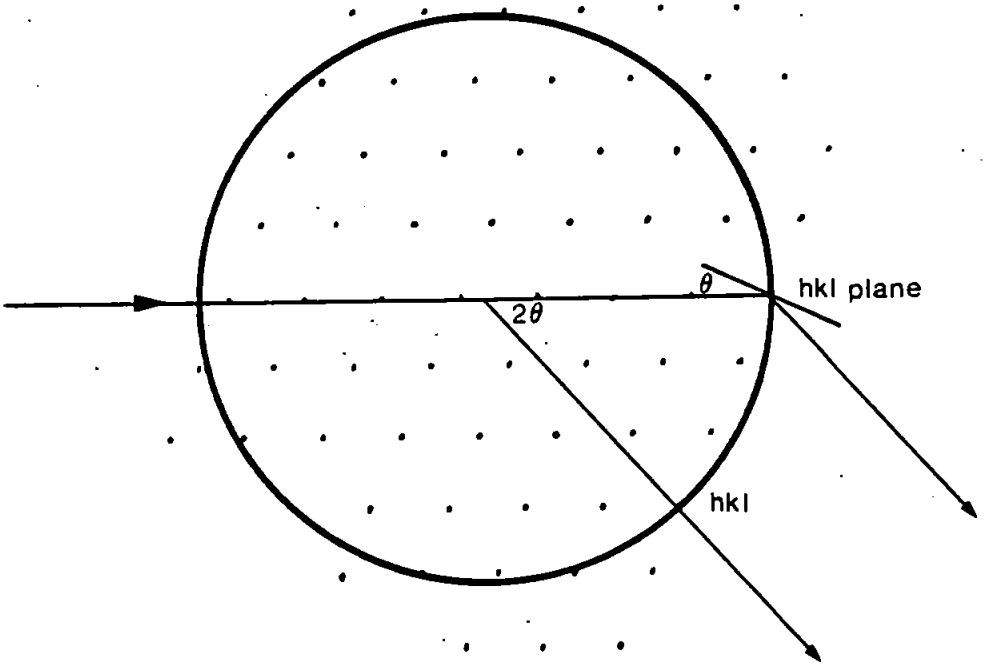

Figure 1.1.2. Reciprocal space and its relationship to diffraction in real space.

located away from such a plane.

Consider the reciprocal lattice vector

$$\underline{r}^*_{\alpha\beta\gamma} = \alpha\underline{a}^* + \beta\underline{b}^* + \gamma\underline{c}^*$$

If this vector is perpendicular to the vectors $(-1/h,0,1/\ell)$ and $(-1/h,1/k,0)$, then the scaler products are zero

$$((1/-h)\underline{a} + (1/k)\underline{b})\cdot(\alpha\underline{a}^* + \beta\underline{b}^* + \gamma\underline{c}^*) = 0$$

$$((-1/h)\underline{a} + (1/\ell)\underline{c})\cdot(\alpha\underline{a}^* + \beta\underline{b}^* + \gamma\underline{c}^*) = 0$$

$$\alpha/h = \beta/k = \gamma/\ell$$

An obvious solution is $\alpha = nh$, $\beta = nk$, $\gamma = n\ell$, n integer, so that associated with the plane $(hk\ell)$ are the points $\underline{r}^*_{nh\ nk\ n\ell}$, with the values of n corresponding to the orders of reflexion from $(hk\ell)$.

Examining the Bragg equation it is obvious that the maximum value of $n < 2d_{hk\ell}/\lambda$.

In terms of the Ewald sphere the only r.l points that can be observed lie within 2 r.l. units of the origin, the so called limiting sphere.

This introduces one of the problems of X-ray crystallography, namely series termination effects.

As the r.l. points correspond to the coefficients of a three-dimensional Fourier series, a series formed from diffraction data is truncated. This is equivalent to multiplying the reciprocal lattice by a three-dimensional top hat function; by the convolution theorem this results in $\rho(x,y,z)$ being multiplied by

$$(\sin(4\pi s) - 2\pi s\cos 4\pi s)/2\pi^2 s^3$$

$$s = (x^2 + y^2 + z^2)^{\frac{1}{2}}$$

producing so called diffraction ripples, peaks and troughs around atoms, which make it difficult to pick out from an electron density map, light atoms in the proximity of a heavy atom. However, if, using

known atomic positions to calculate F_c, a Fourier series is computed with coefficients $|F_o|-|F_c|$, a difference synthesis is produced

$$\rho(x,y,z) = \Sigma\Sigma\Sigma\,(|F_o| - |F_c|)e^{-2\pi i(hx+ky+\ell z-\alpha_{hk\ell})}$$

Since Fourier series calculated using both F_c and F_o as coefficients produce diffraction ripples, the difference will almost eliminate the ripples, indeed all common features, leaving, hopefully, the light atoms revealed.

In practice, though refinement using only high order reflexions has been found to give accurate bond lengths[5], the light atoms are often located geometrically or increasingly, from neutron diffraction data, thereby avoiding problems with the hydrogen scattering factor[6].

1.2 Data Reduction

Before the structure factors can be used in calculations they must first be found from the measured intensities, which, in the case of a diffractometer, are proportional to the total count (corrected with background readings):

$$K\, e_{hk\ell}\, A_{hk\ell}\, L_{hk\ell}\, p_{hk\ell} |F_{hk\ell}|^2 V = E_{hk\ell}\omega/I_o = \text{Integrated reflexion}$$

K = constant

$e_{hk\ell}$ = primary extinction correction

$A_{hk\ell}$ = absorption and secondary extinction correction

$L_{hk\ell}$ = Lorentz factor

$p_{hk\ell}$ = polarisation factor

I_o = beam intensity

The integrated reflexion is used as the reciprocal lattice points have finite volume, not only due to finite crystal size, but also thermal effects and the non-monochromatic nature of the X-ray beam.

If the Bragg equation is differentiated

$$\lambda = 2d_{hk\ell} \sin\theta$$

$$d\lambda = 2d_{hk\ell} \cos\theta\, d\theta$$

$$d\theta = d\,\lambda/2d \cos\theta$$

one sees, as well as a lengthening in the direction of the origin, that there exists an exceptionally large range $d\theta$ over which the Bragg equation is satisfied at $\theta = 90^{\circ}$; furthermore, the incident beam is never ideally collimated and so the incident beam impinges on the crystal over a range of incident angles.

Earlier it had been assumed that the nuclear positions were constant. In fact, thermal agitation causes each atom to execute vibrations about the equilibrium position. If 'u' is taken to indicate the displacement of the atom, then the magnitude of the thermal motion can

be expressed by $\langle u^2 \rangle$ the mean square displacement.

Generally the field of restoring forces and hence the mean square displacement varies with direction and can be shown to mark out a quadric surface; regarding the restoring forces as linear, this surface is an ellipsoid. Unless restricted by the symmetry of the atoms location the mutually perpendicular axes of the ellipsoid are not parallel with the axes of the unit cell.

If the atoms of a crystal were motionless, then each atom of a set of translation equivalent atoms would be fixed relative to one another. Under such circumstances every atom on a particular plane scatters exactly in-phase with all other atoms on that plane and exactly 2π out of phase with the atoms on the next plane. As a result all atoms of the translation equivalent set scatter in phase with an amplitude corresponding to f_j.

With thermal motion the atoms are somewhat displaced from their planes and this spoils the in-phase relations of their combined scattering; consequently the amplitude is reduced by a factor of the form e^{-W}, the temperature factor.

The temperature factor for isotropic temperature vibrations is

$$\begin{aligned} T_{hk\ell} &= e^{-2\pi^2\langle u^2\rangle/d^2_{hk\ell}} \\ &= e^{-2\pi^2\langle u^2\rangle(2\sin\theta/\lambda)^2} \\ &= e^{-B(\sin\theta/\lambda)^2} \qquad B = 8\pi^2\langle u^2\rangle \\ &= e^{-2\pi^2\langle u^2\rangle r^*_{hk\ell}{}^2} \qquad r^*_{hk\ell} = 1/d \end{aligned}$$

The most general form of the temperature factor is then

$$1.2.1 \quad T_{hk\ell} = e^{-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}\ell^2c^{*2}+2U_{12}hka^*b^*+2U_{23}k\ell b^*c^*+2U_{13}h\ell a^*c^*)}$$

Other forms commonly used have

$$2\pi^2 U_{11} a^{*2} = \frac{1}{4} B_{11} a^{*2} = \beta_{11}$$

$$4\pi^2 U_{12} a^* b^* = \frac{1}{2} B_{12} a^* b^* = \beta_{12}$$

The exponent of 1.2.1 has the form of an ellipsoid referred to an arbitrary coordinate system

$$Ax^2 + By^2 + Cz^2 + 2Dxy + 2Eyz + Fzx = a$$

with $A = 2\pi^2 U_{11}$

and $h^2 a^{*2} = x^2$ etc.

which can readily be converted to the neater form

$$x^2/a^2 + y^2/b^2 + z^2/c^2 = 1$$

where a, b and c are the three orthogonal principal axes of the ellipsoid; the directions of these axes are, in general, oblique to each of the crystal axes, so a complete description includes the angles between the ellipsoid axes and the crystal axes.

After the temperature factor correction 1.1.2 becomes

$$F_{hk\ell} = \Sigma g_i \, e^{2\pi i (hx_i + ky_i + \ell z_i)}$$

$$g_i = T_{hk\ell} f_i$$

Lorentz Factor

As the r.l points have volume they spend a finite time on the Ewald sphere, a time proportional to the velocity normal to the sphere. Considering the zero level as a simple case (Figure 1.2.1)

$$OP = 2\sin\theta$$

$$\nu_n = \nu\cos\theta$$

$$= OP.\omega\cos\theta$$

$$= 2\sin\theta\cos\theta\omega$$

$$\omega/\nu_n = 1/\sin 2\theta = L_{hk\ell}$$

For other geometries the Lorentz factor will take different forms, the

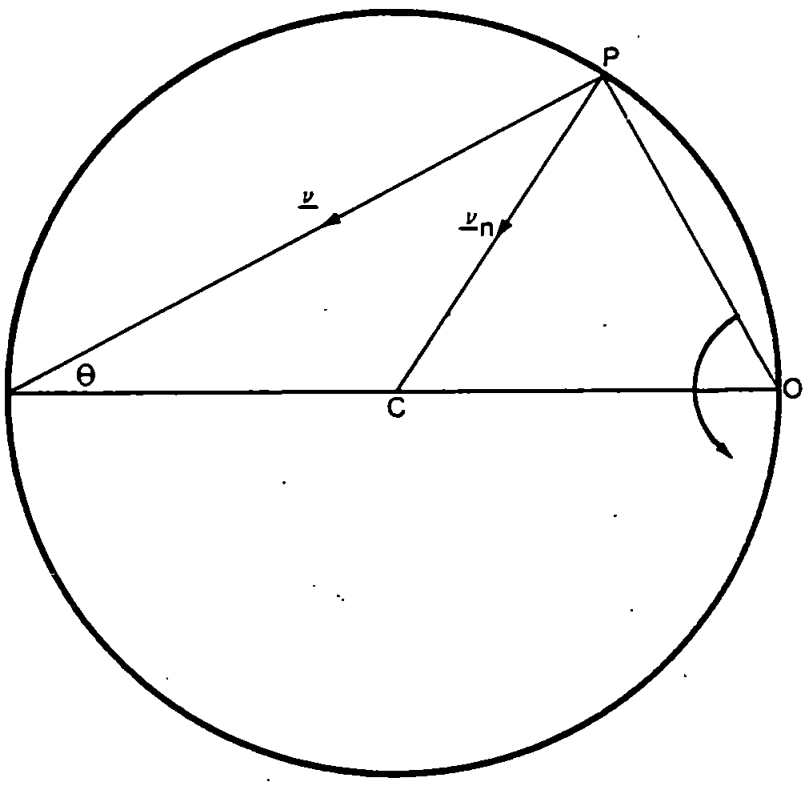

Figure 1.2.1. A diagrammatic rationalisation of the Lorentz correction.

various expressions being found in Vol. II of International Tables.

Polarisation Factor

The need for $p_{hk\ell}$, the polarisation correction, can be understood by considering the randomly polarised incident X-ray beam I_i, which notionally consists of two equal plane polarised mutually perpendicular beams. The beam in the plane presents no problems; however, the beam whose plane of polarisation is perpendicular to the reflecting plane will be reduced in intensity. The scattered beam can be thought of as being produced by electrons moving up and down the electric vector of the incident beam. The component of the electron motion in the direction of the electric vector of the reflected beam I_s is proportional to cos 2θ. Hence:

$$I_i = A_x^2 + A_y^2$$

$$A_x = A_y = (I_i/2)^{\frac{1}{2}}$$

$$I_s = K\, I_i (\tfrac{1}{2} + \tfrac{1}{2} \cos^2 2\theta)$$

$$I_s \propto (1 + \cos^2\theta)/2 = p_{hk\ell}$$

If the beam has been monochromated by reflexion from a crystal plane, the $p_{hk\ell}$ has to be modified to allow for the partial polarisation of the incident beam.

Primary Extinction $(e_{hk\ell})$[38,39]

This arises from the scattered beam being π/2 out of phase with the incident beam and scattering from a parallel plane, resulting in interference effects.

It is difficult to allow for, if only because the calculation of tanh $(nq)/nq(e_{hk\ell})$, requires the determination of 'n', the average number of perfectly parallel planes within the crystallites, which is

difficult. However, as $\lim_{x \to 0} \tanh(x)/x = 1$

if 'n' can be made small, by for example breaking up the crystallites with a sudden temperature drop, then $e_{hk\ell}$ will approach unity; generally, however, the correction is small and ignored.

Secondary Extinction

This results from the diminution in energy of an incident beam due to scattering; it means that the incident beam is less intense on internal planes than on superficial planes; it behaves rather like absorption and the correction is of a similar form

$$I_o = I_c e^{-2gI_c} \qquad I_c = \text{corrected intensity}$$

The 'g' can be found by expanding the expression and neglecting higher terms

$$I_c/I_o = 1 + 2gI_c.$$

A plot of I_c/I_o v I_c will give g, assumed to be a constant for a particular crystal, as the gradient.

In practice, because of temperature factor and atomic scattering factor dependence upon $\sin\theta/\lambda$, secondary extinction only effects significantly $\sin\theta/\lambda < 0.2$ reflexions, which can be detected by looking for $I_c > I_o$ by an amount greater than the residual index, R.

Absorption

The intensity, I_T of a beam passing through a thickness 'x' is given by

$$I_T = I_i e^{-\mu_\lambda x}$$

μ_λ = the linear absorption coefficient.

Knowing the size and shape of a crystal, preferably spherical or cylindrical, and with μ_λ being a computable quantity, the attenuation

can be calculated for a given reflexion.

To obviate the need for correction, at least for organic structures, highly penetrating radiations such as Mo, may be used, especially in diffractometry. Where intensities are recorded on film this is less true because of inefficiency.

Point Atom Structures

It has been shown previously that $F_{hk\ell}$ decreases with $\sin\theta/\lambda$; this introduces serious restrictions when inequalities and probabilities are used, where the magnitudes of the reflexions are of paramount importance.

In an attempt to circumvent this limitation $F_{hk\ell}$ is transformed into the form it would have had if the structure consisted of point, stationary atoms.

$$F_{hk\ell} = \Sigma g_j e^{2\pi i(hx_j+ky_j+\ell z_j)}$$

$$g_i = T_{hk\ell} f_j$$

For one atomic type $F = gE$

E being the sum of the exponential terms.

With point atoms $g = Z$, Z being the atomic number.

$$F_{point}/F_{real} = Z\ E/E\ f\ T_{hk\ell}$$

$$F_{point} = Z/f\ T_{hk\ell} F_{real}$$

As however, generally, crystals contain more than one type of atom, some average value of Z/g, such as $\Sigma Z_j/\Sigma g_j$ must be used.

Noting that $\Sigma Z_j = F_{ooo}$, an early point atom function was the unitary structure factor

$$U_{hk\ell} = (F_{hk\ell})_{point}/F_{ooo} = (F_{hk\ell})_{real}/\Sigma g_j.$$

However, for an accurate comparison of intensities allowance must be made for the enhancement in intensity for certain classes of re-

flexion[7].

For this, and other reasons 'E', a normalised structure factor was introduced[8].

$$E^2_{hk\ell} = U^2_{hk\ell}/\overline{U^2}$$

$\overline{U}^2$ is the average over all reflexions, excepting systematically absent reflexions, for a particular set of reflexions.

Equivalently

1.2.2 $$E_{hk\ell}{}^2 = |F_{hk\ell}|^2/\varepsilon\Sigma g_j{}^2$$

with ε compensating for the enhancement mentioned earlier.

Note that the denominator in 1.2.2 is the local average intensity:

$$|F_{hk\ell}|^2 = F_{hk\ell}F^*_{hk\ell}$$
$$= \Sigma g^2{}_j + 2\ \Sigma\ \Sigma\ g_k g_j \cos(\underline{h}\cdot(\underline{r}_j - \underline{r}_k))$$

If reflexions within a shell centred on the origin, so $\sin\theta/\lambda$ is constant, are averaged, then the second term on the right hand side vanishes as it is as likely to be plus as minus.

The temperature factors are initially either specified from experience or estimated from a Wilson plot[9].

Wilson Plot[10,11]

As shown above, at constant $\sin\theta/\lambda$

$$|F_{hk\ell}|^2 = \Sigma g^2{}_i$$

If equal isotropic temperature factors are assumed this equals

$$e^{-2B(\sin\theta/\lambda)}\Sigma f^2{}_i$$

As measured intensities are naturally on a relative scale

$$I_{rel} = K\ I_{abs} = K\ e^{-2B(\sin\theta/\lambda)^2}\Sigma f^2{}_i$$
$$I_{rel}/\Sigma f^2{}_i = K\ e^{-2B(\sin\theta/\lambda)^2}$$
$$\ln(I_{rel}/\Sigma f_i{}^2) = \ln K - 2B(\sin\theta/\lambda)^2$$

Plotting $\ln(I_{rel}/\Sigma f_i{}^2)$ against $(\sin\theta/\lambda)^2$ gives $-2B$ as the slope and $\ln K$ when $(\sin\theta/\lambda)^2 = 0$.

1.3 Direct Methods

This is the generic term given to methods which use intensities directly to solve the structure.

The growth in the importance of direct methods can be dated from 1948[12], when classical inequalities were used to derive relationships between reflexions, although earlier work had been done[13].

For example, with centrosymmetric structures, the unitary structure factor $U_{hk\ell}$ takes the form:

$$2\Sigma n_j \cos 2\pi(hx_j + ky_j + \ell z_j)\ n_j = g_j/\Sigma g_j$$

Adopting the notation $U_h = U_{hk\ell} = 2\Sigma n_j \cos(h)$

$$U_k = U_{h'k'\ell'} = 2\Sigma n_j \cos(k)$$

$$U_h + U_k = 2\ \Sigma n_j(\cos(h) + \cos(k)) = 4\ \Sigma n_j \cos((h + k)/2)\cos((h - k)/2)$$

Using the Cauchy inequality $(\Sigma a_i b_i)^2 < (\Sigma a_i^2)(\Sigma b_i^2)$

$$(U_h + U_k)^2 < 16\ \Sigma n_j \cos^2((h + k)/2)\ \Sigma n_j \cos^2((h - k)/2)$$

$$< 16\ \Sigma n_j\ ½\ (1 + \cos(h + k))\ \Sigma n_j\ ½\ (1 + \cos(h - k))$$

$$< (1 + U_{h+k})\ (1 + U_{h-k})$$

Similarly

$$(U_h - U_k)^2 < (1 - U_{h+k})\ (1 - U_{h-k})$$

These relationships have recently found use in symmorphic space groups[14,15,16] based on the fact that if

$$|U_h|,\ |U_{h-k}|,\ |U_{h+k}| \text{ are large, } |U_k| = 0$$

and

$$|U_h|^2 > (1 - |U_{h+k}|)\ (1 - |U_{h-k}|)$$

then

$$S(h + k)S(h - k) = -1.$$

More general inequalities, based on $\rho(x,y,z)$ being non-negative

(which the Harker-Kasper inequalities implicitly assumed) are the Karle-Hauptmann Determinants[17].

$$1.3.1 \quad \begin{vmatrix} E_{ooo} & E_{-h_1} & E_{-h_2} & \ldots E_{-h_n} \\ E_{h_1} & E_{ooo} & E_{h_1-h_2} & \ldots E_{h_1-h_n} \\ E_{h_2} & E_{h_2-h_1} & E_{ooo} & \ldots E_{h_2-h_n} \\ \cdot & \cdot & \cdot & \cdot \\ E_{h_n} & E_{h_n-h_1} & E_{h_n-h_2} & \ldots E_{ooo} \end{vmatrix} > 0$$

However, the use of inequalities has been restricted mainly to relatively small molecules[18].

In more recent years, probability methods have predominated, with the normalised structure factor, E, being used almost universally. If equal temperature factors and profiles for f_j are assumed then

$$f_j/\sigma_2^{\frac{1}{2}} = \phi_j = Z_j/(\Sigma Z_j^2)^{\frac{1}{2}} = N^{-\frac{1}{2}} \text{ for an equal atom structure}$$

$$E_{hk\ell} = \Sigma\phi_j \, e^{2\pi i(hx_j+ky_j+\ell z_j)}$$

Consider the product $E(h')E(h-h')$ for an equal atom structure

$$E(h')E(h-h') = N^{-1} \Sigma e^{2\pi i \underline{h}.\underline{r}_j} + N^{-1} \Sigma \Sigma e^{2\pi i(\underline{h}'.\underline{r}_j+(h-h').\underline{r}_k)}$$

Averaging over h', the double summation, assuming random atomic positions, is zero.

$$1.3.2 \quad E(h) = N^{\frac{1}{2}} \langle E(h')E(h-h') \rangle_{h'}$$

It can be shown that for an unequal atom structure 1.3.2 takes the form

$$1.3.3 \quad E(h) = \sigma_3^{-1}\sigma_2^{3/2} \langle E(h')E(h-h') \rangle_{h'}$$

Superficially 1.3.3 appears useless since it is necessary to know the magnitude and phase of all 'E's to determine one. It was pointed out[19] however, that where $E_{hk\ell}$ is large, the series must lean strongly

in one direction and this direction will tend to be dominated by products between large E's.

For centrosymmetric structures 1.3.3 is adequate, but for non-centrosymmetric structures, where the values of the phases must be determined, rather than the sign, 1.3.3 must be modified:

1.3.4 $E_h = |E_h| \cos\phi_h + i|E_h| \sin\phi_h$

Equating real and imaginary components

$$|E_h| \cos\phi_h = \sigma_3^{-1}\sigma_2^{3/2} \langle |E_{h'}||E_{h-h'}| \cos(\phi_{h'} + \phi_{h-h'}) \rangle_{h'} = C$$

$$|E_h| \sin\phi_h = \sigma_3^{-1}\sigma_2^{3/2} \langle |E_{h'}||E_{h-h'}| \sin(\phi_{h'} + \phi_{h-h'}) \rangle_{h'} = S$$

1.3.5 $\text{Tan}\ \phi_h = S/C$

The tangent formula, 1.3.5 is only an equality of the summation ranges over all h'; if there is only one term 1.3.5 reduces to

1.3.6 $\phi_h \simeq \phi_{h'} + \phi_{h-h'}$

1.3.5 may be improved by the use of weights[20].

$$B_h = \langle W_h, W_{h-h'} |E_{h'}||E_{h-h'}| \cos(\phi_{h'} + \phi_{h-h'}) \rangle_{h'}$$

$$T_h = \langle W_h, W_{h-h'} |E_{h'}||E_{h-h'}| \sin(\phi_{h'} + \phi_{h-h'}) \rangle_{h'}$$

1.3.7 $\text{Tan}\ \phi_h = T_h/B_h$

$$W_h = 0.2\ \alpha_h \qquad 5 > \alpha_h$$

$$= 1 \qquad \alpha_h > 5$$

but these weights have been criticised[21].

1.3.7 is up to four times faster than 1.3.5, the weights being based on a commonly used measure of variance of the indicated phase, α_h[22].

1.3.8 $\alpha_h = 2\sigma_3\sigma_2^{-3/2}|E_h|(T_h^2 + B_h^2)^{\frac{1}{2}}$

If there is only one contributor, 1.3.8 becomes

1.3.9 $\alpha_h = \kappa_{hh'} = 2\sigma_3\sigma_2^{-3/2}|E_h E_{h'} E_{h-h'}|$

Table 1.3.1

Statistical Properties of E

	Centric	Acentric[23]
$P(\|E\|)$	$(2\pi)^{-\frac{1}{2}} e^{-\|E\|^2/2}$	$\|E\| e^{-\|E\|^2}$
$<\|E\|>$	$(2/\pi)^{\frac{1}{2}} = .798$	$\pi^{\frac{1}{2}}/2 = .886$
$<E>$	0	0
$<\|E\|^2>$	1	1
$<\|E\|^2-1>$	0	0
$<(\|E\|^2-1)>$	$4/(2\pi e)^{\frac{1}{2}} = .968$	$2/e = .735$
$<(\|E\|^2-1)^2>$	2	1
$<(\|E\|^2-1)^3>$	8	2
$\%\|E\|>1$	31.7	36.8
$\%\|E\|>2$	4.6	1.8
$\%\|E\|>3$	.3	.1

The question as to whether a crystal is centrosymmetric or not can often be resolved by the statistical properties shown in Table 1.3.1 (though non-crystallographic symmetry can cause confusion[24,25,26]). Other information, such as the presence of unusually high Patterson overlap can also be gleaned (e.g. from $\langle(|E_h^2|-1)^2\rangle$ or $\langle(|E_h^2|-1)^3\rangle$)[27].

The Starting Set of Phases

Formulae such as 1.3.6 are of little use however, unless some phases are known; happily some phases, generally three, may be allocated specific values, to fix the origin, and, if appropriate for the space group, an addition phase to fix the enantiomorph. Before continuing a few definitions may be helpful:

A structure invariant is a reflexion, or group of reflexions, whose phase, or sum of whose phases, is determined solely by the crystal structure, i.e. is independent of origin.

Equivalent points are points which are (geometrically) related to all symmetry elements in the same way.

A permissable origin is one related in such a way to the symmetry elements, that full advantage is taken of space group symmetry.

A seminvariant is a reflexion, or group of reflexions, whose phase, or the sum of whose phases, is independent of the choice of origin within the equivalence class (the equivalence class being implicitly selected by the functional form of the structure factor); obviously structure invariants are structure seminvariants.

The intensity invariants are a subset of the structure invariants whose phases, as a consequence of space group symmetry, are either 0 or π.

In International Tables, the forms of the structure invariants and seminvariants are indicated by ω_I and ω_s, the invariant, and seminvariant, moduli respectively, with a reflexion 'h' being an invariant or seminvariant according as 'h' is divisible by ω:

$$\omega_j = 0 \quad \text{implies } h_j = 0$$

$$\omega_j \neq 0 \quad \text{implies } h_j/\omega_j \text{ is integer}$$

To clarify matters consider P2:

$$(202) = \omega_I = \omega_s \text{ (as there is only one equivalence class)}$$

$$A = 2\cos 2\pi(hx + \ell z)\cos 2\pi(ky)$$

$$B = 2\cos 2\pi(hx + \ell z)\sin 2\pi(ky)$$

Moving from (0,y,0) as origin, to for example $(\frac{1}{2},y,\frac{1}{2})$ requires, if A and B are to be unchanged that h,ℓ = g(erade) and k = 0.

Origin Specification[28]

To select the origin of a unit cell, the phases of, generally, three reflexions are specified

$$1.3.10 \quad \sum_{i=1}^{3} h_i X + k_i Y + \ell_i Z = K_i + n_i \quad (0 < K_i < 1)$$

1.3.10, the planes of equal phase for the three reflexions, solve to give:

$$1.3.11 \quad X = \Delta^{-1} \begin{vmatrix} k_1 & \ell_1 & K_1 + n_1 \\ k_2 & \ell_2 & K_2 + n_2 \\ k_3 & \ell_3 & K_3 + n_3 \end{vmatrix}$$

$$= \Delta^{-1} \left(\begin{vmatrix} k_1 & \ell_1 & K_1 \\ k_2 & \ell_2 & K_2 \\ k_3 & \ell_3 & K_3 \end{vmatrix} + \begin{vmatrix} k_1 & \ell_1 & n_1 \\ k_2 & \ell_2 & n_2 \\ k_3 & \ell_3 & n_3 \end{vmatrix} \right)$$

$$\Delta = \begin{vmatrix} h_1 & k_1 & \ell_1 \\ h_2 & k_2 & \ell_2 \\ h_3 & k_3 & \ell_3 \end{vmatrix}$$

Y and Z are of a similar form.

Since the same origin is required for each unit cell, $\Delta = \overline{+}\ 1$ (symmetry allow less restrictive conditions). An equivalent result can be obtained by considering the effect of a shift of origin. The phase ψ' of E, with respect to the new origin, related to the old by $\underline{r}_o$ is given by:

$$E = \Sigma\phi_i e^{2\pi i \underline{h}.\underline{r}_i}$$

$$E' = \Sigma\phi_i e^{2\pi i \underline{h}.(\underline{r}_i - \underline{r}_o)}$$

1.3.12 $$\psi' + 2\pi m = \psi - 2\pi \underline{h}.\underline{r}_o$$

If $\underline{h} = \Sigma a_i \underline{h}_i$ where a_i are rational and $\underline{h}_i$ are independent vectors then 1.3.12 gives:

1.3.13 $$2\pi m + \psi' = \psi - 2\pi(\Sigma(a_i \underline{h}_i . \underline{r}_o)).$$

$$= \psi + \Sigma a_i(\psi_i' - \psi_i + 2\pi m_i)$$

It is clear that unless a_i are integer, i.e. as

1.3.14 $$\Delta^{-1} = a_1/\begin{vmatrix} h_2 & h_3 & h \\ k_2 & k_3 & k \\ \ell_2 & \ell_3 & \ell \end{vmatrix} = -a_2/\begin{vmatrix} h_1 & h_3 & h \\ k_1 & k_3 & k \\ \ell_1 & \ell_3 & \ell \end{vmatrix} = a_3/\begin{vmatrix} h_1 & h_2 & h \\ k_1 & k_2 & k \\ \ell_1 & \ell_2 & \ell \end{vmatrix}$$

that the base reflexions form a primitive set ($\Delta = \overline{+}\ 1$), ψ has values differing by $2\pi/D$ ($\Delta = GD$, G is the greatest common divisor (g.c.d.) of the determinants).

To define the ambiguous origin more closely ψ may be given one of its D values and adjoined to the basic set; the g.c.d., G, of the non-

zero 3 x 3 subdeterminants of the matrix

$$\begin{vmatrix} h_1 & k_1 & \ell_1 \\ h_2 & k_2 & \ell_2 \\ h_3 & k_3 & \ell_3 \\ h_4 & k_4 & \ell_4 \end{vmatrix}$$

not all of whose 3 x 3 subdeterminants vanish, will give the number of permitted origins. If G > 1 the process is continued until one finally attains a primitive set (a matrix the g.c.d. of whose 3 x 3 subdeterminants is unity).

$$\begin{vmatrix} h_1 & k_1 & \ell_1 \\ h_2 & k_2 & \ell_2 \\ h_3 & k_3 & \ell_3 \\ \cdot & \cdot & \cdot \\ h_n & k_n & \ell_n \end{vmatrix}$$

As an example consider P2 again. A convenient origin specifying set is h_g 0 ℓ_u, h_u 0 ℓ_g, h_g k ℓ_g ($k \neq 0$). The first two reflexions have two possible values (o or π) either of which may be chosen; the third reflexion may be assigned an arbitrary phase. It can readily be shown that for the triple to be primitive $k_3 = \overline{+}\,1$ and $h_1\ell_2 - h_2\ell_1 = \overline{+}1$.

While an origin specifying set, as above, can often be put in a simple general form by making indices zero, this has the disadvantage of reducing the number of distinct symmetry related reflexions. For example, the number of known phases is reduced in the P2 case from twelve, with general reflexions, to eight.

Specification of Enantiomorph.

The question only arises, of course, in non-centrosymmetric space groups. If one enantiomorph has co-ordinates (x_j, y_j, z_j) $j = 1,N$, then the other enantiomorph has co-ordinates $(\bar{x}_j, \bar{y}_j, \bar{z}_j)$,

$j = 1,N$ (except for Fdd2).

As $\sin 2\pi(hx + ky + \ell z)$ is an odd function, the enantiomorph is specified by restricting a structure (sem)invariant to one side of the real axis, in the complex plane.

However, in some space groups single phase (sem)invariants are also intensity invariants (phases are 0 or π) and therefore unsuitable for enantiomorph specification. Multi-phase invariants can be derived by considering a linear combination of phases with coefficients A_h. If the origin is moved by $\underline{r}_o$ then:

$$\phi_{new} = \phi_{old} - 2\pi(\underline{h}.\underline{r}_o)$$

$$\Sigma A_h \phi_{h(new)} = \Sigma A_h \phi_{h(old)} - 2\pi(\Sigma A_h \underline{h}).\underline{r}_o$$

1.3.15 $\quad \Sigma A_h \underline{h} = 0$

and the value is independent of origin, i.e., is a structure invariant. As an example consider C2.

The equivalent positions referred to a primitive cell[29,30] are

$$\begin{vmatrix} X \\ Y \\ Z \end{vmatrix} = \begin{vmatrix} 1 & 1 & 0 \\ 1 & \bar{1} & 0 \\ 0 & 0 & \bar{1} \end{vmatrix} \begin{vmatrix} x \\ y \\ z \end{vmatrix}$$

Primitive Centred

$(x,y,z) \quad (x + y,\ x - y,\ \bar{z}) \quad (X,Y,Z)$

$(\bar{x},y,\bar{z}) \quad (\bar{x} + y,\ \bar{x} - y,\ z) \quad (\bar{Y},\bar{X},\bar{Z})$

The seminvariant modulus $\omega_s = (2\ 0\ 2)$. In the primitive cell, as

$$h' = h + k$$

$$k' = h - k$$

$$\ell' = \bar{\ell}$$

the seminvariant vector is $(h - k, \ell)$ and ω_s is $(0,2)$.

A convenient origin defining set (O.D.S.) is

$h_1 k_1 \ell_1$ $\quad h_1 = k_1$ $\quad \ell_1 = 2n + 1$ $\quad 0$ or π

$h_2 k_2 \ell_2$ $\quad h_2 \neq k_2$ $\quad \ell_2 = 2n$ $\quad$ arbitrary phase

The set will be primitive if $h_2 - k_2 = \bar{+} 1$. However, the seminvariants $\phi_{2h02\ell}$ (with respect to the centred cell) can only be, by space group symmetry, 0 or π. Applying 1.3.15 and writing $h_1 k\ \ell_1$ and $h_2 \bar{k}\ \ell_2$ as h_1 and h_2 respectively, then if

$$h_1 + h_2 = 0 \mod(\omega_s)$$

implying, in this case, h_1, h_2, and ℓ_2, ℓ_2, have the same parity, then the linear combination

$$\phi_{h_1} + \phi_{h_2} + \phi_{2h02\ell} \quad (2h = h_1 + h_2,\ 2\ell = \ell_1 + \ell_2)$$

is a structure seminvariant (generalising, $\Sigma A_h h = 0 \mod(\omega_s)$ implies $\Sigma A_h \phi_h$ is a structure seminvariant) which suggests, as $\phi_{2h02\ell}$ is a structure seminvariant, that $\phi_{h_1} + \phi_{h_2}$ is as well. The enantiomorph for C2 can be specified by a $0 < \phi_{h_1} + \phi_{h_2} < \pi$ restriction.

A systematic method has been developed of isolating a large set of reflexions which specify enantiomorph strongly, using cosine invariants; it relies upon formulae for calculating approximately, from intensity data alone $\cos(\phi_h + \phi_k + \phi_\ell)$ $(h + k + \ell = 0)$, these formulae being particularly useful when the cosine, due to space group symmetry must be $\bar{+} 1$.

Even when the cosines must be $\bar{+} 1$, the value may be ambiguous, so checks on internal consistency are desirable.

Consider:

$$\phi_1 = \phi_{h_1} + \phi_{h_2} + \phi_{h_3}$$

$$\phi_2 = \phi_{-h_1} + \phi_{-k} + \phi_{h_1+k}$$

$$\phi_3 = \phi_{-h_3} + \phi_{k} + \phi_{h_3-k}$$

$$\phi_4 = \phi_{-h_1-k} + \phi_{-h_2} + \phi_{-h_3+k}$$

With $\Sigma h_i = 0$, $\Sigma \phi_i = 0$ is a structure invariant, so if, for example $\cos\phi_i = 1$ $i = 1,3$, then $\cos\phi_4$ must also be 1.

By using these quadrupoles, by requiring consistency between the formulae, and, especially where from space group symmetry the cosine must be $\bar{+}$ 1, using only a percentage (the most strongly indicated) of the expected number of a sign, error may be minimised.

To illustrate how these cosine invariants are used consider $P2_1$[31]:

By space group symmetry

$$\cos\phi_{\bar{h}\bar{k}\bar{\ell}} = (-1)^k \cos\phi_{h\bar{k}\ell}$$

Reflexions $hk\ell$, with k fixed, if $|E|_{02k0}$ is not too large, will take values distributed over 0 to 2π.

With the origin chosen so 0 2k 0 = 0

$k = 2n$ $\cos(\phi_{h\bar{k}\ell} + \phi_{\bar{h}\bar{k}\bar{\ell}} + \phi_{02k0}) = \cos 2\phi_{h\bar{k}\ell} \simeq \pm 1$

according as $\phi_{h\bar{k}\ell} \simeq 0, \pi$ or $\pm \pi/2$ respectively

$k = 2n + 1 = -\cos 2\phi_{h\bar{k}\ell} \simeq \bar{+} 1$ according as

$\phi_{h\bar{k}\ell} \simeq 0, \pi$ or $\pm \pi/2$ respectively.

The basic idea is to find an integer k and two clases of reflexions such that

1) $|E|_{02k0}$ is moderately large

2) Any two phases in class 1 differ by 0 or π

3) Any two phases in class 11 differ by 0 or π

4) Any phase in class 1 differs from any in class 11 by approximately $\pi/2$

5) Every $|E|$ in class 1 and 11 be large

Assuming 1) and 5) are satisfied, the classes are created by placing in class 1 cosine invariants having high values (presumably

+1) and in class 11 those having small values (presumably -1) to produce:

Class 1

$$\phi_{h\bar{k}\ell} = \tfrac{1}{2}\phi_{02k0} \quad \text{or} \quad \tfrac{1}{2}\phi_{02k0} + \pi \qquad k = 2n$$

$$= \tfrac{1}{2}\phi_{02k0} \pm \pi/2 \qquad k = 2n + 1$$

Class 11

$$\phi_{h\bar{k}\ell} = \tfrac{1}{2}\phi_{02k0} \pm \pi/2 \qquad k = 2n$$

$$= \tfrac{1}{2}\phi_{02k0} \quad \text{or} \quad \tfrac{1}{2}\phi_{02k0} + \pi \qquad k = 2n + 1$$

To ensure 2) and 3) pertain, only phases $\phi_{hk\ell}$, $\phi_{h'k\ell'}$ which interact strongly are retained, i.e. have large

$$A = 2/N^{\frac{1}{2}} |E_{hk\ell} E_{h'k\ell'} E_{h\pm h'o\ell\pm\ell'}|$$

and large (calculated) values ($\simeq +1$) for at least one of the following cosines

$$\cos(\phi_{\bar{h}k\bar{\ell}} + \phi_{\bar{h}'\bar{k}\bar{\ell}'} + \phi_{h+h'o\ell+\ell'})$$

$$\cos(\phi_{\bar{h}k\bar{\ell}} + \phi_{h'\bar{k}\ell'} + \phi_{h-h'o\ell-\ell'})$$

In a similar manner 4) is verified by retaining those phases which interact weakly with the other class and have small calculated cosines ($\simeq 0$).

A second method uses a generalisation of the tangent formula. It can be shown (Appendix A) that

$$\langle \sin(\phi_{\bar{h}} + \phi_{h-k} + \phi_k) | A \rangle_k = 0$$

$$= \langle | E_k \, E_{h-k} \sin(\phi_{\bar{h}} + \phi_{h-k} + \phi_k) | A \rangle_k = 0$$

(as E_h is a constant so is $|E_k E_{h-k}|$ for fixed A).

If $\underline{k}$ ranges over an arbitrary set of reciprocal space then it can be considered as composed of subsets within which A is constant. Therefore,

1.3.16 $\langle |E_k E_{h-k}| \sin(\phi_{\bar{h}} + \phi_{h-k} + \phi_k) \rangle_k = 0$

With

$$C = \langle |E_k E_{h-k}| \cos(\phi_k + \phi_{h-k}) \rangle_k$$

$$S = \langle |E_k E_{h-k}| \sin(\phi_k + \phi_{h-k}) \rangle_k$$

1.3.16 can be put in the form

$$C \sin\phi_h - S \cos\phi_h = 0$$

$$\mathrm{Tan}\phi_h = S/C$$

While ϕ_h will satisfy 1.3.16 it will not necessarily satisfy

1.3.17 $\langle \cos(\phi_{\bar{h}} + \phi_{h-k} + \phi_k) | A \rangle = I_1(A)/I_o(A)$

To incorporate both 1.3.16 and 1.3.17 a function Φ is defined thus:

$$\Phi = \langle w_s \sin^2(\phi_h + \phi_{h-k} + \phi_k) + w_c[\cos(\phi_{\bar{h}} + \phi_{h-k} + \phi_k) - I_1(A)/I_o(A)]^2 \rangle_k$$

W_s and w_c are the reciprocals of the variances of $\sin(\phi_{h-k} + \phi_{\bar{h}} + \phi_k)$ and $\cos(\phi_{\bar{h}} + \phi_k + \phi_{h-k})$ respectively, and $I_1(A)$ and $I_o(A)$ are modified Bessel functions.

If Φ is plotted over the interval 0 to 2π, then for enantiomorph sensitive reflexions (assuming more than one term in the summation) two equal minima will be found, preferably well defined, at approximately $\pm \pi/2$.

Starting Set Selection

The starting set, which contains reflexions that specify origin, and, if appropriate, enantiomorph, as well as reflexions that take a selection of values (or a symbolic value), has many possible members.

To ensure a good phase development, members of the starting set clearly should have large $|E|$ values and a high degree of interaction with other strong reflexions, requirements met by reflexions with a high α_h.

As there is no phase information initially, an approximation for α_h must be used:

$$\langle\alpha_h^2\rangle^{32} = \Sigma\kappa^2_{hh'} + \Sigma\Sigma\kappa_{hh'}\kappa_{hh''}(I_1(\kappa_{hh'})/I_0(\kappa_{hh'}) \times (I_1(\kappa_{hh''})/I_0(\kappa_{hh''}))$$

$$I_1(\kappa)/I_0(\kappa) \simeq 0.5658\kappa - 0.1304\kappa^2 + 0.0106\kappa^3$$

(with a maximum error of 4% for $5 > \kappa$).

If one calculates $\langle\alpha_h^2\rangle$ for all reflexions, removes from the data set the reflexion with the lowest value, modifies $\langle\alpha^2_h\rangle$ to allow for the removal, repeats the process, all the time listing eliminated reflexions and $\langle\alpha_h^2\rangle$ values, until the process terminates, then the result is a list that 'converges' onto the reflexions that interact most strongly with the data set; a consequence of the listing is that $\langle\alpha_h^2\rangle$ is calculated only from reflexions lower down the list; a low value for $\langle\alpha_h^2\rangle$ means that the phase is not well indicated by the reflexions below; in the extreme case of $\langle\alpha_h^2\rangle = 0$ there is a break in the phase expansion necessitating the reflexion being given a selection of values ($\pm \pi/4$, $\pm 3\pi/4$).

However, a large number of multisolution reflexions is clearly very expensive in computing time; hence the development of the method of magic integers[33].

This is based on a set {n} of carefully chosen integers and the proposition that a value x($o<x<1$) exists that satisfies approximately for n phases ϕ_i the following equations:

$$\phi_i = n_i\, x \bmod (1) \qquad i = 1,n$$

where ϕ_i are phases expressed in cycles.

For example:

ϕ_1 = 2 x mod (1) ϕ_5 = 2 y mod (1)

ϕ_2 = 3 x mod (1) ϕ_6 = 3 y mod (1)

ϕ_3 = 7 x mod (1) ϕ_7 = 7 y mod (1)

ϕ_4 = 13 x mod (1) ϕ_8 = 13 y mod (1)

If there are Σ_2 relationships between these phases (and known phases) then a convenient notation is

$$\text{Cos } 2\pi(Hx + Ky + a) \overset{\uparrow}{\overset{}{\uparrow}} 1$$

(will tend to be close to, but less than, one).

Finding the maximum (s) of the function

$$\psi(x,y) = \Sigma w_i \cos(H_i x + K_i y + a_i)$$

w_i = weight of Σ_2 interaction, $|E_h E_{h-k} E_k|$

by evaluation of ψ along x and y gives the required phases, which can then be refined independently[34], the magic integer link being broken, using as a criterion the maximisation of ψ.

Using the sequence 4 6 7 a r.m.s. (root mean square) error of 26.6° for the phases is obtained compared with a r.m.s. error for random phases of $\pi/\sqrt{3}$ (103.9°).

Figures of Merit (F.O.M.'s)

Since starting sets usually contain multisolution reflexions, various figures of merit have been developed to isolate the correct phase expansion.

One of the earliest was the ψ_o test[35]. It is based on the Sayre equation and uses reflexions of high magnitude $|E_{h-k}|$, $|E_k|$ in calculating reflexions of low magnitude E_h.

$$\psi_o = \Sigma |\Sigma E_k E_{h-k}|$$

Another F.O.M. based on the Sayre equation is R_K.[22] For reflexions with known phase the calculated structure factor is

$$E_{h\ calc} = c\Sigma E_{h-k} E_k \qquad E_k = |E_k| e^{i\phi_k} \text{ etc.}$$

As the summation is only over known phases, $c \neq \sigma_3^{-1}\sigma_2^{3/2}$, but instead is obtained by requiring

$$\Sigma(|E_h|_{calc})^2 = \Sigma(|E_h|_{obs})^2$$

$$R_K = \Sigma||E_h|_{obs} - |E_h|_{calc}|/\Sigma|E_h|_{obs}$$

F.O.M.'s based on the self consistancy of the phase set, such as Z ($= \Sigma\alpha_\eta^2$),[36] have some use, but should be avoided with certain types of space groups, especially symmorphic space groups, where the most favourable F.O.M.'s will correspond to trivial solutions, such as all $\phi_h = 0$.

An interesting attempt at an absolute figure of merit is represented by NQEST[40]. It is based on the four phase invariants, the negative quartets.

If, $h + k + \ell + m = 0$, $|E_h|, |E_k|, |E_\ell|, |E_m|$ and $B(2|E_hE_kE_\ell E_m|/N)$ are large (e.g. > 1.7 and > 1.0 respectively), and $|E_{h+k}|, |E_{h+\ell}|, |E_{\ell+k}|$ are small (e.g. < 0.7) then

$$\cos(\phi_h + \phi_k + \phi_\ell + \phi_m) \simeq -1 \text{ and}$$

$$\text{NQEST} = \Sigma B \cos(\phi_h + \phi_k + \phi_\ell + \phi_m)/\Sigma B.$$

Phases are derived by tangent expansion from the S.S.P.'s[41]. An ideal value would, of course, be -1.

A similar F.O.M. is H.K.C.[14,16,42]. Other F.O.M.'s proposed include those based on a Σ_1 criterion[43] and a more general Sayre equation[44].

1.4 Least Squares

Consider an experiment in which we make m measurements g_i. Each measurement is subject to an unknown error e_i. These are assumed to be uncorrelated.

It is desired to obtain from these measurements the best estimates of the values of n parameters x_j, related to the observed quantities by m linear equations, with known coefficients d_{ij}, henceforth referred to as the observational equations:

$$g_1 = d_{11}\, x_1 + d_{12}\, x_2 + \ldots\ldots\ldots d_{1n}\, x_n + e_1$$

$$g_2 = d_{21}\, x_1 + d_{22}\, x_2 + \ldots\ldots\ldots d_{2n}\, x_n + e_2$$

$$\vdots$$

$$g_m = d_{m1}\, x_1 + d_{m2}\, x_2 + \ldots\ldots\ldots d_{mn}\, x_n + e_m$$

In matrix form

$$DX + E = G$$

D = Design matrix of coefficients d_{ij}

X = Matrix of parameters x_j

E = Matrix of random errors e_m

G = Matrix of measurements g_i

A necessary, but not sufficient condition for any progress to be made is that $m \geq n$.

To obtain the best (minimum variance) estimates for x_j the function $M = \Sigma w_i (g_i - \Sigma d_{ij}\, x_j)^2$ where w_i is the weight for an observation, is minimised.

In matrix notation

$$M = (G-DX)^T\, W\, (G-DX)$$

with w_{ii}, the elements of the m x m diagonal matrix W, giving a measure of the reliability of the observation g_i; ideally w_{ii} is in-

versely proportional to the variance σ_i^2 of the observation. Upon minimising M, i.e. the weighted squared differences between the observed values and the calculated values from DX, if the weights are correctly chosen, minimum variance estimates can be obtained. To minimise M, n partial derivatives $\partial M/\partial x_j$ are found.

$$\partial M/\partial x_j = 2\Sigma w_i d_{ij}(g_i - \Sigma_j d_{ij} x_j) = 0$$

$$j = 1,n$$

The normal equations are obtained by rearranging these n equations

1.4.1 $$\Sigma w_i d_{i1} g_i = x_1 \Sigma w_i d_{i1}^2 + x_2 \Sigma d_{i1} d_{i2} w_i + \ldots x_n \Sigma w_i d_{i1} d_{in}$$

$$\Sigma w_i d_{i2} g_i = x_1 \Sigma w_i d_{i2} d_{i1} + x_2 \Sigma d_{i2}^2 w_i + \ldots x_n \Sigma w_i d_{i2} d_{in}$$

$$\vdots$$

$$\Sigma w_i d_{in} g_i = x_1 \Sigma w_i d_{in} d_{i1} + x_2 \Sigma w_i d_{in} d_{i2} + \ldots x_n \Sigma w_i d_{in}^2$$

In matrix notation

$$M = (G-DX)^T W (G-DX)$$

$$= G^T WG - (DW)^T W G - G^T W DX + (DX)^T WDX$$

Differentiating

$$O = O - D^T WG - D^T WG + 2D^T WDX$$

Rearranging as before we get the normal equations in the form

$$D^T WDX = D^T W G = NX$$

In order that N have an inverse, the matrix D must be of rank n. As N is an nxn matrix, having as elements the coefficients on the right hand side of 1.4.1, it is clear that the matrix is symmetric, with diagonal terms being necessarily positive, and of high magnitude, relative to off-diagonal terms.

N^{-1} has the useful property of being proportional to C, the covariance matrix, whose diagonal terms are the variances of the

parameter estimates; the off-diagonal terms are generally much smaller and represent correlation between parameters.

$\rho_{jk} = C_{jk} / \sqrt{C_{jj}C_{kk}}$ with ρ_{jk} the correlation between the parameters x_j, x_k.

The way least squares are utilised in crystallography is to use a linear approximation. By Taylors theorem of the mean

$$f(x_1 + \Delta x_1, x_2 + \Delta x_2 \ldots x_n + \Delta x_n) = f(x_1, x_2 \ldots x_n) +$$

$$(\Delta x_1 \partial/\partial x_1 + \Delta x_2 \partial/\partial x_2 \ldots \Delta x_n \partial/\partial x_n)$$

$$\times f(x_1, x_2, \ldots x_n) \ldots + 1/n!(\Delta x_1 \partial/\partial x_1 + \Delta x_2 \partial/\partial x_2 \ldots \Delta x_n \partial/\partial x_n)^n$$

$$\times f(x_1, x_2, \ldots x_n) + R_n$$

Neglecting all except the first two terms

$$f(x_1 + \Delta x_1, x_2 + \Delta x_2, \ldots x_n + \Delta x_n) - f(x_1, x_2, \ldots x_n) \simeq$$

$$(\Delta x_1 \partial/\partial x_1 + \Delta x_2 \partial/\partial x_2 \ldots + \Delta x_n \partial/\partial x_n)\ f(x_1, x_2, \ldots x_n)$$

If $f(x_1 + \Delta x_1, x_2 + \Delta x_2, \ldots x_n + \Delta x_n) \equiv |F_o|$, the observed structure factor, and $f(x_1, x_2, \ldots x_n) \equiv |F_c|$, the calculated structure factor, then the observational equations, after weighting, take the form

$$W^{\frac{1}{2}}DX = W^{\frac{1}{2}}G$$

$$W_i^{\frac{1}{2}}G_i = \sqrt{w_i}\Delta_i$$

$$X_j = \Delta x_j$$

$$W_i^{\frac{1}{2}}D_{ij} = \sqrt{w_i}\partial|F_c|_i/\partial x_j$$

so that after minimising M, the normal equations are

$$NX = D^T WDX = D^T WG$$

$$(D^T WD)_{jk} = \Sigma w_i \partial|F_c|_i/\partial x_j \partial|F_c|_i/\partial x_k$$

$$(D^T WG)_j = \Sigma w_i \Delta_i \partial|F_c|_i/\partial x_j$$

W_i are estimated from counting statistics, with an additional component for instrumental instability.

Assuming the weights are of the form $\sigma^2/\sigma_i^2(F_i)$ and there is a random, normal distribution of errors $\Sigma w_i \Delta_i^2/(m-n) (= S^2)$ will have a $\chi^2_{(m-n)}/(m-n)$ distribution[46]. The expectation value of a $\chi^2_{(m-n)}$ distributed function is (m-n). Ideally then, with correct weighting, $\sigma^2 = 1$ and S^2, sometimes called the variance (estimated) of observations of unit weight, should also equal one. However, as for observations of small magnitude $\sigma^2(|F|)$ may be of the same order as $|F|$, clearly estimates for $\sigma^2(F)$ will tend to be unreliable, leading to S values that differ from unit. Analysis of S^2 in terms of $\sin\theta/\lambda$, h,k,ℓ or in any other systematic manner is a useful check for systematic error. S should have a nearly constant value[47].

The variance of the parameters is given by

$$\sigma^2(x_j) = S^2(N^{-1})_{jj}$$

while the covariance between parameters x_j, x_k can be estimated as

$$S^2(N^{-1})_{jk}$$

K, the scale factor, when refined presents a few problems when off-diagonal terms of $D^T W D$ are neglected to save storage, as it correlates with the temperature factor[45,48].

As mentioned earlier, for the inverse of N(n x n) to exist, it must be of rank n. Singular normal matrixes arise from treating as independent parameters that are not; for example in a symmorphic space group such as P2 the y coordinate of one atom must be fixed to specify the origin; if it is not then one y coordinate will be linearly dependent upon the others and hence cause singularity. Another instance arises where an atom has a four-fold axis so that

$$U_{11} = U_{22} \text{ and } U_{12} = U_{23} = U_{13} = 0.$$

These difficulties can be obviated by using parameters that are distinct from, though they may be made equal to, one or more atomic

parameters. In such a case

$$dw = dx_1 = dx_2 \ldots dx_n$$

$$d|F_c|/dw = \partial|F_c|/\partial x_1 + \partial|F_c|/\partial x_2 \ldots + \partial|F_c|/\partial x_n$$

For structures, such as proteins, where the number of reflexions, due to disorder, only exceeds the number of atomic parameters by a relatively small margin, conventional refinement is clearly inappropriate.

Although a priori calculation of the structure is conceivable[49,50], for larger structures the computing effort becomes prohibitive. To improve the atomic coordinates therefore, a slightly different technique must be used[51]. One approach tried was to assume 'ideal' bond lengths and angles (planar trans amide groups in proteins, for example) and then, by a least squares procedure, fit this idealised structure to the X-ray co-ordinates. Finally, an energy minimisation procedure was applied[51-55].

A more elegant method is to incorporate distance and angle restraints between atoms in the observational equations; as all the information about the structure is considered, refinement to a chemically reasonable steroechemistry is very rapid, even if only a relatively small number of reflexions are used[56,57].

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CHAPTER TWO

DEHYDRO-PEPTIDES: CHEMISTRY AND OCCURRENCE

2.1 Introduction

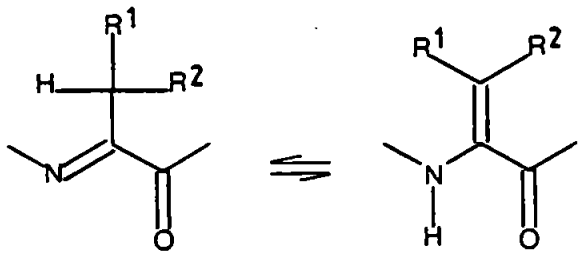
In recent years the number of biochemically active small molecules discovered has increased greatly.

An especially interesting group are the dehydro-peptides. The biological existence of dehydro-peptides, while having been suspected for many years, was strongly indicated by the discovery of a dehydro-peptidase[1] in 1932. Dehydro-peptidase activity was subsequently found in all plant and animal tissues studied[2,3].

These dehydro-peptidases were purified and separated into dehydro-peptidase I and II. It was subsequently shown that neither was specific for dehydro-peptides, but operated on saturated systems as well, being an amino acid acylase and amino peptidase respectively. Their dehydro-peptidase activity must be considered adventitious; a specific dehydro-peptidase has not been shown to exist (at least in higher organisms).

Over the years several dehydro-peptides were isolated[4-6] but it was not until dehydro-amino acid residues were identified in more familiar compounds, such as nisin that widespread interest began to be shown. Table 2.1.1 lists a selection of the dehydro-peptides and derivatives that have been found.

Whether dehydro-peptides have a significant role in mammalian biochemistry is unclear, though dehydro-alanine is believed to be at the active site of rat (liver) L-His ammonia lyase[7]. Also dehydro-amino acids have an ephemeral existence during the degradation of hydroxy and sulphur containing amino acids (by dehydrases and desulphydrases respectively), while other amino acids can go via the imino acid (under the influence of L-oxidases, though interestingly D-oxidases of greater activity are also present), which is tautomeric with the dehydro-amino acid:



Knowledge of the general structural characteristics of these compounds, relatively unexplored[8,9], to facilitate relation of biochemical activity to structure, is clearly desirable. To this end, the structures of a series of N-acyl (acetyl) dehydro-amino acids and peptides were studied and compared with peptides. N-acyl derivatives allowed study of the interaction of the amide system with the unsaturated carbon as well as providing an uncharged derivative (usually essential for stable N-terminal dehydro-amino acid peptides).

Table 2.1.1

Peptide	Dehydro-amino Acid
Nisin[10]	Alanine
Yeast phenylalanine ammonia lyase[11,12]	Alanine
Alternaria Mali Toxin[13]	Alanine
Stendomycin[14]	Butyrine
Berninamycin[15]	Butyrine
Oestreogrysin A[16]	Proline
Albonoursin[17]	Leucine, Phenylalanine } cyclic dipeptide
Telomycin[18]	Tryptophan
Tentoxin[19]	N-methyl Phenylalanine

2.2 Preparation

The first dehydro-peptides were prepared by Erlenmeyer[20] by the hydrolysis of unsaturated oxazolones, themselves prepared from aromatic aldehydes and glycine or acylated glycine (Figure 2.2.1, R=CH_3).

Though widely used, the method achieved its greatest flowering in the hands of Bergmann and co-workers. They extended dehydro-peptides at the carboxyl end by opening the oxazolone with an aqueous solution of a sodium salt of an amino acid or with an amino acid ester in a non-aqueous solvent[21-23] (Figure 2.2.1). Furthermore by generalising, using for example, as the acylated glycine derivative, N-acetyl Δ Phe-Gly-OH (Figure 2.2.1, R=G), an oxazolone can be formed, which can then yeild a peptide with two (or more) dehydro-phenylalanyl residues.

Peptides containing dehydro-aliphatic amino acid residues cannot be practically prepared by the original Erlenmeyer procedure, as the aliphatic aldehydes required contain acidic hydrogens. However, it is practicable if the reaction is split so acetic anhydride is absent when the aldehydes/ketones are added[24]. Also, by the use of a related reaction the use of aldehydes can be avoided altogether. Thus, if N-chloroacetyl-leucine is warmed with acetic anhydride (especially in the presence of pyridine), the unsaturated azlactone is formed, by elmination of hydrogen chloride and water (Figure 2.2.2(a)).

For biochemical studies it is often desirable that the substrate has both free amino and carboxyl groups; the first representative of this class of compound, Gly Δ Phe-OH, was prepared by careful reaction of N-chloroacetyl-phenylserine with acetic anhydride, to form, via β elmination, 2-chloromethyl-4-benzylidene-oxazolin-5-one, which, after hydrolysis, was reacted with ammonia (Figure 2.2.2(b))[25-27]; by removing the N blocking group it is even possible to obtain the free amino group

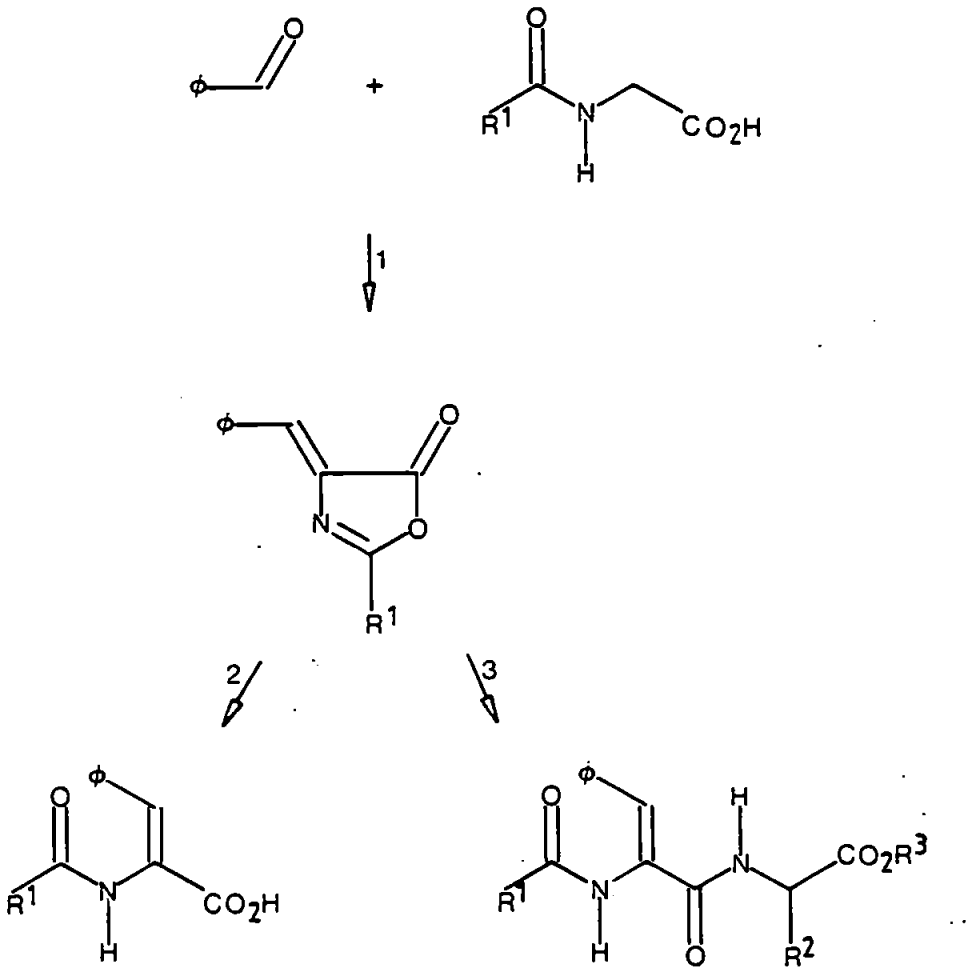
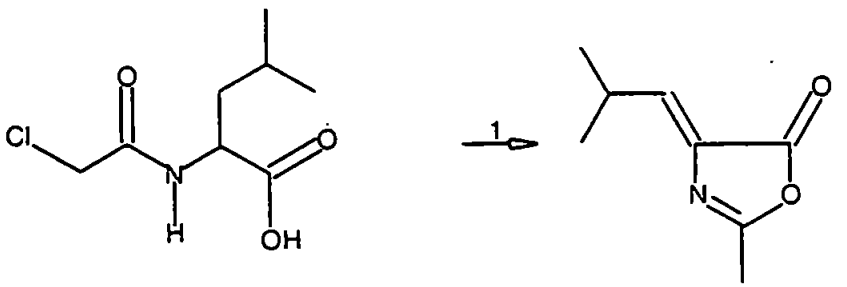
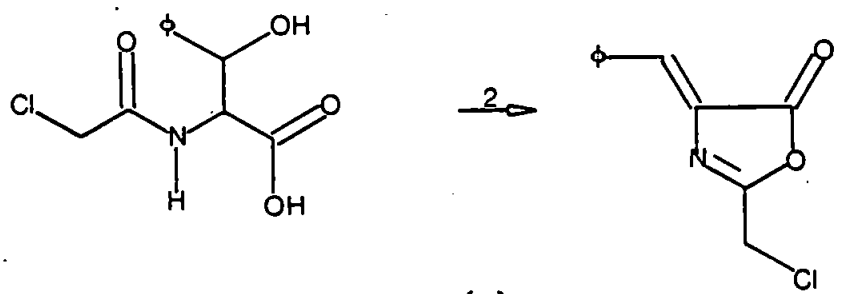


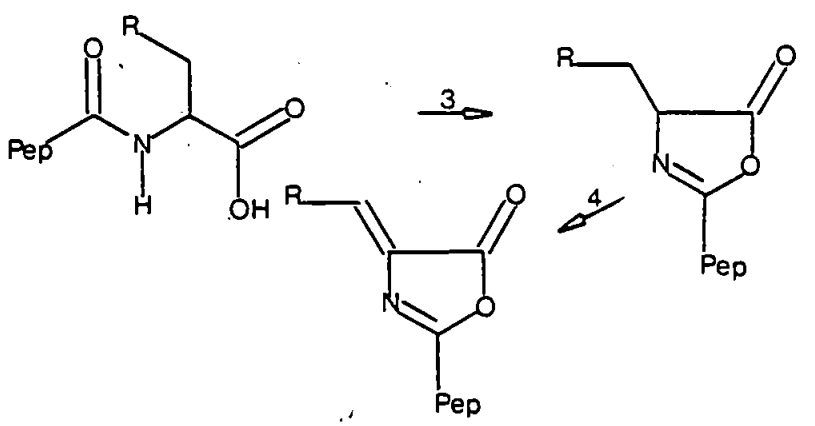
Figure 2.2.1. The Erlenmeyer synthesis; R^1 is a suitable group such as CH_3 or $CH_3C(O)N(H)C(CH\phi)$ (G); 1 and 2 are Ac_2O/NaOAc and OH^- respectively while 3 is an amino acid salt or ester.



(a)



(b)



(c)

Figure 2.2.2. Variations on the Erlenmeyer reaction; 1 is Ac_2O/pyridine, 2 Ac_2O, 3 D.C.C.I./T.H.F./5° C and 4 D.D.Q.; Pep is the amino end of a peptide chain and R is appropriate for the amino acid residue.

on at least some unsaturated amino acid residues[28-30].

A recent variation on the Erlenmeyer procedure, essentially involves formation of the saturated oxazolone with D.C.I.I.[31] and oxidation[32] with D.D.Q. (2,3-dichloro-5,6-dicyano-1,4 benzoquinone) to the unsaturated oxazolone (see Figure 2.2.2(c)).

Using the observation that acetamide and pyruvic acid, heated under reduced pressure, lead to the formation of a mixture of N-acetyl Δ Ala-OH (α acetamido-acrylic acid) and 2,2-diacetamido propanoic[33] acid (Figure 2.2.3), a convenient procedure for preparing N-acetyl Δ Ala-OH (and derivatives), involving heating excess pyruvic acid with acetamide (or derivatives) and removing water azeotropically has evolved[34]. Heating 2,2-acetamido propanoic acid (conveniently prepared by the Böttinger synthesis[35] (Figure 2.2.3)) also results in the same product.

A rather similar reaction involves mixing the appropriate nitrile (though only if it has an α halogen) with an excess of pyruvic acid and saturating the mixture with dry HCL (Figure 2.2.4(a)), though hydrolysis of the nitrile becomes more significant as R becomes larger[2].

An elegant general method for producing dehydro-amino acid esters is shown in Figure 2.2.4(b). It involves N-chlorination by tertiary butyl hypochlorite (tert-B.H.C.), dehydrochlorination to the corresponding imino acid ester and tautomerising to the thermodynamically more favoured, α,β dehydro-amino acid[36-39].

Within the last twenty years interest in protein sequence determination has prompted study of dehydro-peptide formation by β elimination from O derivatives of seryl residues (Figure 2.2.5)[40-43].

An elegant use of this reaction was in a study of the role of serine in chymotrypsin[44]; previous studies had sought to show its necessity by forming an O derivative, but this was open to the objec-

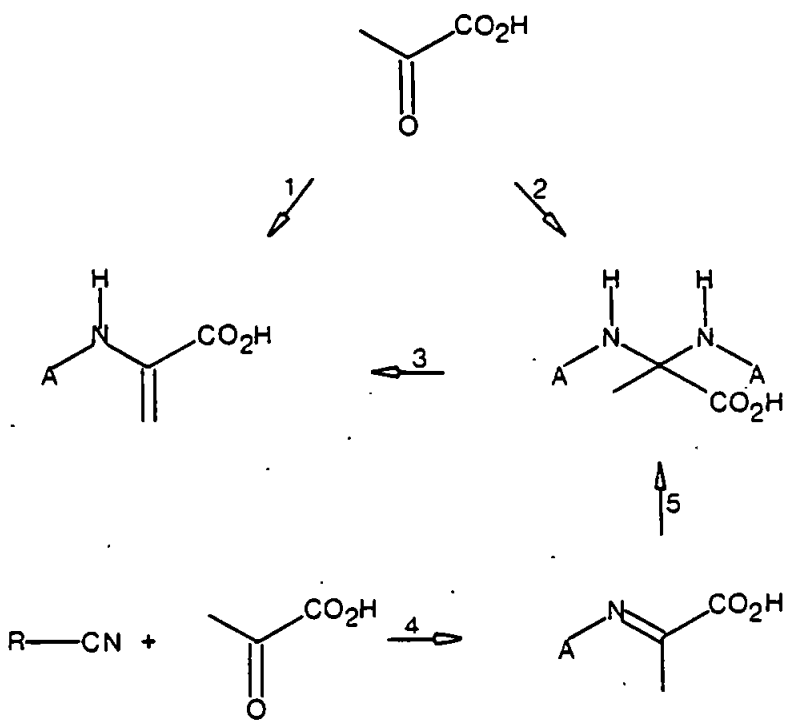


Figure 2.2.3. Dehydro-alanine formation: 1 and 2 consume $RCONH_2$ and 2 $RCONH_2$ respectively (A is RCO-); 1 is favoured when the water is removed; 3, 4 and 5 require glacial acetic acid, chilled H_2SO_4 and RCN/H_2O respectively.

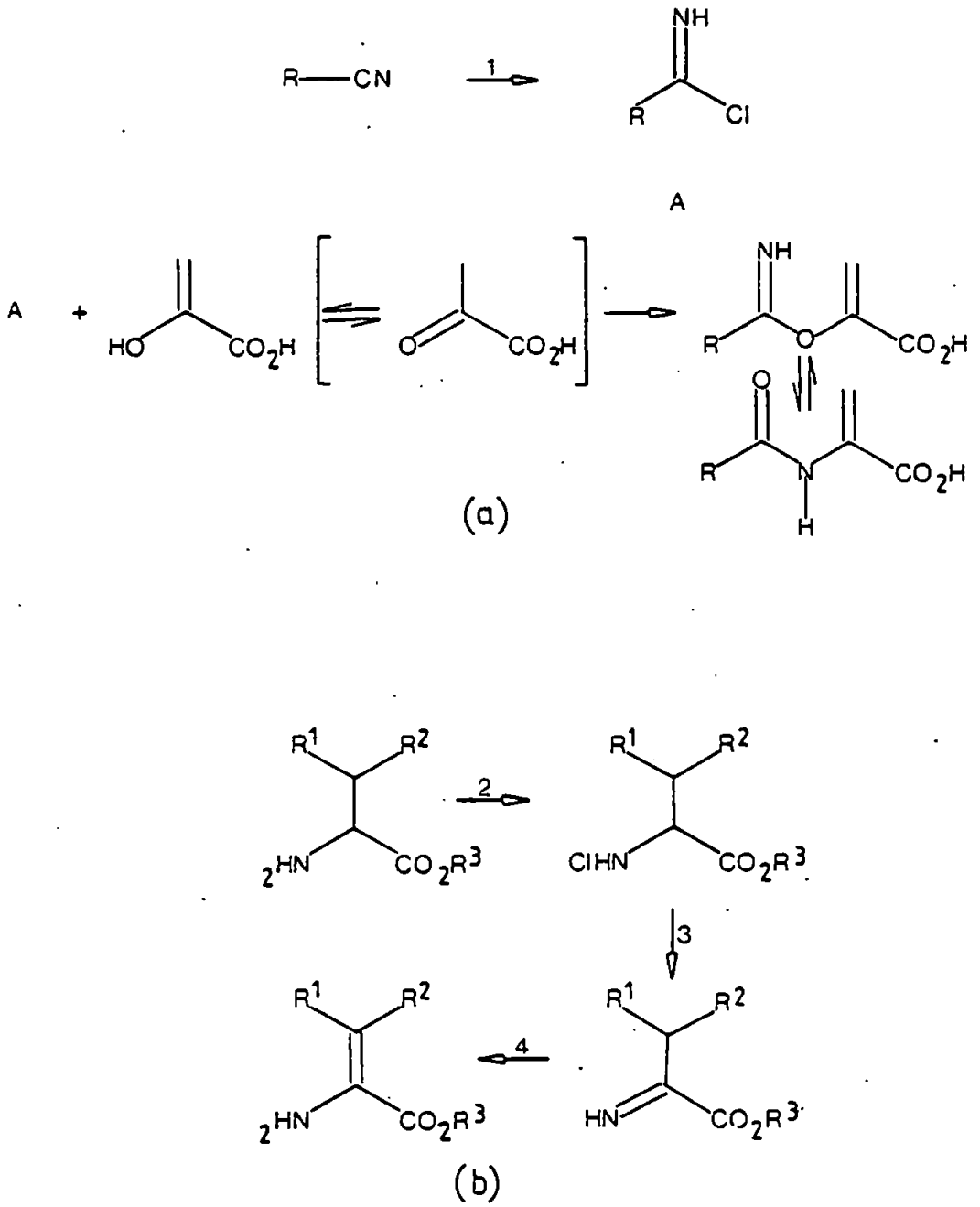


Figure 2.2.4. 1, 2, 3 and 4 require dry HCl/-5° C, tert-B.H.C., D.B.U. and ECl followed by NH_3 respectively.

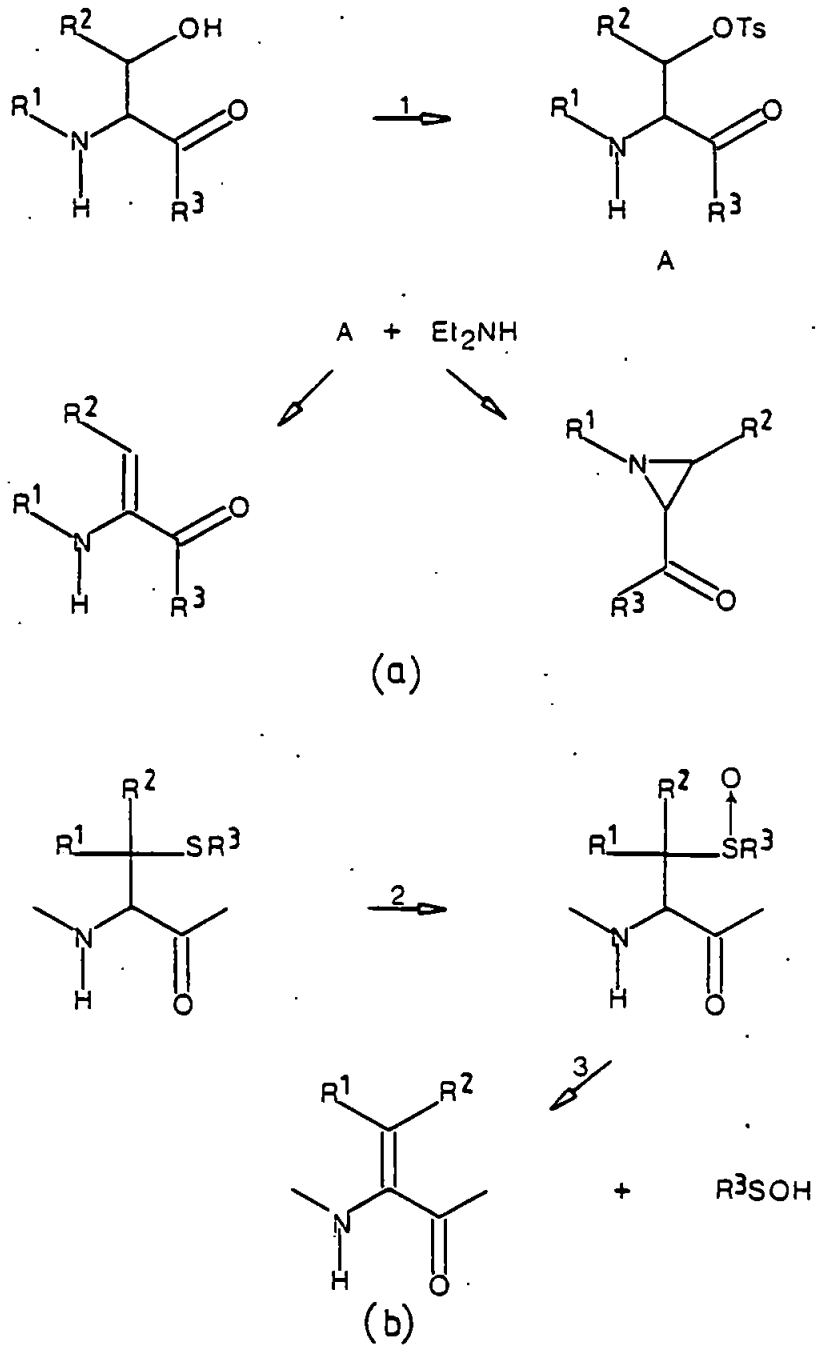


Figure 2.2.5(a) β elimination pathways. (b) Thermolytic formation of dehydro-peptides; 1 is TsCl/pyridine/-5° C while 2 and 3 are [O] and $\Delta/P\Phi_3$ respectively.

tion that it could be a steric effect; forming the dehydro-alanyl (inactive) derivative demonstrated conclusively that the hydroxyl group was essential.

However, β elimination may not be the only reaction, e.g. O-tosyl derivatives, amongst other by-products[45,46], can give rise to aziridines[47] (stereospecifically) (Figure 2.2.5(a)), especially when R is CH_3 (or presumably an alkyl group generally) and/or R_3 is NH-X (a general amide). Other leaving groups can also give rise to undesirable by-products[48,49].

For these and other reasons a method that requires only mild, neutral conditions has recently been developed[50]. It relies upon thermolytic elimination from β alkyl sulphinyl derivatives (Figure 2.2.5(b)), themselves prepared from the readily available amino acid sulphides[51]. The conversion, by oxidation, however, introduces the serious drawback that cysteine, cystine and tryptophan are oxidised irreversably. The temperature required for thermolysis was also sometimes rather high (140° C); to obviate this difficulty use was made of the observation that elimination is reversible; by adding thiophiles, such as triphenyl phosphine, the reaction temperature is lowered considerably. As it has been shown that aromatic sulphenic acids are better leaving groups than alkyl sulphenic acids[52], replacement of the S-benzyl or S-methyl groups used by S-aromatic groups should allow elimination at any reasonable temperature.

The 'obvious' method of dehydro-peptide synthesis, by incorporation of dehydro-amino acids using standard coupling techniques has a number of drawbacks:

The conditions for the removal of carboxyl blocking groups would be inimical to the integrity of the dehydro-peptide; the use of hydrogenolysis for blocking group removal is totally precluded in subsequent steps and, until recently, the preparation of dehydro-amino acids with

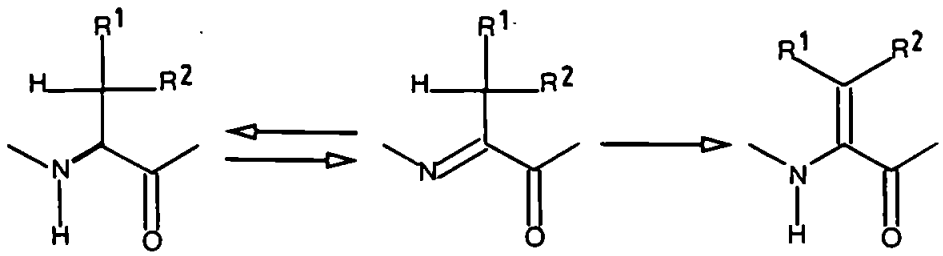
free amino groups was not practicable[28,53,54]. The propensity of dehydro-peptides to react with various reagents[55-58] makes desirable the introduction of the double bond as late in the synthesis as possible. Finally, and most importantly, the carboxyl group may be difficult or impossible to activate in a manner that produces coupling[59].

The coupling may be accomplished however, if the N-acyl group or stereo/chemical factors (proline) make azlactone formation difficult[60,61].

2.3 Biosynthesis and biochemistry

The biosynthesis of dehydro-peptides obviously cannot proceed by the usual mechanism for protein synthesis, with the same applying to proteins containing D amino acids.

A proposed mechanism[62] that produces both is shown below:



D/L I II

This mechanism produces α epimerisation naturally, in conformation with the observation that where there is more than one chiral centre, inversion generally only occurs at the α carbon[63] (though allo-derivatives have been isolated).[64] Additionally it is clear that derivatives without an amide hydrogen, and N-methyl amino acids occur frequently in antibiotics, could not follow this mechanism and indeed, such derivatives with a D configuration have not so far been found. Although a dehydro-peptide, tentoxin, with a methylated amide group exists, there is no obvious reason why methylation should not have occured after synthesis of II. The isolation of a tryptophan side chain α,β-oxidase provides support for this route[63].

Imines or dehydro-peptides provide possibly a plausable intermediate in the synthesis of the large number of exotic amino acids that have, in recent years been isolated from various fungal, plant and bacterial sources. For example, hydration of I would produce the α hydroxyalanine and α hydroxyvaline systems found in ergotamine and ergocristine[66]. These and similar reactions could of course occur

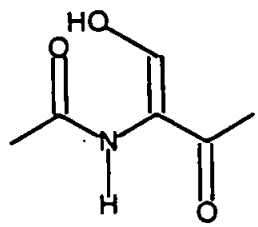
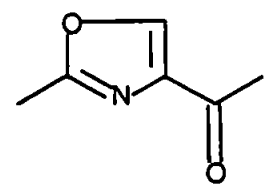
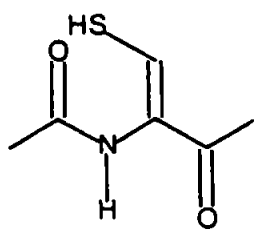
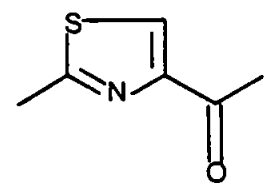
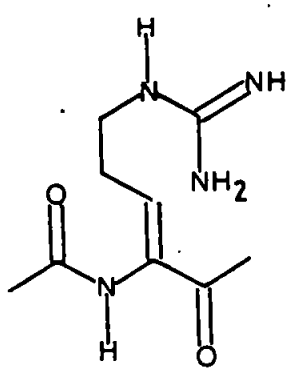
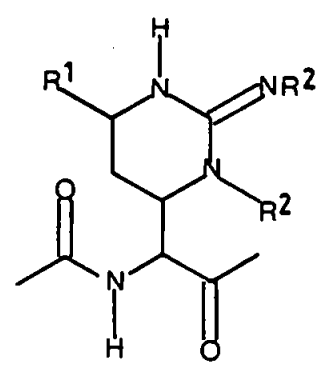
intramolecularly and it has been proposed that the formation of a number of compounds proceeds in this manner (Table 2.3.1). However the generality of this proposal has been restricted by observations showing that the D-Val residue in penicillin is not formed via an α,β dehydrovaline[67].

Chemists have shown interest in such reactions nevertheless, as there is presently no direct or stereospecific way to introduce substituents into a peptide. Incorporation of substituted amino acids by standard coupling techniques suffers from the disadvantage that substituted amino acids are generally synthesised by the difficult and laborious process of condensing fragments, which themselves often have a lengthy preparation. The introduction of double bonds along the carbon chain would enable direct[14,58,68] and possibly stereospecific derivatization[69,70]. By varying the reaction conditions the position of substitution can be made α or β[71]. More adventurous reactions such as photochemical cycloadditions are also possible[72]. Additionally, unsaturated analogues of biologically active peptides may themselves show desirable characteristics[73].

In studies of the complement system it was found that peptides containing the Phe-Tyr sequence inhibited an enzyme (EAC 1423) responsible for the mobilisation of the complement response[74]. In a search for more effective inhibitors a number of dehydro-peptides were tried of which two, N-AcΔ-3-(2-R)Ala-Tyr-OH (R is thienyl or furyl) were active, but in the opposite sense expected; there was a dose dependent, delayed (reaching a peak 48 hours after treatment of the mice) activation (measured by in vitro cancer cell destruction) of the murine macrophages presumably mediated by an allosteric effect on the enzymes responsible for complement activation (attempts at in vitro activation of the macrophages were unsuccessful)[75].

Table 2.3.1.

Antibiotics and their putative precursors

Dehydro-amino acid residue	Antibiotic
	
Serine	Oestreorgrysin A[16] Griseoviridin[78]
	
Cysteine	Micrococcin[76] Thiostrepton[77]
	
Arginine	Capreomycin (R^1 = R^2 = H)[79,80] Viomycin (R^1 = OH, R^2 = H)[81] Stendomycin (R^1 = H, R^2 = CH_3)

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CHAPTER THREE

EXPERIMENTAL DETAILS

3.1 Preparations

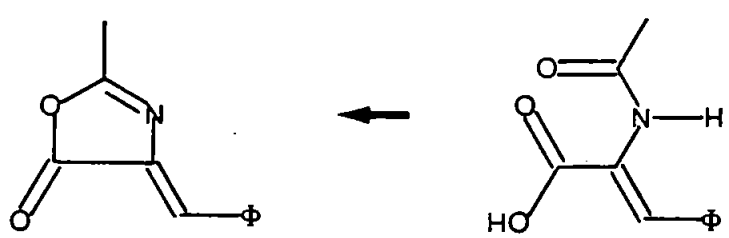
The aim was to prepare crystalline peptide and dehydropeptide derivatives and determine their molecular structures by X-ray diffraction techniques; N-acetyl derivatives were favoured as it allows study of an extra amide link.

A number of preparative methods were tried:

Carbodiimide Method

The coupling of N-acetyl dehydro-alanine or N-acetyl dehydro-phenylalanine with various amino acid esters was attempted.

In the case of N-acetyl dehydro-alanine (N-AcΔAla-OH) the attempt was totally unsuccessful; with N-acetyl dehydro-phenylalanine (N-AcΔPhe-OH), instead of the expected product, 2-methyl 4-benzylidene oxazolin-5-one was formed in appreciable yield. With hindsight the latter result is not unexpected, as, in contrast to saturated azlactones, unsaturated azlactones are, because of conjugation, rather stable.



An examination of the structures of N-Ac-ΔPhe-OH and N-Ac-ΔAla-OH (Figure 6.2.1 and Figure 4.2.1 respectively) makes clear why azlactone formation would be slower in the latter case; while N-Ac-ΔPhe-OH has the correct stereochemistry for azlactone formation, N-Ac-ΔAla-OH requires a 180° rotation about N4–C5 to product a suitable stereochemistry.

β elimination

Two peptides, N-Ac D, L-Ser-L-Ala-OEt and N-AcL-Ala-L-Ser-OEt, were prepared using D.C.C.I. and, in the latter case, HOBT (not being used in the former case because of the danger of lactone formation[1]).

The hydroxyl group of the serine residue was then reacted to form a suitable derivative for β elimination. The leaving group chosen was the toluene sulphonate anion. In an effort to simplify isolation 'polytosyl chloride' was prepared by chlorosulphonation of a polystyrene matrix[2]. However, handling characteristics proved unsatisfactory and so tosyl chloride chloride was used instead.

It was found in both cases β elimination occured spontaneously giving rise to non-crystalline products.

Bergmann Synthesis

The N-acetyl dehydro-peptide N-AcΔPheGly-OH and analogues with Gly replaced by L-Ala, L-Leu, L-Phe, L-Pro, L-Ser-OEt were prepared from 2-methyl 4-benzylidene oxazolin-5-one in the usual manner[3-5]; N-AcΔPheΔPhe-OH was also prepared.

Although the products were crystalline, the crystals were, with the exception of N-AcΔPhe-L-Pro-OH, unsuitable for single crystal diffraction. The dicyclohexyl ammonium salt of N-AcΔPhe-L-Leu-OH was prepared in an effort to obtain a suitable crystal, but to no avail.

Miscellaneous Methods

A method that was tried a number of times was that of Greenstein for N-chloroacetyl dehydro-alanine[6]. Despite azeotropic drying of the reactants, in every case the principal product was chloroacetamide. The preparation of the same compound was tried by a modification of Wielands method[7], but with no success.

N-AcΔLeu-OMe was prepared from the imine[8], but could not be induced

to crystallise. The free acids preparation from the corresponding azlactone was tried, but the purification of the azlactone was not achieved.

The growth of crystals, suitable for diffraction work, of Z-GlyΔAla-OEt, BOC-D,L-PheΔAla-OMe and $Tos^{-+}H_3N$ D,L-PheΔAla-OMe was attempted, but unsuccessfully. $Tos^{-}\ ^{+}H_3N$ D,L-PheΔAla-OMe was converted to the chloride by passage through C.G.401[Cl^{-}], but proved to be an oil.

Infra-red spectra were recorded on a Perkin-Elmer 357 while u.v. spectra were obtained from a Perkin-Elmer 402. T.l.c. used air dried SiO_2, the solvent system being EtOAc/C_6H_6 (4:1).

Experimental

N-AcΔPhe-L-Ser-OEt

N-AcΔPhe-OH (5 mmol) was dissolved in 20 mL T.H.F., D.C.I.I. and HOBT (5 mmol each) washed in with 10 mL T.H.F. and the reaction mixture cooled to 0^{o} C with a freezing mixture.

After 1.5 hours D.C.U. (1.02 g) was filtered off. HCl.Ser-OEt (5 mmol) was added to the filtrate in 30 mL T.H.F./acetonitrile (2:1) together with diisopropylethylamine (5 mmol). The solvent was removed under reduced pressure after a further 2 hours and the resultant solid mixed with 70 mh H_2O/EtOH (4:3) and filtered.

Following unsuccessful efforts to isolate the expected product from the filtrate, the H_2O/EtOH insoluble residue was dissolved in chloroform, D.C.U. filtered off and the solvent removed; the solid remaining was shown by m.p. (150^{o} C), n.m.r., u.v., i.r. and t.l.c. to be identical with 2-methyl 4-benzylidene oxazolin-5-one.

Yield (based on reacted reagent) was 0.46 g (50%). The desired compound was subsequently prepared in the following manner:

5 mmol of 2-methyl 4-benzylidene oxazoline-5-one (azlactone) was refluxed in acetone with HCl.L-Ser-OEt/diisopropylethylamine (5 mmol) for 5 hours. The solvent was removed, 120 mL EtOH/H_2O (1:5) added, and the mixture filtered to remove unreacted azlactone (0.25 g). T.l.c. revealed the main product at R_f = 0.19. The product was purified with a column (65 g Kieselgel 60 : 40 mL H_2O), the column being developed with EtOAc/C_6H_6 and the eluant being analysed by t.l.c.

m.p. = 2 147° C, i.r. (KBr) 3300, 1730, 1640 cm^{-1}

Yield = 0.33 g (29%).

N-AcΔPhe-L-Pro-OH

To a solution of proline (10 mmol) in 16.7 mL of 0.6 M NaOH was added 10 mmol of azlactone and 8 mL of acetone. The mixture was shaken until the azlactone dissolved and allowed to stand until t.l.c. indicated reaction was complete (4 hours). 11 mL of IMHCl were then added and the acetone blown off. Tarry material was removed and the solution left overnight in the fridge. The resulting crystalline precipitate was filtered off and recrystallised from EtOH/H_2O.

m.p. = 141° - 143° C, i.r. (KBr) 3200, 1730, 1660 cm^{-1}

Yield = 1.7 g (56%).

Analogues of this compound with L-Pro replaced by other amino acids were prepared in a similar manner.

N-AcL-Ala-L-Ser-OEt

10 mmol of N-AcL-Ala-OH and HCl.L-Ser-OEt were suspended in 60 mL of acetonitride at 0° C. A solution of HoBT, diisopropylethylamine and D.C.C.I. (10 mmol each) in 15 mL acetonitride was then added and the reactants left stirring overnight.

After filtering off D.C.U. (2.0 g), the acetonitrile was removed under reduced pressure and the resultant oil mixed with cold water (30 mL). The precipitate of HOBT was filtered off and the filtrate passed

through a column of cation exchange resin (Amberlite C.G. 120[Na^+]). Following removal of the water, ethyl acetate was added and NaCl filtered off. Upon removal of the solvent the product separated as an oil which solidified when left overnight in the fridge. It was re-crystallised from EtOH/n-C_6H_{14}.

$[\alpha]_D$ = -75° (c = 1, H_2O), m.p. = 136° - 138° C

i.r. (KBr) 3310, 3090, 1620, 1550 cm^{-1}

Yield = 2.1 g (85%)

N-AcD,L-Ser-L-Ala-OEt (but with no HoBT) and N-AcL-Ala-L-Ala-OEt were prepared in a similar manner.

N-AcL-AlaO-Tosyl-L-Ser-OEt

N-AcL-Ala-L-Ser-OEt (2 mmol) was dissolved in 5 mL of dry pyridine (stored at 3° C over 3 Å molecular sieves) and 2.1 mmol of tosyl chloride (purified by the Pelletier method[10]).

After 30 hours t.l.c. showed that reaction was complete and indicated that β elimination had spontaneously occurred (strong R_f = 0, presumably toluene sulphonic acid). However, to ensure complete reaction diethylamine was still added. The reaction mixture had water added and was passed through a bed of ion exchange resin (C.G. 120[Na^+]). The solvent was removed under reduced pressure (pyridine forms an azeotrope with water) and the residue dissolved in acetone/water. The undissolved portion was filtered off (sodium tosylate, m.p. > 260° C) and the solvent removed to leave an oil which could not be crystallised.

u.v. 230 n.m. i.r. (NaCl disc) 3300, 1640, 1530 cm^{-1}

Yield = 0.55 mmol (27.5%)

The preparation of N-AcO-Tosyl D,L-Ser-L-Ala-OEt proceeded in a similar manner; the product was again non-crystalline.

3.2 Data Collection, Computing and Miscellaneous Details

The unit cell parameters and space group were usually determined initially from Weissenberg photographs. Data were collected on a Nonius CAD4 four circle diffractometer using the $\omega/2\theta$ scan mode. Crystal integrity was monitored by periodically remeasuring reflexions.

The geometry of the CAD4 differs somewhat from that of the classical four circle diffractometer (Figure 3.2.1).

The goniometer head, mounted on the Φ (PHIK) axis, is supported by the κ block. This can be rotated about the κ axis (which makes an angle α, nominally 50°, with the Φ axis), while the block on which it is carried, the ω block, is itself rotatable about the ω(OMK) axis. Additionally, the detector rotates on an axis (2θ) which is coaxial with the ω axis.

The zero positions for κ, ω, and 2θ are defined in terms of the geometry of the instrument; the point in κ rotation, where PHIK and OMK coincide, is defined as $\kappa = 0$; the zero for ω is defined as the point in ω rotation where the κ axis lies in the XZ plane and the κ block is most distant from the collimator, with a similar definition for 2θ. The point where the key on the goniometer head mount is parallel to the Y axis and κ and ω are zero defines $\Phi = 0$.

Data consistency is estimated from

$$R' = (\Sigma N \Sigma w_{ij} (\bar{F}_j - F_{ij})^2 / \Sigma (N - 1) \Sigma w_{ij} F^2_{ij})^{\frac{1}{2}}$$

where internal summations are over equivalent reflexions and $\bar{F}$ is the average of equivalent reflexions.

Computing was done on the I.C.L. 1900, 2980 or C.D.C. 7600. The structures were solved using either SHELX 76 or MULTAN 78. Indices used to measure progress in structure determination are defined below:

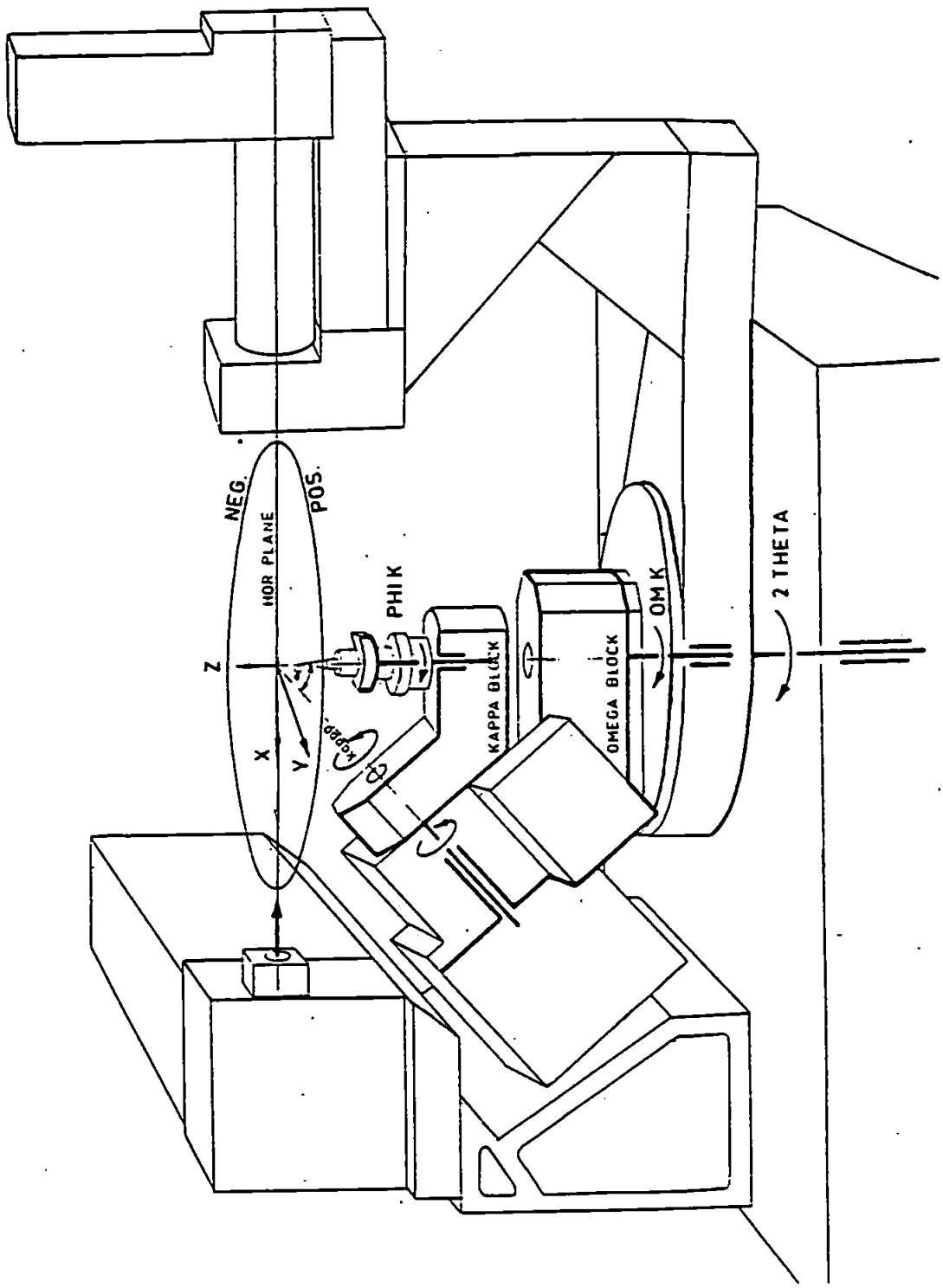


Figure 3.2.1. The CAD4 diffractometer and its geometry.

$$R = \Sigma\Delta_i / \Sigma|F_o|_i$$

$$R_w = \Sigma(w^{\frac{1}{2}}\Delta)_i / \Sigma(w^{\frac{1}{2}}|F_o|)_i$$

$$R_G^2 = \Sigma(w\Delta^2)_i / \Sigma(w|F_o|^2)_i$$

R_M = R_G calculated with a scale factor that minimises R_G.

Molecular geometry was calculated using XANADU. Least-squares planes were calculated using atoms at unit weight; hydrogen atoms were not used. The equations of the planes are given in right-handed Cartesian coordinates with X_o parallel to X, Y_o parallel to ZxX* and Z_o parallel to Z.

Structures were drawn using ORTEP; hydrogen was given the dummy temperature factor of B = 1.

In the absence of units, distances are quoted in Angstroms, angles in degrees, i.r. peaks in cm^{-1} and u.v. values in n.m.

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CHAPTER FOUR

N-ACETYL DEHYDRO-ALANINE

4.1 Introduction

The dehydro-alanyl residue occurs with frequency in two classes of biologically active molecules: antibiotics and enzymes.

It was first detected in nisin, and later in subtilin, as part of the carboxyl terminal sequence, dehydro-alanyl lysine; significantly this feature appears essential for the antibiotic activity.[1] The necessity or otherwise of the other dehydro-alanyl residues (one each for subtilin and nisin plus a β methyl dehydro-alanyl (butyrine) residue for nisin) is unknown.

Interestingly nisin (and subtilin) contain lanthionine and β methyl lanthionine residues, which could plausably be formed by addition of cysteine to dehydro-alanyl and butyrine residues respectively, as mercapto derivatives generally add readily[2]. A special feature of nisin activity that was predicted (and found) on this basis was antimaterial activity, as the malarial parasite is known to be inhibited by a shortage of Co-enzyme A(HS-CoA)[3]. Another suggested role for addition (after the intermediate production of dehydro-alanine) is as the final stage of a mechanism for replacement of β substituents[4].

The inactivating activity of nisinase, which appears to act as a reductase or dehydro-peptidase on both nisin and subtilin[5], suggests its use as a quick screening method for antibiotics (and other molecules?) containing dehydro-alanyl residues.

Enzymes containing dehydro-alanine are generally ammonia lyases, with dehydro-alanyl residue at the active site. A mechanism involving a Schiff base has been proposed[6].

Following the observation of in vitro inactivation of His-ammonia lyase by nitromethane, the in vivo inactivation (in rats) was

attempted (successfully), by the same means, to model a human genetic disorder, histidinaemia[7]. However, because another degrading enzyme existed (His-pyruvate transaminase) the modelling was unsuccessful; it would seem to have shown, none-the-less, at least provisionally, that dehydro-alamine has no essential structural biochemical role in mammals.

Further details of the chemistry and biochemistry can be found in Chapter 2.

4.2 N-Acetyl Dehydro-Alanine

Experimental

The compound was prepared by Wielands method[8] and recrystallised from methanol.

Formula - $C_5H_7NO_3$
Space group = $P2_1/n$
F(000) = 272

$a = 3.941$ Å

$b = 10.156$ Å

$c = 14.898$ Å

$\beta = 91.64^{\circ}$

$V = 596.05$ Å^3

$Z = 4$

$D_o = 1.43$ Mg m^{-3} (n-C_6H_{14}/CCl_4)

$D_c = 1.45$ Mg m^{-3}

$\mu = 0.078$ mm^{-1}

Data were collected using Mo-K_α radiation monochromated with graphite ($1.5 < \theta < 27^{\circ}$); 1570 reflexions (30 were intensity controls) were measured, 1489 of which were systematically present (1283 unique, 1133, 88.3% $|F| > 3\sigma(|F|)$.

After data reduction SHELX was used to produce an E-map, from which the structural skeleton could be picked out. After three cycles of refinement with isotropic temperature factors R = 16%, three cycles with anisotropic temperature factors produced R = 8.7%. The hydrogens were located on a difference map and after insertion and six further cycles, R = 4.4%.

An attempted weighted refinement, with the weighting parameter (g) being refined did not converage. 'g' was therefore fixed during refinement, being altered between refinements until the analysis of

variance was satisfactory. The final values are shown below.

	R	R_W	$R_M (= R_G)$	S^2
all $\|F\|$	4.8	4.9	5.9	0.043
$\|F\| > 3\sigma(\|F\|)$	4.3	4.7	5.9	1.000

A final difference map revealed quite a noisy background with significant ripples between most of the bonded atoms.

The final atomic parameters are shown in Tables 4.2.1 and 4.2.2. $10|F_o|/10|F_c|$ tables are in Appendix E (Table E.1).

Discussion

The initial impression of a planar molecule was confirmed by least squares plane analysis (Table 4.2.3, plane 1). Although the planarity might be expected due to the resultant conjugation of the carboxylic, olefin and amide systems, it produces some very small intra-molecular non-bonded distances (Table 4.2.4).

Rather more surprising, considering the very small a axis, is that the angle between the least squares plane of the molecules normal and the a axis is as large as 35^{o}.

A comparison of the bond lengths and angles with those of peptides (Table 4.2.8) show the angles agree within two degrees except for $C-\hat{N}-C^{\alpha}$ (C2-$\hat{N}$4-C5). Other dehydro-amino acids (Chapter 6) still show this angle as anomalously large. Examination of the intra-molecular non-bonded distances, especially involving O3, suggest, together with the N4-$\hat{C}$5-C6 value of 127^{o}, the angular expansion occurs to relieve steric strain.

The bond lengths are similar except for the $N-C^{\alpha}$ and C-N distances which are significantly shorter and longer respectively than those in peptides[9]; the shortening of the first bond would be expected as it is an sp^2 - sp^2 link, but together with the lengthening of the second bond it suggests some delocalisation is taking place. N-Ac-ΔPhe-OH (see 6.2) shows a similar but less pronounced effect, which is consistent with less delocalisation as the amide plane is skewed out of the plane of the olefinic system.

Fumaramic acid[10], a closely related, essentially planar molecule, shows several similarities to N-Ac-ΔAla-OH; the most noteworthy are an insensitivity of the olefinic bond length to molecular planarity, a characteristic often found[11-14], and a significant difference in carbonyl bond distances, the amide carbonyl being long (1.233 Å) than

the carboxylic (1.206 Å). The last observation is related to the first in that it implies that contributions from resonance hybrids involving the carbonyl are not significantly changed from the isolated carboxylic acid group.

An analysis of hydrogen bonding (Table 4.2.5) reveals that, although constraints are placed upon hydrogen bonding in such an inflexible molecule, it takes place to the maximum, albeit limited, extent. A detailed examination of the hydrogen bonding shows a number of interesting features; the C7-$\hat{O}$8...H4 (168°) and C7-$\hat{O}$8...N4 (172.7°) values show the oxygen lone pair to be in an sp orbital, which is fairly unusual for a carboxylic carbonyl and probably differs from the situation in N-Ac-ΔPhe-OH (see 6.2); also the C2-$\hat{O}$3...H9 (124°) and C2-$\hat{O}$3...O9 (120.7°) values suggest the lone pairs on the amide oxygen are in sp^2 orbitals which, while being usual for amides in general and agreeing with the other two dehydro-peptides (see 6.2 and 6.3), is in contrast with the usual situation in peptides (see for example 5.2 and 5.3). The bond formed by H9, while being, not unexpectedly, shorter than the bond involving H4 is, nevertheless, longer than observed for equivalent bonds in most amide-carboxylic complexes (2.50 ± 0.02 Å)[15].

The carboxylic acid group is planar (Table 4.2.3, plane 4) and its parameters C7-O9 (1.310 Å), C7-O8 (1.206 Å), O8-$\hat{C}$7-O9 (124.8°) agree well with those expected (1.31 Å, 1.21 Å and 123° respectively)[16]. As the aforementioned planarity, somewhat surprisingly, even includes the hydrogen, which only deviates from the least squares plane by 0.04 Å (with an approximate e.s.d. of 0.03 Å) no accommodation for the hydrogen bond to O3 seems to have been necessary. The hydrogen is in the conformation (synplanar) which minimises the distance to the carbonyl oxygen, presumably due to an electrostatic interaction, though

packing considerations may also be important. In fact the synplanar conformation has been variously estimated as being more stable than the antiplanar by 2 Kcal/mole[17] or at least 4 Kcal/mole[18]. This is consistent with the observation of the antiplanar form only when an intra-molecular hydrogen bond is formed.

The inflexible nature of the molecule makes a rigid body librational correction appropriate as can be seen from the excellent agreement between $(U_{ij})_{OBS}$ and $(U_{ij})_{CALC}$ (Table 4.2.6) and R_G(10.7%).

Figure 4.2.2, a projection down the b axis, shows the molecular packing. It can be rationalised as hydrogen bonded ribbons, parallel to the a c diagonal, the ribbons being held together by hydrogen bonding to form a distorted sheet, and sheets cohering by Van der Waals forces.

The carboxylic carbonyl group C7-O8 is antiplanar to the olefinic bond C5-C6 (see figure 4.2.1). A comparison, assuming similar bond lengths and angles, with the non-bonded distances of the synplanar conformation O9...N4 (2.52 Å) O8...C6 (2.79 Å) provides at least a partial rationalisation. While being a very useful rule-of-thumb for saturated acids, producing the 'correct' synplanar conformation (for unbranched acids), in unsaturated (α,β) acids steric factors are often ambiguous and it has been suggested, not altogether convincingly, using the bend bond model for double bonds[19], that the antiplanar conformation will then be found. However, for less simple molecules more distant parts can influence the conformation (see 6.2).

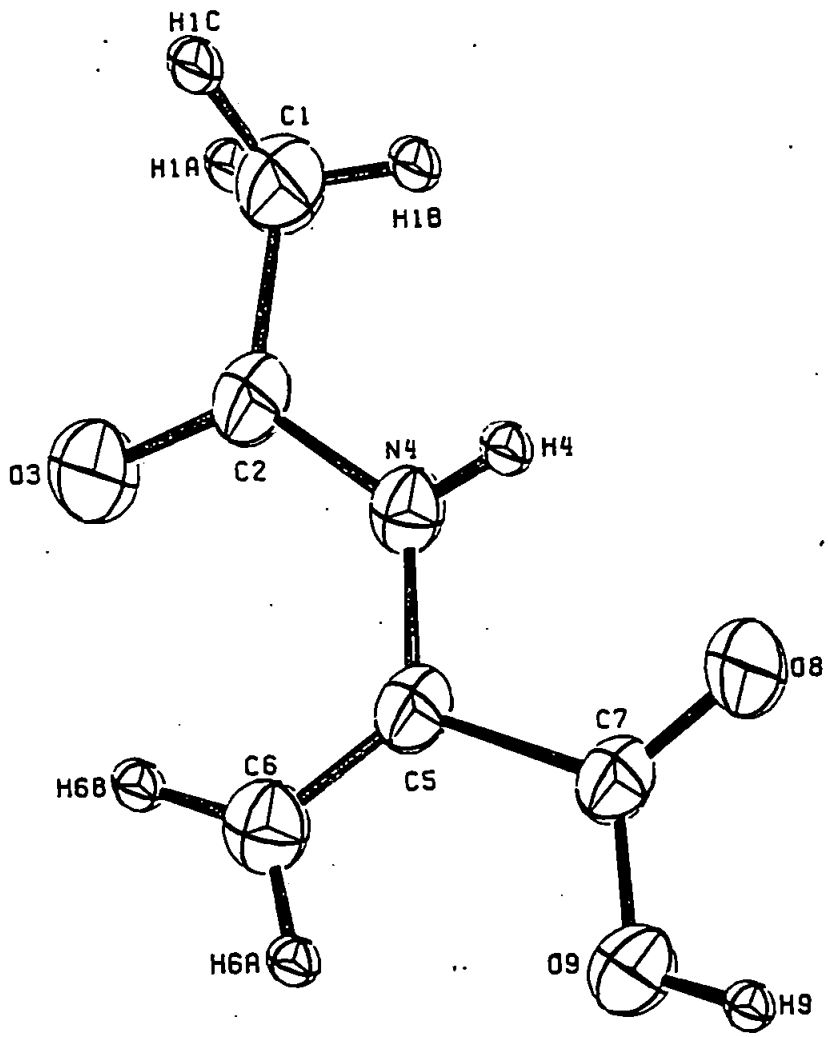

Figure 4.2.1. ORTEP drawing of the molecular structure of N-AcΔAla-OH with 50% probability ellipsoids; the view is parallel to the axis.

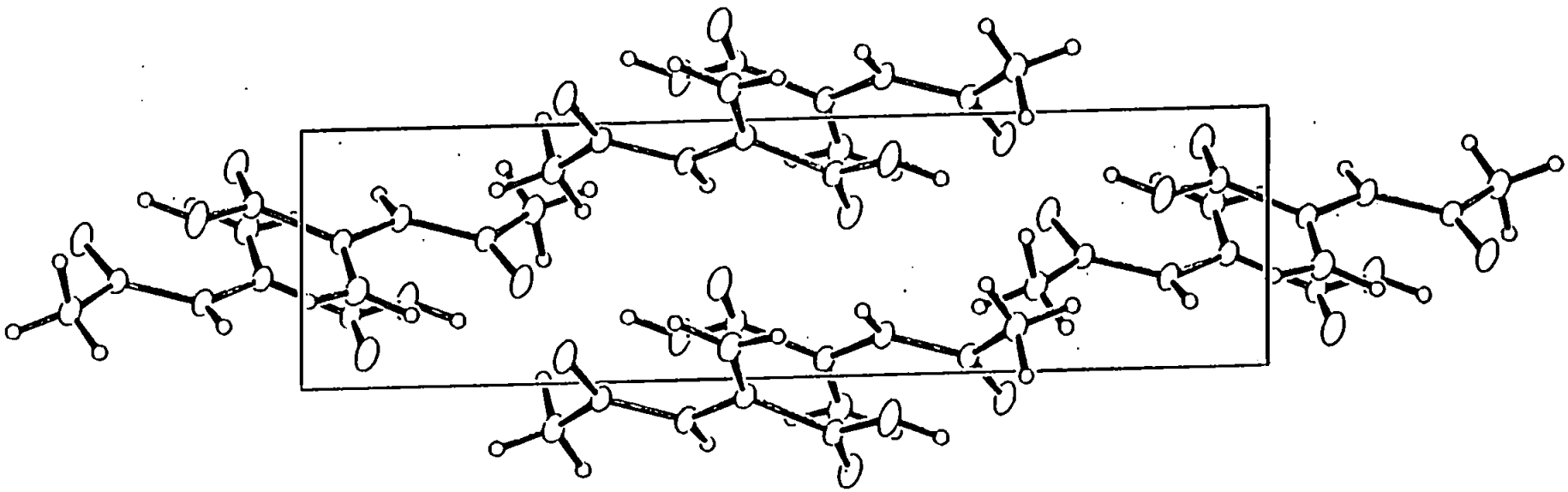

Figure 4.2.2. A projection down to the b axis showing the molecular packing.

Table 4.2.1

Atomic fractional co-ordinates with the e.s.d.'s in parenthesis and of the same magnitude as the final digit.

	x	y	z
C1	0.3274(4)	0.4872(1)	1.2393(1)
C2	0.4365(3)	0.3667(1)	1.1905(1)
O3	0.6025(3)	0.2781(1)	1.2275(1)
N4	0.3472(3)	0.3608(1)	1.1023(1)
C5	0.4322(3)	0.2620(1)	1.0410(1)
C6	0.6234(4)	0.1571(1)	1.0566(1)
C7	0.2819(3)	0.2902(1)	0.9493(1)
O8	0.1317(3)	0.3910(1)	0.9324(1)
O9	0.3323(3)	0.1951(1)	0.8918(1)
H1A	0.254(6)	0.462(2)	1.298(2)
H1B	0.164(6)	0.534(2)	1.209(2)
H1C	0.519(8)	0.548(3)	1.250(2)
H4	0.252(4)	0.427(2)	1.080(1)
H6A	0.659(4)	0.098(2)	1.007(1)
H6B	0.721(4)	0.138(2)	1.114(1)
H9	0.251(6)	0.216(2)	0.838(2)

Table 4.2.2

Bond angles (degrees). The e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

H1A-C1-H1B	111(2)
H1A-C1-H1C	106(2)
H1B-C1-H1C	106(2)
C2-C1-H1A	109(1)
C2-C1-H1B	113(1)
C2-C1-H1C	111(2)
C1-C2-O3	122.4(1)
C1-C2-N4	116.0(1)
O3-C2-N4	121.5(1)
H4-N4-C2	117(1)
H4-N4-C5	116(1)
C2-N4-C5	127.1(1)
N4-C5-C6	127.4(1)
N4-C5-C7	111.1(1)
C6-C5-C7	121.4(1)
C5-C6-H6A	117.7(9)
C5-C6-H6B	123(1)
H6A-C6-H6B	119(1)
C5-C7-O8	122.1(1)
C5-C7-O9	113.1(1)
O8-C7-O9	124.8(1)
C7-O9-H9	111(1)

Table 4.2.3

Deviations from least squares planes (in Å)

	1	2	3	4
C1	0.014		0.002	
C2	-0.023		-0.005	
O3	-0.039		0.002	
N4	-0.018	0.002	0.002	
C5	0.016	-0.007		0.000
C6	0.086	0.003		
C7	-0.004	0.002		0.000
O8	0.048			0.000
O9	-0.081			0.000

i	a_i	b_i	c_i	d_i
1	0.8409	-0.4787	-0.2526	-3.4359
2	0.8167	-0.5172	-0.2558	-3.5244
3	0.8509	-0.4589	-0.2558	-3.4620
4	0.8568	-0.4301	-0.2845	-3.5638

Table 4.2.4

Intra-molecular non-bonded distances

(< Van der Waals + 0.35 Å)

Cl ...H4	2.46
H1B...N4	2.49
H1B...H4	2.24
O3 ...C5	2.844
O3 ...C6	2.830
O3 ...H6B	2.28
C6 ...C2	3.022
C7 ...H4	2.40
O8 ...H4	2.27
O8 ...N4	2.665
O8 ...H9	2.32
O9 ...C6	2.708
O9 ...H6A	2.34

Table 4.2.5

Hydrogen bonding

Donor X-H	Acceptor Y	Angle XHY°	Distance HY	Distance XY	Position of Acceptor
N4-H4	O8	159	2.4	3.18	(-x,1-y,2-z)
O9-H9	O3	168	1.7	2.60	(x-½,½-y,z-½)

Table 4.2.6

Observed and calculated U_{ij} (upper and lower line respectively). Hydrogen U_{ij} were not analysed. R_G = 10.7 %.

	U_{11}	U_{12}	U_{13}	U_{22}	U_{23}	U_{33}
C1	0.0478	-0.0011	-0.0090	0.0495	0.0046	0.0300
	0.0495	-0.0009	-0.0100	0.0505	0.0050	0.0296
C2	0.0341	0.0073	-0.0072	0.0419	-0.0030	0.0246
	0.0396	0.0040	-0.0081	0.0425	-0.0018	0.0255
O3	0.0639	-0.0065	-0.0165	0.0503	-0.0023	0.0279
	0.0615	-0.0053	-0.0154	0.0500	-0.0020	0.0280
N4	0.0404	-0.0002	-0.0103	0.0372	-0.0011	0.0249
	0.0292	0.0077	-0.0058	0.0358	-0.0033	0.0249
C5	0.0344	0.0069	-0.0074	0.0373	-0.0028	0.0250
	0.0348	0.0047	-0.0072	0.0366	-0.0027	0.0259
C6	0.0478	-0.0014	-0.0105	0.0434	-0.0010	0.0337
	0.0493	-0.0041	-0.0122	0.0418	0.0001	0.0321
C7	0.0380	0.0042	-0.0076	0.0401	-0.0006	0.0251
	0.0500	-0.0019	-0.0118	0.0432	0.0001	0.0267
O8	0.0649	-0.0105	-0.0162	0.0468	-0.0007	0.0319
	0.0634	-0.0083	-0.0171	0.0474	-0.0001	0.0290
O9	0.0765	-0.0141	-0.0202	0.0538	0.0088	0.0294
	0.0704	-0.0110	-0.0172	0.0525	0.0066	0.0308
H1A	0.084					
H1B	0.074					
H1C	0.090					
H4	0.037					
H6A	0.043					
H6B	0.056					
H9	0.082					

Table 4.2.7

Librational corrections and corrected bond lengths (in Angstroms)

C1-H1A	0.005	0.973
C1-H1B	0.004	0.919
C1-H1C	0.005	0.990
C2-C1	0.004	1.498
C2-O3	0.005	1.239
C2-N4	0.005	1.357
N4-H4	0.004	0.839
C5-N4	0.004	1.407
C5-C6	0.005	1.327
C6-H6A	0.003	0.965
C6-H6B	0.004	0.945
C7-C5	0.006	1.507
C7-O8	0.005	1.210
C7-O9	0.003	1.313
O9-H9	0.004	0.880

Table 4.2.8

	Peptide	N-Ac-ΔAla-OH
C^{α}-C(O)	1.51	1.493
C=O	1.24	1.233
C(O)-N	1.32	1.352
N-C^{α}	1.45	1.403
C^{α}-$\hat{C}$(O)-O	120.5	122.4
C^{α}-$\hat{C}$(O)-N	116	116.0
O-$\hat{C}$-N	123.5	121.5
C(O)-$\hat{N}$-C^{α}	122	127.1
N-$\hat{C}^{\alpha}$-C(O)	111	111.1

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CHAPTER FIVE

N-ACETYL-L-ALA-L-ALA-OET

AND

N-ACETYL-L-ALA-L-SER-OET

5.1 Introduction

Because of their biological importance, peptides and proteins have been an area of intensive study.

As the peptide linkage, at least to a first approximation, is planar, the conformation of a peptide chain may be described by the angle between the planes $C^{\alpha}_{i-1}C_{i-1}O_{i-1}N_iC^{\alpha}_i$ and $C^{\alpha}_iC_iO_iN_{i+1}C^{\alpha}_{i+1}$ i.e. $\Phi(C_{i-1}N_iC^{\alpha}_iC_i)$ and $\Psi(N_iC^{\alpha}_iC_iN_{i+1})$. Not all pairs of these angles are possible (due to steric clash) or, if possible, likely; certain combinations of Φ and Ψ are specially favoured as they produce conformations stabilised by well directed hydrogen bonds, in the general case, between amide hydrogen and oxygen; two of the more commonly encountered are the α helix (3.6 residues per repeat unit) and the anti-parallel pleated sheet (two residues per repeat unit), so-called because adjacent hydrogen bonded chains are N → C, C → N, N → C etc., and the sheet produced has 'folds' in it.

Peptide conformations have been actively studied by model building and computer simulation and islands of stability established[1,2]. These are usually presented in the form of a Ramachandran diagram, which is a plot of Φ against Ψ contoured to show potential energy values.

Naturally if premises such as peptide bond planarity or Van der Waals radii are incorrect the 'islands' of stability move, but the Ramachandran plot allows a convenient initial analysis of a conformation.

The relationships between Φ, Ψ, n (the number of residues per repeat unit, $n = 360^{\circ}/\theta^{\circ}$) and d, the distance per residue in the axial direction, assuming average values for the peptide bond, are shown below.

5.1.1. $\cos(\theta/2) = 0.817 \sin((\Phi + \Psi)/2) + 0.045 \sin((\Phi - \Psi)/2)$

5.1.2. $d \sin(\theta/2) = -2.967 \cos((\Phi + \Psi)/2) - 0.664 \cos((\Phi - \Psi)/2)$.

The structure of N-Ac-L-Ala-L-Ala-OEt was determined to compare it with

N-Ac-L-AlaΔAla-OEt. However, as N-Ac(L-Ala)$_2$OEt suffers from domain anisotropy, which has effects on bond lengths, temperature factors, etc., the structure of N-AcL-Ala-L-Ser-OEt was also determined in the hope (mistaken) that it would be free from such an effect.

Details of preparative methods and chemistry are to be found in Appendix B.

5.2 N-Acetyl-L-Ala-L-Ala-OEt

Experimental

The compound was prepared by the carbodiimide method[3] and recrystallised from acetone/n-Hexane.

Formula - $C_{10}H_{18}N_2O_4$

Space group = C2

F(000) = 496

a = 14.656 Å

b = 9.931 Å

c = 9.631 Å

β = 112.501°

Z = 4

V = 1295.06 $Å^3$

D_o = 1.18 Mg m^{-3} (CCl_4/cyclo-C_6H_{12})

D_c = 1.18 Mg m^{-3}

μ = 0.057 mm^{-1}

Data were collected on a CAD4 diffractometer using Mo-K_α radiation monochromated with graphite ($1.5^\circ < \theta < 27^\circ$). 1609 reflexions were measured, 1499 of which were unique (1031, 69% $|F|>3\sigma(|F|)$). Attempts to solve the structure using SHELX were unsuccessful, probably due to the lack of weight given to Ψ_o in the figure of merit. The structure was subsequently solved with the assistance of Dr. G. M. Sheldrick, using his private program. The structure was then refined, using SHELX until R = 8.6, $R_M = R_G$ = 7.0 (all reflexions). As some of the bond angles, bond lengths and temperature factors were highly variable, domain anisotropy was suspected. Compensation for the effect was achieved by a refinement procedure incorporated in SHELX. Actually it was found that suppression of 001, 020, $\bar{1}12$ and $\bar{2}02$ (selected in the

light of the $|F_o|/|F_c|$ analysis) was equally effective.

Weighted refinement then commenced; 'g' was varied until the analysis of variance was satisfactory.

The final indices are shown below:

	R	R_W	$R_G = R_M$	S^2
all $\|F\|$	8.0	6.5	7.3	0.037
$\|F\| > 2\sigma(\|F\|)$	5.1	5.8	7.1	1.498

The final atomic positions are listed in Table 5.2.1 and Table 5.2.2. $10|F_o|/10|F_c|$ are listed in Appendix E (Table E.4).

Discussion

The peptide groups have the trans disposition that, with the notable exception of proline (which, when associated with reverse open turns, is often in the cis form), is usually found. The energy difference between cis and trans is actually quite small ($\sim$ 2.8 Kcal/mole)[4] but cis is sterically unfavourable in the context of an otherwise trans chain[5,6]. Least squares plane analysis (Table 5.2.2) shows that only one of the peptide groups (plane 7, ω_1 = 180.0°) has the planarity expected; the other has the chiral carbon (C6) deviating from the plane (plane 5, ω_2 = 172.0°). The estimated standard deviation (e.s.d.) in the direction of the plane normal may be approximated by the mean of the e.s.d.'s in the directions of the cell axes; 'exact' calculation would require knowledge of the correlation between the axes, which is not readily available; the deviation of C6, at 0.168 A is significant at the 3σ level, though naturally the e.s.d.'s represent only lower limits for standard deviations.

Table 5.2.8 compares the values of Ψ and Φ with those of related compounds; it is clear that Φ_1 and Ψ_1 roughly agree with the values for an anti-parallel pleated sheet; the number of residues per repeat unit, at 1.91, compares well with the anti-parallel pleated sheet value of 2.00.[7]

The analysis of hydrogen bonding (Table 5.2.6) shows the anti-parallel effect to be produced by the two fold axis, molecules related by the two fold being hydrogen bonded; infinite ribbons, parallel to the ac plane are therefore formed, held together along the b axis by Van der Waals forces between the methyl side groups. A projection down the b axis (Figure 5.2.2) shows the molecular packing.

The hydrogen bond lengths are in the expected range for amide hydrogen bonds. The C14-O$\hat{1}$5...H8(179°), C14-O15...N8(176.2°) and C9-O$\hat{1}$O...H13(161°), C9-O$\hat{1}$O...N13(166.8°) angles are those expected from hydrogen bonding to sp lone pairs.

Φ_2 and Ψ_2, which aren't constrained by hydrogen bonding considerations have values close to but outside the limits of the γ information ($-85^{\circ} < \Phi < -60^{\circ}$, $95^{\circ} < \Psi < 160^{\circ}$)[8], which is stabilised by non-bonded interaction between the amide hydrogen (H8) and the side chain (in this case a methyl group C7) and is favoured by a large side chain, T(C7, C6, N8, H8) is 31°.

A comparison of the bond lengths and angles with those expected in a peptide[9] (Table 5.2.9) show good agreement.

The ester group parameters[10] C6-C$\hat{4}$-O3 (11.6°), C6-C4-O5 (126.6°), C4-O5 (1.181 Å), C4-O3 (1.343 Å) agree reasonably well with the average values for esters (methyl) of 111°, 125°, 1.20 Å, 1.34 Å. The latter bond length is, a little surprisingly, longer than the equivalent length in carboxylic acids (1.31 Å).

The ethyl (C1-C2) bond distance is very short (1.42 Å) with a high temperature factor (Table 5.2.2) for C1, but detailed examination of the electron density map showed no evidence of another stable conformation. The distance, although short, was longer than before suppression of reflexions. The ethyl group is practically planar (Table 5.2.5, plane 1) with the carboxylate group, in contrast to the situation in N-Ac-L-Ala-L-Ser-OEt (see 5.3).

The intersheet distance, perpendicular to the ac plane is clearly 4.96 Å (b/2, the C-centring producing the halfing) compared with the 5.7 Å[11] expected for an antiparallel pleated sheet, indicating a somewhat denser packing.

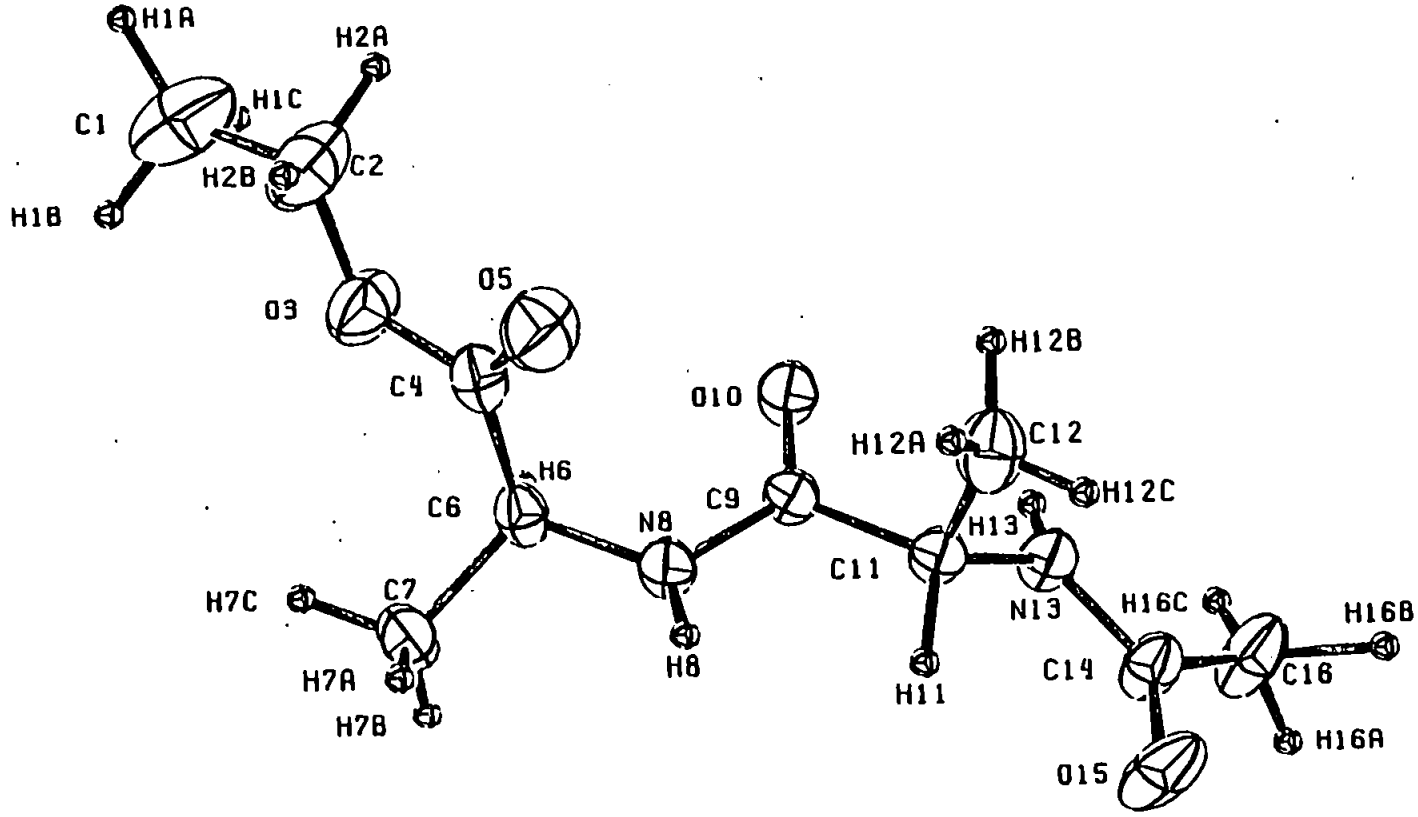

Figure 5.2.1. ORTEP drawing of the molecular structure of N-AcL-Ala-L-Ala-OEt.

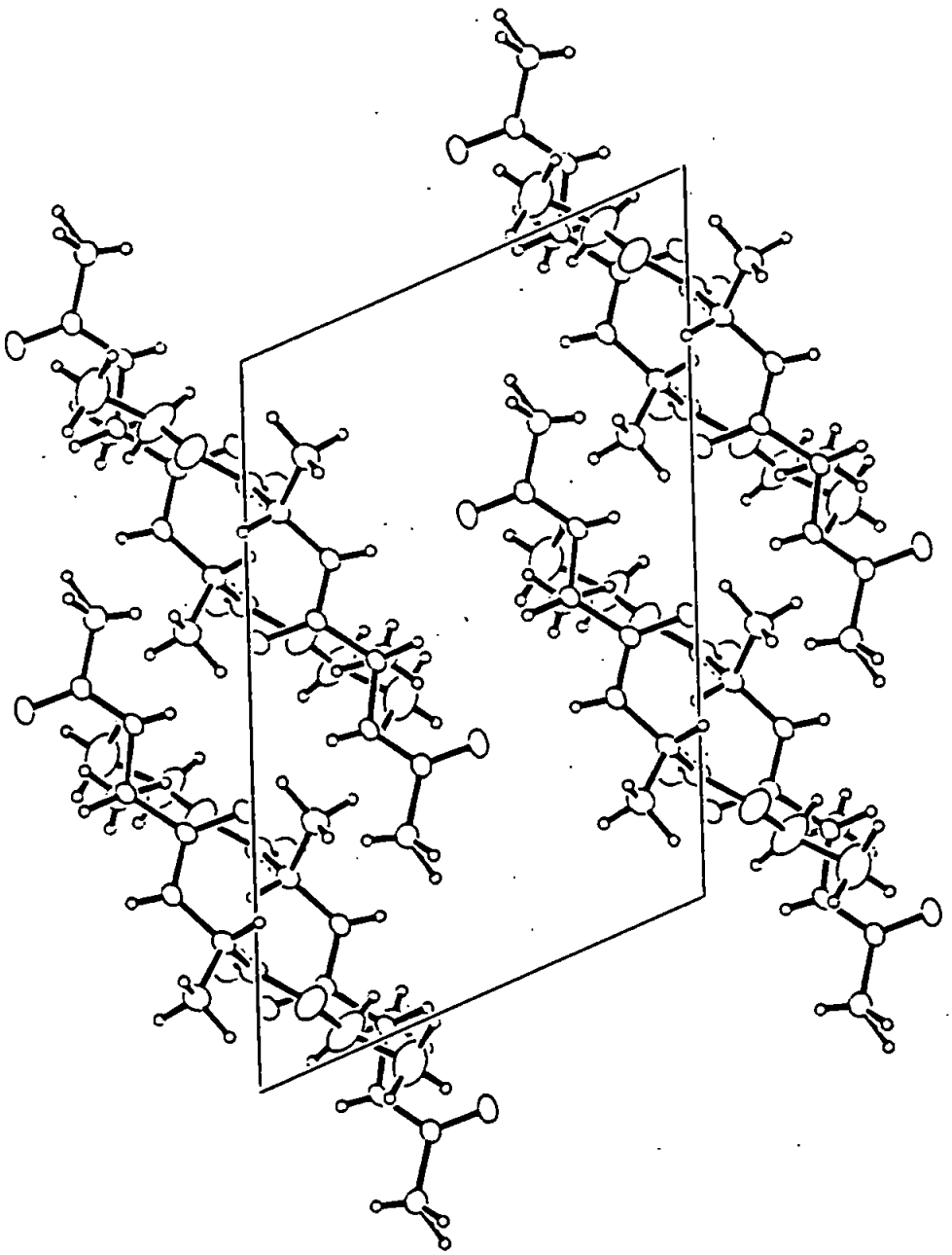

Figure 5.2.2. A projection down the b axis showing the molecular packing.

Table 5.2.1

Atomic fractional co-ordinates. The e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

x	x	y	z
C1	-0.0413(7)	0.211(1)	-0.3310(9)
C2	0.0316(5)	0.2547(8)	-0.1929(9)
O3	0.0911(2)	0.1381(5)	-0.1174(4)
C4	0.1702(3)	0.1603(5)	0.0097(4)
O5	0.1917(3)	0.2695(4)	0.0599(4)
C6	0.2247(2)	0.0315(5)	0.0728(4)
C7	0.1664(3)	-0.0569(6)	0.1369(5)
N8	0.3204(2)	0.0621(0)	0.1854(3)
C9	0.3948(2)	0.1079(4)	0.1509(3)
O10	0.3901(2)	0.1141(4)	0.0213(2)
C11	0.4853(2)	0.1527(5)	0.2822(3)
C12	0.4837(4)	0.3054(6)	0.2954(6)
N13	0.5736(2)	0.1066(5)	0.2614(3)
C14	0.6542(2)	0.0686(6)	0.3762(3)
O15	0.6578(2)	0.0689(6)	0.5050(2)
C16	0.7401(3)	0.0238(9)	0.3400(5)
H6	0.231(2)	-0.013(4)	-0.007(4)
H7A	0.158(4)	-0.017(6)	0.220(6)
H7B	0.196(4)	-0.142(7)	0.164(6)
H7C	0.093(3)	-0.068(5)	0.065(5)
H8	0.333(2)	0.069(3)	0.275(4)
H11	0.485(2)	0.112(3)	0.376(3)
H12A	0.447(4)	0.350(7)	0.319(6)

Table 5.2.1 continued

	x	y	z
H12B	0.476(3)	0.344(5)	0.194(6)
H12C	0.540(4)	0.324(5)	0.373(5)
H13	0.567(3)	0.096(4)	0.180(5)
H16A	0.783(5)	-0.043(7)	0.399(7)
H16B	0.814(6)	0.091(9)	0.401(8)
H16C	0.723(3)	0.006(5)	0.251(6)

Table 5.2.2

Temperature factors - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.163(7)	0.165(7)	0.109(5)	0.028(5)	0.010(5)	0.040(6)
C2	0.098(4)	0.101(4)	0.139(5)	0.004(3)	-0.017(4)	0.013(3)
O3	0.083(2)	0.080(2)	0.095(2)	-0.002(2)	-0.002(2)	-0.003(2)
C4	0.058(2)	0.072(2)	0.070(2)	-0.009(2)	0.026(2)	-0.013(2)
O5	0.101(2)	0.072(2)	0.109(2)	-0.016(2)	0.018(2)	-0.012(2)
C6	0.056(2)	0.071(2)	0.053(2)	-0.012(1)	0.027(1)	-0.012(1)
C7	0.075(3)	0.086(3)	0.074(2)	0.001(2)	0.036(2)	-0.022(2)
N8	0.055(1)	0.084(2)	0.040(1)	-0.006(1)	0.024(1)	-0.008(1)
C9	0.051(2)	0.074(2)	0.043(1)	0.002(1)	0.025(1)	0.001(1)
O10	0.059(1)	0.122(2)	0.040(1)	-0.001(1)	0.025(1)	-0.011(1)
C11	0.050(2)	0.079(2)	0.038(1)	0.001(1)	0.022(1)	-0.001(1)
C12	0.072(3)	0.096(3)	0.082(3)	-0.021(3)	0.028(2)	-0.006(2)
N13	0.053(1)	0.110(2)	0.036(1)	0.001(1)	0.024(1)	-0.001(1)
C14	0.054(2)	0.118(3)	0.040(1)	-0.005(2)	0.019(1)	0.004(2)
O15	0.080(2)	0.210(4)	0.038(1)	0.009(2)	0.022(1)	0.040(2)
C16	0.057(2)	0.187(6)	0.052(2)	-0.009(3)	0.017(2)	0.023(3)
H6	0.05(1)					
H7A	0.09(1)					
H7B	0.10(2)					
H7C	0.09(1)					
H8	0.04(1)					
H11	0.05(1)					

Table 5.2.2 continued

	U_{11}
H12A	0.10(2)
H12B	0.08(1)
H12C	0.08(1)
H13	0.06(1)
H16A	0.11(2)
H16B	0.15(2)
H16C	0.08(1)

Table 5.2.3

Bond lengths (in Angstroms) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

C1-C2	1.42(1)	C9-C11	1.508(4)
C2-O3	1.464(7)	C11-C12	1.523(7)
O3-C4	1.343(4)	C11-N13	1.456(4)
C4-O5	1.181(5)	C11-H11	0.99(3)
C4-O6	1.508(6)	C12-H12A	0.80(7)
C6-C7	1.512(5)	C12-H12B	1.02(5)
C6-N8	1.439(4)	C12-H12C	0.89(5)
C6-H6	0.92(4)	N13-H13	0.76(4)
C7-H7A	0.95(6)	N13-C14	1.327(4)
C7-H7B	0.93(6)	C14-O15	1.221(4)
C7-H7C	1.04(5)	C14-C16	1.498(5)
N8-H8	0.82(3)	C16-H16A	0.94(7)
N8-C9	1.335(4)	C16-H16B	1.22(8)
C9-O10	1.225(3)	C16-H16C	0.82(5)

Table 5.2.4

Bond angles (degrees) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

C1-C2-O3	108.3(6)
C2-O3-C4	117.7(4)
O3-C4-O5	121.8(4)
O3-C4-C6	111.6(3)
O5-C4-C6	126.6(3)
C4-C6-H6	106(2)
C4-C6-C7	111.2(3)
C4-C6-N8	109.8(3)
H6-C6-C7	109(2)
H6-C6-N8	111(2)
C6-C7-H7A	112(3)
C6-C7-H7B	111(3)
C6-C7-H7C	113(3)
H7A-C7-H7B	110(5)
H7A-C7-H7C	100(4)
H7B-C7-H7C	110(4)
C6-N8-H8	125(2)
H8-N8-C9	112(2)
C6-N8-C9	122.5(2)
N8-C9-O10	122.6(3)
N8-C9-C11	115.6(2)
O10-C9-C11	121.8(2)
C9-C11-H11	110(2)
C9-C11-C12	109.1(3)
C9-C11-N13	109.6(2)

Table 5.2.4 continued

H11-C11-C12	109(2)
H11-C11-N13	108(2)
C11-C12-C12A	127(4)
C11-C12-C12B	107(3)
C11-C12-C12C	103(3)
H12A-C12-H12B	103(5)
H12B-C12-H12C	99(5)
H12B-C12-H12C	117(4)
C11-N13-H13	114(3)
C11-N13-C14	121.9(2)
H13-N13-C14	123(3)
N13-C14-O15	121.7(3)
N13-C14-C16	116.7(3)
O15-C14-C16	121.6(3)
C14-C16-H16A	120(4)
C14-C16-H16B	113(4)
C14-C16-H16C	111(3)
H16A-C16-H16B	80(5)
H16A-C16-H16C	111(6)
H16B-C16-H16C	119(5)

Table 5.2.5

Deviations (in Angstroms) from the least squares plane. Asterisked atoms are not used in the least squares calculation.

	1	2	3	4	5	6	7
C1	-0.046						
C2	0.054						
O3	0.025	-0.001					
C4	-0.013	0.004				-0.058	
O5	-0.021	-0.002				0.034	
C6		-0.001	0.013	0.050	0.168*	0.048	
C7							
N8			-0.028	-0.064	0.001	-0.024	
C9			0.030	-0.016	-0.002		
O10			-0.015	-0.008	0.001		
C11				0.038	0.001		0.007*
C12							
N13							-0.001
C14							0.003
O15							-0.001
C16							-0.001

Table 5.2.5 continued

Equations of least squares planes

	a_i	b_i	c_i	d_i
1	-0.5923	-0.1157	0.7974	-2.229
2	-0.5629	-0.1279	0.8165	-2.2082
3	-0.2967	0.9497	0.1002	-0.6751
4	-0.3335	0.9410	0.0583	-0.8030
5	-0.3731	0.9256	0.0637	-1.0493
6	-0.4123	-0.1072	0.9047	-1.8416
7	0.3414	0.9397	-0.0198	3.6612

Table 5.2.6

Hydrogen bonding

Donor X-H	Acceptor Y	Angle XHY°	Distance HY	Distance XY	Position of Acceptor
N13-H13	O10	155	2.3	2.97	(1-x, y, -z)
N8-H8	O15	171	2.1	2.88	(1-x, y, 1-z)

Table 5.2.7

Intra-molecular non-bonded close contacts

(< Van der Waals + 0.35Å)

O3...H6	2.43	O1O...C6	2.778
O3...C7	2.982	O1O...H13	2.45
O5...C2	2.661	O1O...N13	2.797
O5...N8	2.742	N13...H12C	2.54
H8...C11	2.36	N13...H16C	2.44
H8...H11	2.11	C14...H11	2.51
N8...H11	2.46	O15...C11	2.745
C9...C4	3.088	O15...H11	2.39
C9...H13	2.43	C16...H13	2.52

Table 5.2.8

Comparison of the conformational angles with similar compounds

	ϕ_1	ϕ_2	ϕ_3	ψ_1	ψ_2	ψ_3
Anti-parallel pleated sheet[12]		-142		145		
β-Poly-L-Ala[13]		-139		135		
$(L\text{-Ala})_2.HCl$[14]		-153		157	163	
$(L\text{-Ala})_2$[15]		-113		165	103	
$(L\text{-Ala})_3$ Molecule A[16]		-146	-147	153	146	172
$(L\text{-Ala})_3$ Molecule B		-156	-160	162	150	144
N-Acetyl $(L\text{-Ala})_2$-OEt	-145	-74		138	166	

Table 5.2.9

	1st Amide	2nd Amide	Expected Value
$C^{\alpha}-C(O)$	1.498	1.508	1.51
C=O	1.221	1.225	1.24
C-N	1.327	1.335	1.32
$N-C^{\alpha}$	1.456	1.439	1.45
$C^{\alpha}-C^{\beta}$	1.523	1.512	1.53
$C^{\alpha}-\hat{C}(O)-O$	121.6	121.8	120.5
$C^{\alpha}-\hat{C}(O)-N$	116.7	115.6	116
$O-\hat{C}-N$	121.7	122.6	123.5
$C-\hat{N}-C^{\alpha}$	121.9	122.5	122
$N-\hat{C}^{\alpha}-C(O)$	109.6	109.8	111

5.3 N-Acetyl-L-Ala-L-Ser-OEt

Experimental

The compound was prepared by the carbodiimide method[3] and recrystallised from $EtOH/Et_2O$.

Formula $C_{10}H_{18}N_2O_5$

$a = 15.283$ Å

$b = 9.822$ Å

$c = 9.710$ Å

$\beta = 112.94^{\circ}$

$Z = 4$

$V = 1342.29$ Å^3

$D_o = 1.22$ Mg m^{-3} (CCl_4/C_6H_{14})

$D_c = 1.22$ Mg m^{-3}

Space group C2

$\mu = 0.062$ mm^{-1}

F(000) = 528

Data were collected using Mo-K_α radiation monochromated with graphite ($1.5 < \theta < 30^{\circ}$). 2210 reflexions were measured (44 of which were intensity controls), 2067 being unique (1386, 67% $|F| > 3\,\sigma(|F|)$).

After data reduction, a convergence map was calculated and used to select a starting set. Tangent expansion using SHELX with $E \geq 1.2$ and examination of E-maps with higher figures of merit (RA) failed to reveal the structure.

Consequently a two pronged approach was used:

A. N-Acetyl (L-Ala)$_2$-OEt

The compound is almost isomorphic with the desired compound. A rough index of how closely they are related is given by:

$$ISOM = N\Sigma(|E|_i - |E|'_i)^2/n$$

= o for 'perfect' isomorphism

= 1 for a random relationship

$$N = (2(1 - m^2))^{-1}$$

m = 0.798 for centrosymmetric end

= 0.886 for non-centrosymmetric crystals

For N-Ac-L-Alu-L-Ser-OEt and N-Ac-L-Alu-L-Ma-OEt

ISOM = 0.427

Nine atomic positions from N-Ac-L-Ala-L-Ala-OEt were used to phase the reflexions (one atom having a fixed y coordinate), the atoms being chosen so that their positions hopefully wouldn't be altered too much by distortions introduced by the hydroxyl group (such as hydrogen bonding), and a difference map calculated. At this point R = 52%, R_G = R_M = 55%. Atoms revealed in the map were inserted and the process continued until the entire molecule had been found. Least squares refinement then continued isotropically until R = 25%, R_G = 21%, R_M = 17% and thereafter anisotropically. At R = 13%, R_M = R_G = 11%, hydrogen atoms were inserted.

After weighting (g = 0.003) and with all reflexions R = 10%, R_W = 9% = R_M = R_G. This was after a domain anisotropy correction when an F_o/F_c analysis showed evidence of extinction. As well as the reduction in peaks close to atoms, the C-C ethyl bond length 'improved' from 1.38A to 1.43A. A detailed examination of the electron density map didn't reveal any splitting of the Cl peak. A refinement using atoms with variable occupancy was not successful.

The final atomic parameters are shown in Table 5.3.1 and Table 5.3.2. Structure factor tables are in Appendix E (Table E.2).

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By giving the Ψ_o component of FOM a high weight (1.3) the structure was solved. This contrast with N-Ac(L-Ala)$_2$OEt can be explained by noting the beneficial effects of an increase in data. For a fixed number of strongest reflexions (300) and Σ_2 interactions an increase (from 1499 to 2067) in the number of reflexions leads to an increase in E_{min}, 1.41 for N-Ac-L-Ala-L-Ser-OEt compared with 1.24 for N-Ac(L-Ala)$_2$OEt and κ_{min}, 1.50 for N-Ac-L-Ala-L-Ser-OEt and 1.39 for N-Ac(L-Ala)$_2$OEt. This means that any fragmentation of the data set is reduced and a better phase development obtained.

Discussion

While both amide groups have the usual trans configuration, only one of the amide groups shows the expected planarity (Table 5.3.5, plane 1) with $\omega_1 = 179^{\circ}$; the other amide group has the chiral carbon (C8) deviating significantly from the plane (plane 3, $\omega_2 = 173^{\circ}$). Although the resonance stabilisation energy associated with a planar amide group is almost 20 Kcal/mole[17], there is only a small energy penalty for limited rotations about $N_i - C_i$. Both theoretical and experimental studies performed on amides and other peptide model compounds suggest that rotations of up to 15° are energetically allowable[18-20].

Theoretical modelling of the peptide system with ω as a variable indicates that there is an increased conformational flexibility of the peptide chain, with the gain in stability from non-bonded, electrostatic and hydrogen bonding more than compensating for the energy expenditure required for peptide bond non-planarity. The effect is greater with larger side chains[21].

The values of Φ_1 and Ψ_1 (Table 5.3.8) approach quite closely those for an anti-parallel pleated sheet, as can be seen by computing 'n', the number of residues per repeat unit; the value of 1.94 is quite close to the sheet value of 2.0, bearing in mind that mean bond lengths and angles were assumed in the calculation. The position given by Φ_1 and Ψ_1 on a Ramachandran plot (as it is usually drawn) is to the right of the n = 2 line and corresponds to a righthand twist (about an axis along the peptide chain) to the sheet.

It has been argued[22], with some experimental support[23], from a survey of Ψ, Φ values in lysozyme, carboxypeptidase A, α-chymotrypsin, myoglobin and ribonuclease S, that a sheet with a right hand twist is more stable than either a 'perfect' anti-parallel sheet or one with a left

handed twist. The basis of the argument is as follows:

By definition the stablest state has the lowest free energy G:

$$G = H - TS$$

As

$$S = k \log \Omega$$

where Ω is the number of a priori equally probably microstates of the assembly, and assuming that all Φ,Ψ values within the allowed region are equally likely, then, because the n = 2 line splits the allowed region so that the area to the left is less than the area to the right, peptides with a right hand twist have a higher entropy and, other things being equal, a greater stability than sheets with no twist or a left hand twist.

Since sheets with a right-hand twist are relatively pliable (especially near the centre of the allowed region) they are able to modify their environments locally to achieve the tight packing that 'good' packing in a crystal or protein generally entails.

The hydrogen bonding analysis (Table 5.3.6) shows bonding between molecules related by the two fold axis; a projection down the b axis (Figure 5.3.2) shows the effect of this on the molecular packing; infinite sheets parallel to the a c plane, are formed, being held together along the b axis by Van der Waals forces between the $-CH_3$ and $-CH_2OH$ groups.

The value expected of the inter-sheet distance for an anti-parallel pleated sheet is provided by silk, which can be considered as (Gly-Ser-Gly-Ala-Gly-Ala)$_n$. The sheets are held together by Van der Waals forces between the side chains; Gly and Ala/Ser alternately (along the sheet normal) pack together so that there are two inter-sheet distances, one for Gly (3.5 Å) and the other for Ala/Ser (5.7 Å)[11]. The inter-sheet distance perpendicular to the a c plane, at 4.911 Å (b/2), is therefore considerably smaller than 5.7 Å or even, surprisingly, the equivalent N-Ac(L-Ala)$_2$-OEt distance (4.96 Å).

The values of Φ_2 and Ψ_2, which are not constrained by hydrogen bonding considerations, have values close to of the γ conformation, (T(C7,C8,N9,H9)=- 33) which was indicated by a shoulder in the i.r. (KBr) at 3440 cm^{-1} (v(N-H)). Overall, Table 5.3.8 shows that substitution of Ser for Ala produces relatively little change in the Φ and Ψ angles.

Table 5.3.9 shows the bond lengths and angles conform quote closely to the weighted average for small peptides[9]. The parameters of the ester group C5-O3 (1.319 Å), C5-O4 (1.195 Å), C8-C5-O4 (125.2°), and C8-C5-O3 (111.8°) compared quite well with the expected values of 1.34 Å, 1.20 Å, 125° and 111° respectively[10].

A more detailed examination of the hydrogen bonding, particularly the C15-$\hat{O}$16...H9 (174°), C15-$\hat{O}$16...N9 (177.2°) and C10-$\hat{O}$11...H14 (161°), C10-$\hat{O}$11...N14 (167.0°) angles show the amide hydrogens donating to sp lone pairs. As O16 is also an acceptor for H6, the second hydrogen bond would be expected to interact with the lone pair in the 2p orbital implying a C15-$\hat{O}$16...H6 angle of 90°. The observed value is 116° with C15-O16...O6 at 120.4°.

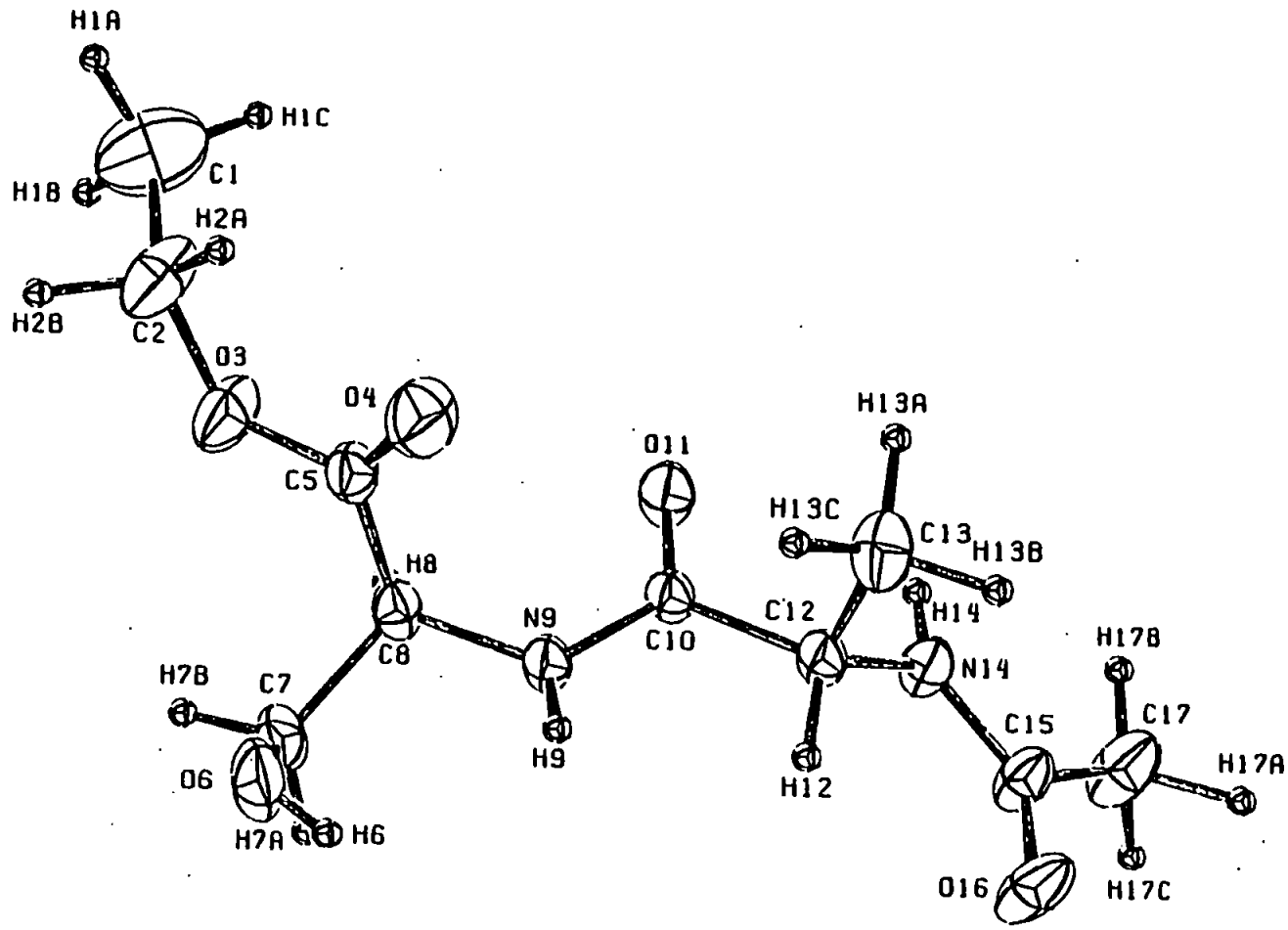

Figure 5.3.1. ORTEP drawing of the molecular structure of N-AcL-Ala-L-Ser-OEt

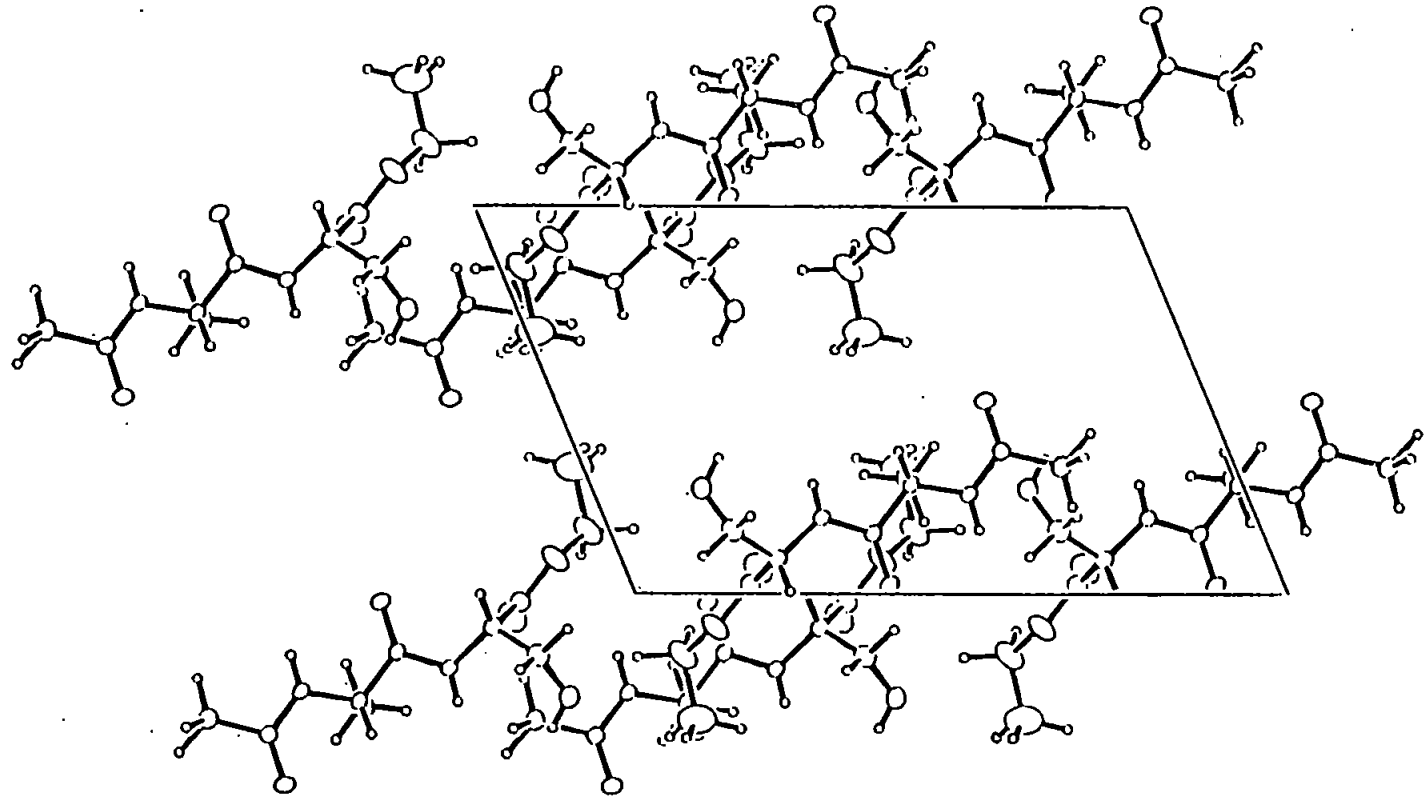

Figure 5.3.2. Projection down the b axis showing the molecular packing.

Table 5.3.1

Atomic fractional co-ordinates; the e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

	x	y	z
C1	0.017(1)	0.233(1)	-0.313(1)
C2	0.0331(4)	0.2358(9)	-0.1594(8)
O3	0.1007(2)	0.1248(7)	-0.0880(4)
O4	0.2040(3)	0.2695(6)	0.0647(5)
C5	0.1815(2)	0.1557(7)	0.0233(4)
O6	0.1675(3)	0.0104(8)	0.2699(4)
C7	0.1888(3)	-0.0594(7)	0.1622(5)
C8	0.2392(2)	0.0322(6)	0.0877(4)
N9	0.3331(2)	0.0678(6)	0.1954(3)
C10	0.4023(2)	0.1087(6)	0.1546(3)
O11	0.3953(2)	0.1105(6)	0.0245(2)
C12	0.4920(2)	0.1568(7)	0.2820(4)
C13	0.4902(4)	0.3129(8)	0.2925(8)
N14	0.5744(2)	0.1082(7)	0.2573(3)
C15	0.6518(2)	0.0654(0)	0.3686(4)
O16	0.6588(2)	0.0635(7)	0.4991(3)
C17	0.7342(3)	0.0210(9)	0.3283(5)
H6	0.209(5)	0.025(7)	0.342(8)
H7A	0.226(2)	-0.160(4)	0.202(4)
H7B	0.127(4)	-0.095(5)	0.095(5)
H8	0.238(3)	-0.021(5)	0.003(5)
H9	0.340(2)	0.076(3)	0.280(4)
H12	0.492(3)	0.118(4)	0.369(5)

Table 5.3.1 continued

	x	y	z
H13A	0.487(4)	0.364(7)	0.182(7)
H13B	0.510(4)	0.356(6)	0.376(7)
H13C	0.445(7)	0.34(1)	0.33(1)
H14	0.568(3)	0.111(4)	0.162(5)
H17A	0.7237(3)	0.0339(9)	0.2125(5)
H17B	0.7542(3)	-0.0830(9)	0.3617(5)
H17C	0.7898(3)	0.0886(9)	0.3971(5)

Table 5.3.2

Temperature factors. The e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.20(1)	0.160(8)	0.088(5)	0.015(5)	0.034(6)	0.059(8)
C2	0.071(3)	0.117(5)	0.103(5)	0.004(4)	-0.003(3)	0.025(3)
O3	0.061(2)	0.082(2)	0.083(2)	-0.011(2)	-0.007(2)	0.000(2)
O4	0.084(3)	0.068(2)	0.108(3)	-0.005(2)	0.010(2)	-0.014(2)
C5	0.048(2)	0.067(2)	0.049(2)	-0.005(2)	0.015(2)	-0.013(2)
O6	0.057(2)	0.177(4)	0.061(2)	-0.005(2)	0.027(2)	-0.040(2)
C7	0.059(2)	0.082(3)	0.064(2)	-0.002(2)	0.017(2)	-0.037(2)
C8	0.047(2)	0.062(2)	0.043(2)	-0.011(2)	0.020(1)	-0.012(1)
N9	0.041(1)	0.078(2)	0.033(1)	-0.005(1)	0.017(1)	-0.013(1)
C10	0.042(1)	0.059(2)	0.037(2)	-0.002(2)	0.020(1)	-0.007(1)
O11	0.054(1)	0.123(3)	0.036(1)	-0.001(1)	0.023(1)	-0.017(2)
C12	0.039(1)	0.076(2)	0.038(2)	0.000(2)	0.021(1)	-0.007(2)
C13	0.061(3)	0.079(3)	0.096(4)	-0.018(3)	0.020(3)	-0.016(2)
N14	0.040(1)	0.101(2)	0.034(1)	-0.001(2)	0.018(1)	-0.003(2)
C15	0.042(2)	0.111(3)	0.038(2)	-0.002(2)	0.014(1)	0.011(2)
O16	0.059(2)	0.172(4)	0.036(1)	0.010(2)	0.017(1)	0.031(2)
C17	0.053(2)	0.165(5)	0.055(2)	-0.001(3)	0.024(2)	0.025(3)
H6	0.09(2)					
H7A	0.04(1)					
H7B	0.07(1)					
H8	0.05(1)					
H9	0.027(7)					

Table 5.3.2 continued

	U_{11}
H12	0.05(1)
H13A	0.10(2)
H13B	0.08(1)
H13C	0.13(3)
H14	0.05(1)
H17A	0.17(3)
H17B	0.24(5)
H17C	0.16(4)

Table 5.3.3

Bond lengths (in Angstroms) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

C1-C2	1.42(1)	C10-C12	1.520(5)
C2-O3	1.476(7)	C12-H12	0.92(4)
O3-C5	1.322(5)	C12-C13	1.538(8)
O4-C5	1.192(6)	C13-H13A	1.16(7)
O6-H6	0.75(7)	C13-H13B	0.97(6)
O6-C7	1.390(6)	C13-H13C	0.9(1)
C7-H7A	1.13(4)	N14-C12	1.451(4)
C7-H7B	0.99(5)	N14-H14	0.90(4)
C7-C8	1.536(5)	N14-C15	1.323(4)
C8-H8	0.96(5)	C15-O16	1.229(4)
C8-C5	1.486(6)	C15-C17	1.521(5)
C8-N9	1.451(4)	C17-H17A	1.08(0)
N9-H9	0.79(3)	C17-H17B	1.08(0)
N9-C10	1.327(4)	C17-H17C	1.08(0)
C10-O11	1.226(4)		

Table 5.3.4

Bond angles (degrees) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

C1-C2-O3	106.4(7)	C10-C12-H12	107(3)
C2-O3-C5	118.3(4)	C10-C12-C13	109.3(4)
O3-C5-O4	123.1(4)	C10-C12-N14	109.2(3)
O3-C5-C8	111.6(3)	H12-C12-C13	110(3)
O4-C5-C8	125.3(3)	H12-C12-N14	109(2)
H6-O6-C7	116(5)	C13-C12-N14	112.2(3)
O6-C7-H7A	114(2)	C12-C13-H13A	111(3)
O6-C7-H7B	103(3)	C12-C13-H13B	118(3)
O6-C7-C8	111.8(4)	C12-C13-H13C	113(6)
H7A-C7-H7B	98(3)	H13A-C13-H13B	109(5)
C8-C7-H7A	114(2)	H13A-C13-H13C	115(7)
C8-C7-H7B	115(3)	H13B-C13-H13C	89(7)
C5-C8-H8	106(3)	C12-N14-H14	114(3)
C5-C8-C7	110.7(3)	C12-N14-C15	121.8(3)
C5-C8-N9	111.4(3)	C15-N14-H14	124(2)
C7-C8-H8	104(3)	N14-C15-O16	122.5(3)
C7-C8-N9	109.8(3)	N14-C15-C17	116.6(3)
N9-C8-H8	116(3)	O16-C15-C17	120.9(3)
C8-N9-H9	118(2)	C15-C17-H17A	115.6(2)
C8-N9-C10	122.5(3)	C15-C17-H17B	111.1(3)
C10-N9-H9	118(2)	C15-C17-H17C	101.3(3)
N9-C10-O11	123.5(3)	H17A-C17-H17B	109.5(0)
N9-C10-C12	115.0(2)	H17A-C17-H17C	109.5(0)
O11-C10-C12	121.5(3)	H17B-C17-H17C	109.5(0)

Table 5.3.5

Deviations (in Angstroms) from the least squares planes.

Asterisked atoms are not used in the least squares calculation.

	1	2	3	4
C17	0.002			
O16	0.003			
C15	-0.008			
N14	0.003			
C12	0.038*	0.002		
O11		0.002	-0.011	
C10		-0.006	0.022	
N9		0.002	-0.020	
C8		0.139*	0.009	0.000
C5				-0.001
O4				0.000
O3				0.000
C2				0.064*
C1				-1.087*

Table 5.3.5 continued

Equations of the least squares planes

	a_i	b_i	c_i	d_i
1	0.3529	0.9356	-0.0047	3.8486
2	-0.3625	0.9313	0.0366	-1.0842
3	-0.2971	0.9527	0.0649	-0.7439
4	-0.4442	-0.0888	0.8915	-2.0329

Table 5.3.6

Hydrogen bonding

Donor X-H	Acceptor Y	Angle XHY°	Distance H-Y	Distance X-Y	Position of Acceptor
N9-H9	O16	167	2.1	2.94	(1-x,y,1-z)
O6-H6	O16	165	2.0	2.78	(1-x,y,1-z)
N14-H14	O11	159	2.1	2.95	(1-x,y,-z)

Table 5.3.7

Intra-molecular contact distances (< Van der Waals + 0.35Å)

C2...O4	2.690	O11...C8	2.793
C5...C1	3.342	O11...H14	2.44
C5...O6	2.866	O11...N14	2.789
C5...C10	3.141	C12...H9	2.44
C7...O3	2.905	C12...O16	2.755
C7...H9	2.53	H12...H9	2.18
H7A...H6	2.34	H12...H13C	2.33
H8...O3	2.40	H12...C15	2.49
H8...H7B	2.32	H12...O16	2.42
N9...O4	2.735	C13...C15	3.337
N9...O6	2.944	H14...C10	2.50
N9...H12	2.41		

Table 5.3.8

Conformational angles (in degrees)

	ϕ_1	ϕ_2	ψ_1	ψ_2
N-Ac-L-Ala-L-Ser-OEt	-142	-78	140	172
N-Ac-L-Ala-L-Ala-OEt	-145	-74	138	166

Table 5.3.9

Significant bond lengths and angles (in Angstroms and degrees respectively).

	First Amide	Second Amide	Expected Value
C-C(O)	1.521	1.520	1.51
C=O	1.229	1.226	1.24
C-N	1.323	1.327	1.32
$N-C^{\alpha}$	1.451	1.451	1.45
$C^{\alpha}-C^{\beta}$	1.538	1.536	1.53
$C-\hat{C}(O)-O$	120.9	121.5	120.5
$C-\hat{C}(O)-N$	116.6	115.0	116
$O-\hat{C}-N$	122.5	123.5	123.5
$C-\hat{N}-C^{\alpha}$	121.8	122.5	122
$N-\hat{C}^{\alpha}-C(O)$	109.2	111.4	111

5.4 Structure Solution Strategies

The problems raised by the initial failure to solve the structure of N-Ac-(L-Ala)$_2$OEt provoked the study of the constitution of a good starting set.

A starting set may be selected very satisfactorily by a convergence map, which isolates those reflexions that interact most strongly with the data set. However, it can happen, when these reflexions are used, that subsets of reflexions, poorly linked with the rest of the data set, are not satisfactorily phased.

To obviate that possibility, representative reflexions from the subsets are required in the starting set, i.e. what might be called core reflexions, that interact minimally with the main data set, while being well indicated by some subset. The latter requirement is produced by a high $\langle\alpha^2\rangle$, while to satisfy the second involves looking for reflexions which are badly determined by Σ_2 relationships with some strong reflexions.

The obvious way is to search through Ψ_o reflexions (defined to be the strong reflexions of a triplet with two strong and one weak reflexion) looking for reflexions that are present in a number of relationships. However, it is by no means clear, once a list of such reflexions has been prepared, what criterion to use for ordering, whether number of Ψ_o interactions, or the magnitudes of the strong reflexions, or a mixture of both. For this reason, it was decided to look at a restricted group of reflexions $E_{-h-k-\ell}$ which have a Ψ_o interaction with three other reflexions E_h, E_k, E_ℓ (5.4.1 and 5.4.2). This will be recognised as the definition of a negative quartet (N.Q.)[24].

5.4.1 $\quad |E|_h,\ |E|_k,\ |E|_\ell,\ |E|_{-h-k-\ell} > \text{EMIN}$

5.4.2 $\quad |E|_{h+k},\ |E|_{h+\ell},\ |E|_{k+\ell} < \text{EMAX}$

The other three reflexions naturally have a similar relationship.

N.Q.s are of course used in the NQEST test precisely because the phases are largely independent of the phase expansion process, i.e. they are not strongly linked by Σ_2. The use of N.Q. reflexions in the starting set would be expected to remove some of this independence as has been found when negative quartet relationships are used in the phase expansion (NQEST becomes a less discriminating F.O.M.)[25].

The criterion used for ordering reflexions is the strength of the indication of the phase by N.Q. relationships. For one relationship it is proportional to

$$5.4.3 \quad B = [2/N]|E|_h|E|_k|E|_\ell|E|_m(Y + \sum^{n}(|E|^2_{cross} - 1)$$

where Y and n are usually 1 and 3 respectively and $h + k + \ell + m = 0$. For multiple indications of phase, by a similar derivation to $\langle\alpha^2\rangle$ (see Appendix B), the appropriate measure is

$$\langle\beta^2\rangle = \Sigma B^2 + 2 \sum_i \sum_j \sum_i B_i B_j (I_1(B_i) I_1(B_j))/(I_o(B_i) I_o(B_j))$$

For a centrosymmetric structure[26], the appropriate measure is ΣB^2.

The foregoing analysis rationalizes the use, in the starting set, of reflexions that occur frequently in the NQEST test, a procedure found to be of use[27]. It would be expected that the number of N.Q.s would vary with the fragmentation of the data set, and it has indeed been noted that the number is highly structure dependent[24].

Program Description

Data are converted from SHELX LIST 3 format to H, K, L, $|F|$, ID; ID is zero if $|F| > 3\sigma$ ($|F|$) otherwise one. As a necessary condition for a reflexion to be designated as strong is an ID of zero, the cut-off point can alter the reflexions chosen.

The reflexions with high $\langle\beta^2\rangle$ are isolated by using the SIGMA2 subroutine of MULTAN 78 to provide the reflexions of the Ψ_o test; be-

cause symmetry is being ignored, to prevent quartet duplication[28], symmetry-invariant weak reflexions are ignored; in the case of C2 they are reflexions of the form O k O. For a quartet to be retained all reflexions must be distinct. If the number of quartets is greater than 250, the quartets with the highest B values are retained. The latter operations are performed by an appended segment (KWICORE) that isolates and processes the quartets.

Possible Development

Symmetry effects could be incorporated and quartets having systematically absent cross-reflexions (not lattice extinctions)[29].

When B > O the quartet is probably O while when B < O it is π. Thus when $Y \approx \Sigma\ (1 - |E|^2_{cross})$ the quartet is somewhere between O and π and hence potentially an enantiomorphically sensitive invariant. As lack of enantiomorphic definition is often a problem these quartets could be of value in choosing the starting set or selecting the 'best' (which is not to say correct) solution by a F.O.M. of the type defined below:

$$\Sigma W \cos(\Phi_h + \Phi_k + \Phi_\ell + \Phi_m)/\Sigma W$$

A good solution would have a value near zero. Possible weights are $\langle\alpha_h\rangle\langle\alpha_k\rangle\langle\alpha_\ell\rangle\langle\alpha_m\rangle$.

Utlilisation

In order to assess the effectiveness of the procedure, a comparison with a run of MULTAN 78, where the starting set was chosen automatically, was undertaken.

The starting set chosen, from which the structure solution could not be isolated, is shown below.

				$\lvert E \rvert$
Origin	11	1	$\bar{8}$	2.892
	12	0	$\bar{1}$	2.569
Enantiomorph	6	2	$\bar{1}\bar{0}$	3.489
	6	0	$\bar{1}\bar{0}$	4.015
	12	2	$\bar{1}$	1.902
	5	5	1	1.811
	13	1	$\bar{1}$	2.659
	1	1	$\bar{2}$	1.712
	2	0	$\bar{2}$	2.389

The number of strong reflexions was 300 ($\lvert E \rvert \leq 1.235$)

The number of Σ_2 relationships was 3500.

The number of reflexions per non-hydrogen atom (17.6) and Σ_2 relationships per reflexion (11.7) were greatly in excess of the values usually required ($\sim$ 10 and $\sim$ 8 respectively). Examination of the starting set shows eight out of the nine reflexions to be of the form h k $\bar{\ell}$, leaving the other half of the data set under-represented. Possibly by inputting molecular geometry and changing the balance of the starting set the structure could have been solved, but instead a starting set was selected from reflexions with high $\langle\beta^2\rangle$ (and reasonably high $\langle\alpha^2\rangle$).

These were isolated with $\lvert E \rvert_{max} \leq 0.7$ (388 reflexions, one of which was a symmetry-invariant). The number of strong reflexions (130) involved in Ψ_o relationships was adjusted to maximise the number of relationships while not producing so many that they needed to be sorted. The N.Q.s isolated had a $\langle\cos(\Phi_h + \Phi_k + \Phi_\ell + \Phi_m)\rangle$ of -0.354 and a B weighted $\langle\cos(\Phi_h + \Phi_k + \Phi_\ell + \Phi_m)\rangle$ (i.e. NQEST) of 0.399 based on the refined structure.

The starting set was as follows:

				|E|
Origin	7	1	$\bar{10}$	2.618
	6	2	9	2.537
	10	2	$\bar{7}$	2.496
	9	5	1	2.092
	4	0	$\bar{2}$	2.492
	4	0	3	2.592
	3	1	7	2.961
Enantiomorph	13	1	$\bar{1}$	2.659
	1	1	$\bar{2}$	1.712

The final two reflexions were left for the program to choose to ensure there would be no break in the phase expansion generated by CONVERGE. The phase expansion, using the same number of strong reflexions and Σ_2 relationships as in the previous run, produced an E-map from which the structure could be found.

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CHAPTER SIX

N-ACETYL DEHYDRO-PHENYLALANINE

AND

N-ACETYL DEHYDRO-PHENYLALANYL-L-PROLINE

6.1 Introduction

While dehydro-alanyl residues are constituents of a wide range of natural products, dehydro-phenylalanyl residues have, so far, been found in only two: albonoursin[1] and tentoxin[2]. They are, remarkably, both cyclic peptides (dipeptide and tetrapeptide respectively).

The first compound, albonoursin, has been isolated from a number of organisms, where its function is not clear, but is possibly related to its sometimes present antibiotic properties; it also displays anti-tumour activity (non-dose dependent)[3]. Although all the geometrical isomers have been synthesised[4], no structure-activity correlations have been reported. The isolation of a number of similar compounds (cyclic dipeptides with dehydro-tryptophan residues) has been reported, but with no details of biological activity[5].

Tentoxin is a phytotoxin isolated from the fungus Alternaria tenuis, which, when applied to germinating seedlings, causes chlorosis; the effect is species specific and is associated with a tentoxin binding site on CF_1 (chloroplast coupling factor 1, a vital protein in A.T.P. synthesis) in sensitive species[6].

Chemically it would be expected that dehydro-phenylalanyl derivatives would be easier to isolate than dehydro-alanyl derivatives since tantomerism with the imino form is restricted by the conjugation of the olefin bond with the phenyl ring. Indeed even derivatives with free amino groups have been synthesised[7]. In fact, β substitution of dehydro-alamine generally appears to increase stability to electrophiles[8] and similar derivatives with a range of β substituents have been synthesised[9].

The presence of a dehydro-phenylalamine residue has been found to confer resistance to enzymolysis by both thermolysin, an endopeptidase with specificity for the amino sites of hydrophobic amino acid residues

and chymotrypsin, an endopeptidase specific for the carboxyl sites of aromatic amino acid residues. Thus the substitution of a dehydro-phenylalanyl residue for a phenylalanine residue in an encephalin analogue (Tyr-D-Ala-Gly-Phe-Met-NH_2) produced resistance to in vivo enzymolysis as well as the bonus of increased potency (x 5)[10].

Further details of the chemistry can be found in Chapter 2.

6.2 N-Acetyl Dehydro-phenylalanine

Experimental

The compound was prepared by hydrolysis of 2-methyl 4-benzylidene oxazolin-5-one. Chunky prisms were grown by cooling slowly an aqueous solution.

The measured density and a molecular weight calculated on the basis of $C_{11}H_{11}NO_3$ gave Z = 4.69. Drying in vacuo over silica gel indicated eight water molecules per unit cell, confirmed later by the structural determination.

Formula = $C_{11}H_{11}NO_3.2H_2O$

Space group = $P2_1/a$

F(000) = 512

a = 18.281 Å

b = 6.080 Å

c = 11.401 Å

β = 105.94°

Z = 4

V = 1218.75 $Å^3$

D_o = 1.31 Mg m^{-3}

D_c = 1.31 Mg m^{-3}

μ = 0.066 mm^{-1}

Data were collected on a CAD4 diffractometer by the θ/2θ mode, using Mo-K_α radiation monochromated with graphite.

Of the 2589 reflexions measured (100 intensity control measurements, $1.5^\circ < \theta < 27^\circ$) 2361 were systematically present, of which 2154 were unique (1297, 60.2% $|F| > 3\sigma(|F|)$).

The structure was solved using the EEES facility of SHELX. The first E-map revealed 15 atoms (R = 41%, R_G = 40.5%, R_M = 40%). At R = 33%, $R_M = R_G$ = 37% a difference map revealed the two oxygens.

Refinement continued until R = 12%, = R_G = R_M after which anisotropic refinement commenced. At R = 9% = R_M = R_G a difference map revealed the hydrogens and refinement continued until:

	R	$R_M = R_G$
all|F|	10.5	8.6
$\|F\| > 2\sigma(\|F\|)$	5.7	5.7

Following weighted refinement

	R	$R_M = R_G$	R_W	S^2	g
all|F|	10.6	7.0	6.6	0.0027	0.0015
$\|F\| > 2\sigma(\|F\|)$	5.8	6.8	5.7	1.65	0.0015

The high percentage of weak reflexions probably explains the high R factor with all reflexions. The final atomic parameters are listed in Table 6.2.1 and Table 6.2.2. $10|F_o|/10|F_c|$ tables are in Appendix E (Table E.5).

Discussion

The first impression, confirmed by least squares plane analysis (Table 6.2.5, plane 5), was of a plane from which the amide group skews.

Examination of the intra-molecular non-bonded distances (Table 6.2.7) reveals severe steric crowding between the amide oxygen (O3) and C5, amide nitrogen (N4) and 'hydroxyl' oxygen (O15), and the carboxylic acid carbon (C13) and the carbonyl carbon; these make it clear why the amide group isn't in the plane. Possibly an auxillary factor is to facilitate hydrogen bonding (by H1W1) to O3 and H4 to O14.

An analysis of the hydrogen bonding (6.2.6) shows how extensive it is, with all possible hydrogen bond donors donating. Hydrogen bonds involving the water molecules are clearly shorter (average value 2.72 Å) than the amide hydrogen bond (2.98 Å) as is usually found.

Despite the hydrogen positions being uncertain it is quite instructive to examine the water molecules in detail. The H-$\hat{O}$-H values at 103° (W1) and 108° (W2), as expected, are less than $\cos^{-1}(-1/3)$.

The angles involving donating hydrogen atoms for the first water molecule (W1), H2W1...H1W2(120°), H2W1-$\hat{W1}$...H2W2(110°), H1W1-W1...H1W2 (117°) and H1W1-W1...H2W2(114°) show the hydrogens are roughly tetrahedrally arrayed around the oxygen. Although the interaction of the donated hydrogens might be expected to alter the repulsion between lone pairs, it is still surprising that H2W2...$\hat{W1}$...H1W2(93°) is less than $\cos^{-1}(-1/3)$. The relevant angles for the second water molecule (W2), H2W2-$\hat{W2}$...H15(128°) and H1W2-W2...H15(123°) show a similar tendency.

An equivalent analysis of the hydrogen bonding to the other donors shows some interesting features. C2-$\hat{O3}$...H1W1(124°), C2-$\hat{O3}$...W1(125°) and, less convincingly C13-$\hat{O14}$...H4(143°), C13-$\hat{O14}$...N4(140.0°) indicate sp^2 hybridisation of the carbonyl oxygens. The H15-$\hat{O15}$...W1(91.7°)

H15-$\hat{O}$15...H2W1(92°), C13-$\hat{O}$15...W1(153.1°), C13-$\hat{O}$15...H2W1(153°) and H15-$\hat{O}$15-C13(115°) angles indicate that H2W1 is in the plane of H15-O15-C13 as the sum of the first, third and fifth angles is 359.8°. Despite the non-ideal values, the oxygen (O15) must be presumed to be sp^2 hybridised.

Figure 6.2.2, a projection down the b axis, shows the molecular packing. It can be rationalised as molecular sheets, parallel to the ab plane, held together by chains of water molecules parallel to the b axis.

The phenyl group is planar (Table 6.2.5, plane 5) with an average bond length of 1.384 Å. The bond length, after a rigid body librational correction, despite the reasonably low value of R_G(11.3%), at 1.387 Å is considerably below the spectroscopic value for benzene (1.395 Å).

The average ring angle is 120.0°, with the angle centred on the ipso atom, i.e. the atom bonded to the substituent, C8-$\hat{C}$7-C12 at 118.6°. The values, for a series of cinnamic acids[11], of the equivalent angle at 118.4°, 119.0° and 118.8° are similarly below the average value. The effect of substituents on the bond lengths and angles of the phenyl ring has been an area of active study. Most cases are adequately covered by a valence bond interpretation[12] though several other explanations exist.

If the substituent (x) is a pure σ acceptor, i.e. more electro negative than ring atoms, then the p character of the hybrid orbital donating the x is increased (as the p electron is more loosely held), producing a concomitant increase in s character for the other two hybrid orbitals. This results in a decrease in the bond length of the bonds from the ipso atom to adjacent ring atoms and an increase in the ring angle (α) centred on the ipso atom. For a σ donor the changes are in the opposite directions.

For a π donor/acceptor, by equating a presumed decrease in the

C_{ipso} - x distance with an increase in s character of the hybrid orbital a similar situation to that for a σ donor is produced resulting in similar effects[13]. Naturally the effect would be expected to be conditioned by the rotation about C_{ipso} - x, but although a trend is evident it isn't a rigid relationship.

The dihedral angles corresponding to Ψ and Φ in peptides are Φ'(C2,N4,C5,C13) = -74° and Ψ'(N4,C5,C13,O15) = -11°.

Table 6.2.8 shows significant bond lengths and angles compared with those in peptides[14]. The most obvious difference in the bond lengths is in the N-C^{α}, C-N distances, being significantly shorter and longer respectively than the corresponding peptide distance; this reflects the conjugation of the amide system with the olefinic system, even though this is reduced by the rotation about N-C(τ(C2,N4,C5,C6) = 106°); the topic is discussed further in 6.3.

The bond angles broadly agree, with the exception of N-$\hat{C}^{\alpha}$-C(O) which is anomalous even when compared with other dehydro-amino acids (Table 6.2.8). The intra-molecular non-bonded distances show severe N4...O15 clash, which is relieved by expansion of this angle.

The carboxylic acid group is planar, with the acid hydrogen (H15) deviating from the plane by only 0.04 Å (with an approximate e.s.d. of 0.04 Å), despite being a donor to W2. The bond formed is in fact exceptionally strong, the hydrogen being well directed towards the acceptor (O15-H15...W2 = 174°). As is usually found H15-O15 is synplanar to C13-O14. A comparison of the carboxylic acid group parameters C13-O14(1.207 Å), O15-$\hat{C}$13-O14(123.1°), C13-O15(1.319 Å), with the expected values 1.21 Å, 123°, 1.31 Å showing good agreement[15].

The disposition of the phenyl group to the carbonyl group (C13-O14) about the double bond is trans, while the double bond is

synplanar to the carbonyl group. The latter situation contrasts with the case of N-Ac-ΔAla-OH (see 4.2) and suggests the use of steric clash between the carboxyl oxygens and the β substituents (and the bend bond model for ambiguous cases) as a criterion is limited. The molecule in fact betrays its origins, as the parent oxazolin-5-one ring is seen to be formed by O3 attack on C13 (Figure 6.2.1).

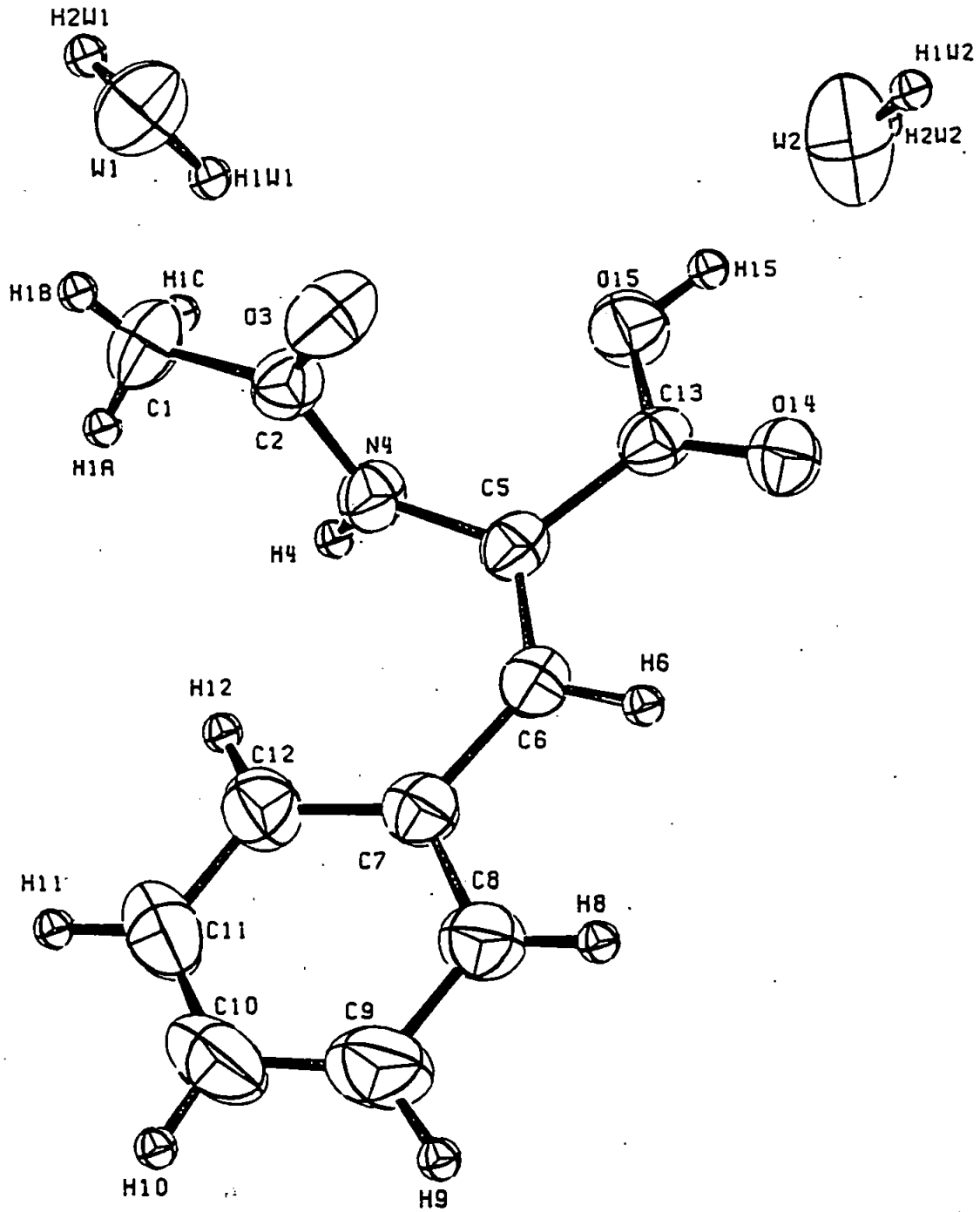


Figure 6.2.1. ORTEP drawing of the molecular structure of N-AcΔPhe-OH.$2H_2O$ with 50% probability ellipsoids.

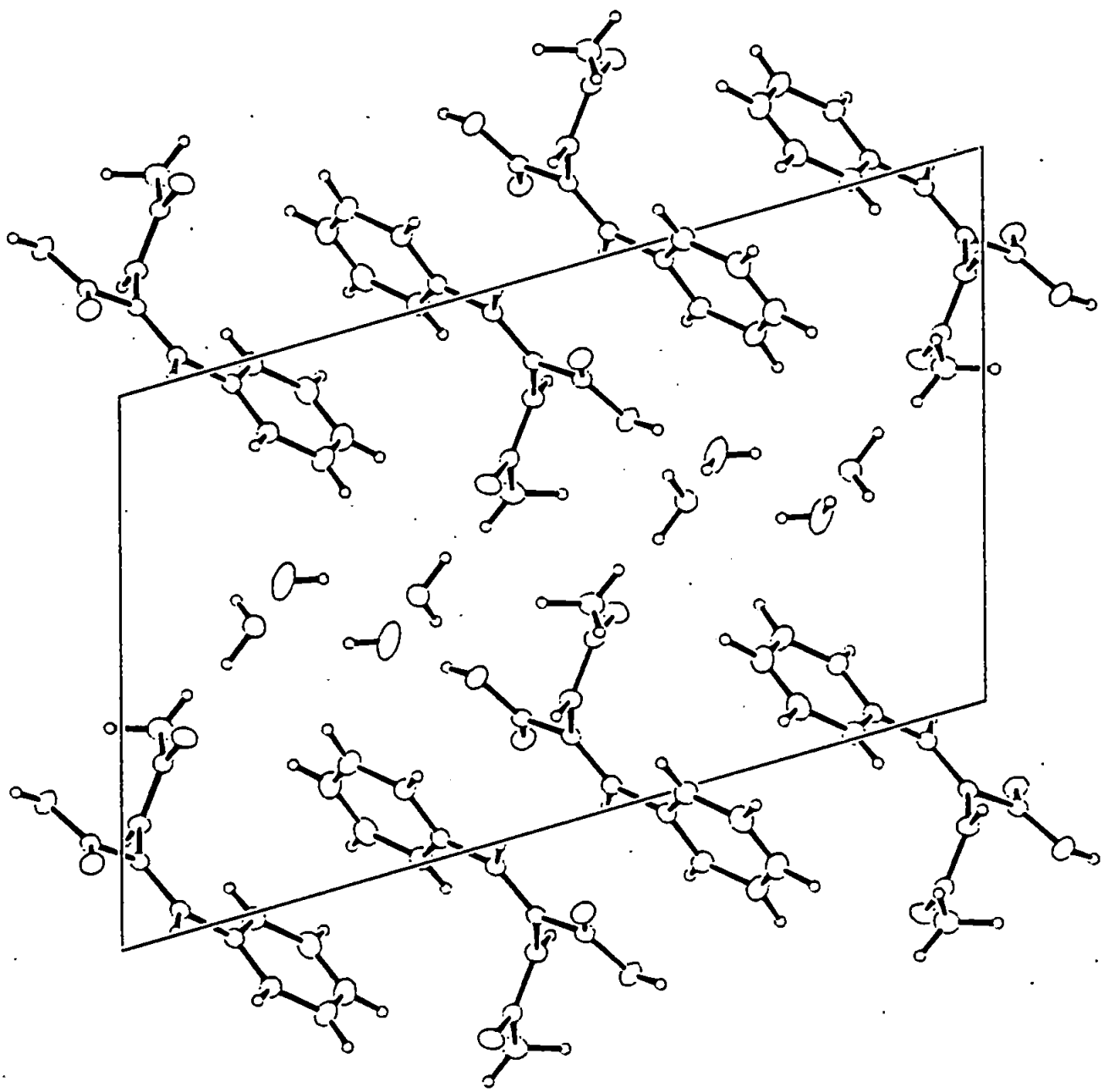


Figure 6.2.2. Projection down the b axis showing the molecular packing.

Table 6.2.1

Atomic fractional co-ordinates with the e.s.d.'s in parenthesis and of the same magnitude as the final digit.

	x	y	z
C1	0.3790(3)	-0.2956(5)	0.4545(2)
C2	0.3162(2)	-0.0796(4)	0.4515(1)
O3	0.3515(2)	0.0884(3)	0.4266(1)
N4	0.2186(2)	-0.0742(3)	0.4793(1)
C5	0.1524(2)	0.1234(3)	0.4794(1)
C6	0.0427(2)	0.1661(4)	0.4326(1)
C7	-0.0360(2)	0.0395(4)	0.3694(1)
C8	-0.1430(2)	0.1444(5)	0.3282(1)
C9	-0.2192(3)	0.0455(6)	0.2644(2)
C10	-0.1901(3)	-0.1598(6)	0.2420(2)
C11	-0.0868(3)	-0.2659(5)	0.2833(2)
C12	-0.0103(3)	-0.1681(4)	0.3468(2)
C13	0.2101(2)	0.2952(4)	0.5361(1)
O14	0.1725(1)	0.4813(3)	0.5342(1)
O15	0.3073(2)	0.2248(3)	0.5881(1)
H1A	0.324(4)	-0.407(8)	0.445(3)
H1B	0.427(3)	-0.301(6)	0.423(2)
H1C	0.407(4)	-0.346(7)	0.513(3)
H4	0.196(2)	-0.201(5)	0.496(2)
H6	0.007(2)	0.309(4)	0.438(1)
H8	-0.160(2)	0.292(4)	0.343(1)
H9	-0.291(3)	0.142(5)	0.239(2)
H10	-0.245(3)	-0.213(5)	0.199(2)
H11	-0.068(3)	-0.410(6)	0.267(2)

Table 6.2.1 continued

	x	y	z
H12	0.056(2)	-0.249(4)	0.375(1)
H15	0.341(3)	0.320(7)	0.623(2)
H1W1	0.462(3)	0.094(5)	0.377(2)
H2W1	0.571(3)	0.003(6)	0.365(2)
H1W2	0.439(3)	-0.126(7)	0.179(2)
H2W2	0.435(3)	0.020(6)	0.235(2)

Table 6.2.2

Temperature factores - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.057(2)	0.050(2)	0.069(2)	0.002(1)	0.022(2)	0.018(1)
C2	0.037(1)	0.042(1)	0.040(1)	0.002(1)	0.008(1)	0.006(1)
O3	0.050(1)	0.054(1)	0.070(1)	0.015(1)	0.027(1)	0.010(1)
N4	0.040(1)	0.028(1)	0.052(1)	0.003(1)	0.015(1)	0.002(1)
C5	0.035(1)	0.033(1)	0.040(1)	0.005(1)	0.014(1)	0.003(1)
C6	0.038(1)	0.037(1)	0.041(1)	0.001(1)	0.014(1)	0.002(1)
C7	0.040(1)	0.046(1)	0.039(1)	0.000(1)	0.014(1)	-0.003(1)
C8	0.045(1)	0.058(2)	0.048(2)	-0.003(1)	0.010(1)	-0.001(1)
C9	0.053(2)	0.096(3)	0.053(2)	-0.007(2)	0.000(1)	-0.004(2)
C10	0.070(2)	0.090(3)	0.053(2)	-0.021(2)	0.010(2)	-0.028(2)
C11	0.080(2)	0.059(2)	0.059(2)	-0.019(2)	0.026(2)	-0.016(2)
C12	0.055(2)	0.048(2)	0.056(2)	-0.005(1)	0.016(1)	-0.005(1)
C13	0.034(1)	0.086(1)	0.042(1)	0.006(1)	0.013(1)	0.003(1)
O14	0.045(1)	0.033(1)	0.062(1)	-0.003(1)	0.007(1)	0.005(1)
O15	0.047(1)	0.047(1)	0.048(1)	-0.001(1)	-0.004(1)	0.007(1)
W1	0.052(1)	0.057(1)	0.052(1)	0.012(1)	0.016(1)	0.013(1)
W2	0.126(2)	0.071(2)	0.055(1)	-0.007(1)	-0.020(1)	0.038(2)
H1A	0.14(2)					
H1B	0.11(1)					
H1C	0.13(1)					
H4	0.07(1)					
H6	0.03(1)					
H8	0.05(1)					

Table 6.2.2 continued

	U_{11}
H9	0.09(1)
H10	0.08(1)
H11	0.08(1)
H12	0.06(1)
H15	0.11(1)
H1W1	0.08(1)
H2W1	0.09(1)
H1W2	0.10(1)
H2W2	0.09(1)

Table 6.2.3

Bond lengths (in Angstroms) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

W1-H1W1	0.95(4)	C6-H6	0.97(2)
W1-H2W1	0.88(4)	C7-C8	1.400(3)
W2-H1W2	0.87(4)	C7-C12	1.385(4)
W2-H2W2	0.81(4)	C8-C9	1.385(4)
C1-H1A	0.91(5)	C8-H8	0.97(3)
C1-H1B	0.89(4)	C9-C10	1.382(5)
C1-H1C	1.07(5)	C9-H9	1.01(3)
C1-C2	1.490(4)	C10-C11	1.373(4)
C2-O3	1.230(3)	C10-H10	0.92(3)
C2-N4	1.345(3)	C11-C12	1.380(4)
N4-C5	1.419(3)	C11-H11	0.97(3)
N4-H4	0.89(3)	C12-H12	0.93(3)
C5-C6	1.332(3)	C13-O14	1.207(3)
C5-C13	1.491(3)	C13-O15	1.319(3)
C6-C7	1.470(3)	O15-H15	0.86(4)

Table 6.2.4.

Bond angles (degrees) - e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

H2W1-W1-H1W1	103(3)
H2W2-W2-H1W2	108(3)
H1A-C1-H1B	111(4)
H1A-C1-H1C	88(3)
H1A-C1-C2	111(3)
H1B-C1-H1C	124(3)
H1B-C1-C2	113(3)
H1C-C1-C2	108(2)
O3-C2-C1	122.9(2)
O3-C2-N4	120.5(2)
C1-C2-N4	116.5(2)
C2-N4-C5	121.1(2)
C2-N4-H4	117(2)
C5-N4-H4	122(2)
N4-C5-C6	124.8(2)
N4-C5-C13	117.4(2)
C6-C5-C13	117.8(2)
C5-C6-C7	131.7(2)
C5-C6-H6	117(1)
C7-C6-H6	111(1)
C6-C7-C8	116.0(2)
C6-C7-C12	125.4(2)
C8-C7-C12	118.6(2)
C7-C8-C9	120.6(3)
C7-C8-H8	119(1)

Table 6.2.4 continued

C9-C8-H8	120(1)
C8-C9-C10	119.7(3)
C8-C9-H9	112(2)
C10-C9-H9	128(2)
C9-C10-C11	120.1(3)
C9-C10-H10	114(2)
C11-C10-H10	126(2)
C10-C11-C12	120.5(3)
C10-C11-H11	119(2)
C12-C11-H11	121(2)
C11-C12-C7	120.5(3)
C11-C12-H12	118(2)
C7-C12-H12	122(2)
C5-C13-O14	123.5(2)
C5-C13-O15	113.4(2)
O14-C13-O15	123.1(2)
C13-O15-H15	115(2)

Table 6.2.5

Deviations (in Angstroms) from the least squares plane. Asterisked atoms are not included in the least squares calculation.

Plane	1	2	3	4	5	6
C1	0.002		1.117*			
C2	-0.008		1.217*			
O3	0.003		2.263*			
N4	0.002		0.085*			
C5		-0.008	0.068			-0.091
C6		-0.019	-0.014	0.040		0.071
C7		0.015	-0.050	-0.022	0.013	
C8			-0.032	-0.030	-0.009	
C9			0.028	0.005	-0.002	
C10			0.052	0.029	0.008	
C11			0.002	0.005	-0.003	
C12			-0.054	-0.026	-0.007	
C13		0.012	0.148*			-0.012
O14			0.352*			-0.019
O15			-0.011*			0.052

Table 6.2.5 continued

i	a_i	b_i	c_i	d_i
1	0.5891	0.2174	0.7783	7.5979
2	0.4381	0.4096	-0.8002	5.5841
3	0.4850	0.4136	-0.7705	5.3325
4	0.5030	0.4134	-0.7590	5.2890
5	0.5147	0.4229	-0.7458	5.2356
6	-0.5333	-0.2603	0.8049	5.6749

Table 6.2.6

Hydrogen bond lengths (Å) and angles (°)

Donor X-H	Acceptor Y	Angle XHY	Distance HY	Distance XY	Position of Acceptor
O15-H15	W2	174	1.7	2.53	(x, y, z)
W2-H2W2	W1	164	2.0	2.81	(x-½, ½-y, 1+z)
W2-H1W2	W1	177	1.8	2.71	(1-x, 1-y, 1-z)
W1-H2W1	O15	178	2.0	2.86	(1-x, -y, 1-z)
W1-H1W1	O3	174	1.7	2.69	(x, y, z)
N4-H4	O14	170	2.1	2.98	(x, y-1, z)

Table 6.2.7

Intra-molecular non-bonded distances (< Van der Waals + 0.35Å)

O3 ... H1B	2.53
O3 ... C5	2.708
N4 ... H1A	2.52
N4 ... C7	3.120
N4 ... H12	2.50
N4 ... O15	2.680
H4 ... C1	2.48
H4 ... H1A	2.30
H4 ... H12	2.36
C6 ... H8	2.56
C6 ... O14	2.794
H6 ... H8	2.20
H6 ... C8	2.46
H6 ... C13	2.51
H6 ... O14	2.44
C12... N4	3.088
C12... C5	3.161
C13... C2	3.174

Table 6.2.8

Bond lengths (Å) and angles (°) compared with those of peptides

	Peptide	N-Ac-ΔPhe-OH
C^{α}-C(O)	1.51	1.490
C=O	1.24	1.230
C-N	1.32	1.345
N-C^{α}	1.45	1.419
C-$\hat{C}$(O)-O	120.5	122.9
C-$\hat{C}$(O)-N	116	116.5
O-$\hat{C}$-N	123.5	120.5
C-$\hat{N}$-C	122	121.1
N-$\hat{C}^{\alpha}$-C	111	117.4

6.3 N-Acetyl Dehydro-phenylalanyl-L-Proline

Experimental

The compound was prepared by Bergmanns method and recrystallised a number of times from methanol/water[16].

Formula = $C_{16}H_{18}N_2O_4.\frac{1}{2}H_2O$

Space group = C2

F(000) = 636

a = 18.516 Å

b = 9.515 Å

c = 10.538 Å

β = 120.102°

V = 1606.3 Å^3

D_o = 1.28 Mg m^{-3} (CCl_4/n-C_6H_{14})

D_c = 1.29 Mg m^{-3}

Z = 4

μ = 0.055 mm^{-1}

The cell parameters were determined on the diffractometer from high angle reflexions.

Data were collected using graphite monochromated Mo-K_α radiation ($1.5^\circ < \theta < 30^\circ$); 2667 reflexions (82 intensity controls) were measured 2476 being unique (82.3% (2037) $|F| > 3\sigma(|F|)$). Because of previous difficulty in solving symmorphic space groups[17] using SHELX, it was decided to use MULTAN, which allowed the weights of the F.O.M. to be altered. ABSFOM, Ψ_o and R_k were given weights of 0.7, 1.3, and 1.0 respectively. The geometry of the phenyl group was supplied for calculation of a molecular scattering factor to aid in scaling[18].

The phase set with the highest F.O.M. and incidentally, the lowest Ψ_o, produced an E-map with eighteen atoms of the structure. Subsequent calculation was done on SHELX.

Fourier refinement revealed the missing atoms. Isotropic least

squares refinement commenced interspersed with difference map calculation. At R = 22%, R_m = 23%, an atom lying on the two fold axis, presumed to be the oxygen of water, was admitted for refinement.

At R = 19.58, R_m = 18.76, anisotropic refinement commenced; instead of the expected large drop in R, it stopped at R = 18.1%, R_M = 17.1%.

Eventually an error was discovered in the data processing, an inappropriate attenuation factor having been used. It is remarkable that MULTAN was able to solve the structure with the forty-six largest ($|F|$, admittedly, not $|E|$) reflexions overvalued.

The data were reprocessed and refinement continued. After four cycles of refinement R = 8.4%, $R_G = R_M$ = 9.6%. The hydrogen atoms, located from the difference map were introduced and the refinement continued to R = 6.1%, $R_M = R_G$ = 7.11%. Five reflexions, 9 7 3, 14 6 3, 0 2 1, 8 6 3, 3 7 3, were suppressed due to very large Δ/e.s.d.

At this point R = 5.16%, $R_G = R_M$ = 4.67%. A weighting scheme with

$$w_i = (\sigma_i^2(|F|) + g(|F|^2|))^{-1}$$

was then introduced. 'g' was not refined, as previous attempts had not converged, but varied until the analysis of variance was satisfactory. The final value of the refinement indices are shown below:

	R	R_W	$R_M = R_G$	g	S^2
all $\|F\|$*	5.83	4.92	5.61	0.00115	0.040
all $\|F\|$	6.21	5.02	6.15	0.00115	0.083
$\|F\| > 2\sigma(\|F\|)$	4.57	4.66	5.53	0.00115	1.045

The final atomic parameters are shown in Table 6.3.1 and Table 6.3.2 The structure factors ($10|F_o|/10|F_c|$) are listed in Appendix E (Table E.3).

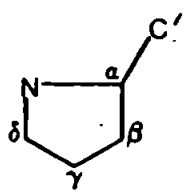
*except for noted suppressed reflexions.

Discussion

This, as far as is known, is the first structural determination of a dipeptide with an unsaturated residue.

Least squares analysis (Table 6.2.5) shows that the molecule consists of six planes, formed by the benzal, two amide, carboxylic acid, olefin and pyrrolidine (-C17) groups, with C17 lying out of the plane.

In all reported crystal structures of molecules containing proline residues, it has been found that four of the atoms of the pyrrolidine ring



form a plane from which the fifth, usually C^{γ},[19-25] but occasionally C^{α}[26] or C^{β}[27] deviates. Potential energy calculations show the pyrrolidine ring to be rather flexible, with a large number of almost iso-energetic conformations. However, two minima, one with C^{γ} displaced on the same side as C', of the plane formed by the other four atoms, and the other, higher, minimum with C^{γ} on the opposite side to C', have been indicated[28].

The proline residue in the present compound shows (Table 6.2.5, plane 6) C^{γ}(C17) deviation on the opposite side to C'(C20).

The position of the phenyl group trans to the carbonyl confirms previous observations on the stereochemical course of the Bergmann synthesis[29].

The first amide link has a trans configuration, i.e. the nitrogen

hydrogen is trans to the carbonyl oxygen, with ω_1 = 166°. Comparison with the values for a peptide (Table 6.3.8) show the C2-N4 and N4-C5 bond lengths to be significantly longer and shorter respectively than in a peptide, reflecting conjugation with the olefin system. This conjugation will depend upon the twist about N4-C5(Φ_1' = -51.5°) as can be seen, for example, by comparing C-N in N-Ac-ΔPhe-OH(A) and N-Ac-ΔPhe-L-Pro-OH(B).

$(C-N)_B > (C-N)_A$ (1.352 and 1.345 respectively) while τ(C2,N4,C5,C6) at 134° is greater than the equivalent torsion angle in A (106°) which is exactly the expected ordering. Other peptide structures containing dehydro-phenylalanyl residues ($N\text{-Ac}(\Delta\text{Phe})_2\text{Gly-OH}$[29] and $N\text{-Ac-}(\Delta\text{Phe})_2\text{-L-Ala-OH}$)[30] were not published in sufficient detail to permit comparison.

The second amide linke is planar and again has a trans configuration, i.e. N-C^{δ} is trans to the carbonyl oxygen, with ω_1 = 178.3°. The C-N distance is rather longer than the peptide equivalent quoted[14] in Table 6.3.8, but much closer to another estimate[31]; the angles are in broad agreement. The C5-C13 at 1.51 A is a little surprising as both atoms are sp^2 hydridized.

The phenyl group is planar (Table 6.3.5, plane 4) with an average bond length of 1.384 Å. The value of the angle centred on the atom bonded to the rest of the molecule (C12-$\hat{C}$7-C8) at 118.4°, is, as usual (see 6.2), below the average value (120.0°).

The styryl group is non-planar with τ(C5,C6,C7,C8) at 38°. The twist appears to produce little effect on the C6-C7 bond length (1.467A). The equivalent bond lengths in a series of cinnamic acids are 1.486, 1.469, 1.484 with torsion angles of 11.7°, 65.4 and 83.3° respectively[11]. The bond length and angle in N-Ac-ΔPhe-OH, 1.470 and

5° respectively, follows this lack of trend. It confirms the insensitivity of the sp^2 - sp^2 bond lengths shown in a comparison of bond lengths in planar butadienes (zero torsion angle) and non-planar cyclo-octatetraenes (torsion angle of 60°).

The carboxylic and group is planar (Table 6.3.5, plane 5) but with the hydrogen (H21) deviating from the plane by 0.13A. With an approximate e.s.d. of 0.04Å this is clearly significant. Certainly such a compromise of the carboxylic and groups planarity will be expensive in loss of resonance energy ($\propto A \sin^2 \tau$, τ being the twist about C20-021, A being approximately 15 Kcal/mole), and is clearly an accommodation to allow the hydrogen to donate more easily to the water molecule. Of the conformations for the and hydrogen that maintain planarity of the group the one which minimises the distance to the carbonyl oxygen (the synplanar conformation) was the one found, suggesting an electrostatic interaction; possibly packing is also a factor. Experimentally, the syn conformation has been estimated as being more stable by around 4 Kcal/mole, and is, except where an intra-molecular hydrogen bond is formed, the observed conformation in the crystalline phase.

The C20-02$\hat{1}$-H21 (111°), 022-C20-021 (123.7°), C20-022 (1.196A) values agree reasonably with expected values[15] of 110 - 114.5° (neutron determinations), 123°, 1.21A respectively, though C20-021 (1.336) is longer than expected (1.31A).

The molecular conformation (Figure 6.3.1) may be grossly described by the conventional torsion angles of peptides, with Φ_1'(C2,N4,C5,C13) = -51.5°, Ψ_1'(N4,C5,C13,N15) = 135.8, Φ_2(C13,N15,C19,C20) = -70.2° and Ψ_2(N15,C19,C20,021) = 164.7°. Naturally, the significance of the angles of the dehydro-phenylalanyl residue is not the same as for saturated residues as the spatial relationships differ. Comparison

with N-Ac-ΔPhe-OH(Φ' = -74°, Ψ' = -11°) show considerable change.

Figure 6.3.2 shows a view parallel to the plane defined by the three labled atoms (the olefinic plane), while Figure 6.3.3, perpendicular to the plane, shows the less hindered side.

Hydrogenation of the double bond, assuming:

a) a similar conformation under the reaction conditions;

b) the validity of the Prelog rule (that the substrate approach the catalyst with the least sterically hindered side);

and c) simple cis attack

would be expected to produce an excess of N-Ac-D-Phe-L-Pro-OH over N-Ac-L-Phe-L-Pro-OH, a result actually observed[32].

The justification for believing the conformation would be similar in solution lies in consideration of the intra-molecular non-bonded distances, particularly the H4...H8, H6...H12, O14...C19 distances (Table 6.3.7); these indicated a drive to co-planarity of the phenyl, olefin and amide groups which leaves little conformational freedom. Certainly, under the conditions of hydrogenation, which takes place in a protic solvent (methanol), this conformation seems closer to reality than the ring structure (formed by an intra-molecular hydrogen bond between the acidic hydrogen and amide oxygen) proposed.

There is however in N-Ac-$(\Delta Phe)_2$-Res (Res being an amino acid residue) some evidence, from circular dichroism (C.D.) measurements, for a ring structure, as addition of urea produces significant change.

The hydrogen bond analysis (Table 6.3.6) shows the bond lengths to be within the expected range, with the amide hydrogen bond being longer (and presumably weaker) than the bonds involving the water molecule.

H23A-O23-H23B at 103° is, as expected, less than $\cos^{-1}(-1/3)$.

The H23A-$\hat{O}$23...H21(92°) and H23B-$\hat{O}$23...H21(119°) values deviate somewhat from the tetrahedral values. The distorsion is probably real and doesn't reflect uncertainty in the hydrogen positions, as the H23A-O23...O21(92.3°) and H23B-$\hat{O}$23...O2(122.0°) are very similar; this would be expected if the hydrogen bonds are assumed to be linear.

The C13-$\hat{O}$14...H4(112°) and C13-O14...N4(114.8) and, slightly less convincingly C2-$\hat{O}$3...H23B(133°) and C2-$\hat{O}$3...O23(137.1) values, again assuming hydrogen bond linearity (though O.3...H23A-O23 is only 162°), suggest that the lone pairs on the carbonyl oxygen are in sp^2 orbitals. Certainly in some carbonyl systems such as dehetopiperazine and cyanuric acid[33] there are lone pair lobes at about 110° to C=O.

A projection down to b axis (Figure 6.3.4) shows the molecules packed so as to form a layer, roughly parallel to the a b plane, held together by hydrogen bonding involving the water molecule, while the layers are held together by hydrogen bonding between the amide hydrogen (H4) and the amide oxygen (O14).

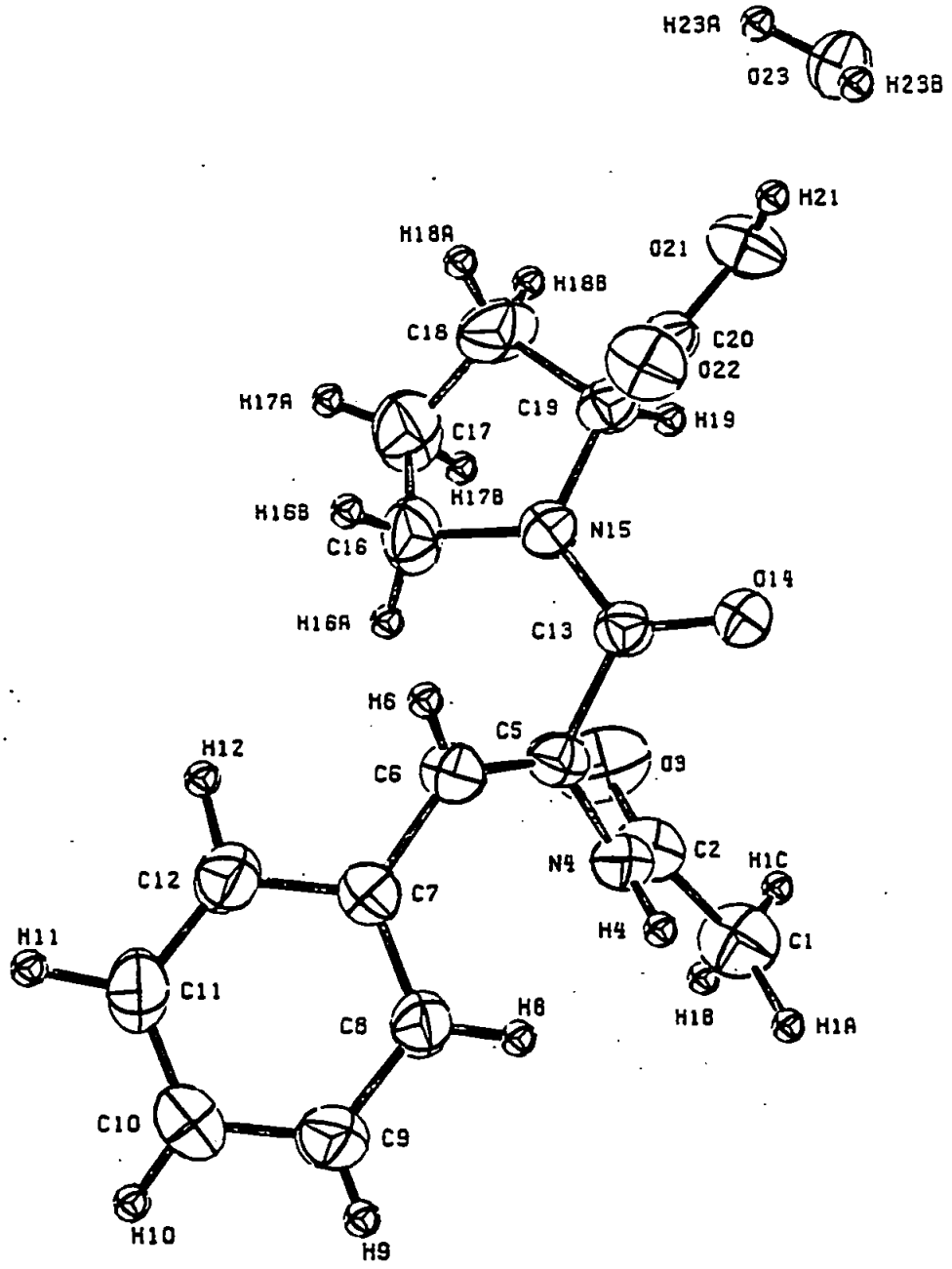


Figure 6.3.1. ORTEP drawing of the molecular structure of N-AcΔPheL-Pro-OH.½H_2O with 50% probability ellipsoids.

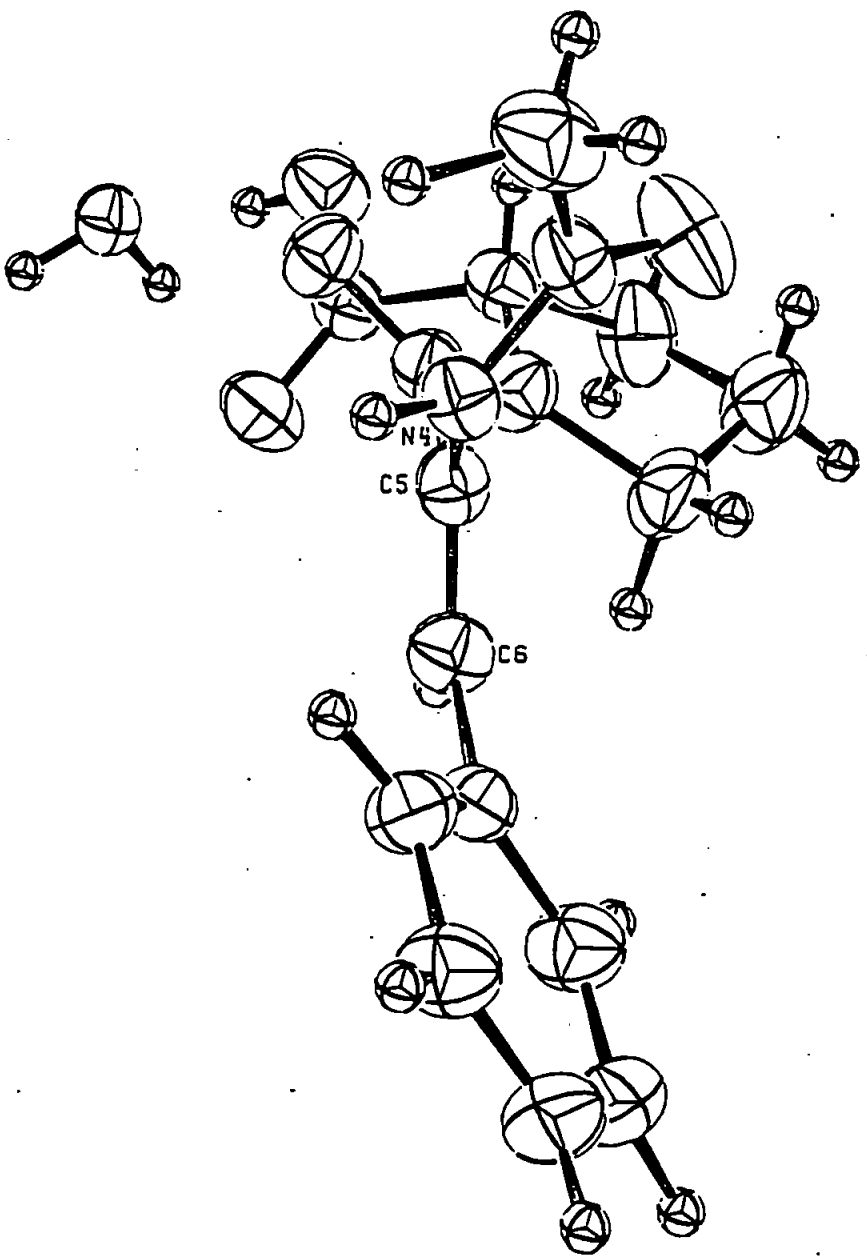


Figure 6.3.2. A view of the molecule parallel to the plane defined by the labelled atoms.

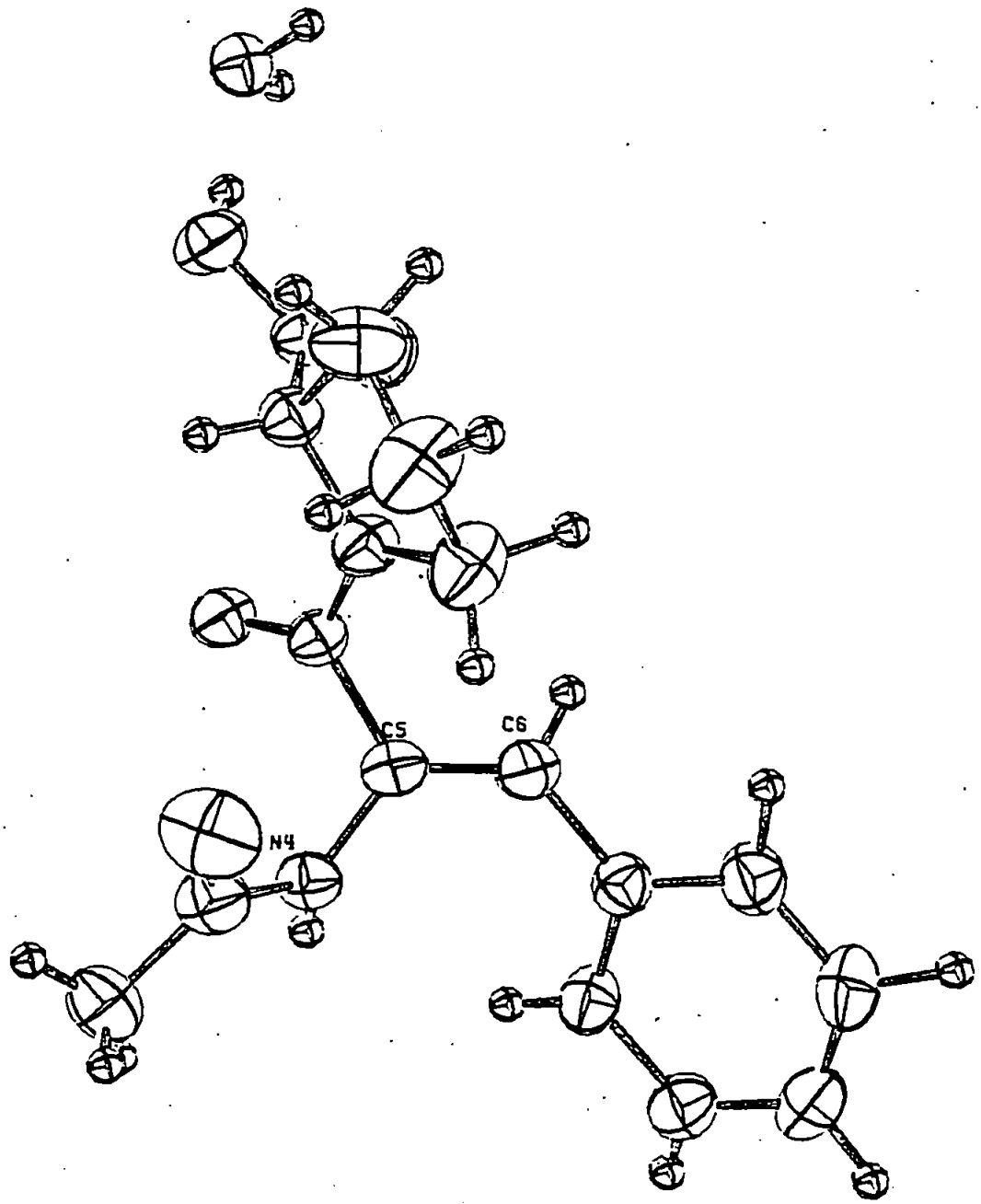


Figure 6.3.3. View of the molecule normal to the plane defined by the labelled atoms.

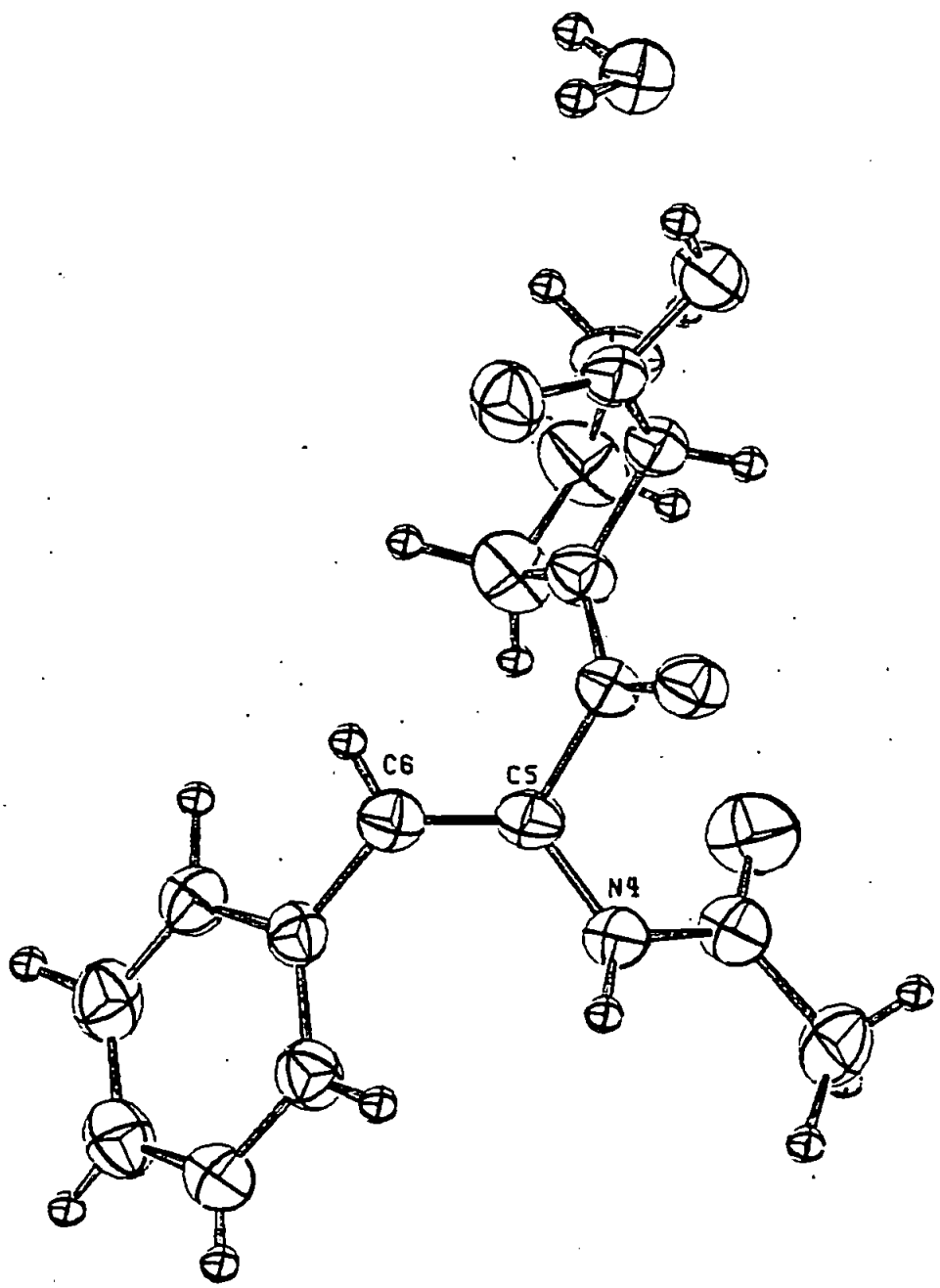


Figure 6.3.4. View normal to the plane defined by the atoms, but antiparallel to that of Figure 6.3.3.

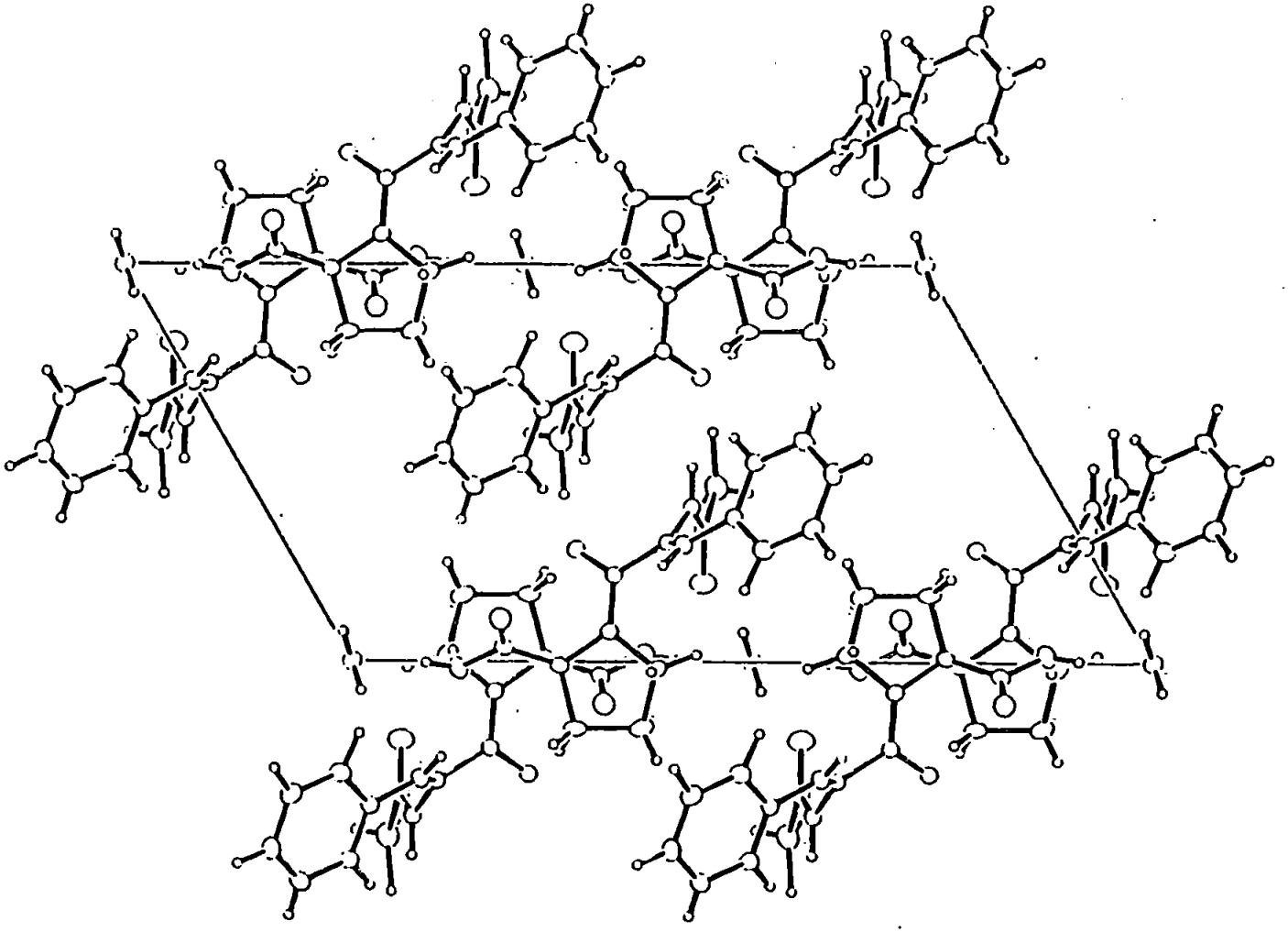


Figure 6.3.5. A projection down the b axis showing the molecular packing.

Table 6.3.1

Atomic fractional co-ordinates with e.s.d.'s in parenthesis and of the same magnitude as the final digit.

	x	y	z
C1	0.4195(2)	0.9457(4)	0.5600(4)
C2	0.4658(1)	0.8307(3)	0.6676(2)
O3	0.5051(1)	0.8471(3)	0.8018(2)
N4	0.4648(1)	0.7031(0)	0.6102(2)
C5	0.5211(1)	0.5968(3)	0.6997(2)
C6	0.5015(1)	0.4634(3)	0.7048(2)
C7	0.4192(1)	0.3961(3)	0.6367(2)
C8	0.3537(1)	0.4297(3)	0.4974(2)
C9	0.2769(1)	0.3644(3)	0.4431(3)
C10	0.2641(1)	0.2667(3)	0.5251(3)
C11	0.3286(2)	0.2320(3)	0.6636(3)
C12	0.4054(1)	0.2955(3)	0.7181(3)
C13	0.6110(1)	0.6446(3)	0.7828(2)
O14	0.6401(1)	0.7100(3)	0.7177(1)
N15	0.6568(1)	0.6086(3)	0.9241(2)
C16	0.6257(2)	0.5560(4)	1.0202(3)
C17	0.6857(2)	0.6185(5)	1.1667(3)
C18	0.7691(2)	0.6185(4)	1.1686(2)
C19	0.7440(1)	0.6566(3)	1.0098(2)
C20	0.8000(1)	0.5847(3)	0.9642(2)
O21	0.8722(1)	0.6541(3)	1.0170(2)
O22	0.7843(1)	0.4793(2)	0.8934(2)
O23	1.0000(0)	0.5227(3)	1.0000(0)

Table 6.3.1 continued

	x	y	z
H1A	0.385(4)	0.913(8)	0.423(8)
H1B	0.384(3)	0.975(6)	0.576(5)
H1C	0.455(3)	1.018(7)	0.609(6)
H4	0.435(2)	0.694(4)	0.510(4)
H6	0.543(2)	0.406(3)	0.759(3)
H8	0.362(2)	0.493(4)	0.435(3)
H9	0.238(2)	0.378(4)	0.357(4)
H10	0.211(2)	0.230(3)	0.487(3)
H11	0.326(2)	0.148(4)	0.729(4)
H12	0.458(2)	0.281(4)	0.819(3)
H16A	0.565(2)	0.582(5)	0.983(4)
H16B	0.634(2)	0.440(5)	1.027(4)
H17A	0.689(3)	0.575(5)	1.249(5)
H17B	0.669(3)	0.721(7)	1.147(6)
H18A	0.807(2)	0.530(4)	1.209(4)
H18B	0.805(2)	0.680(4)	1.225(4)
H19	0.745(2)	0.751(3)	0.998(3)
H21	0.908(2)	0.606(4)	1.004(4)
H23	1.010(2)	0.464(4)	1.074(4)

Table 6.3.2

Temperature factors. The e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.062(1)	0.047(1)	0.083(2)	-0.002(1)	0.035(1)	0.011(1)
C2	0.0441(9)	0.049(1)	0.051(1)	-0.0113(9)	0.0250(8)	-0.0024(8)
O3	0.084(1)	0.079(1)	0.053(1)	-0.024(1)	0.0265(9)	0.012(1)
N4	0.0356(6)	0.0420(7)	0.0370(7)	-0.0035(7)	0.0172(6)	0.0014(6)
C5	0.0330(7)	0.0450(9)	0.0357(7)	-0.0039(7)	0.0169(6)	-0.0001(7)
C6	0.0372(8)	0.0436(9)	0.046(1)	-0.0011(8)	0.0182(7)	-0.0005(8)
C7	0.0406(8)	0.0349(8)	0.0411(9)	-0.0040(7)	0.0207(7)	-0.0020(7)
C8	0.049(1)	0.046(1)	0.0397(9)	-0.0003(8)	0.0211(8)	-0.0101(8)
C9	0.0443(9)	0.051(1)	0.047(1)	-0.003(1)	0.0158(8)	-0.0071(9)
C10	0.048(1)	0.055(1)	0.066(1)	-0.007(1)	0.032(1)	-0.0131(9)
C11	0.068(1)	0.051(1)	0.057(1)	0.003(1)	0.037(1)	-0.012(1)
C12	0.055(1)	0.046(1)	0.046(1)	0.0053(9)	0.0205(9)	-0.0035(9)
C13	0.0351(7)	0.0394(8)	0.0346(7)	-0.0019(7)	0.0160(6)	-0.0018(7)
O14	0.0394(6)	0.0550(8)	0.0365(6)	0.0037(6)	0.0179(5)	-0.0040(6)
N15	0.0391(7)	0.0518(9)	0.0350(7)	0.0003(7)	0.0176(6)	-0.0052(7)
C16	0.070(1)	0.075(2)	0.044(1)	-0.003(1)	0.035(1)	-0.019(1)
C17	0.081(2)	0.010(2)	0.042(1)	-0.011(1)	0.033(1)	-0.028(2)
C18	0.059(1)	0.087(2)	0.0302(9)	-0.006(1)	0.0145(8)	0.003(1)
C19	0.0402(8)	0.0415(9)	0.0339(8)	-0.0025(7)	0.0134(6)	-0.0011(7)
C20	0.0395(8)	0.0393(9)	0.0329(7)	-0.0002(7)	0.0126(6)	0.0001(7)
O21	0.0410(7)	0.0540(9)	0.063(1)	-0.0129(8)	0.0216(7)	-0.0060(7)
O22	0.0581(8)	0.0471(8)	0.0606(9)	-0.0152(7)	0.0288(7)	-0.0050(7)
O23	0.051(1)	0.047(1)	0.040(1)	0.000(0)	0.0239(8)	0.000(0)
H1A	0.17(2)					

Table 6.3.2 continued

	U_{11}
H1B	0.10(1)
H1C	0.11(2)
H4	0.07(1)
H6	0.05(1)
H8	0.06(1)
H9	0.08(1)
H10	0.05(1)
H11	0.06(1)
H12	0.06(1)
H16A	0.08(1)
H16B	0.08(1)
H17A	0.09(1)
H17B	0.12(2)
H18A	0.07(1)
H18B	0.07(1)
H19	0.03(1)
H21	0.07(1)
H23	0.09(1)

Table 6.3.3

Bond lengths (in Å); e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

C1-H1A	1.29(7)	C11-C12	1.378(3)
C1-H1B	0.81(6)	C12-H12	1.03(3)
C1-H1C	0.91(6)	C13-O14	1.231(2)
C1-C2	1.498(4)	C13-N15	1.337(2)
C2-O3	1.234(3)	N15-C19	1.472(2)
C2-N4	1.352(3)	N15-C16	1.481(3)
N4-H4	0.92(3)	C16-H16A	1.02(4)
N4-C5	1.419(3)	C16-H16B	1.11(4)
C5-C13	1.511(2)	C16-C17	1.500(4)
C5-C6	1.328(3)	C17-H17A	0.93(5)
C6-H6	0.88(3)	C17-H17B	1.01(6)
C6-C7	1.467(3)	C17-C18	1.536(4)
C7-C12	1.392(3)	C18-H18A	1.04(4)
C7-C8	1.393(3)	C18-H18B	0.86(4)
C8-H8	0.96(3)	C18-C19	1.538(3)
C8-C9	1.386(3)	C19-H19	0.91(3)
C9-H9	0.84(4)	C19-C20	1.508(3)
C9-C10	1.369(4)	C20-O22	1.196(2)
C10-H10	0.93(3)	C20-O21	1.336(2)
C10-C11	1.385(4)	O21-H21	0.87(4)
C11-H11	1.08(4)	O23-H23	0.90(4)

Table 6.3.4

Bond angles (degrees). The e.s.d.'s, in parenthesis, are of the same magnitude as the final digit.

H23A-O23-H23B	103(5)
H21-O21-C20	111(2)
O21-C20-O22	123.7(2)
O21-C20-C19	110.3(2)
O22-C20-C19	126.0(2)
C20-C19-C18	111.0(2)
C20-C19-H19	110(2)
C18-C19-H19	112(2)
N15-C19-H19	108(2)
C20-C19-N15	112.5(2)
C18-C19-N15	103.6(2)
C19-C18-H18A	114(2)
C19-C18-H18B	108(2)
H18A-C18-H18B	98(3)
C19-C18-C17	103.4(2)
C17-C18-H18A	118(2)
C17-C18-H18B	115(2)
C18-C17-H17A	113(3)
C18-C17-H17B	102(3)
H17A-C17-H17B	119(4)
C18-C17-C16	103.5(2)
C16-C17-H17A	117(3)
C16-C17-H17B	100(3)
C17-C16-N15	103.2(2)
C17-C16-H16A	114(2)

Table 6.3.4 continued

C17-C16-H16B	109(2)
H16A-C16-H16B	111(3)
N15-C16-H16A	113(2)
N15-C16-H16B	107(2)
C19-N15-C16	111.7(2)
C19-N15-C13	119.4(2)
C16-N15-C13	126.9(2)
N15-C13-O14	122.6(2)
N15-C13-C5	117.9(2)
O14-C13-C5	119.4(2)
C13-C5-N4	113.5(2)
C13-C5-C6	120.5(2)
C6-C5-N4	125.7(2)
C7-C6-H6	114(2)
C7-C6-C5	129.4(2)
C5-C6-H6	117(2)
C6-C7-C8	123.9(2)
C6-C7-C12	117.7(2)
C12-C7-C8	118.4(2)
C7-C8-C9	120.2(2)
C7-C8-H8	121(2)
C9-C8-H8	119(2)
C8-C9-C10	120.7(2)
C8-C9-H9	121(3)
C10-C9-H9	118(3)
C9-C10-C11	119.8(2)
C9-C10-H10	118(2)

Table 6.3.4 continued

C11-C10-H10	122(2)
C10-C11-C12	120.0(2)
C10-C11-H11	124(2)
C12-C11-H11	116(2)
C11-C12-C7	121.0(2)
C7-C12-H12	111(2)
C11-C12-H12	128(2)
C5-N4-C2	120.1(2)
C5-N4-H4	121(2)
C2-N4-H4	118(2)
N4-C2-C1	116.3(2)
N4-C2-O3	119.6(2)
C1-C2-O3	124.0(2)
C2-C1-H1A	116(3)
C2-C1-H1B	108(4)
C2-C1-H1C	98(3)
H1A-C1-H1B	109(4)
H1A-C1-H1C	129(5)
H1B-C1-H1C	93(5)

Table 6.3.5

Deviations from least squares planes (in Angstroms). Atoms with asterisks are not used in the least squares plane calculation.

	1	2	3	4	5	6	7	8
C1	0.002	3.229*						
C2	-0.008	2.663*						
O3	0.003	3.246*						
N4	0.003	1.422*					-0.010	-0.012
C5	0.290*	0.690*	-0.004				0.030	0.026
C6		0.021					-0.011	-0.030
C7		-0.014		0.004				0.014
C8		-0.010		0.000				
C9		0.001		-0.003				
C10		0.013		0.002				
C11		0.006		0.003				
C12		-0.016		-0.005				
C13		0.610*	0.013				-0.009	0.002
O14		0.317*	-0.005					
N15		0.812*	-0.005			-0.028		
C16						0.017		
C17						0.571*		
C18						-0.016		
C19			0.050*		0.002	0.026		
C20					-0.006	-1.133*		
O21					0.002			
O22					0.003			

Table 6.3.5 continued

i	a_i	b_i	c_i	d_i
1	0.8229	0.2340	- 0.5178	6.5953
2	-0.2997	0.7179	0.6283	2.4774
3	-0.2699	0.8542	0.4444	3.7278
4	-0.2903	0.7224	0.6275	2.5373
5	0.3940	-0.5491	0.7370	4.0144
6	-0.2804	0.9181	0.2800	3.4136
7	-0.1306	0.2435	0.9611	2.6979
8	-0.1228	0.2527	0.9597	2.8166

Table 6.3.6

Hydrogen bonding - bonding expected by symmetry is not tabulated

Donor X-H	Acceptor Y	Angle XHY	Distance HY	Distance XY	Position of Donor
N4-H4	O14	170	2.1	3.00	(-1-x,y,-1-z)
O21-H21	O23	170	1.9	2.76	(x, y, z)
O23-H23A	O3	162	1.8	2.71	(-x-½,y-½,-z)

Table 6.3.7

Close intra-molecular non-bonded contacts

(< Van der Waals + 0.35Å)

H1C	...O3	2.39
C2	...C13	2.926
O3	...C13	2.827
N4	...C7	3.092
N4	...O14	2.852
H4	...C1	2.50
H4	...H8	2.25
H4	...H1A	2.28
C5	...O3	2.690
C5	...C8	3.170
C5	...C16	2.957
C6	...H12	2.47
C6	...C16	3.072
H6	...H12	2.31
H6	...C13	2.55
H9	...H8	2.29
H9	...H10	2.20
O14	...C19	2.738
N15	...C6	2.975
N15	...H17B	2.49
N15	...O22	2.820
H16A	...H17B	2.26
H17B	...H18B	2.25
C19	...H17B	2.53
H19	...H18B	2.18

Table 6.3.7 continued

H19...O21	2.44
C20...C13	3.085
C20...O14	3.037
H21...O22	2.32

Table 6.3.8

Comparison of the important bond lengths (Å) and angles (°)

	Peptide	1st Amide group	2nd Amide group	N-Ac-ΔPhe-OH
C-C(O)	1.51	1.498	1.511	1.490
C=O	1.24	1.234	1.231	1.230
C-N	1.32	1.352	1.337	1.345
$N-C^{\alpha}$	1.45	1.419	1.472	1.419
$C-\hat{C}(O)-O$	120.5	124.0	119.4	122.9
$C-\hat{C}(O)-N$	116.0	116.3	117.9	116.5
$O-\hat{C}-N$	123.5	119.6	122.6	120.5
$C-\hat{N}-C^{\alpha}$	122	120.1	119.4	121.1
$N-\hat{C}^{\alpha}-C(O)$	111	113.5	112.5	117.4

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APPENDIX A

PROBABILITY ASPECTS OF STRUCTURE SOLUTION

Application of probability theory[1] produces a very useful relationship between intensities and the triplet invariants.

A.1 $P(\Omega|A) \simeq [1/2\pi I_0(A)] \exp(A\cos\Omega)$

$A = 2|E_h E_{h-k} E_k|/N^{\frac{1}{2}}(1-|E_h|^2/N) \simeq 2|E_h E_{h-k} E_k|/N^{\frac{1}{2}}$

I_0 is a Bessel function and $\Omega = \phi_h + \phi_{-h-k} + \phi_k$

Using A.1, the conditional expectation for a given A of:

a) $\phi_h + \phi_k + \phi_{-h-k}$ is

$$E((\phi_h + \phi_k + \phi_{-h-k})|A) = [1/2\pi I_0(A)]\int_0^{2\pi} \Omega \exp(A\cos\Omega)d\Omega = 0$$

b) $\sin m(\phi_h + \phi_{-h-k} + \phi_k)$ is

$$E(\sin m(\phi_h + \phi_{-h-k} + \phi_k)|A) = [1/2\pi I_0(A)] \times \int_0^{2\pi} \sin m\Omega \exp(A\cos\Omega)d\Omega = 0$$

c) $\cos m(\phi_h + \phi_{-h-k} + \phi_k)$ is

A.2 $$E(\cos m(\phi_h + \phi_{-h-k} + \phi_k)|A) = [1/2\pi I_0(A)] \times \int_0^{2\pi} \cos m\Omega \exp(A\cos\Omega)d\Omega$$

As $\exp(A\cos\Omega) = I_0(A) + 2\Sigma I_m(A)\cos m\Omega$

$A.2 = I_m(A)/I_0(A)$

d) $\cos^2(\phi_h + \phi_k + \phi_{-h-k})$ and $\sin^2(\phi_h + \phi_k + \phi_{-h-k})$

$$E(\cos^2(\phi_h + \phi_k + \phi_{-h-k})|A) = [1/2\pi I_0(A)] \times \int_0^{2\pi} \cos^2\Omega \exp(A\cos\Omega)d\Omega = \Lambda$$

As $\sin^2\Omega = 1 - \cos^2\Omega$

$$E(\sin^2(\phi_h + \phi_k + \phi_{-h-k})|A) = [1/2\pi I_0(A)] \times \int_0^{2\pi} \exp(A\cos\Omega)d\Omega - \Lambda = 1 - \Lambda$$

Using $\cos^2\Omega = \frac{1}{2}(1 + \cos 2\Omega)$ and $I_2(A) = I_0(A) - 2I_1(A)/A$

$$\Lambda = 1 - I_1(A)/(AI_0(A))$$

The variance is found using

$$\sigma^2(x) = E(x^2) - (E(x))^2$$

$$\sigma^2(\sin(\phi_h + \phi_k + \phi_{-h-k})|A)$$

$$= E(\sin^2(\phi_h + \phi_k + \phi_{-h-k})|A) - E(\sin(\phi_h + \phi_k + \phi_{-h-k})|A)^2$$

$$= E(\sin^2(\phi_h + \phi_k + \phi_{-h-k})) = I_1(A)/AI_0(A))$$

Similarly

$$\sigma^2(\cos(\phi_h + \phi_k + \phi_{-h-k})|A)$$

$$= E(\cos^2(\phi_h + \phi_k + \phi_{-h-k})|A) - (E(\cos(\phi_h + \phi_k + \phi_{-h-k})|A))^2$$

$$= \Lambda - I_1^2(A)/I_0^2(A)$$

Use of these relationships has been made in selecting a good starting set of reflexions by estimating α_h.

$$\alpha_h^2 = \Sigma\kappa_{hh'}\sin(\phi_{h'} + \phi_{h-h'} - \phi_h)^2 +$$

$$\Sigma\kappa_{hh'}\cos(\phi_{h'} + \phi_{h-h'} - \phi_h)^2$$

$$= \Sigma\kappa^2_{hh'} + \Sigma\Sigma\kappa_{hh'}\kappa_{hh''}(\cos(\phi_{h'} + \phi_{h-h'} - \phi_h)$$

$$\cos(\phi_{h''} + \phi_{h-h''} - \phi_h) + \sin(\phi_{h'} + \phi_{h-h'} - \phi_h)$$

$$\sin(\phi_{h''} + \phi_{h-h''} - \phi_h))$$

As the trigonometric terms are unknown, expectation values are substituted to give an estimate of α_h^2

$$\langle\alpha_h^2\rangle = \Sigma\kappa^2_{hh'} + \Sigma\Sigma\kappa_{hh'}\kappa_{hh''}(I_1(\kappa_{hh'})/I_0(\kappa_{hh'}))$$

$$\times (I_1(\kappa_{hh''})/I_0(\kappa_{hh''}))$$

The estimate can be weighted[2] by substituting $W_{h'}W_{h-h'}\kappa_{hh'}$ for $\kappa_{hh'}$ where $W_h = \tanh[\langle\alpha_h^2\rangle^{\frac{1}{2}}/2]$.

A similar relationship to A.1 exists for quartets (four phase invariants) :

A.3 $P(\psi|B) \simeq [1/2\pi I_0(B)] \exp B\cos(\psi)$

$B = 2|E_h E_k E_\ell E_{-h-k-\ell}|/N$

$\psi = \phi_h + \phi_k + \phi_\ell + \phi_{-h-k-\ell}$

However, A.3 can be drastically modified if the magnitudes of the cross products, $|E_{h+k}|$, $|E_{h+\ell}|$, $|E_{\ell+k}|$ are known. If they are large A.3 remains unchanged, but if they are (all) zero or small the relationship becomes[3]

A.4 $[1/2\pi I_0(2B)]\exp -2B\cos(\psi)$

The way in which expectations about the invariant can be altered just from knowledge of three reflexions is a consequence of the concept of nested neighbourhoods, a neighbourhood being a set of reflexions, relatively effective, compared with the body of the data, in determining the invariant[4]. In the case considered $|E_h|$, $|E_k|$, $|E_\ell|$, $|E_{-h-k-\ell}|$ constitute the first neighbourhood, which nests in the second neighbourhood $|E_h|$, $|E_k|$, $|E_\ell|$, $|E_{-h-k-\ell}|$, $|E_{h+\ell}|$, $|E_{h+k}|$, $|E_{\ell+k}|$, which nest in the third, in a similar manner[3].

Utilization of A.4 produces the following results

A.5 $E(\psi|B) = \pi$

$E(\sin(m\psi)|B) = 0$

$E(\cos(m\psi)|B) = -I_m(2B)/I_0(2B)$

If there are several indications of $\phi_{-h-k-\ell}$ by A.4, the conditional probability distribution will take the form

A.6 $N^{-1} \pi_i P(\psi_i|B_i)$

where N is a normalising term.

The exponent of A.6 can be simplified in the following manner:

A.7 $\Sigma B_i \cos(\phi_{h+k+\ell} - \gamma_i)$

$= \cos\phi_{h+k+\ell} \Sigma B_i \cos(\gamma_i) + \sin\phi_{h+k+\ell} \Sigma B_i \sin(\gamma_i)$

$\gamma_i = \phi_{h_i} + \phi_{k_i} + \phi_{\ell_i}$

Using $\langle \sin(\phi_h + \phi_k + \phi_\ell - \phi_{h+k+\ell}) \rangle = 0$

$$\text{Tan}(\delta) = \Sigma B_i \sin(\gamma_i) / \Sigma B_i \cos(\gamma_i) = S/C$$

$$\text{Sin}(\delta) = \Sigma B_i \sin(\gamma_i)/\beta_h \quad \text{Cos}(\delta) = \Sigma B_i \cos(\gamma_i)/\beta_h$$

$$\beta_h = (s^2 + C^2)^{\frac{1}{2}}$$

A.6 becomes

$$\text{A.8} \qquad [2\pi I_0(2\beta_h)]^{-1} \exp -2\beta_h \cos(\phi_{h+k+\ell} - \delta)$$

Higher order invariants have similar distributions to the triplets and quartets but since the strength of indication of a phase varies as $(N^{-\frac{1}{2}})^{m-2}$ where 'm' is the invariant order, they are less useful, though the idea of 'embedding' shows much promise[5,6].

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APPENDIX B

PEPTIDE CHEMISTRY

B.1 Synthesis

Since the carbodiimide method only was used, other methods will be mentioned only briefly.

Mixed Anhydride Method

The reactions involved are shown in Figure B.1.1(a). The amine base must not be too nucleophilic if racaemisation is to be minimised, but if the reaction with the chloroformate is to occur, a hindered base such as di-isopropyl ethylamine cannot be used[2]. N-methyl morpholine has been found to be a suitable compromise.

The fact that Cl^- is a fairly good nucleophile, means that even if the exact quantity of amine is used, free base is present; replacing Cl^- by BF_4^-, a very poor nucleophile, produces a crystalline complex[5], which reacts with minimal racaemisation[2].

An alternative means of anhydride preparation is represented by E.E.D.Q.[3] and derivatives[4] (Figure B.1.1(b)). E.E.D.Q. has also been incorporated in an insoluble polymer[6].

The Azide Procedure

At one time, this was the method of choice when racaemate-free coupling was required (though racaemisation occurs under certain conditions[7,8,9]), but faster methods are now preferred. Figure B.1.2(a) shows the coupling stages.

N-carboxyamino Acid Anhydrides (N.C.A.'s Leuch's anhydrides)

Although originally used only to generate polyamino acids[10], because of the speed of reaction and lack of racaemisation, attempts have been made, with some success[11,12], to adapt it for general synthesis (Figure B.1.2(a))

The pH requires very careful control, as at low pH there is a tendency for the carbamate ion to lose carbon dioxide, leading to

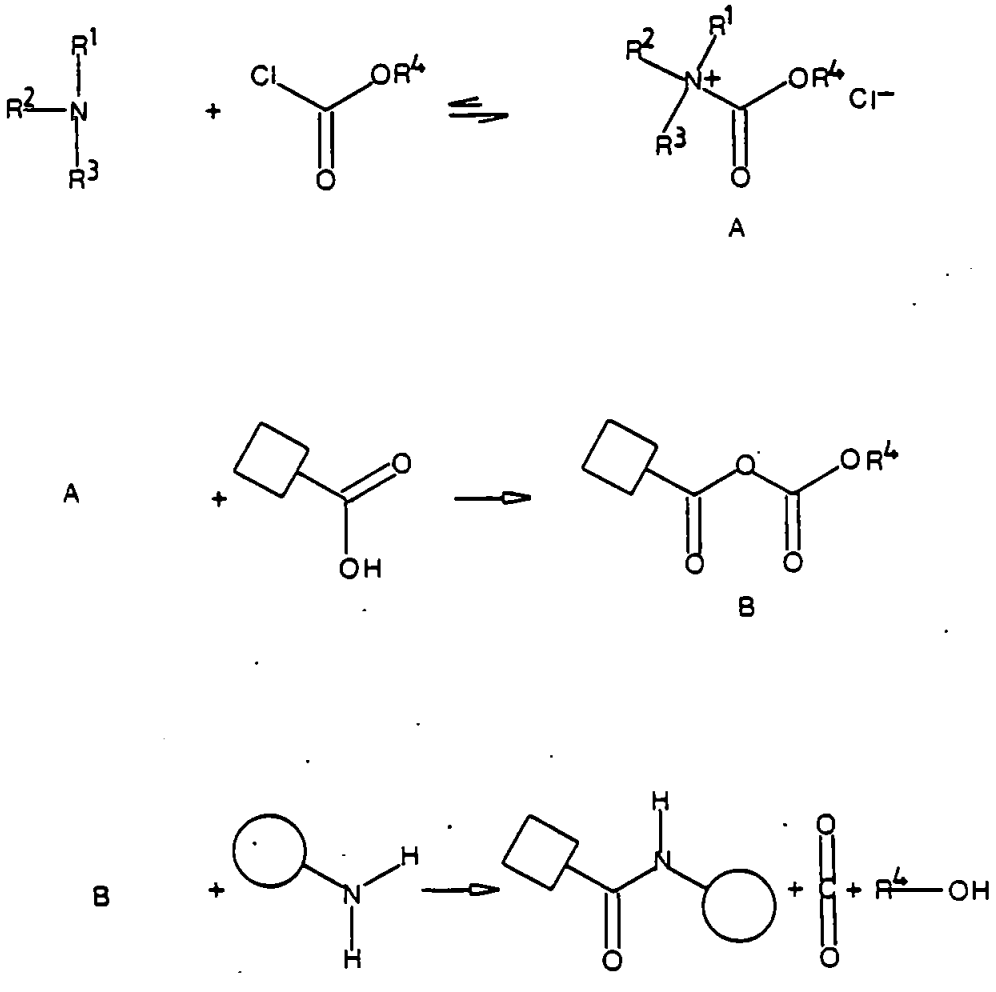


Figure B.1.1 (a) The mixed anhydride method;

for optimum yields R^4 is isobutyl.

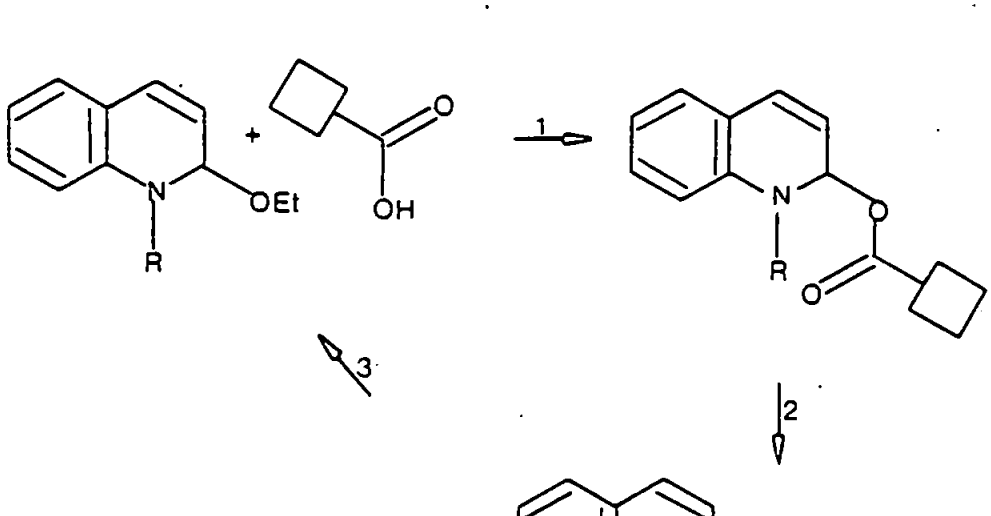
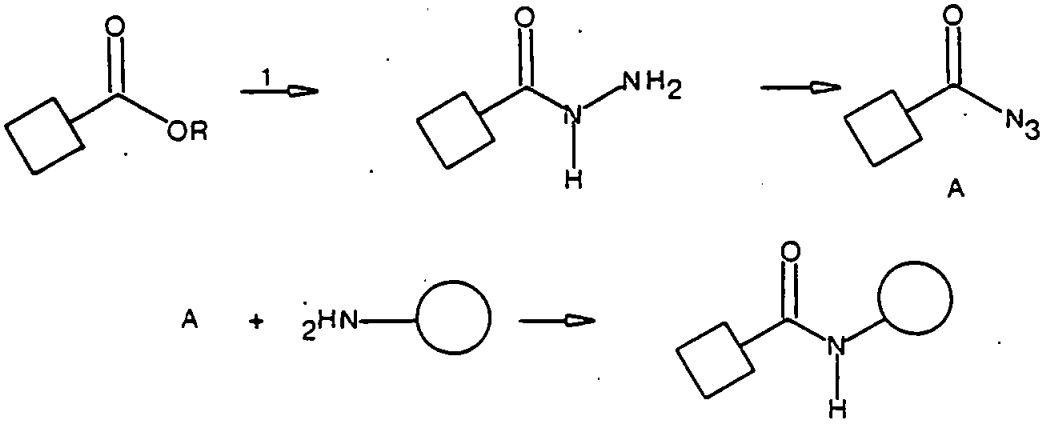
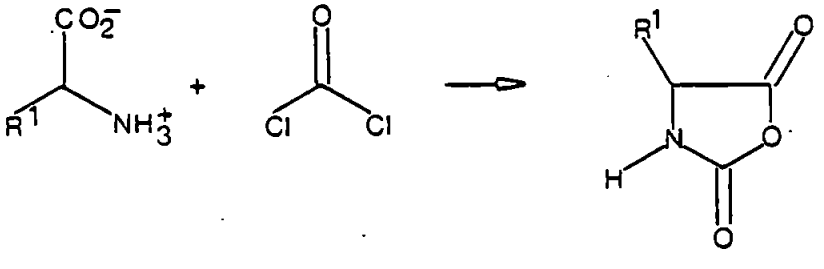


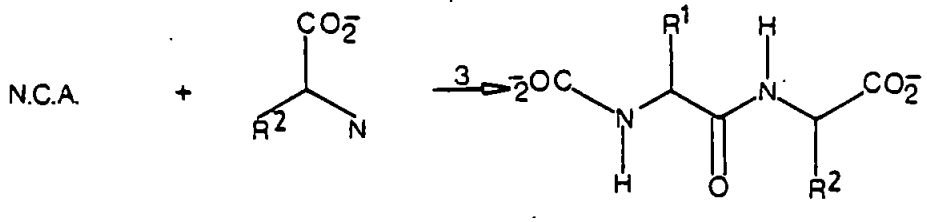
Figure B.1.1 (b) E.E.D.Q. variation on the mixed anhydride method; because reaction 2 is slow, B· (mixed anhydride) reacts with the amino component before side-reactions can occur; R is -COOEt and ☐- the body of the molecule; 3 requires $EtOCOCl/EtOH/Et_3N$.



(a)



N.C.A.



(b)

Figure B.1.2 (a) The azide procedure; the ester (R is usually Me or Et) is converted to the hydrazide, which upon reaction with nitrous acid (2) forms the water insoluble azide. (b) The N.C.A. method; 3 requires pH ≈10/H_2O/~0° C.

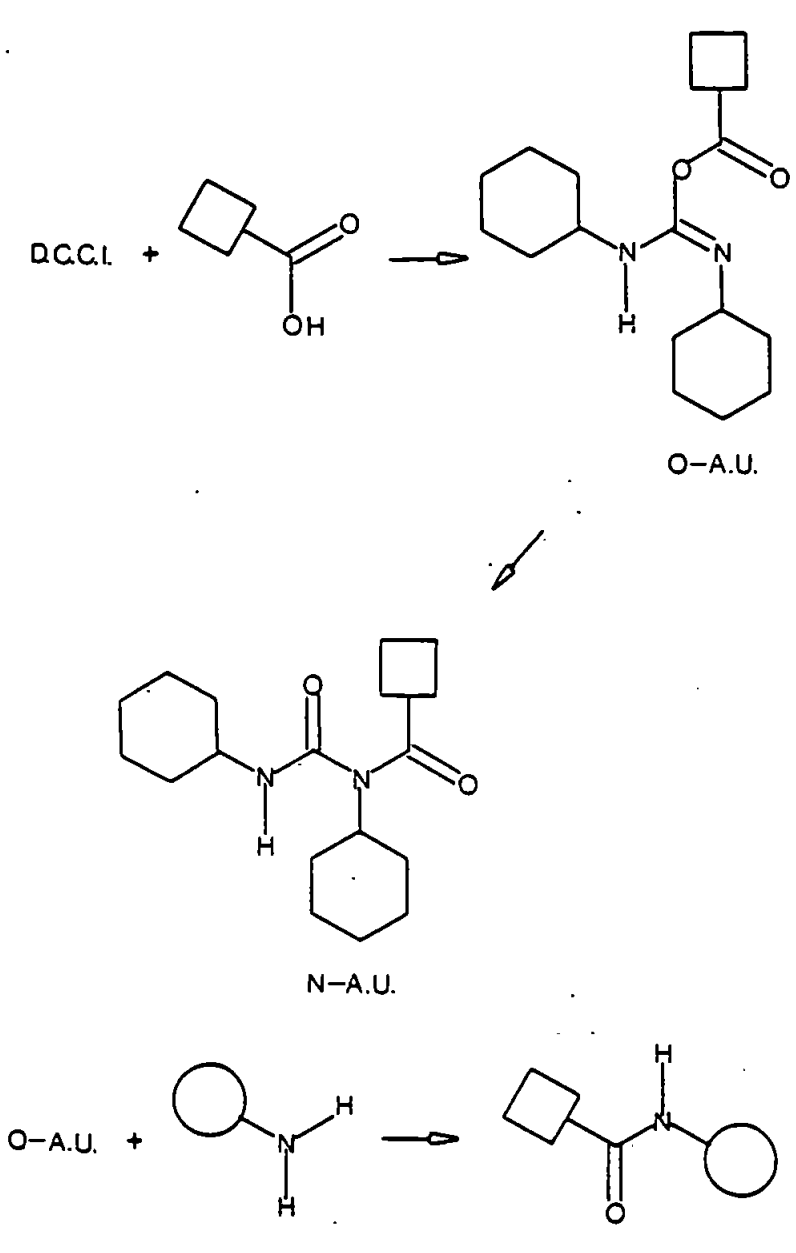


Figure B.1.3 The carbodiimide method:- the O-acyl urea (O-A.U.) can go to the N-acyl urea (N-A.U.) if the amino component is absent. □ and ○ represent the remainder of the molecule.

over-reaction, while at high pH there is significant reaction with hydroxide ion.

The D.C.C.I. Method

This method (Figure B.1.3) combines the advantages of cheap, readily available, chemicals, with not too rigorous reaction conditions and easily separated by-products.

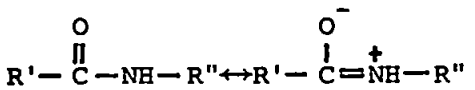
In addition, should high optical purity be required, an additive such as HOBT[14] (1-hydroxybenzotriazole, preferable to the earlier HOSu, which can form β alanine[13] side products) will usually ensure it, a point of special importance when N-acetyl derivatives are being synthesised; the reaction in the 'Eintopf Methode' proceeds via the active ester; these newer active esters are superseding the older generation of active ester, which are tedious to prepare[16], slow to react and often react incompletely[15].

Other methods of interest include condensation by oxidation - reduction[17] and via phosphorus compounds[18].

B.2 Racaemisation

The reactions and mechanisms that produce racaemisation during peptide synthesis have received much attention.

It has been well established that racaemisation of N-benzoyl-amino acid active esters is base catalysed and proceeds via oxazolone (azlactone) formation[19-21]. It is clear, considering the canonical forms



the carbonyl oxygen is more, or less, nucleophilic according as R' is electron donating or not. In the case of derivatives such as the urethanes, the diminished nucleophilicity of the carbonyl oxygen does not allow ring closure to form oxazolone.

Oxazolone formation is believed to result from the reactions shown in Figure B.2.1[22]. As well as kinetic evidence, a diminution in the racaemisation rate with N-methyl amide derivatives and imino acids such as proline support the mechanism.

The observed degree of racaemisation is very considerably effected by the ratio between the rate of oxazolone formation and racaemisation, and the rate of coupling. This is influenced greatly by the following factors:

Basicity

In addition to solvent basicity, there is the base added to neutralise the hydrochloride; ideally this base should be a considerably stronger base than the amino component while being as weak a nucleophile as possible; D.I.E.A. represents a good compromise[23].

Dielectric Constant

As reactions involving charged components usually show a marked

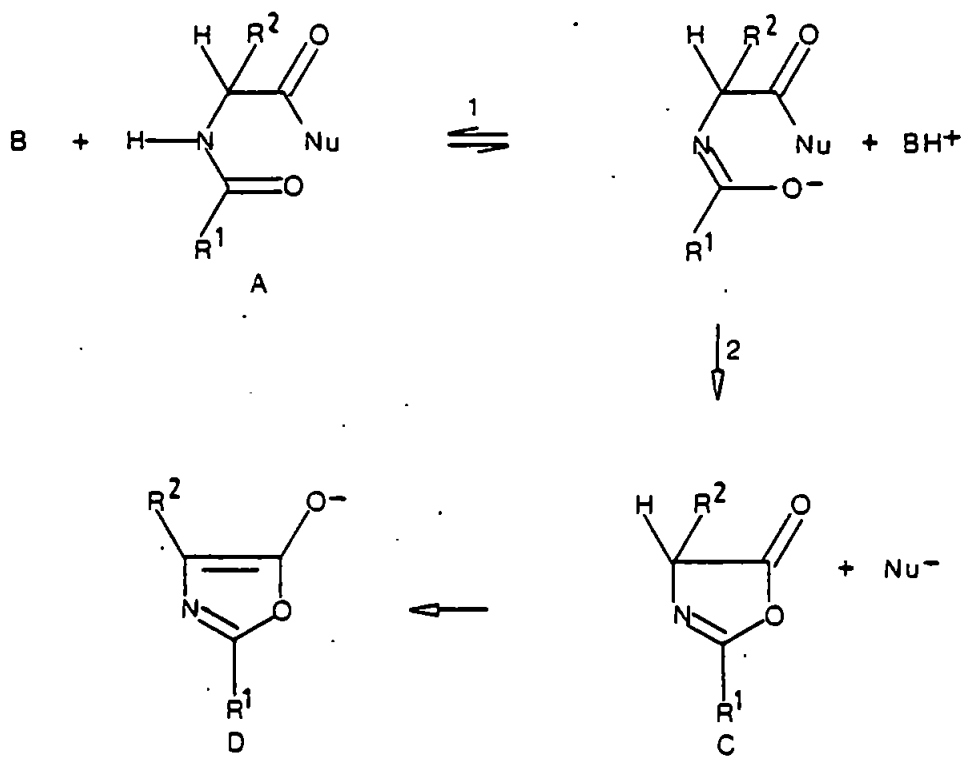


Figure B.2.1. Racaemisation via oxazolone formation. 1 is fast and 2 is slow. C (L-oxazolone) ionises far more readily than A (L-amino acid residue) as the anion is stabilised by conjugation. D ⇋ D,L-oxazolone ⇋ D,L-amino and residue.

dependence on dielectric constant, racaemisation occurs most readily in solvents, such as water, with high dielectric constants.

Ionic Strength

This is an influence for the same reasons as the dielectric constant, and probably accounts for the 'chloride ion effect'[19,24].

Nucleophilicity of Reaction Components

If a nucleophile reacts with the oxazolone rapidly, then racaemisation is prevented. The most important nucleophile during coupling is usually the amino component and, not unexpectedly, the least hindered ester is the most effective nucleophile (indicated by the degree of optical purity)[25].

Temperature

A low temperature is generally found to be beneficial due both to the increased stability of some reactants and a suppression of side reactions.

To minimise racaemisation during coupling clearly it is desirable that it proceed as rapidly as possible; to this end the minimum amount of solvent is used. In addition, with the D.C.C.I. method, an additive such as HOBT may be added; this has two beneficial effects:

The coupling proceeds very rapidly (via the active ester) e.g. the HOBT ester of Z-L-Phe reacts with HCl.L-Val-OMe/N-ethyl morpholine to give the dipeptide at over 90% yield in 5 minutes at $0^{o}C$[26].

HOBT is a fairly good nucleophile so it can block racaemisation at the oxazolone level (Figure B.2.1).

In derivatives such as the urethanes, which do not form oxazolones, the principal means of racaemisation is direct α-hydrogen abstraction[27-31], this being true even for derivatives of amino acids like cystine, well known for its tendency to racaemise, which at one

time were believed to racaemise by reversible β elimination. The effect of the side chain on the rate of racaemisation by direct proton abstraction has been determined for a series of benzoyl amino acid anilides[32] (which cannot form oxazolones); the rate of racaemisation increased from valine to phenylglycine in the following manner:

Val<But<Leu<Ala<Phe<Ph Gly

The rate is clearly related to the electronegativity of the side group, except for valine where the steric effect predominates.

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APPENDIX C

STRUCTURES ATTEMPTED

C.1 N-Acetyl Dehydro-Phenylalanyl-L-Leucine

Experimental

The compound was prepared by the method of Bergmann[1] and crystals grown by cooling slowly a water/methanol/n-hexane solution; the first crystals obtained were large, off-white, hexagonal prisms and these were used for determination of the space group and cell parameters. After many recrystallisations, small pure crystals with a sharp melting point, but tiny cross section and unsatisfactory extinction under polarised light, were obtained; they were unsuitable for data collection.

Crystal characteristics

Formula $C_{17}\ H_{22}\ N_2\ O_4$

$a = b = 12.555\ \text{Å}$

$c = 21.711\ \text{Å}$

$\gamma = 60^{\circ}$

$D_o = 1.26\ g.cm^{-3}$

$D_c = 1.07\ g.cm^{-3}$

$Z = 6$

Space group $P6_1$

An attempt was made to collect data on the CAD 4 using an impure crystal, but the reflexions were too weak to be worth collecting.

C.2 N-Acetyl Dehydro-Phenylalanyl-L-Alanine

Experimental

The compound was prepared by the method of Bergmann[2] and crystals grown from water.

Data collection was attempted but not continued due to the weak nature of the reflexions.

Other compounds that proved unsuitable are mentioned in Chapter 3.

References

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APPENDIX D

RECENT DEVELOPMENTS

Recent Developments

The last couple of years have seen the emergence of components of the likely successor to MULTAN, MAGLIN (MAGic integers and LINear equations)[1,2].

Magic integers have already been introduced into later versions of MULTAN, but recent progress promises to make them an even more efficient procedure[3]; the use of linear equations in this way is new.

In cycles Σ_2 relationships take the form:

$$\phi_{1i} \pm \phi_{2i} \pm \phi_{3i} \pm b_i = n_i$$

where 'n' is integer.

As the number of Σ_2 relationships greatly exceed the number of phases least squares solution suggests itself.

Putting the κ weighted Σ_2 relationships in matrix form gives

$$A\phi = C$$

which has a least squares solution

$$\phi = (A^T A)^{-1} A^T C$$

The original technique was to use estimates of the phases to solve for 'n', make 'n' the nearest integer, and substitute in C (after κ weighting) to obtain new estimates for the phases, the only change from one phase set to the next being in the column vector C. This last point is important as matrix inversion is very time consuming (increasing as the cube of the matrix order), though the matrix order can be reduced by keeping constant certain phases (recognisable from the elements of $(A^T A)^{-1} A^T$) which are stable from one cycle to the next.

The question arises of what to do, if for example, 'n' is calculated as 1.5 or, for that matter, values clustered around a midpoint. An explicit weighting to reflect the uncertainty would mean A changing and consequent matrix inversion, every cycle. However, if the

example is written thus:

$$\phi_{1i} + \phi_{2i} + \phi_{3i} + b_i = n_i = n_i' + \alpha_i$$

with $\alpha = 0.5$, the equation is effectively eliminated from the least squares, while $\alpha = 0$ will tend to decrease ϕ_{ji} $j = 1,3$. De facto weighting can be achieved by a function $f(\alpha)$ such that $f(0.5) = .5$ and $f(o) = 0$. $4\alpha^3$ has been found to be suitable. The example now takes the form

$$\kappa(\phi_{1i} + \phi_{2i} + \phi_{3i}) = \kappa(n_i' - b_i + f_i(\alpha)) = C_i$$

so that only C varies with each cycle.

Sophistications, like extrapolation of phases, produce more efficient computer use, but lack of an adequate indicator of refinement progress, lessens the effect.

The linear equation procedure, like tangent refinement, by requiring the triplet invariants to be close to zero, blurs enantiomorph discrimination[4,5]. Definition is possible, by rather empirical, ad hoc methods or, far more satisfactorily, by restrictions on phases related by magic integers[6].

Renewed interest in Karle-Hauptman (K-H) determinants has been prompted by the derivation of the maximum determinant rule[7-10]: that the most probable set of phases for the reflexions in the K-H determinant is that which maximises its value.

$$\Delta_{m+1} = N^{-1} \begin{vmatrix} \overbrace{1 & \cdots & U_{1p} & \cdots & U_{1m}}^{U_m} & E_{1,m+1} \\ \vdots & & \vdots & & \vdots & \vdots \\ U_{p1} & \cdots & 1 & \cdots & U_{pm} & E_{p,m+1} \\ \vdots & & \vdots & & \vdots & \vdots \\ U_{m1} & \cdots & U_{mp} & \cdots & 1 & E_{m,m+1} \\ \vdots & & \vdots & & \vdots & \vdots \\ E_{m+1,1} & \cdots & E_{m+1,p} & & E_{m+1,m} & 1 \end{vmatrix}$$

i.e. given U_m and denoting by $E_1 \ldots . E_m$, $E_{m+1,1} \ldots . E_{m+1,m}$, it can be shown that

$$P(E_1 \ldots . E_m | U_m) = (2\pi)^{-m/2} U_m^{-\frac{1}{2}} e^{-N} \exp(N\Delta_{m+1}/2U_m) \text{ for centro-symmetric structures}$$

$$= (2\pi)^{-m} U_m^{\frac{1}{2}} e^{-N} \exp(N\Delta_{m+1}/U_m) \text{ for non-centrosymmetric structures.}$$

They have been used most interestingly, combined with the magic integer method, as a figure of merit. The determinant is evaluated as a function of magic integer variables, with the peaks giving values to the variables, which are then refined by a novel method[11,12].

On the basis of a comprehensive theoretical framework[13-15], structural information is increasingly being utilized in direct methods to solve large or difficult structures. Proteins, an area resistant to direct methods[16,17,18] hitherto, is an obvious field where progress can be expected.

Other areas of interest include a geometric interpretation of direct methods[19], and the use of weak reflexions in refinement[20,21]

and scaling[22].

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APPENDIX E

STRUCTURE FACTOR TABLES

Table E.1

Observed and calculated structure factor moduli for N-Ac Δ Ala-OH. Symmetry related reflexions showing large inconsistencies are shown below:

h	k	ℓ	e.s.d./F	Δ/F	N
0	11	5	0.280	4.245	2
0	7	8	0.207	0.156	2
0	5	9	0.216	0.189	2
0	1	11	0.229	0.354	2

R' = 0.0096

H	K	L	10F0	10FC
2	0	0	175	274
4			54	43
6			327	355
8			12	12
10			135	119
12			268	270
14			69	69
16			38	38
18			31	35
1	1		471	537
3			178	160
5			391	370
7			249	229
9			63	38
11			102	95
13			176	169
15			17	24
17			31	32
19			52	42
0	2		1429	1654
2			979	939
4			79	78
6			96	82
8			51	50
10			218	221
12			246	255
14			68	58
16			53	57
18			89	85
1	3		451	422
3			178	175
5			90	87
7			123	116
9			34	92
11			22	22
13			38	34
15			37	32
17			7	15
19			125	606
0	4		445	437
2			471	487
4			190	187
6			52	48
8			223	229
10			119	114
12			29	27
14			54	62

H	K	L	10F0	10FC
18	4	0	10	20
1			345	337
3			394	396
5			82	84
7			100	102
9			184	181
11			104	114
13			52	57
15			39	58
17			25	19
0	2		250	247
2			131	124
4			167	177
6			88	94
8			107	116
10			208	202
12			25	22
14			31	22
16			51	51
1	4		345	346
3			226	220
5			125	125
7			61	66
9			97	97
11			26	26
13			30	25
15			40	45
17			23	6
0	6		100	103
2			78	82
4			129	133
6			25	28
8			38	41
10			34	26
12			29	22
14			32	23
16			56	60
1	5		62	62
3			33	30
5			74	80
7			18	15
9			29	24
11			38	23
13			21	10
15			44	37
17			44	47
19			32	26

H	K	L	10F0	10FC
-20	1	1	66	56
-18			53	51
-16			36	21
-14			24	7
-12			30	7
-10			20	8
-8			32	26
-6			24	21
-4			15	8
-2			17	9
0			9	11
2			14	16
4			7	9
6			36	37
8			22	12
10			33	8
12			15	17
14			25	17
16			21	26
18			33	22
-19	1	1	21	18
-17			138	178
-15			238	241
-13			165	158
-11			206	191
-9			267	284
-7			805	842
-5			154	120
-3			852	966
-1			402	432
1			376	338
3			635	541
5			41	42
7			361	368
9			118	123
11			83	85
13			19	7
15			30	26
17			23	13
19			28	25
-18	2		65	63
-16			197	204
-14			94	93
-12			125	128
-10			389	366
-8			256	252
-6			738	718
-4			688	689
-2			1	1
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2			1	1
4			1	1
6			1	1
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0			1	1
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-2	20		1	1
0			1	1
-1	21		1	1
1			1	1
0	22		1	1

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
2	6	1	79	90	-1	9	1	68	73	1	13	1	10	10	-8	2	2	320	311	12	4	2	51	66
4	6	1	120	116	1	9	1	28	19	3	13	1	23	2	-6	2	2	229	219	14	4	2	51	53
6	6	1	113	111	3	9	1	47	44	5	13	1	37	2	-4	2	2	526	492	16	4	2	37	25
8	6	1	57	78	5	9	1	16	28	-20	0	2	26	14	-2	2	2	927	932	-19	5	2	16	16
10	6	1	122	127	7	9	1	48	50	-18	0	2	47	49	0	2	2	183	218	-17	5	2	26	16
12	6	1	28	36	9	9	1	21	21	-16	0	2	39	31	2	2	2	786	791	-15	5	2	32	16
14	6	1	18	27	11	9	1	24	19	-14	0	2	169	194	4	2	2	155	139	-13	5	2	46	19
16	6	1	61	63	13	9	1	10	11	-12	0	2	154	155	6	2	2	136	119	-11	5	2	121	125
-17	7	1	43	26	-14	10	1	13	11	-10	0	2	100	96	8	2	2	103	178	-9	5	2	155	150
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-9	7	1	90	90	-6	10	1	21	24	-2	0	2	1238	1323	16	2	2	9	18	-1	5	2	256	251
-7	7	1	63	65	-4	10	1	18	31	0	0	2	522	517	18	2	2	39	32	1	5	2	373	337
-5	7	1	61	60	-2	10	1	26	22	2	0	2	55	58	-19	3	2	42	39	3	5	2	[illegible]	[illegible]
-3	7	1	60	56	0	10	1	22	24	4	0	2	112	113	-17	3	2	9	16	5	5	2	115	113
-1	7	1	45	43	2	10	1	13	39	6	0	2	484	483	-15	3	2	21	31	7	5	2	74	69
1	7	1	54	59	4	10	1	34	37	8	0	2	43	40	-13	3	2	56	91	9	5	2	24	24
3	7	1	57	58	6	10	1	46	46	10	0	2	7	21	-11	3	2	164	162	11	5	2	25	19
5	7	1	80	86	8	10	1	12	19	12	0	2	91	89	-9	3	2	245	257	13	5	2	61	32
7	7	1	47	45	10	10	1	14	11	14	0	2	8	14	-7	3	2	211	192	15	5	2	39	25
9	7	1	35	26	12	10	1	31	17	16	0	2	45	49	-5	3	2	77	77	-18	6	2	40	26
11	7	1	20	29	-11	11	1	10	2	18	0	2	48	52	-3	3	2	327	312	-16	6	2	9	2
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2	8	1	109	113	-10	12	1	13	5	3	1	2	465	445	-16	4	2	[illegible]	0	8	6	2	151	177
4	8	1	65	67	-8	12	1	43	24	5	1	2	350	329	-14	4	2	116	121	10	6	2	[illegible]	47
6	8	1	50	52	-6	12	1	9	6	7	1	2	172	169	-12	4	2	96	85	12	6	2	[illegible]	19
8	8	1	15	11	-4	12	1	10	8	9	1	2	95	85	-10	4	2	142	144	14	6	2	57	57
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14	8	1	8	23	2	12	1	18	11	15	1	2	25	36	-4	4	2	301	294	-15	7	2	[illegible]	32
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-7	9	1	57	55	-5	13	1	26	10	-14	2	2	150	152	6	4	2	61	69	-5	7	2	174	[illegible]
-5	9	1	36	41	-3	13	1	10	3	-12	2	2	139	137	8	4	2	147	152	-3	7	2	15	152
-3	9	1	50	88	-1	13	1	10	3	-10	2	2	139	128	10	4	2	24	37	-1	7	2	14	42

XTXXX

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
1	7	2	107	99	4	10	2	8	11	12	0	3	28	34	-7	3	3	155	152	15	5	3	35	33
3	7	2	121	89	6	10	2	9	27	14	0	3	29	31	-5	3	3	241	251	-18	6	3	33	31
5	7	2	44	43	8	10	2	9	11	16	0	3	34	20	-3	3	3	209	214	-16	6	3	34	20
7	7	2	82	77	10	10	2	9	9	-21	1	3	33	39	-1	3	3	67	64	-14	6	3	15	22
9	7	2	25	39	12	10	2	10	20	-19	1	3	9	20	1	3	3	260	262	-12	6	3	74	55
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6	0	8	17	3
8	0	8	43	40
10	0	8	34	37
-19	1	8	20	9

H	K	L	10FO	10FC
-17	1	8	21	8
-15	1	8	39	44
-13	1	8	60	67
-11	1	8	100	108
-9	1	8	75	70
-7	1	8	32	35
-5	1	8	7	7
-3	1	8	138	140
-1	1	8	26	32
1	1	8	195	197
3	1	8	63	66
5	1	8	88	95
7	1	8	41	43
9	1	8	31	32
11	1	8	15	23
-20	2	8	48	47
-18	2	8	22	12
-16	2	8	9	5
-14	2	8	32	29
-12	2	8	78	74
-10	2	8	110	109
-8	2	8	114	108
-6	2	8	112	112
-4	2	8	124	142
-2	2	8	51	57
0	2	8	125	125
2	2	8	37	40
4	2	8	25	28
6	2	8	37	19
8	2	8	56	49
10	2	8	29	20
-19	3	8	29	24
-17	3	8	9	26
-15	3	8	21	5
-13	3	8	31	26
-11	3	8	65	71
-9	3	8	18	20
-7	3	8	111	106
-5	3	8	68	74
-3	3	8	133	131
-1	3	8	19	26
1	3	8	89	93
3	3	8	70	76
5	3	8	52	53
7	3	8	39	52
9	3	8	9	4
-18	4	8	19	29
-16	4	8	24	21

H	K	L	10FO	10FC
-14	4	8	37	46
-12	4	8	50	65
-10	4	8	[illegible]	29
-8	4	8	59	61
-6	4	8	21	26
-4	4	8	7	29
-2	4	8	28	26
0	4	8	69	71
2	4	8	68	65
4	4	8	59	61
6	4	8	52	54
8	4	8	9	20
10	4	8	11	15
-19	5	8	[illegible]	[illegible]
-17	5	8	29	14
-15	5	8	29	16
-13	5	8	63	65
-11	5	8	51	47
-9	5	8	8	12
-7	5	8	61	61
-5	5	8	61	58
-3	5	8	63	84
-1	5	8	56	83
1	5	8	78	84
3	5	8	[illegible]	14
5	5	8	24	9
7	5	8	64	60
9	5	8	36	12
-18	6	8	23	42
-16	6	8	33	22
-14	6	8	31	36
-12	6	8	[illegible]	18
-10	6	8	25	28
-8	6	8	10	29
-6	6	8	[illegible]	4
-4	6	8	19	21
-2	6	8	[illegible]	12
0	6	8	20	16
2	6	8	43	43
4	6	8	33	28
6	6	8	53	51
8	6	8	25	6
-17	7	8	37	29
-15	7	8	19	18
-13	7	8	31	37
-11	7	8	25	16
-9	7	8	15	15
-7	7	8	41	52

H	K	L	10FO	10FC
-5	7	8	27	9
-3	7	8	[illegible]	22
-1	7	8	17	[illegible]
1	7	8	55	[illegible]
3	7	8	31	13
5	7	8	25	15
7	7	8	36	[illegible]
-16	[illegible]	8	[illegible]	22
-14	[illegible]	8	[illegible]	15
-12	[illegible]	8	23	[illegible]
-10	[illegible]	8	22	[illegible]
-8	[illegible]	8	18	16
-6	[illegible]	8	17	[illegible]
-4	[illegible]	8	20	13
-2	[illegible]	8	33	[illegible]
0	[illegible]	8	37	17
2	[illegible]	8	41	[illegible]
4	[illegible]	8	17	9
6	[illegible]	8	23	17
-13	9	8	25	6
-11	9	8	9	16
-9	9	8	24	17
-7	9	8	41	36
-5	9	8	24	26
-3	9	8	16	15
-1	9	8	17	15
1	9	8	9	16
3	9	8	20	18
-12	10	8	10	12
-10	10	8	25	13
-8	10	8	17	5
-6	10	8	9	6
-4	10	8	15	7
-2	10	8	33	21
0	10	8	[illegible]	7
2	10	8	13	10
-7	11	8	10	6
-5	11	8	[illegible]	[illegible]
-3	11	8	35	21
-20	[illegible]	9	[illegible]	[illegible]
-18	[illegible]	9	9	9
-16	[illegible]	9	74	73
-14	[illegible]	9	19	17
-12	0	9	143	149
-10	0	9	180	190
-8	0	9	225	[illegible]
-6	[illegible]	9	105	110
-4	[illegible]	9	21	15

H	K	L	10FO	10FC
-2	0	9	38	44
0	0	9	156	153
2	0	9	101	101
4	0	9	73	76
6	0	9	74	74
8	0	9	36	37
-19	1	9	10	10
-17	1	9	60	61
-15	1	9	43	37
-13	1	9	115	105
-11	1	9	204	212
-9	1	9	75	70
-7	1	9	28	26
-5	1	9	52	48
-3	1	9	65	64
-1	1	9	31	85
1	1	9	95	92
3	1	9	21	36
5	1	9	9	29
7	1	9	63	60
9	1	9	29	27
-20	2	9	6	24
-18	2	9	19	27
-16	2	9	73	74
-14	2	9	22	33
-12	2	9	147	147
-10	2	9	115	114
-8	2	9	171	171
-6	2	9	107	111
-4	2	9	68	66
-2	2	9	62	62
0	2	9	74	73
2	2	9	80	78
4	2	9	100	99
6	2	9	41	35
8	2	9	32	37
-19	3	9	19	22
-17	3	9	27	41
-15	3	9	48	48
-13	3	9	77	74
-11	3	9	173	179
-9	3	9	71	69
-7	3	9	107	105
-5	3	9	23	33
-3	3	9	8	22
-1	3	9	118	116
1	3	9	87	88
3	3	9	61	64

H	K	L	10FO	10FC
5	3	9	44	37
7	3	9	9	35
-18	4	9	49	46
-16	4	9	61	63
-14	4	9	10	22
-12	4	9	95	97
-10	4	9	66	64
-8	4	9	108	105
-6	4	9	116	116
-4	4	9	76	72
-2	4	9	43	45
0	4	9	42	46
2	4	9	8	26
4	4	9	51	52
6	4	9	9	13
8	4	9	24	26
-17	5	9	21	11
-15	5	9	54	51
-13	5	9	70	70
-11	5	9	81	85
-9	5	9	49	54
-7	5	9	86	89
-5	5	9	32	31
-3	5	9	41	40
-1	5	9	109	108
1	5	9	44	58
3	5	9	52	48
5	5	9	35	38
7	5	9	40	36
-16	6	9	17	20
-14	6	9	9	18
-12	6	9	52	55
-10	6	9	30	37
-8	6	9	58	56
-6	6	9	78	75
-4	6	9	26	17
-2	6	9	45	50
0	6	9	42	41
2	6	9	9	29
4	6	9	27	29
6	6	9	10	21
-15	7	9	18	23
-13	7	9	38	33
-11	7	9	7	19
-9	7	9	23	31
-7	7	9	69	72
-5	7	9	42	44
-3	7	9	36	29

H	K	L	10FO	10FC
-1	7	9	44	46
1	7	9	28	34
3	7	9	11	17
5	7	9	31	34
-14	8	9	22	27
-12	8	9	30	37
-10	8	9	9	12
-8	8	9	7	18
-6	8	9	36	44
-4	8	9	23	30
-2	8	9	22	32
0	8	9	29	15
2	8	9	11	16
-11	9	9	14	14
-9	9	9	9	11
-7	9	9	35	43
-5	9	9	33	28
-3	9	9	25	17
-1	9	9	14	12
1	9	9	33	11
-8	10	9	26	2
-6	10	9	29	21
-4	10	9	24	25
-2	10	9	25	19
-18	0	10	79	75
-16	0	10	27	18
-14	0	10	7	20
-12	0	10	58	62
-10	0	10	28	34
-8	0	10	66	72
-6	0	10	177	177
-4	0	10	14	26
-2	0	10	113	109
0	0	10	24	28
2	0	10	9	11
4	0	10	14	11
6	0	10	10	29
-19	1	10	59	57
-17	1	10	42	37
-15	1	10	41	36
-13	1	10	29	29
-11	1	10	18	12
-9	1	10	56	58
-7	1	10	152	152
-5	1	10	153	157
-3	1	10	154	161
-1	1	10	21	40
1	1	10	3	22

H	K	L	10FO	10FC
3	1	10	41	26
5	1	10	31	32
7	1	10	10	36
-18	2	10	63	64
-16	2	10	17	24
-14	2	10	42	51
-12	2	10	43	49
-10	2	10	46	49
-8	2	10	48	55
-6	2	10	169	168
-4	2	10	9	33
-2	2	10	117	115
0	2	10	19	22
2	2	10	9	24
4	2	10	9	33
6	2	10	33	25
-17	3	10	36	37
-15	3	10	59	63
-13	3	10	29	35
-11	3	10	28	37
-9	3	10	62	68
-7	3	10	83	90
-5	3	10	87	87
-3	3	10	100	106
-1	3	10	103	103
1	3	10	34	24
3	3	10	9	15
5	3	10	10	23
-18	4	10	41	32
-16	4	10	19	21
-14	4	10	60	56
-12	4	10	14	31
-10	4	10	49	49
-8	4	10	59	56
-6	4	10	107	110
-4	4	10	33	32
-2	4	10	71	72
0	4	10	47	38
2	4	10	9	16
4	4	10	23	30
6	4	10	24	31
-17	5	10	27	34
-15	5	10	54	55
-13	5	10	31	33
-11	5	10	12	14
-9	5	10	47	51
-7	5	10	55	55
-5	5	10	53	49

H	K	L	10FO	10FC
-3	5	10	62	66
-1	5	10	59	41
1	5	10	20	1
3	5	10	9	12
5	5	10	30	21
-16	6	10	10	[illegible]
-14	6	10	41	[illegible]
-12	6	10	52	46
-10	6	10	37	38
-8	6	10	24	22
-6	6	10	31	31
-4	6	10	9	14
-2	6	10	35	38
0	6	10	40	44
2	6	10	20	10
4	6	10	25	22
-15	7	10	40	38
-13	7	10	32	26
-11	7	10	36	26
-9	7	10	44	42
-7	7	10	21	31
-5	7	10	22	1
-3	7	10	12	23
-1	7	10	45	25
1	7	10	10	17
-12	8	10	35	43
-10	8	10	15	5
-8	8	10	[illegible]	16
-6	8	10	29	14
-4	8	10	13	7
-2	8	10	10	12
0	8	10	21	20
-9	9	10	10	17
-7	9	10	13	16
-5	9	10	23	7
-3	9	10	30	7
-18	0	11	37	29
-16	0	11	31	26
-14	0	11	9	13
-12	0	11	69	68
-10	0	11	18	4
-8	0	11	19	15
-6	0	11	14	13
-4	0	11	23	[illegible]
-2	0	11	32	45
0	0	11	37	55
2	0	11	5	31
4	0	11	10	8

H	K	L	10FO	10FC
-17	1	11	30	27
-15	1	11	56	65
-13	1	11	18	21
-11	1	11	38	47
-9	1	11	8	19
-7	1	11	8	21
-5	1	11	29	35
-3	1	11	9	13
-1	1	11	27	25
1	1	11	49	49
3	1	11	48	41
-18	2	11	33	21
-16	2	11	9	29
-14	2	11	40	36
-12	2	11	58	61
-10	2	11	17	4
-8	2	11	21	20
-6	2	11	39	25
-4	2	11	28	29
-2	2	11	45	45
0	2	11	42	41
2	2	11	13	25
4	2	11	10	25
-17	3	11	20	15
-15	3	11	41	37
-13	3	11	39	35
-11	3	11	15	29
-9	3	11	39	28
-7	3	11	9	18
-5	3	11	68	51
-3	3	11	22	22
-1	3	11	28	28
1	3	11	31	46
3	3	11	31	13
-16	4	11	10	15
-14	4	11	34	48
-12	4	11	40	18
-10	4	11	9	18
-8	4	11	32	14
-6	4	11	31	22
-4	4	11	9	21
-2	4	11	40	42
0	4	11	27	14
2	4	11	49	26
-15	5	11	10	5
-13	5	11	42	40
-11	5	11	9	17
-9	5	11	34	22
-7	5	11	9	13
-5	5	11	9	20
-3	5	11	42	42
-1	5	11	9	2
1	5	11	10	11
-14	6	11	23	30
-12	6	11	21	13
-10	6	11	31	22
-8	6	11	9	22
-6	6	11	9	14
-4	6	11	9	12
-2	6	11	24	32
0	6	11	8	9
-11	7	11	20	[illegible]
-9	7	11	16	17
-7	7	11	10	3
-5	7	11	10	6
-3	7	11	22	26
-1	7	11	6	8
-8	8	11	23	26
-6	8	11	10	5
-16	0	12	10	14
-14	0	12	9	12
-12	0	12	9	9
-10	0	12	46	60
-8	0	12	19	23
-6	0	12	66	65
-4	0	12	9	4
-2	0	12	19	23
0	0	12	33	34
2	0	12	35	19
-15	1	12	38	30
-13	1	12	49	48
-11	1	12	23	17
-9	1	12	43	43
-7	1	12	74	77
-5	1	12	9	12
-3	1	12	40	25
-1	1	12	9	34
1	1	12	10	28
-16	2	12	42	28
-14	2	12	11	6
-12	2	12	14	18
-10	2	12	43	12
-8	2	12	53	33
-6	2	12	56	51
-4	2	12	13	37
-2	2	12	9	18
0	2	12	10	30
-15	3	12	24	33
-13	3	12	10	22
-11	3	12	41	61
-9	3	12	23	27
-7	3	12	47	52
-5	3	12	9	11
-3	3	12	33	27
-1	3	12	16	8
1	3	12	13	23
-14	4	12	21	8
-12	4	12	[illegible]	18
-10	4	12	9	23
-8	4	12	51	47
-6	4	12	34	31
-4	4	12	48	49
-2	4	12	33	18
0	4	12	29	11
-13	5	12	10	19
-11	5	12	36	40
-9	5	12	20	16
-7	5	12	19	23
-5	5	12	15	11
-3	5	12	10	18
-10	6	12	42	43
-8	6	12	21	29
-6	6	12	39	7
-4	6	12	58	30
-14	0	13	[illegible]	9
-12	0	13	74	69
-10	0	13	[illegible]	9
-8	0	13	[illegible]	20
-6	0	13	29	10
-4	0	13	37	19
-2	0	13	10	2
-13	1	13	57	50
-11	1	13	22	22
-9	1	13	16	16
-7	1	13	[illegible]	[illegible]
-5	1	13	10	10
-3	1	13	40	24
-12	2	13	62	60
-10	2	13	24	26
-8	2	13	36	22
-6	2	13	41	19
-4	2	13	10	21
-11	3	13	[illegible]	20
-9	3	13	10	17
-7	3	13	[illegible]	8
-5	3	13	[illegible]	15
-8	4	13	22	21

Table E.2

Observed and calculated structure factor moduli for N-Ac-L-Ala-L-Ser-OEt. Symmetry related reflexions showing large inconsistencies are shown below:

h	k	ℓ	e.s.d./F	Δ/F	N
19	3	0	0.274	4.247	2
14	6	0	0.209	0.166	2
17	7	0	0.221	0.401	2
4	10	0	0.215	0.161	2
3	11	0	0.235	0.422	2
4	12	0	0.271	4.407	2

$R' = 0.0063$

H	K	L	10FO	10FC
3	6	1	83	82
2	6	1	48	-51
1	6	1	24	24
0	6	1	119	120
1	6	1	11	-12
2	6	1	49	48
3	6	1	25	-25
4	6	1	10	15
5	6	1	60	60
6	6	1	100	89
7	6	1	116	-111
8	6	1	26	25
9	6	1	139	139
10	6	1	64	-63
11	6	1	13	12
12	6	1	36	37
13	6	1	59	62
14	6	1	11	-9
15	6	1	102	93
16	6	1	24	-10
17	6	1	35	-37
18	6	1	10	16
19	6	1	17	16
20	6	1	53	55
21	6	1	133	-136
22	6	1	102	107
23	6	1	33	37
24	6	1	61	-62
25	6	1	16	-17
26	6	1	42	37
27	6	1	18	18

H	K	L	10FO	10FC
0	10	1	82	82
1	10	1	90	92
2	10	1	8	-11
3	10	1	11	6
4	10	1	8	5
5	10	1	57	57
6	10	1	63	64
7	10	1	50	-48
8	10	1	3	1
9	10	1	26	-4
10	10	1	15	26
11	10	1	38	28
12	10	1	24	-18
13	10	1	137	-135
14	10	1	25	25
15	10	1	40	42
16	10	1	28	30
17	10	1	39	38
18	10	1	252	-253
19	10	1	46	47
20	10	1	89	87
21	10	1	153	153
22	10	1	55	55
23	10	1	97	89
24	10	1	34	33
25	10	1	26	26
26	10	1	54	55
27	10	1	27	26
28	10	1	57	-57
29	10	1	29	-32
30	10	1	50	-47
31	10	1	219	207

H	K	L	10FO	10FC
0	1	0	125	-136
1	1	0	66	-61
2	1	0	58	54
3	1	0	101	96
4	1	0	46	-45
5	1	0	13	11
6	1	0	41	41
7	1	0	19	-19
8	1	0	41	37

H	K	L	10FO	10FC
0	1	1	134	138
1	1	1	47	47
2	1	1	64	63
3	1	1	46	48
4	1	1	64	65
5	1	1	42	45
6	1	1	66	64
7	1	1	71	75
8	1	1	24	20
9	1	1	117	117
10	1	1	83	88
11	1	1	155	154
12	1	1	70	82
13	1	1	12	-9
14	1	1	42	42
15	1	1	83	84
16	1	1	30	28
17	1	1	54	54
18	1	1	82	77
19	1	1	21	21
20	1	1	27	27
21	1	1	86	85
22	1	1	32	32
23	1	1	21	21
24	1	1	42	46
25	1	1	15	14
26	1	1	82	73

H	K	L	10FO	10FC
1	2	1	734	729
2	2	1	314	346
3	2	1	77	80
4	2	1	35	34
5	2	1	14	14
6	2	1	19	17
7	2	1	31	36
8	2	1	19	19
9	2	1	96	94
10	2	1	42	46
11	2	1	96	86
12	2	1	36	35
13	2	1	24	26
14	2	1	102	95
15	2	1	114	108
16	2	1	48	48
17	2	1	33	43
18	2	1	45	43
19	2	1	145	186
20	2	1	159	195
21	2	1	149	145
22	2	1	162	139
23	2	1	39	37
24	2	1	49	46
25	2	1	139	144
26	2	1	19	18

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
3	2	2	109	106	1	6	2	73	68	-2	11	2	3	-2	0	3	3	38	-36	-2	7	3	31	-33
4	2	2	50	-52	2	6	2	43	-42	-1	11	2	21	21	1	3	3	320	315	-1	7	3	102	-106
-4	3	2	16	60	3	6	2	4	5	0	11	2	77	77	2	3	3	257	238	0	7	3	149	150
-3	3	2	75	60	4	6	2	14	-15	1	11	2	12	-13	3	3	3	59	-61	1	7	3	26	-28
-2	3	2	374	350	-4	7	2	15	21	2	11	2	19	-19	4	3	3	20	-19	2	7	3	12	18
-1	3	2	366	370	-3	7	2	3	1	-1	12	2	39	37	-4	4	3	24	26	3	7	3	65	66
0	3	2	93	-108	-2	7	2	9	15	0	12	2	10	11	-3	4	3	97	96	4	7	3	20	21
1	3	2	84	-79	-1	7	2	115	-120	1	12	2	25	-21	-2	4	3	59	-58	-3	8	3	10	-14
2	3	2	215	-194	0	7	2	44	44	-3	0	3	27	27	-1	4	3	115	-104	-2	8	3	69	-68
3	3	2	3	-9	1	7	2	41	46	-1	0	3	260	-251	0	4	3	34	-30	-1	8	3	54	56
4	3	2	36	-39	2	7	2	25	-25	1	0	3	602	583	1	4	3	139	-129	0	8	3	58	61
-4	4	2	33	33	3	7	2	24	22	3	0	3	93	-93	2	4	3	142	133	1	8	3	10	-12
-3	4	2	9	5	4	7	2	3	0	-4	1	3	15	-15	3	4	3	138	-137	2	8	3	14	10
-2	4	2	230	226	-3	8	2	8	4	-3	1	3	3	-11	4	4	3	10	4	3	8	3	3	-1
-1	4	2	218	212	-2	8	2	78	-77	-2	1	3	211	204	-4	5	3	30	33	-3	9	3	34	-31
0	4	2	201	-218	-1	8	2	127	130	-1	1	3	24	19	-3	5	3	154	156	-2	9	3	29	28
1	4	2	77	-74	0	8	2	23	-24	0	1	3	129	141	-2	5	3	19	17	-1	9	3	26	28
2	4	2	90	-84	1	8	2	57	-54	1	1	3	34	33	-1	5	3	8	9	0	9	3	34	-30
3	4	2	40	-34	2	8	2	132	137	2	1	3	131	-123	0	5	3	108	-98	1	9	3	69	71
4	4	2	60	69	3	8	2	24	-23	3	1	3	3	8	1	5	3	256	-248	2	9	3	18	-18
-4	5	2	72	-72	-3	9	2	3	8	4	1	3	10	-13	2	5	3	29	31	3	9	3	28	-30
-3	5	2	5	2	-2	9	2	40	38	-4	2	3	4	-13	3	5	3	32	31	-3	10	3	6	-2
-2	5	2	147	-145	-1	9	2	11	16	-3	2	3	92	-83	4	5	3	57	-57	-2	10	3	4	5
-1	5	2	92	-82	0	9	2	162	-162	-2	2	3	76	-70	-4	6	3	3	2	-1	10	3	61	-60
0	5	2	137	136	1	9	2	80	-83	-1	2	3	60	-55	-3	6	3	21	-22	0	10	3	58	-58
1	5	2	77	79	2	9	2	3	-5	0	2	3	241	-248	-2	6	3	167	163	1	10	3	96	99
2	5	2	106	104	3	9	2	19	19	1	2	3	88	75	-1	6	3	54	-56	2	10	3	18	20
3	5	2	43	44	-3	10	2	16	-1	2	2	3	23	-25	0	6	3	9	10	3	10	3	10	-13
4	5	2	33	34	-2	10	2	8	8	3	2	3	112	106	1	6	3	120	127	-2	11	3	41	-38
-4	6	2	12	-4	-1	10	2	81	-82	4	2	3	42	41	2	6	3	70	-64	-1	11	3	23	-25
-3	6	2	30	-34	0	10	2	13	-12	-4	3	3	52	52	3	6	3	44	45	0	11	3	29	-28
-2	6	2	37	40	1	10	2	31	-33	-3	3	3	159	-158	4	6	3	23	-26	1	11	3	48	-49
-1	6	2	18	15	2	10	2	36	-38	-2	3	3	396	-386	-4	7	3	28	-29	2	11	3	29	27
0	6	2	66	-64	3	10	2	23	21	-1	3	3	126	124	-3	7	3	20	17	-1	12	3	31	-29

H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC	H	K	L	10FO	10FC
0	12	3	15	-18	-4	4	4	92	-97	3	7	4	24	-23	-4	1	5	28	-28	3	4	5	34	-32
1	12	3	35	-33	-3	4	4	5	0	4	7	4	18	22	-3	1	5	27	-28	4	4	5	16	19
-4	0	4	12	-13	-2	4	4	37	-41	-3	8	4	3	-3	-2	1	5	77	75	-4	5	5	35	37
-2	0	4	30	-32	-1	4	4	37	-34	-2	8	4	46	-44	-1	1	5	30	25	-3	5	5	3	3
0	0	4	136	139	0	4	4	354	356	-1	8	4	59	57	0	1	5	24	-25	-2	5	5	9	-1
2	0	4	181	174	1	4	4	125	-128	0	8	4	57	59	1	1	5	653	643	-1	5	5	92	88
4	0	4	25	-25	2	4	4	3	-13	1	8	4	46	50	2	1	5	175	-170	0	5	5	272	-277
-4	1	4	6	-1	3	4	4	55	53	2	8	4	48	53	3	1	5	35	-34	1	5	5	22	23
-3	1	4	5	-3	4	4	4	50	56	3	8	4	7	9	4	1	5	11	9	2	5	5	124	125
-2	1	4	124	120	-4	5	4	3	-6	-3	9	4	29	-28	-4	2	5	49	50	3	5	5	56	56
-1	1	4	133	127	-3	5	4	162	-165	-2	9	4	22	21	-3	2	5	13	14	4	5	5	20	20
0	1	4	229	250	-2	5	4	132	-127	-1	9	4	120	124	-2	2	5	70	66	-4	6	5	71	-77
1	1	4	26	33	-1	5	4	78	81	0	9	4	71	-74	-1	2	5	200	196	-3	6	5	68	-69
2	1	4	260	-258	0	5	4	7	-1	1	9	4	8	-8	0	2	5	328	-345	-2	6	5	72	69
3	1	4	55	-52	1	5	4	240	243	2	9	4	54	55	1	2	5	175	-175	-1	6	5	106	104
4	1	4	56	51	2	5	4	16	-17	3	9	4	17	-18	2	2	5	16	-13	0	6	5	132	133
-4	2	4	30	37	3	5	4	19	18	-3	10	4	8	9	3	2	5	101	100	1	6	5	46	41
-3	2	4	68	68	4	5	4	48	-49	-2	10	4	28	-27	4	2	5	11	-8	2	6	5	58	56
-2	2	4	60	-61	-4	6	4	20	26	-1	10	4	13	12	-4	3	5	18	-17	3	6	5	8	-11
-1	2	4	43	40	-3	6	4	41	-38	0	10	4	9	6	-3	3	5	31	-30	4	6	5	3	-3
0	2	4	66	73	-2	6	4	90	94	1	10	4	14	-18	-2	3	5	58	54	-4	7	5	50	-51
1	2	4	8	9	-1	6	4	107	-100	2	10	4	6	-10	-1	3	5	98	-93	-3	7	5	15	-14
2	2	4	143	-134	0	6	4	91	-90	-2	11	4	13	-8	0	3	5	121	121	-2	7	5	46	50
3	2	4	45	31	1	6	4	148	138	-1	11	4	15	13	1	3	5	94	-87	-1	7	5	58	-60
4	2	4	55	-54	2	6	4	138	-145	0	11	4	104	106	2	3	5	16	15	0	7	5	92	87
-4	3	4	6	-12	3	6	4	70	-78	1	11	4	20	-20	3	3	5	90	-88	1	7	5	46	-50
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-2	3	4	50	54	-4	7	4	29	34	-1	12	4	56	-52	-4	4	5	3	11	3	7	5	21	-21
-1	3	4	50	55	-3	7	4	80	87	0	12	4	22	21	-3	4	5	117	115	-3	8	5	15	-12
0	3	4	40	45	-2	7	4	3	4	1	12	4	14	15	-2	4	5	61	-55	-2	8	5	90	-88
1	3	4	106	-105	-1	7	4	121	-118	-3	0	5	92	-99	-1	4	5	127	127	-1	8	5	45	-47
2	3	4	180	172	0	7	4	63	-63	-1	0	5	328	-323	0	4	5	70	67	0	8	5	11	-8
3	3	4	57	-55	1	7	4	69	-70	1	0	5	90	88	1	4	5	165	-162	1	8	5	75	-81
4	3	4	20	-21	2	7	4	19	-18	3	0	5	43	-43	2	4	5	110	-103	2	8	5	36	-38

H	K	L	10FO	10FC
3	8	5	10	11
-3	9	5	11	8
-2	9	5	14	-14
-1	9	5	51	-53
0	9	5	20	-33
1	9	5	[illegible]	6
2	9	5	12	-12
3	9	5	20	-19
-2	10	5	12	-11
-1	10	5	7	-14
0	10	5	28	29
1	10	5	12	14
2	10	5	15	15
-2	11	5	40	45
-1	11	5	25	-23
0	11	5	6	0
1	11	5	17	14
2	11	5	15	15
-1	12	5	31	29
0	12	5	15	-16
1	12	5	24	-23
-4	0	6	3	-1
-2	0	6	94	[illegible]
0	0	6	664	-703
2	0	6	159	158
4	0	6	129	128
-4	1	6	6	-9
-3	1	6	3	3
-2	1	6	201	-185
-1	1	6	119	-109
0	1	6	300	-310
1	1	6	54	-56
2	1	6	85	-82
3	1	6	59	57

H	K	L	10FO	10FC
4	1	6	98	100
-4	2	6	33	32
-3	2	6	61	-60
-2	2	6	26	-24
-1	2	6	106	105
0	2	6	101	104
1	2	6	171	-175
2	2	6	55	50
3	2	6	79	-77
4	2	6	55	-54
-4	3	6	38	-37
-3	3	6	65	68
-2	3	6	26	28
-1	3	6	294	-289
0	3	6	281	275
1	3	6	112	108
2	3	6	76	70
3	3	6	27	-26
4	3	6	43	-45
-4	4	6	8	-11
-3	4	6	81	79
-2	4	6	41	-41
-1	4	6	31	29
0	4	6	2	2
1	4	6	131	-128
2	4	6	15	-13
3	4	6	64	62
4	4	6	32	-33
-4	5	6	25	24
-3	5	6	3	2
-2	5	6	16	-17
-1	5	6	10	-15
0	5	6	71	-67
1	5	6	172	-168

H	K	L	10FO	10FC
2	5	6	30	-30
3	5	6	53	52
4	5	6	3	-1
-4	6	6	23	27
-3	6	6	27	-26
-2	6	6	79	78
-1	6	6	76	-76
0	6	6	55	-52
1	6	6	89	91
2	6	6	5	0
3	6	6	36	36
4	6	6	3	-4
-3	7	6	29	29
-2	7	6	100	100
-1	7	6	63	-64
0	7	6	20	-21
1	7	6	125	129
2	7	6	18	-16
3	7	6	44	46
-3	8	6	8	3
-2	8	6	8	-12
-1	8	6	87	90
0	8	6	27	-27
1	8	6	24	26
2	8	6	29	32
3	8	6	42	-42
-3	9	6	3	7
-2	9	6	26	-25
-1	9	6	32	33
0	9	6	32	-35
1	9	6	61	-63
2	9	6	36	-36
3	9	6	15	11
-2	10	6	18	-20

H	K	L	10FO	10FC
-1	10	6	26	-28
0	10	6	42	-41
1	10	6	79	-81
2	10	6	43	41
-2	11	6	3	3
-1	11	6	8	3
0	11	6	37	35
1	11	6	14	18
2	11	6	6	1
-1	12	6	18	12
0	12	6	8	8
1	12	6	10	9
-3	0	7	68	68
-1	0	7	87	88
1	0	7	202	198
3	0	7	132	-130
-4	1	7	38	39
-3	1	7	60	60
-2	1	7	65	-67
-1	1	7	76	71
0	1	7	260	265
1	1	7	168	165
2	1	7	22	26
3	1	7	7	-1
4	1	7	81	-82
-4	2	7	23	20
-3	2	7	52	-50
-2	2	7	123	119
-1	2	7	258	-262
0	2	7	286	-278
1	2	7	2	4
2	2	7	104	103
3	2	7	111	110
4	2	7	46	48

H	K	L	10FO	10FC
-4	3	7	41	-45
-3	3	7	37	-38
-2	3	7	25	-25
-1	3	7	140	-139
0	3	7	120	-127
1	3	7	108	110
2	3	7	3	2
3	3	7	86	86
4	3	7	47	49
-4	4	7	16	-16
-3	4	7	23	22
-2	4	7	29	-27
-1	4	7	124	131
0	4	7	206	210
1	4	7	24	25
2	4	7	110	-112
3	4	7	107	-110
4	4	7	3	-1
-4	5	7	33	37
-3	5	7	12	19
-2	5	7	64	-67
-1	5	7	9	8
0	5	7	5	5
1	5	7	32	-33
2	5	7	34	34
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4	5	7	19	-18
-4	6	7	3	2
-3	6	7	70	-70
-2	6	7	24	24
-1	6	7	21	-20
0	6	7	115	-111
1	6	7	93	96
2	6	7	26	25

H	K	L	10FO	10FC
3	6	7	3	5
4	6	7	40	-44
-3	7	7	5	10
-2	7	7	3	-3
-1	7	7	24	23
0	7	7	72	-70
1	7	7	71	-72
2	7	7	45	44
3	7	7	52	-53
-3	8	7	31	29
-2	8	7	62	-61
-1	8	7	34	-29
0	8	7	6	2
1	8	7	56	60
2	8	7	77	75
3	8	7	21	-19
-3	9	7	30	27
-2	9	7	4	-2
-1	9	7	20	18
0	9	7	129	134
1	9	7	4	5
2	9	7	16	-13
3	9	7	66	70
-2	10	7	35	33
-1	10	7	27	-22
0	10	7	6	-11
1	10	7	42	-43
2	10	7	17	19
-1	11	7	56	-49
0	11	7	27	-29
1	11	7	14	17
0	12	7	20	-17
-4	0	8	53	-51
-2	0	8	65	-64

H	K	L	10FO	10FC
0	0	8	140	-147
2	0	8	39	-34
4	0	8	60	61
-4	1	8	29	29
-3	1	8	76	-76
-2	1	8	82	-78
-1	1	8	168	169
0	1	8	56	62
1	1	8	15	-11
2	1	8	27	27
3	1	8	66	-66
4	1	8	50	-51
-4	2	8	31	33
-3	2	8	9	-7
-2	2	8	96	97
-1	2	8	321	322
0	2	8	45	50
1	2	8	38	-44
2	2	8	165	-167
3	2	8	179	-175
4	2	8	14	-12
-4	3	8	11	9
-3	3	8	32	33
-2	3	8	62	-62
-1	3	8	47	-41
0	3	8	9	6
1	3	8	66	70
2	3	8	118	119
3	3	8	31	-31
4	3	8	21	-21
-4	4	8	49	-53
-3	4	8	30	30
-2	4	8	85	-85
-1	4	8	189	-188

H	K	L	10FO	10FC
0	4	8	199	202
1	4	8	40	43
2	4	8	181	180
3	4	8	62	66
4	4	8	11	-10
-4	5	8	5	-4
-3	5	8	15	-16
-2	5	8	36	37
-1	5	8	22	22
0	5	8	19	-16
1	5	8	71	-74
2	5	8	92	-91
3	5	8	89	89
4	5	8	16	17
-3	6	8	44	-46
-2	6	8	21	24
-1	6	8	38	37
0	6	8	55	58
1	6	8	23	-25
2	6	8	109	-109
3	6	8	38	37
-3	7	8	14	-18
-2	7	8	9	-9
-1	7	8	61	68
0	7	8	10	-10
1	7	8	12	-14
2	7	8	47	46
3	7	8	112	-113
-3	8	8	6	8
-2	8	8	9	-10
-1	8	8	66	-70
0	8	8	46	-49
1	8	8	69	72
2	8	8	82	-81

H	K	L	10FO	10FC
3	8	8	12	-9
-2	9	8	18	-19
-1	9	8	9	-10
0	9	8	27	31
1	9	8	13	12
2	9	8	22	-24
-2	10	8	15	12
-1	10	8	27	30
0	10	8	26	24
1	10	8	8	12
2	10	8	35	38
-1	11	8	27	25
0	11	8	24	23
1	11	8	10	10
-3	0	9	73	73
-1	0	9	120	-117
1	0	9	176	-180
3	0	9	116	118
-4	1	9	2	-2
-3	1	9	3	3
-2	1	9	44	-43
-1	1	9	46	-51
0	1	9	4	-3
1	1	9	6	4
2	1	9	55	57
3	1	9	48	50
4	1	9	47	47
-4	2	9	15	-18
-3	2	9	12	-16
-2	2	9	27	-20
-1	2	9	66	-69
0	2	9	53	-52
1	2	9	28	-30
2	2	9	3	0

H	K	L	10FO	10FC
3	2	9	13	14
4	2	9	6	5
-4	3	9	33	-32
-3	3	9	13	15
-2	3	9	146	148
-1	3	9	78	-78
0	3	9	55	-59
1	3	9	186	-193
2	3	9	67	-68
3	3	9	15	-16
4	3	9	30	-30
-4	4	9	3	-6
-3	4	9	26	26
-2	4	9	96	96
-1	4	9	51	50
0	4	9	47	49
1	4	9	36	-38
2	4	9	186	-185
3	4	9	54	-57
4	4	9	19	19
-4	5	9	23	25
-3	5	9	33	-34
-2	5	9	13	15
-1	5	9	16	-5
0	5	9	9	-8
1	5	9	236	238
2	5	9	118	-118
3	5	9	34	37
-3	6	9	23	-21
-2	6	9	73	-76
-1	6	9	16	11
0	6	9	61	63
1	6	9	15	14
2	6	9	168	169

H	K	L	10FO	10FC
0	4	11	106	-109
1	4	11	269	272
2	4	11	34	32
3	4	11	21	20
4	5	11	25	-27
5	5	11	3	-1
6	5	11	70	-75
7	5	11	171	176
8	5	11	84	86
9	5	11	74	-75
10	5	11	43	43
11	6	11	9	9
12	6	11	51	-55
13	6	11	76	-72
14	6	11	58	-56
15	6	11	19	-19
16	6	11	26	26
17	6	11	19	-18
18	7	11	25	-23
19	7	11	16	-14
20	7	11	154	-153
21	7	11	24	-26
22	7	11	20	18
23	7	11	45	46
24	8	11	22	-24
25	8	11	42	40
26	8	11	28	28
27	8	11	85	85
28	8	11	52	49
29	9	11	81	81
30	9	11	14	-11

H	K	L	10FO	10FC
1	10	10	10	-7
0	11	10	17	-19
3	0	11	24	28
1	0	11	139	138
3	0	11	22	20
4	1	11	99	-102
3	1	11	12	17
2	1	11	65	-56
1	1	11	53	53
0	1	11	30	32
1	1	11	6	2
2	2	11	106	-107
3	1	11	26	-24
4	1	11	8	-1
4	2	11	3	-11
3	2	11	7	7
2	2	11	16	19
1	2	11	99	-102
0	2	11	245	252
1	3	11	87	-89
2	3	11	50	-52
3	3	11	8	-3
4	3	11	14	-15
3	3	11	27	-28
2	3	11	22	22
1	3	11	52	51
0	3	11	85	-49
1	4	11	84	84
2	4	11	6	6
3	4	11	54	-54
4	4	11	28	32
5	4	11	29	31

H	K	L	10FO	10FC
3	5	10	60	63
2	5	10	82	85
1	5	10	84	88
0	5	10	89	91
1	5	10	131	134
2	5	10	178	177
3	5	10	45	46
4	5	10	19	21
5	5	10	16	20
6	5	10	54	57
7	5	10	229	228
8	5	10	65	64
9	5	10	32	31
10	5	10	18	22
11	5	10	79	79
12	5	10	89	86
13	5	10	118	119
14	5	10	15	17
15	5	10	43	42
16	5	10	8	2
17	5	10	13	15
18	5	10	12	13
19	5	10	6	3
20	5	10	5	8
21	5	10	50	49
22	5	10	14	17
23	5	10	3	1
24	5	10	22	19
25	5	10	14	11
26	5	10	22	20

H	K	L	10FO	10FC
3	2	11	9	11
2	2	11	105	111
1	2	11	113	117
0	2	11	120	124
1	2	11	131	134
2	2	11	103	101
3	2	11	1	7
4	2	11	25	24
5	2	11	31	29
6	2	11	65	68
7	2	11	33	35
8	2	11	105	101
9	2	11	39	38
10	2	11	15	12
11	2	11	24	26
12	2	11	23	25
13	2	11	73	72
14	2	11	135	140
15	2	11	22	23
16	2	11	28	33
17	2	11	14	9
18	2	11	7	4
19	2	11	61	59
20	2	11	36	39
21	2	11	22	23
22	2	11	14	11
23	2	11	5	5
24	2	11	16	16
25	2	11	16	16
26	2	11	36	39
27	2	11	5	10

H	K	L	10FO	10FC
3	3	10	37	37
2	3	10	94	93
1	3	10	88	88
0	3	10	60	60
1	3	10	77	77
2	3	10	12	12
3	3	10	88	88
4	3	10	6	5
5	3	10	15	15
6	3	10	43	43
7	3	10	30	31
8	3	10	12	12
9	3	10	55	55
10	3	10	11	11
11	3	10	44	44
12	3	10	2	2
13	3	10	6	6
14	3	10	33	33
15	3	10	6	6
16	3	10	43	42
17	3	10	33	31
18	3	10	1	1
19	3	10	11	11
20	3	10	11	11
21	3	10	11	11
22	3	10	11	11
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34	3	10	11	11
35	3	10	11	11
36	3	10	11	11
37	3	10	11	11
38	3	10	11	11
39	3	10	11	11
40	3	10	11	11
41	3	10	11	11
42	3	10	11	11
43	3	10	11	11
44	3	10	11	11

ATA

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
[illegible]				

H	K	L	10FO	10FC
-1	1	15	43	-45
0	1	15	11	12
1	1	15	[illegible]	[illegible]
2	1	15	[illegible]	[illegible]
3	1	15	[illegible]	[illegible]
4	1	15	[illegible]	[illegible]
5	1	15	[illegible]	[illegible]
-1	2	15	[illegible]	[illegible]
0	2	15	[illegible]	[illegible]
1	2	15	[illegible]	[illegible]
2	2	15	[illegible]	[illegible]
3	2	15	[illegible]	[illegible]
4	2	15	[illegible]	[illegible]
-1	3	15	[illegible]	[illegible]
0	3	15	[illegible]	[illegible]
1	3	15	[illegible]	[illegible]
2	3	15	[illegible]	[illegible]
3	3	15	[illegible]	[illegible]
-1	4	15	[illegible]	[illegible]
0	4	15	[illegible]	[illegible]
1	4	15	[illegible]	[illegible]
2	4	15	[illegible]	[illegible]
-1	5	15	[illegible]	[illegible]
0	5	15	[illegible]	[illegible]
1	5	15	[illegible]	[illegible]
-1	6	15	[illegible]	[illegible]
0	6	15	[illegible]	[illegible]
1	6	15	[illegible]	[illegible]
-1	7	15	[illegible]	[illegible]
0	7	15	[illegible]	[illegible]
1	7	15	[illegible]	[illegible]
-1	8	15	[illegible]	[illegible]
0	8	15	[illegible]	[illegible]
1	8	15	[illegible]	[illegible]
-1	9	15	[illegible]	[illegible]
0	9	15	[illegible]	[illegible]
1	9	15	[illegible]	[illegible]
-1	10	15	[illegible]	[illegible]
0	10	15	[illegible]	[illegible]
1	10	15	[illegible]	[illegible]
-1	11	15	[illegible]	[illegible]
0	11	15	[illegible]	[illegible]
1	11	15	[illegible]	[illegible]
-1	12	15	[illegible]	[illegible]
0	12	15	[illegible]	[illegible]
1	12	15	[illegible]	[illegible]
-1	13	15	[illegible]	[illegible]
0	13	15	[illegible]	[illegible]
1	13	15	[illegible]	[illegible]
-1	14	15	[illegible]	[illegible]
0	14	15	[illegible]	[illegible]
1	14	15	[illegible]	[illegible]
-1	15	15	[illegible]	[illegible]
0	15	15	[illegible]	[illegible]
1	15	15	[illegible]	[illegible]
-1	16	15	[illegible]	[illegible]
0	16	15	[illegible]	[illegible]
1	16	15	[illegible]	[illegible]

H	K	L	10FO	10FC
-1	1	15	81	78
0	1	15	[illegible]	7
1	1	15	[illegible]	51
2	1	15	[illegible]	54
3	1	15	[illegible]	51
4	1	15	[illegible]	13
5	1	15	[illegible]	11
-1	2	15	[illegible]	27
0	2	15	[illegible]	78
1	2	15	[illegible]	18
2	2	15	[illegible]	42
3	2	15	[illegible]	52
4	2	15	[illegible]	57
5	2	15	[illegible]	39
6	2	15	35	36

H	K	L	10FO	10FC
1	1	16	75	-74
2	1	16	35	32
-1	2	16	45	44
0	2	16	36	-36
1	2	16	44	51
-1	3	16	64	64
1	3	16	47	-48
-2	3	16	27	-28
-1	4	16	12	15
0	4	16	24	21
1	4	16	48	48
-2	4	16	104	99
-1	5	16	31	28
0	5	16	14	15
1	5	16	67	65
-2	5	16	57	48
-1	6	16	7	64
0	6	16	3	-4

H	K	L	10FO	10FC
0	5	16	9	7
-1	5	16	3	-2
-1	6	16	28	28
0	6	16	28	26
1	6	16	59	56
-1	7	16	9	-8
1	7	16	82	-84
-2	7	16	24	21
-1	7	16	6	-5
0	7	16	31	-31
1	7	16	30	-28
-2	8	16	9	-8
-1	8	16	17	-13
0	8	16	47	-46
-1	8	16	63	62
-2	9	16	19	18
-1	9	16	55	51

H	K	L	10FO	10FC
0	3	17	29	-28
-1	3	17	58	53
-1	4	17	24	24
0	4	17	30	30
1	4	17	78	-74
-1	5	17	22	-19
1	5	17	14	-15
0	5	17	61	55
1	5	17	98	97
-1	6	18	20	-17
0	6	18	14	-11
-1	7	18	44	-40
1	7	18	21	-21
-1	8	18	51	47
1	8	18	4	-6
-1	9	18	22	-21
0	9	18	28	26
0	4	18	19	18

Table E.3

Observed and calculated structure factor moduli for N-Ac Δ Phe-L-Pro-OH. The following reflexions were omitted because of suspected extinction or multiple reflexion effects.

h	k	ℓ	10 $\|F_o\|$	10 $\|F_c\|$
0	2	1	1479	1648
3	7	3	30	153
8	6	3	387	179
9	7	3	369	100
14	6	3	335	15

R' = 0.0051

H	K	L	10F0	10FC
5	-	1	33	33
2	-	1	17	18
10	-	1	33	31
12	-	1	1	1
14	-	1	16	16
16	-	1	8	8
18	-	1	2	2
1	-	1	13	13
3	-	1	5	7
5	-	1	9	11
7	-	1	5	5
9	-	1	11	11
11	-	1	5	5
13	-	1	7	9
15	-	1	11	13
17	-	1	5	5
19	-	1	9	10
21	-	1	2	2
0	-	2	46	46
2	-	2	68	68
4	-	2	12	12
6	-	2	46	46
8	-	2	68	68
10	-	2	12	12
12	-	2	46	46
14	-	2	68	68
16	-	2	12	12
18	-	2	46	46
20	-	2	68	68
1	-	2	13	13
3	-	2	57	57
5	-	2	91	91
7	-	2	13	13
9	-	2	57	57
11	-	2	91	91
13	-	2	13	13
15	-	2	57	57
17	-	2	91	91
19	-	2	13	13
21	-	2	57	57
0	-	3	46	46
2	-	3	68	68
4	-	3	12	12
6	-	3	46	46
8	-	3	68	68
10	-	3	12	12
12	-	3	46	46
14	-	3	68	68
16	-	3	12	12
18	-	3	46	46
20	-	3	68	68
1	-	3	13	13
3	-	3	57	57
5	-	3	91	91
7	-	3	13	13
9	-	3	57	57
11	-	3	91	91
13	-	3	13	13
15	-	3	57	57
17	-	3	91	91
19	-	3	13	13
21	-	3	57	57
0	-	4	46	46
2	-	4	68	68
4	-	4	12	12
6	-	4	46	46
8	-	4	68	68
10	-	4	12	12
12	-	4	46	46
14	-	4	68	68
16	-	4	12	12
18	-	4	46	46
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15	-	4	57	57
17	-	4	91	91
19	-	4	13	13
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13	-	5	13	13
15	-	5	57	57
17	-	5	91	91
19	-	5	13	13
21	-	5	57	57
0	-	6	46	46
2	-	6	68	68
4	-	6	12	12
6	-	6	46	46
8	-	6	68	68
10	-	6	12	12
12	-	6	46	46
14	-	6	68	68
16	-	6	12	12
18	-	6	46	46
20	-	6	68	68
1	-	6	13	13
3	-	6	57	57
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9	-	6	57	57
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10	-	7	12	12
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21	-	7	57	57
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2	-	8	68	68
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21	-	8	57	57
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2	-	9	68	68
4	-	9	12	12
6	-	9	46	46
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10	-	9	12	12
12	-	9	46	46
14	-	9	68	68
16	-	9	12	12
18	-	9	46	46
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21	-	9	57	57
0	-	10	46	46
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10	-	10	12	12
12	-	10	46	46
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17	-	16	91	91
19	-	16	13	13
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H	K	L	10FO	10FC
-4	4	13	36	32
-17	5	13	45	46
-15	5	13	37	29
-13	5	13	62	65
-11	5	13	57	55
-9	5	13	19	20
-7	5	13	14	21
-5	5	13	10	18
-14	6	13	12	16
-12	6	13	56	54
-10	6	13	36	36
-8	6	13	10	18
-18	0	14	10	12
-16	0	14	38	35

H	K	L	10FO	10FC
-14	0	14	25	1
-12	0	14	76	77
-10	0	14	39	43
-8	0	14	66	63
-6	0	14	18	19
-19	1	14	7	23
-17	1	14	33	36
-15	1	14	47	46
-13	1	14	25	26
-11	1	14	39	47
-9	1	14	10	29
-7	1	14	14	25
-18	2	14	40	35
-16	2	14	37	36

H	K	L	10FO	10FC
-14	2	14	53	50
-12	2	14	1	52
-10	2	14	35	35
-8	2	14	32	32
-6	2	14	10	12
-17	3	14	14	14
-15	3	14	72	72
-13	3	14	71	71
-11	3	14	10	23
-9	3	14	35	29
-7	3	14	37	46
-14	4	14	65	66
-12	4	14	10	23
-10	4	14	66	64

Table E.4

Observed and calculated structure factor moduli for N-Ac-L-Ala-L-Ala-OEt. Symmetry related reflexions showing large inconsistencies are shown below:

h	k	ℓ	e.s.d./F	Δ/F	N
4	10	0	0.202	0.285	2

R' = 0.0146

The following reflexions were omitted because of suspected extinction:

h	k	ℓ	$10\|F_o\|$	$10\|F_c\|$
0	2	0	1384	1646
-2	0	2	1245	1352
-1	1	2	895	1000
0	0	1	766	865

XTX0

H	K	L	10FO	10FC
2	0	0	42	52
6	0	0	135	178
10	0	0	237	270
12	0	0	71	67
14	0	0	161	161
16	0	0	55	61
1	1	0	332	333
3	1	0	55	55
5	1	0	263	257
7	1	0	87	87
9	1	0	56	56
11	1	0	26	26
13	1	0	145	145
15	1	0	63	63
17	1	0	135	135
2	2	0	111	111
4	2	0	117	117
6	2	0	92	91
8	2	0	111	111
10	2	0	176	174
12	2	0	76	76
14	2	0	54	54
16	2	0	54	54
1	3	0	110	110
3	3	0	42	42
5	3	0	146	146
7	3	0	54	54
9	3	0	24	24
11	3	0	135	135
13	3	0	69	69
15	3	0	57	57
0	0	1	35	39
2	0	1	50	51
4	0	1	299	293
6	0	1	189	178
8	0	1	161	165
10	0	1	51	54
12	0	1	93	90
14	0	1	19	21
16	0	1	17	23
1	1	1	43	46
3	1	1	182	136
5	1	1	121	125
7	1	1	74	77
9	1	1	63	63
11	1	1	21	25
13	1	1	216	214
15	1	1	74	71
17	1	1	65	65
2	2	1	112	114
4	2	1	288	250
6	2	1	338	325
8	2	1	78	76
10	2	1	59	59
12	2	1	26	26
14	2	1	12	12
16	2	1	88	88
1	3	1	34	32
3	3	1	64	63
5	3	1	19	19
7	3	1	27	27
9	3	1	12	12
11	3	1	26	26
13	3	1	55	55
15	3	1	13	13
0	0	2	174	179
2	0	2	655	650
4	0	2	350	327
6	0	2	269	274
8	0	2	339	339
10	0	2	237	233
12	0	2	222	225
14	0	2	279	280
16	0	2	155	155
1	1	2	49	52
3	1	2	252	250
5	1	2	194	203
7	1	2	163	169
9	1	2	155	151
11	1	2	310	286
13	1	2	333	330
15	1	2	633	620
2	2	2	421	429
4	2	2	255	249
6	2	2	340	307
8	2	2	160	150
10	2	2	163	166
12	2	2	127	137
14	2	2	75	71
16	2	2	270	282
1	3	2	166	175
3	3	2	206	211
5	3	2	147	143
7	3	2	267	268
9	3	2	291	291
11	3	2	355	339
13	3	2	342	336
15	3	2	423	333
0	0	3	410	404
2	0	3	150	119
4	0	3	93	144
6	0	3	55	66
8	0	3	138	132
10	0	3	66	109
12	0	3	32	32
14	0	3	22	22
16	0	3	55	55
1	1	3	55	55
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13	1	3	55	55
15	1	3	55	55
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6	0	4	55	55
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5	1	9	55	55
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13	1	9	55	55
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3	1	16	55	55
5	1	16	55	55
7	1	16	55	55
9	1	16	55	55
11	1	16	55	55
13	1	16	55	55
15	1	16	55	55

xxx

H	K	L	10FO	10FC
5	9	1	24	29
7	9	1	44	45
9	9	1	21	16
11	9	1	23	21
-10	10	1	12	6
-8	10	1	38	34
-6	10	1	16	10
-4	10	1	11	22
-2	10	1	28	21
0	10	1	36	35
2	10	1	7	18
4	10	1	22	26
6	10	1	57	53
8	10	1	24	19
-9	11	1	22	13
-7	11	1	25	20
-5	11	1	12	15
-3	11	1	12	14
-1	11	1	12	13
1	11	1	12	17
3	11	1	12	9
5	11	1	15	15
7	11	1	13	17
-6	12	1	22	14
-4	12	1	22	5
-2	12	1	21	4
0	12	1	21	15
2	12	1	12	17
4	12	1	23	9
-13	0	2	47	50
-16	0	2	12	2
-14	0	2	10	40
-12	0	2	79	81
-10	0	2	30	27
-8	0	2	137	133
-6	0	2	331	314
-4	0	2	1107	1135
-2	0	2	132	158
0	0	2	326	335
2	0	2	38	27
4	0	2	103	112
6	0	2	45	45
8	0	2	13	19
10	0	2	7	7
12	0	2	11	3
14	0	2	12	11
-17	1	2	17	14
-15	1	2	11	22
-13	1	2	10	105
-11	1	2	111	99
-9	1	2	115	125
-7	1	2	295	294
-5	1	2	106	95
-3	1	2	423	416
-1	1	2	645	639
1	1	2	365	347
3	1	2	512	503
5	1	2	179	178
7	1	2	49	53
9	1	2	102	100
11	1	2	46	44
13	1	2	12	33
15	1	2	37	39
-18	2	2	26	30
-16	2	2	76	78
-14	2	2	113	113
-12	2	2	71	75
-10	2	2	244	256
-8	2	2	314	298
-6	2	2	495	490
-4	2	2	915	968
-2	2	2	208	166
0	2	2	594	572
2	2	2	178	162
4	2	2	8	19
6	2	2	113	108
8	2	2	72	83
10	2	2	11	23
12	2	2	12	20
-17	3	2	12	11
-15	3	2	11	8
-13	3	2	47	51
-11	3	2	101	99
-9	3	2	127	129
-7	3	2	235	210
-5	3	2	166	176
-3	3	2	329	305
-1	3	2	405	410
1	3	2	349	356
3	3	2	147	133
5	3	2	8	41
7	3	2	105	102
9	3	2	122	124
11	3	2	18	10
13	3	2	12	38
15	3	2	30	20
-16	4	2	12	7
-14	4	2	63	64
-12	4	2	70	62
-10	4	2	77	72
-8	4	2	213	216
-6	4	2	179	173
-4	4	2	194	139
-2	4	2	357	350
0	4	2	7	37
2	4	2	316	269
4	4	2	152	166
6	4	2	59	67
8	4	2	119	136
10	4	2	56	54
12	4	2	11	18
14	4	2	41	41
-15	5	2	12	20
-13	5	2	25	28
-11	5	2	56	56
-9	5	2	90	98
-7	5	2	114	118
-5	5	2	81	74
-3	5	2	278	287
-1	5	2	180	183
1	5	2	335	314
3	5	2	113	108
5	5	2	107	107
7	5	2	84	81
9	5	2	60	61
11	5	2	19	13
13	5	2	22	25
-16	6	2	15	23
-14	6	2	44	40
-12	6	2	36	30
-10	6	2	28	19
-8	6	2	113	112
-6	6	2	93	90
-4	6	2	195	201
-2	6	2	110	106
0	6	2	8	13
2	6	2	78	87
4	6	2	60	67
6	6	2	33	31
8	6	2	144	152
10	6	2	33	57
12	6	2	12	3
-15	7	2	31	28
-13	7	2	20	15
-11	7	2	30	31
-9	7	2	10	43
-7	7	2	58	62
-5	7	2	149	154
-3	7	2	80	83
-1	7	2	45	41
1	7	2	125	128
3	7	2	36	31
5	7	2	32	34
7	7	2	52	49
9	7	2	11	9
11	7	2	20	13
-14	8	2	13	27
-12	8	2	31	24
-10	8	2	19	16
-8	8	2	67	66
-6	8	2	49	49
-4	8	2	82	80
-2	8	2	66	65
0	8	2	66	64
2	8	2	77	77
4	8	2	49	51
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8	8	2	37	34
10	8	2	21	31
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-11	9	2	24	3
-9	9	2	19	15
-7	9	2	65	67
-5	9	2	11	34
-3	9	2	101	100
-1	9	2	37	61
1	9	2	15	15
3	9	2	29	32
5	9	2	52	68
7	9	2	29	29
9	9	2	12	4
-10	10	2	8	7
-8	10	2	27	28
-6	10	2	11	12
-4	10	2	19	28
-2	10	2	11	8
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2	10	2	28	25
4	10	2	11	22
6	10	2	25	25
8	10	2	12	4
-9	11	2	11	16
-7	11	2	33	27
-5	11	2	12	4
-3	11	2	26	20
-1	11	2	12	8
1	11	2	25	17
3	11	2	98	93
5	11	2	12	4
-4	12	2	13	6
-2	12	2	12	2
0	12	2	25	12
2	12	2	25	13
-18	0	3	12	9
-16	0	3	11	9
-14	0	3	79	82
-12	0	3	9	3
-10	0	3	105	106
-8	0	3	530	515
-6	0	3	151	159
-4	0	3	143	152
-2	0	3	159	129
0	0	3	218	202
2	0	3	58	62
4	0	3	678	653
6	0	3	265	263
8	0	3	59	56
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14	0	3	12	10
-17	1	3	12	10
-15	1	3	22	57
-13	1	3	83	87
-11	1	3	45	47
-9	1	3	360	358
-7	1	3	151	141
-5	1	3	427	417
-3	1	3	535	553
-1	1	3	98	94
1	1	3	279	270
3	1	3	315	301
5	1	3	109	110
7	1	3	80	79
9	1	3	64	67
11	1	3	30	22
13	1	3	12	20
-18	2	3	13	20
-16	2	3	29	31
-14	2	3	43	43
-12	2	3	113	115

TXXX

H	K	L	10FO	10FC
-10	2	3	47	46
-8	2	3	239	275
-6	2	3	465	495
-4	2	3	288	294
-2	2	3	330	327
0	2	3	302	292
2	2	3	297	267
4	2	3	366	325
6	2	3	149	144
8	2	3	109	111
10	2	3	88	82
12	2	3	39	26
14	2	3	12	9
-17	3	3	13	23
-15	3	3	63	62
-13	3	3	10	46
-11	3	3	80	80
-9	3	3	139	145
-7	3	3	132	127
-5	3	3	437	409
-3	3	3	117	118
-1	3	3	112	110
1	3	3	186	132
3	3	3	183	131
5	3	3	139	109
7	3	3	13	147
9	3	3	13	70
11	3	3	12	19
-14	4	3	1	16
-12	4	3	19	20
-10	4	3	194	27
-8	4	3	116	22
-6	4	3	253	24
-4	4	3	194	190
-2	4	3	101	92
0	4	3	114	142
2	4	3	205	176
4	4	3	339	64
6	4	3	141	333
8	4	3	145	136
10	4	3	1	150
12	4	3	13	92
14	4	3	24	25
-17	5	3	13	16
-15	5	3	37	12
-13	5	3	37	20
-11	5	3	24	37
-9	5	3	102	105
-7	5	3	71	74
-5	5	3	53	51
-3	5	3	172	174
-1	5	3	106	113
1	5	3	192	187
3	5	3	126	133
5	5	3	152	152
7	5	3	89	95
9	5	3	18	22
11	5	3	47	42
13	5	3	12	22
-16	6	3	12	5
-14	6	3	29	30
-12	6	3	23	17
-10	6	3	53	40
-8	6	3	53	52
-6	6	3	96	91
-4	6	3	148	151
-2	6	3	136	139
0	6	3	108	106
2	6	3	137	142
4	6	3	80	77
6	6	3	76	75
8	6	3	75	81
10	6	3	61	66
12	6	3	12	31
-15	7	3	33	23
-13	7	3	22	23
-11	7	3	12	12
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-8	2	7	131	137
-6	2	7	83	82

H	K	L	10FO	10FC
-4	2	7	41	41
-2	2	7	52	56
0	2	7	113	111
2	2	7	210	213
4	2	7	76	71
6	2	7	71	69
8	2	7	24	20
-17	3	7	12	28
-15	3	7	23	19
-13	3	7	53	53
-11	3	7	46	44
-9	3	7	177	178
-7	3	7	162	160
-5	3	7	84	84
-3	3	7	75	79
-1	3	7	104	105
1	3	7	137	146
3	3	7	119	115
5	3	7	81	85
7	3	7	12	27
9	3	7	24	15
-16	4	7	17	26
-14	4	7	12	27
-12	4	7	75	74
-10	4	7	133	129
-8	4	7	95	94
-6	4	7	132	132
-4	4	7	44	47
-2	4	7	52	54
0	4	7	202	203
2	4	7	157	155
4	4	7	17	10
6	4	7	59	58
8	4	7	12	19
-15	5	7	12	26
-13	5	7	47	42
-11	5	7	25	23
-9	5	7	92	86
-7	5	7	142	145
-5	5	7	92	98
-3	5	7	43	47
-1	5	7	56	60
1	5	7	117	112
3	5	7	53	66
5	5	7	41	36
7	5	7	12	16
-14	6	7	31	26
-12	6	7	12	41

H	K	L	10FO	10FC
-10	6	7	44	45
-8	6	7	69	67
-6	6	7	100	93
-4	6	7	76	72
-2	6	7	78	76
0	6	7	128	126
2	6	7	22	42
4	6	7	12	30
6	6	7	12	47
-13	7	7	12	30
-11	7	7	12	19
-9	7	7	23	8
-7	7	7	68	65
-5	7	7	84	81
-3	7	7	71	69
-1	7	7	47	43
1	7	7	40	34
3	7	7	12	11
5	7	7	12	29
-12	8	7	21	19
-10	8	7	5	18
-8	8	7	34	38
-6	8	7	41	46
-4	8	7	62	58
-2	8	7	56	59
0	8	7	18	17
2	8	7	9	3
4	8	7	12	8
-11	9	7	13	17
-9	9	7	26	13
-7	9	7	39	33
-5	9	7	40	40
-3	9	7	57	54
-1	9	7	24	27
1	9	7	12	4
3	9	7	13	3
-8	10	7	23	13
-6	10	7	13	20
-4	10	7	31	25
-2	10	7	13	14
-16	0	8	12	2
-14	0	8	25	10
-12	0	8	25	24
-10	0	8	242	244
-8	0	8	85	20
-6	0	8	29	32
-4	0	8	252	261
-2	0	8	27	23

H	K	L	10FO	10FC
0	0	8	114	108
2	0	8	57	57
4	0	8	94	92
6	0	8	12	4
8	0	8	25	17
-17	1	8	12	12
-15	1	8	43	46
-13	1	8	43	46
-11	1	8	131	172
-9	1	8	45	44
-7	1	8	89	80
-5	1	8	41	54
-3	1	8	99	106
-1	1	8	14	10
1	1	8	117	125
3	1	8	11	7
5	1	8	29	27
7	1	8	12	21
-16	2	8	21	22
-14	2	8	28	27
-12	2	8	63	63
-10	2	8	116	117
-8	2	8	106	103
-6	2	8	66	65
-4	2	8	125	132
-2	2	8	35	37
0	2	8	137	133
2	2	8	68	71
4	2	8	65	64
6	2	8	35	35
8	2	8	27	19
-17	3	8	18	19
-15	3	8	25	21
-13	3	8	56	57
-11	3	8	109	106
-9	3	8	11	13
-7	3	8	125	123
-5	3	8	43	43
-3	3	8	87	83
-1	3	8	53	53
1	3	8	77	76
3	3	8	53	51
5	3	8	33	31
7	3	8	21	12
-16	4	8	11	18
-14	4	8	35	31
-12	4	8	59	52
-10	4	8	47	41
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-6	4	8	44	44
-4	4	8	46	46
-2	4	8	45	46
0	4	8	131	125
2	4	8	45	39
4	4	8	39	44
6	4	8	41	39
8	4	8	14	10
-17	5	8	12	12
-15	5	8	45	46
-13	5	8	39	44
-11	5	8	41	39
-9	5	8	11	17
-7	5	8	55	53
-5	5	8	15	27
-3	5	8	66	67
-1	5	8	60	60
1	5	8	53	54
3	5	8	44	47
5	5	8	21	28
-14	6	8	38	39
-12	6	8	25	32
-10	6	8	23	21
-8	6	8	41	45
-6	6	8	11	24
-4	6	8	34	35
-2	6	8	30	29
0	6	8	52	50
2	6	8	12	14
4	6	8	12	16
-13	7	8	30	33
-11	7	8	12	15
-9	7	8	23	19
-7	7	8	32	44
-5	7	8	25	15
-3	7	8	11	33
-1	7	8	12	22
1	7	8	38	39
3	7	8	23	11
-10	8	8	12	21
-8	8	8	17	19
-6	8	8	12	12
-4	8	8	30	16
-2	8	8	26	19
0	8	8	27	26
2	8	8	28	16
-9	9	8	13	14
-7	9	8	22	30
-5	9	8	5	16

H	K	L	10FO	10FC
-3	4	8	65	64
-6	4	8	38	41
-4	4	8	64	66
-2	4	8	30	36
0	4	8	112	114
2	4	8	36	34
4	4	8	42	42
6	4	8	46	39
-15	5	8	12	16
-13	5	8	75	72
-11	5	8	50	50
-9	5	8	11	17
-7	5	8	55	53
-5	5	8	15	27
-3	5	8	66	67
-1	5	8	60	60
1	5	8	53	54
3	5	8	44	47
5	5	8	21	28
-14	6	8	38	39
-12	6	8	25	32
-10	6	8	23	21
-8	6	8	41	45
-6	6	8	11	24
-4	6	8	34	35
-2	6	8	30	29
0	6	8	52	50
2	6	8	12	14
4	6	8	12	16
-13	7	8	30	33
-11	7	8	12	15
-9	7	8	23	19
-7	7	8	32	44
-5	7	8	25	15
-3	7	8	11	33
-1	7	8	12	22
1	7	8	38	39
3	7	8	23	11
-10	8	8	12	21
-8	8	8	17	19
-6	8	8	12	12
-4	8	8	30	16
-2	8	8	26	19
0	8	8	27	26
2	8	8	28	16
-9	9	8	13	14
-7	9	8	22	30
-5	9	8	5	16

H	K	L	10FO	10FC
-3	9	8	27	20
-1	9	8	13	17
-16	0	9	68	63
-14	0	9	12	12
-12	0	9	67	71
-10	0	9	137	136
-8	0	9	152	153
-6	0	9	10	15
-4	0	9	10	23
-2	0	9	14	11
0	0	9	112	112
2	0	9	16	23
4	0	9	12	33
6	0	9	84	80
-15	1	9	48	53
-13	1	9	66	66
-11	1	9	154	151
-9	1	9	73	77
-7	1	9	32	37
-5	1	9	46	45
-3	1	9	20	25
-1	1	9	101	101
1	1	9	126	123
3	1	9	70	70
5	1	9	32	29
-16	2	9	60	59
-14	2	9	91	91
-12	2	9	91	91
-10	2	9	92	91
-8	2	9	100	99
-6	2	9	50	47
-4	2	9	33	32
-2	2	9	62	54
0	2	9	77	79
2	2	9	11	10
4	2	9	57	58
-15	3	9	45	42
-13	3	9	57	54
-11	3	9	135	136
-9	3	9	53	52
-7	3	9	75	79
-5	3	9	11	21
-3	3	9	32	29
-1	3	9	92	94
1	3	9	71	74
3	3	9	64	62
5	3	9	12	17

H	K	L	10FO	10FC
-14	4	9	12	16
-12	4	9	42	41
-10	4	9	75	70
-8	4	9	71	73
-6	4	9	66	65
-4	4	9	67	67
-2	4	9	70	78
0	4	9	26	21
2	4	9	38	35
-13	5	9	27	46
-11	5	9	52	52
-9	5	9	11	34
-7	5	9	72	71
-5	5	9	25	18
-3	5	9	11	30
-1	5	9	73	91
1	5	9	24	25
3	5	9	12	35
-12	6	9	68	61
-10	6	9	12	18
-8	6	9	55	45
-6	6	9	52	54
-4	6	9	29	30
-2	6	9	56	60
0	6	9	27	31
2	6	9	24	25
-11	7	9	28	20
-9	7	9	18	25
-7	7	9	53	50
-5	7	9	39	37
-3	7	9	37	35
-1	7	9	19	26
1	7	9	13	24
-8	8	9	13	11
-6	8	9	12	27
-4	8	9	9	24
-2	8	9	25	34
-14	0	10	12	8
-12	0	10	67	69
-10	0	10	46	42
-8	0	10	100	99
-6	0	10	135	187
-4	0	10	57	55
-2	0	10	25	42
0	0	10	19	17
2	0	10	12	27
-13	1	10	13	16

H	K	L	10FO	10FC
-15	1	10	9	20
-13	1	10	22	22
-11	1	10	12	2
-9	1	10	45	44
-7	1	10	121	121
-5	1	10	109	116
-3	1	10	122	122
-1	1	10	12	9
1	1	10	12	8
3	1	10	33	33
-14	2	10	12	22
-12	2	10	54	53
-10	2	10	47	52
-8	2	10	46	45
-6	2	10	150	151
-4	2	10	69	71
-2	2	10	83	73
0	2	10	20	13
2	2	10	12	11
-15	3	10	42	34
-13	3	10	21	20
-11	3	10	12	18
-9	3	10	51	57
-7	3	10	83	86
-5	3	10	69	51
-3	3	10	91	94
-1	3	10	53	55
1	3	10	16	16
3	3	10	11	16
-14	4	10	13	39
-12	4	10	27	30
-10	4	10	32	35
-8	4	10	43	42
-6	4	10	84	90
-4	4	10	12	25
-2	4	10	50	54
0	4	10	17	10
2	4	10	13	9
-13	5	10	13	4
-11	5	10	12	8
-9	5	10	44	49
-7	5	10	53	52
-5	5	10	35	35
-3	5	10	65	63
-1	5	10	45	42
1	5	10	25	13
-10	6	10	18	31
-8	6	10	12	33

H	K	L	10F0	10FC
-6	6	10	21	13
-4	6	10	27	22
-2	6	10	25	25
0	6	10	20	24
-9	7	10	45	37
-7	7	10	4	19
-5	7	10	13	6
-3	7	10	30	31
-14	0	11	13	8
-12	0	11	12	25
-10	0	11	12	14
-3	0	11	12	8
-6	0	11	26	29
-4	0	11	13	9
-2	0	11	21	22
0	0	11	22	33
-13	1	11	22	16
-11	1	11	43	47
-9	1	11	12	24
-7	1	11	24	16
-5	1	11	24	7
-3	1	11	12	13
-1	1	11	17	14
1	1	11	41	36
-12	2	11	39	39
-10	2	11	12	8
-8	2	11	12	14
-6	2	11	27	33
-4	2	11	12	25
-2	2	11	12	19
0	2	11	13	36
-11	3	11	33	34
-9	3	11	26	26
-7	3	11	12	18
-5	3	11	27	6
-3	3	11	17	22
-1	3	11	18	5
-10	4	11	13	6
-8	4	11	12	21
-6	4	11	24	29
-4	4	11	12	23
-2	4	11	25	21
-9	5	11	13	12
-7	5	11	13	16
-5	5	11	13	3
-3	5	11	29	31
-10	0	12	41	39
-8	0	12	18	37
-6	0	12	60	54
-4	0	12	13	20
-9	1	12	29	31
-7	1	12	56	58
-5	1	12	28	14
-3	2	12	22	34
-6	2	12	18	31

Table E.5

Observed and calculated structure factor moduli for N-Ac Δ Phe-OH. Symmetry related reflexions showing large inconsistencies are shown below:

h	k	ℓ	e.s.d./F	Δ/F	N
16	3	0	0.213	0.109	2

R' = 0.0114

H	K	L	10FO	10FC
1	0	0	297	291
2	0	0	291	-293
3	0	0	145	-142
4	0	0	36	44
5	0	0	382	396
6	0	0	512	496
7	0	0	170	-153
8	0	0	139	-142
9	0	0	17	1
10	0	0	18	31
11	0	0	116	-127
12	0	0	56	-52
13	0	0	21	42
1	1	0	432	-422
2	1	0	324	-334
3	1	0	60	58
4	1	0	308	-299
5	1	0	28	3
6	1	0	77	-74
7	1	0	185	-184
8	1	0	27	-16
9	1	0	94	93
10	1	0	18	-25
11	1	0	19	8
12	1	0	47	-49
0	1	1	107	123
1	1	1	299	-302
2	1	1	11	12
3	1	1	290	-300
4	1	1	42	39
5	1	1	203	189
6	1	1	48	51
7	1	1	27	-39
8	1	1	33	-16
9	1	1	17	5
10	1	1	76	-74
11	1	1	25	-28
12	1	1	21	42
1	2	1	295	276
2	2	1	102	100
3	2	1	252	-237
4	2	1	141	127
5	2	1	240	241
6	2	1	39	-39
7	2	1	75	80
8	2	1	106	-107
9	2	1	107	-105
10	2	1	107	104
11	3	0	104	107
0	4	0	29	26
1	4	0	33	-1
2	4	0	73	-70
3	4	0	48	53
4	4	0	16	-42
5	4	0	33	64
6	4	0	123	-122
7	4	0	18	13
8	4	0	107	-105
9	4	0	39	-4
10	4	0	77	72
1	5	0	17	12
2	5	0	17	46
3	5	0	34	-29
4	5	0	18	10
5	5	0	108	104
6	5	0	154	156
7	5	0	34	25
8	5	0	41	36
9	5	0	32	31
0	6	0	32	-15
1	6	0	111	110
2	6	0	84	79
3	6	0	27	-27
4	6	0	34	-6
5	6	0	121	113
6	6	0	21	8
7	6	0	72	73
1	7	0	11	2
2	7	0	47	-21
3	7	0	21	17
-13	1	1	30	-6
-12	1	1	55	58
-11	1	1	47	48
-10	1	1	18	32
-9	1	1	150	-158
-8	1	1	45	-45
-7	1	1	54	56
-6	1	1	194	-186
-5	1	1	67	69
-4	1	1	205	-189
-3	1	1	51	-49
-2	1	1	498	-491
-1	1	1	144	-148
0	1	1	639	-739
1	1	1	28	-22
2	1	1	361	364
3	1	1	572	-573
4	1	1	200	-191
5	1	1	254	260
6	1	1	100	-99
7	1	1	154	158
8	1	1	64	-70
9	1	1	34	-10
10	1	1	59	61
11	1	1	175	181
12	1	1	21	14
-12	2	1	21	-28
-11	2	1	105	114
-10	2	1	139	140
-9	2	1	55	-52
-8	2	1	188	-185
-7	2	1	111	111
-6	2	1	78	-76
-5	2	1	341	325
-4	2	1	181	-174
-3	2	1	141	-137
-2	2	1	11	26
-1	2	1	194	198
0	2	1	302	-393
1	2	1	120	110
2	2	1	416	-405
3	2	1	474	469
4	2	1	267	249
5	2	1	34	-31
6	2	1	15	9
7	2	1	67	70
8	2	1	51	50
9	2	1	149	145
10	2	1	30	32
11	2	1	20	-6
-12	3	1	36	38
-11	3	1	20	6
-10	3	1	73	-72
-9	3	1	103	-108
-8	3	1	35	-11
-7	3	1	178	175
-6	3	1	60	57
-5	3	1	117	-117
-4	3	1	227	-219
-3	3	1	65	-61
-2	3	1	65	-52
-1	3	1	347	335
0	3	1	298	277
1	3	1	13	-16
2	3	1	139	129
3	3	1	209	-188
4	3	1	125	118
5	3	1	66	67
6	3	1	254	245
7	3	1	132	128
8	3	1	86	-89
9	3	1	76	-76
10	3	1	20	-24
11	3	1	21	1
-11	4	1	37	23
-10	4	1	20	4
-9	4	1	24	-11
-8	4	1	70	62
-7	4	1	79	81
-6	4	1	38	-52
-5	4	1	56	48
-4	4	1	58	-52
-3	4	1	15	22
-2	4	1	42	-47
-1	4	1	178	176
0	4	1	192	-178
1	4	1	145	-139
2	4	1	60	-56
3	4	1	31	-2
4	4	1	166	-167
5	4	1	102	-99
6	4	1	109	-113
7	4	1	90	-91
8	4	1	72	-71
9	4	1	15	-11
10	4	1	48	-39
-9	5	1	21	-2
-8	5	1	20	-3
-7	5	1	98	-91
-6	5	1	59	65
-5	5	1	154	148
-4	5	1	142	-144
-3	5	1	79	-78
-2	5	1	85	-90
-1	5	1	80	-82
0	5	1	289	281
1	5	1	53	-45
2	5	1	136	-146
3	5	1	182	-180
4	5	1	31	-5
5	5	1	32	37
6	5	1	27	79
7	5	1	67	-64
8	5	1	28	17
9	5	1	15	8
-7	6	1	77	73
-6	6	1	89	-85
-5	6	1	58	-49
-4	6	1	86	-91
-3	6	1	19	-28
-2	6	1	103	100
-1	6	1	40	37
0	6	1	39	-14
1	6	1	104	-101
2	6	1	130	-127
3	6	1	19	10
4	6	1	48	52
5	6	1	20	-36
6	6	1	29	-18
7	6	1	37	-9
8	6	1	37	24
9	6	1	84	-84
-10	7	1	46	-44
-9	7	1	35	36
-8	7	1	42	-25
-7	7	1	30	-32
-6	7	1	21	13
-5	7	2	21	68
-4	7	2	70	-70
-3	7	2	19	30
-2	7	2	30	-30
-1	7	2	16	-56
0	7	2	18	17
1	7	2	84	89
2	7	2	117	109
3	7	2	399	392
4	7	2	461	-457
5	7	2	472	471
6	7	2	359	-371
7	7	2	297	281
8	7	2	590	565
9	7	2	324	-333
-10	8	2	98	-98
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