understanding of the efflux mechanism, it was not attempted to differentiate these two factors in the present study. If 6–CF is replaced with other probes which have no protonated groups such as calcein[12], it can be helpful to explain the cause of the PH effect on the permeability.

This method allows to calculate size and concentration of the prepared vesicles without knowing the molecular weight of vesicles. This is possible because the final concentration of released 6–CF can be measured directly and hence the number of entrapped 6–CF per vesicle can be calculated[11,20]. When 100λ of sample was diluted to 100 ml of buffer, radius of inner aqueous part was estimated to be 53Å and the number of vesicles was 7.8×10^8/ml (ca. 1.3×10^{-12} M). In this case, therefore, vesicle diameter is approximately 210Å and inner volume is 6.2×10^{-19} cm^3. This means that each vesicle contains 75 molecules of dye. The effect of biologically active materials such as insulin and norepinephrine on the permeability was examined and it was observed that these materials influenced significantly the efflux of 6–CF from the vesicles. The effect of lipid composition on the permeablity was also tested with phosphatidylcholine: cholesterol system and the preliminary data showed that the presence of cholesterol in the vesicle eliminated effectively the concentration dependency of the efflux (Table 1). However the pattern of the overall efflux did not change and remained as sigmoidal. In view of the present studies and the simplicity of the procedure, this method can help to produce a large number of permeability data from various vesicles and contribute to the study of permeability mechanisn.

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The Crystal and Molecular Structure of Chloramphenicol Base

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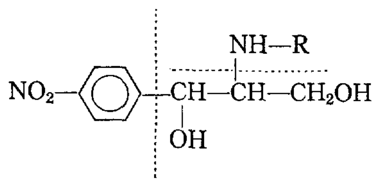
The crystal structure of chloramphenicol base, $C_9H_{12}N_2O_4$, the deacylated base of antibiotic chloramphenicol, has been determined by X–ray diffraction techniques using diffractometer data obtained by the ω–2θ scan technique with CuKα radiation from a crystal with space group symmetry $P2_12_12_1$ and unit cell parameters a = 22.322(6), b = 7.535(6), c = 5.781(5) Å. The structure was solved by direct methods and refined by full–matrix least–squares to a final R = 0.051 for the 573 observed reflections. The overall conformation of the base is quite different from those of the chloramphenicol congeners which are similar despite the presence of many rotatable single bonds. The propane chain in the base is bent with respect to the phenyl ring, while it is extended in the chloramphenicol congeners. There is no intramolecular hydrogen bond between the hydroxyl groups of the propanediol moiety. All of the molecules in the crystal lattice are connected by a three-dimensional hydrogen bonding network.

Introduction

The antibiotic chloramphenicol (CPL; I) is ap owerful inhibitor of protein synthesis in both bacteria and mammalian cells. Extensive studies have established that CPL inhibits peptide bond synthesis catalyzed by ribosomal peptidyltransferase at, or close to, the ribosomal A site.[1,2] However its detailed mode of drug action at the molecular level remains uncertain despite the presence of numerous studies on the structure-activity relationships of CPL.[3]



(I) : R = $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{CHCl_2}$ (II) : R = $-$H

Many structural studies have shown that CPL is a relatively rigid molecule even though there are many rotatable single bonds. Theoretical calculations,[4-6] nmr, IR, Raman, CD,[4,7,8] and crystallographic studies[9-13] on CPL and its congeners have revealed that the stable conformation of the CPL molecule is a folded, V-shaped (sometimes called "curled") one either in solution or in solid, although different in atomic detail. In this conformation, the chain of the three carbon atoms in the propanediol moiety is at the base of the V and fully extended with respect to the phenyl ring, while the phenyl and dichloroacetyl groups are located towards the ends of the wings.

The CPL molecule can be subdivided (see the above scheme) into three parts: (i) the substituted aromatic ring system, (ii) the acyl side chain, and (iii) the propanediol moiety. The propanediol moiety with the D(–)-threo configuration is absolutely required for antibacterial activity. The wide variations are permitted for the aryl moiety whereas the acyl side chain is essential for activity.[2] The deacylated CPL base (CPLB; II), D(–)-threo-2-amino-1-p-nitrophenyl-1, 3-propanediol, is almost devoid of activity both in vivo and in vitro.[14,15] We have undertaken the crystal structure analysis of CPLB in order to determine whether the absence of the dichloroacetyl moiety exerts any structural effects on the remaining parts of the CPL molecule.

Experimental

Transparent crystals were grown from a methanol solution of CPLB in powder form (Sigma) by slow evaporation at room temperature. Oscillation and Weissenberg photographs showed the crystal system to be orthorhombic with the space group $P2_12_12_1$. Accurate cell parameters were obtained by least-squares refinement of the 2θ values for the 24 reflections centered on an automated Rigaku four-circle diffractometer. The crystal data are as follows:

$C_9H_{12}N_2O_4$; Mol. Wt. 212.2; $F(000)=448$

$a=22.322$ (6), $b=7.535$ (6), $c=5.781$ (5) Å; $V=972.3$ Å^3

space group $P2_12_12_1$; $Z=4$; μ(Cu Kα)$=9.903$cm^{-1}

$D_m=1.45$ gcm^{-3} by flotation in CCl_4-cyclohexane

$D_c=1.450$ gcm^{-3}

Reflection data from a crystal with dimensions of 0.5$\times$0.3$\times$0.1 mm were collected with graphite-monochromated Cu Kα radiation using the ω-2θ scan technique over a scan range of $(1.5+0.5\tan\theta)°$ in ω at a scan rate of 4°/min and a 10-s background count at each end of the scan range. Three standard reflections were monitored after every 50 reflections. After corrected for Lorentz and polarization effects, the intensities were converted to structure factor amplitudes.[15] Scanning of the individual reflections showed considerable splits in the peak profiles although the crystals looked clean under the polarizing microscope. Due to the considerably increased background counts, the intensity data beyond $2\theta>100°$ were considered unreliable and not used in the subsequent calculations. Of all 620 independent reflections in the range of $2\theta\leqq100°$, 47 which had $F<6\sigma(F)$ were treated as unobserved.

The structure was solved with the program MULTAN78[17], using the largest 160 E's greater than 1.33. All of the non-hydrogen atoms were located in an E map calculated using the phase set with the highest combined figure of merit. After each cycle of isotropic and anisotrpic full-matrix least-squares refinements, all of the hydrogen atoms could be loacted in a difference Fourier map. Successive refinements using the weighting scheme converged the R value ($R=\sum||F_o|-k|F_c||/\sum|F_o|$) to 0.051 and $R\omega$ ($R\omega=\sum\sqrt{\omega}||F_o|-k|F_c||/\sum\sqrt{\omega}|F_o|$) to 0.054 for the 573 observed reflections. In the final cycle of refinement, the thermal parameters of the hydrogen atoms were not refined but were assigned as the isotropic equivalents of the atoms to which they were bonded. The function minimized in least-squares refinement was $\sum\omega(|F_o|-k|F_c|)^2$ where k is a single scale factor and $\omega=k'/(\sigma^2(F)+gF_*^2)$. k' and g were refined to 1.0 and 0.0062, respectively, in the last cycle of refinement. All of the atomic scattering factors were from International Tables for X-ray Crystallography.[18] All of the calculations were done using the program SHELX.[19] The final atomic parameters are listed in Table 1.[20]

Results and Discussion

The atomic numbering scheme, the bond distances and angles are presented in Figure 1. Most of the bond distances and angles are in the normal range and agree within 3σ with the corresponding ones of CPL[10] and thiamphenicol[13]. The only exception is the O(3)-C(7)-C(4) angle (108.9 (4)°) which is smaller by 8σ than the average value of 112.0 ° found in CPL and thiamphenicol. The phenyl ring is planar within experimental error with the mean deviation of the atoms from the least-squares plane of 0.01 Å. The nitro group is slightly rotated from the phenyl ring plane with a dihedral angle of 10.8°.

Figure 2 shows the stereoscopic PLUTO[21] packing drawings of the structure. An extensive hydrogen bonding network exists (Table 2) in the crystal structure. The molecules related by translation along the c axis are connected by relatively strong O(4)$-$H$\cdots$O(3) (2.807 (6) Å) and weak N(2)$-$H$\cdots$

TABLE 1: Fractional Coordinates and Temperature Factors for Chloramphenicol Base

atom[a]	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	2306(2)	2498(7)	−796(9)	22(3)	28(3)	25(3)	−6(3)	−4(3)	4(3)
C(2)	2677(2)	3384(7)	−2290(10)	34(4)	36(3)	20(3)	3(3)	−3(3)	6(3)
C(3)	3262(2)	3699(8)	−1648(10)	39(4)	36(3)	28(3)	−3(3)	−1(3)	5(3)
C(4)	3479(2)	3074(7)	486(8)	31(3)	30(3)	13(3)	−1(3)	−5(3)	9(2)
C(5)	3081(2)	2218(8)	1938(10)	29(4)	48(4)	19(3)	3(3)	−1(3)	4(3)
C(6)	2494(2)	1929(7)	1339(11)	33(4)	40(3)	30(3)	4(3)	4(3)	1(3)
N(1)	1677(2)	2158(7)	−1487(12)	39(3)	36(3)	48(4)	−1(3)	2(3)	1(2)
O(1)	1537(2)	2420(7)	−3497(8)	46(3)	81(3)	40(3)	5(3)	−16(3)	−3(3)
O(2)	1330(2)	1567(7)	−55(9)	38(3)	92(4)	59(3)	27(3)	9(2)	−14(2)
C(7)	4129(2)	3307(8)	1117(10)	34(3)	29(3)	27(3)	−1(3)	−5(3)	−3(3)
O(3)	4168(2)	3898(6)	3487(6)	43(2)	40(2)	15(2)	−7(2)	0(2)	−5(2)
C(8)	4480(2)	1563(8)	868(10)	21(3)	35(3)	31(3)	7(3)	−1(3)	−3(3)
N(2)	5115(2)	1795(7)	1471(10)	30(3)	49(3)	30(3)	−7(3)	3(2)	−2(2)
C(9)	4423(3)	740(8)	−1480(11)	38(4)	40(3)	36(4)	−5(3)	2(3)	4(3)
O(4)	4732(2)	1746(6)	−3202(7)	53(3)	80(4)	22(2)	7(3)	5(2)	6(3)

atom[b]	x	y	z	U	atom	x	y	z	U
H(C2)	256(3)	371(8)	−348(12)	4	H(O3)	431(2)	484(7)	370(12)	4
H(C3)	353(2)	429(7)	−284(10)	4	H(O4)	454(3)	249(9)	−390(13)	6
H(C5)	323(3)	196(8)	301(10)	4	H1(C9)	398(2)	48(7)	−165(11)	5
H(C6)	220(3)	130(8)	264(10)	4	H2(C9)	463(3)	−46(7)	−137(12)	5
H(C7)	438(3)	414(8)	31(12)	4	H1(N2)	518(3)	249(8)	326(12)	5
H(C8)	433(3)	77(8)	204(10)	4	H2(N2)	533(3)	201(9)	38(12)	5

[a] Estimated standard deviation in parentheses is for the least significant figure. Positional parameters × 10^4; thermal parameters, which are coefficients of the expression $\exp[-2\pi^2(h^2a^{*2}U_{11}+\cdots 2klb^*c^*U_{23}+\cdots)]$, × 10^3. [b] Positional parameters × 10^3: thermal parameter, which is the coefficient for the expression $\exp[-(8\pi^2U)\sin^2\theta/\lambda^2]$, × 10^3.

O(4), (3.196 (7) Å), hydrogen bonds to form a molecular strand. Weak N(2)−H··· O(2) hydrogen bonds, (3.090 (7) Å), interweave the twofold screw-related strands to form a molecular sheet parallel to the *ac* plane. In this sheet, the four molecules which are hydrogen-bonded in a cyclic fashion can be considered as a repeating unit. These planar sheets are in turn connected by strong O(3)−H··· N (2) hydrogen bonds, (2.707 (7) Å), along the *b* direction to form a three-dimensional hydrogen bonding network. The latter hydrogen bond is of special type in that O(3) is hydrogen-bonded to the π electrons of N(2). The amino N(2) may be considered to form an intramolecular hydrogen bond with O(4), in a bifurcated mode, to form a cyclic pentagonal ring.

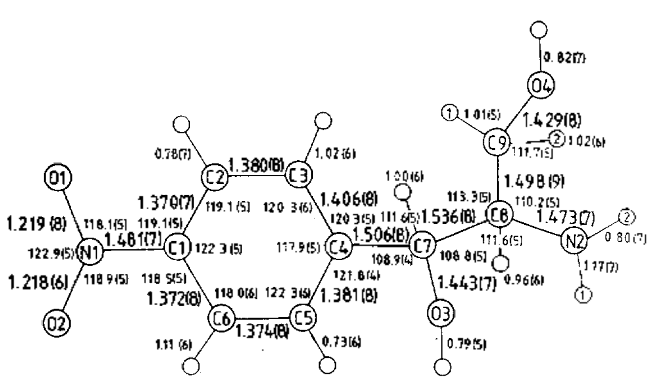


Figure 1. Schematic representation of the chloramphenicol base molecule showing the atomic numbering scheme, the bond distances (Å) and angles (°).

The conformation of the deacylated CPLB is quite different from those of CPL and its congeners as can be seen in the torsion angles in Table 3. The largest differences are in τ_3 and τ_4 which define the orientation of the propane chain with respect to the phenyl ring. The propane chain is fully extended with respect to the phenyl ring in both CPL and its congeners even with the wide variation in molecular environment represented in crystal structures. However, in CPLB, the chain is bent so that C(9) is in the opposite direction to O(3) and the amino group is in the extended position. Moreover τ_1 and τ_2 of CPLB are significantly different from

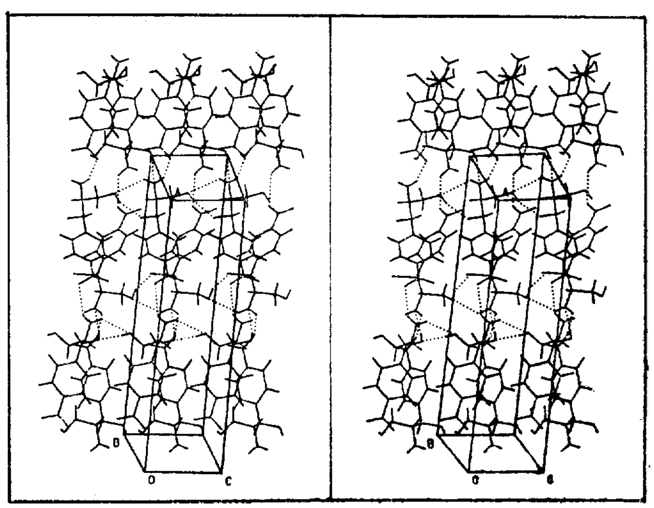


Figure 2. Stereoscopic PLUTO packing diagram of chloramphenicol base.

TABLE 2: Hydrogen Bonds in Chloramphenicol Base

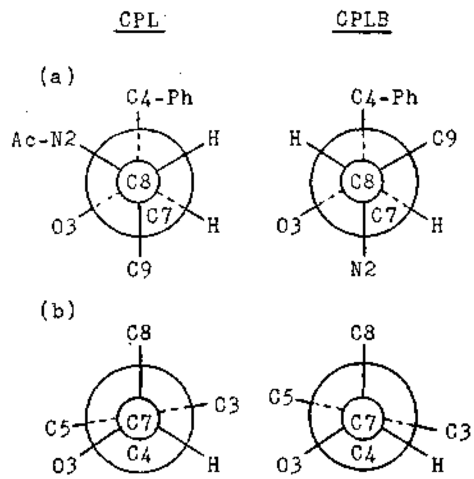
D H A	DA(Å)	HA(Å)	<DHA (°)	Position of A
O(4)−H(O4)···O(3)	2.807(6)	2.02(7)	161(7)	$x, y, -1+z$
N(2)−H1(N2)···O(4)	3.196(7)	2.34(7)	128(6)	$x, y, 1+z$
N(2)−H2(N2)···O(2)	3.090(7)	2.49(7)	132(6)	$\frac{1}{2}+x, \frac{1}{2}-y, -z$
O(3)−H(O3)···N(2)	2.707(7)	1.96(6)	159(6)	$1-x, \frac{1}{2}+y, \frac{1}{2}-z$
H(2)−H2(N2)···O(4)	2.834(7)	2.47(7)	109(6)	x, y, z

TABLE 3: Comparison of Torsion Angles in Chloramphenicol Related Compounds

	τ_1	τ_2	τ_3	τ_4
CPLB	74.6	−45.4	179.6	54.4
CPL[10]	92.7	−27.3	−54.9	179.9
CPL β-Palmitate[12]	102.0	−15.1	−68.7	166.1
Thiamphenicol[13]	99.0	−12.0	−59.0	177.7

τ_1=C(5)-C(4)-C(7)-C(8) τ_2=C(5)-C(4)-C(8)-O(3)

τ_3=C(4)-C(7)-C(8)-N(2) τ_4=C(4)-C(7)-C(8)-C(9)



Ac : dichloroacetyl

Ph : p-nitrophenyl

Figure 3. Newman projections down (a) the C(8)−C(7) bond and (b) the C(7)−C(4) bond in chloramphenicol and its base

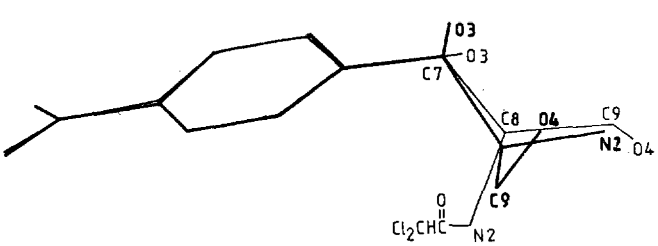


Figure 4. Least-squares fitted molecules of chloramphenicol (light lines) and its base (heavy lines) according to the procedures of Nyburg.[22]

those of CPL congeners. These torsion angles represent the degree of rotation of the phenyl ring with respect to the C(7)-O(3) or C(7)-C(8) bond. These conformational differences are schematically shown in Figures 3 and 4.

According to the nmr studies of the ribosome-CPL complex, binding of CPL to the ribosome seems to be static process and the rigid conformation of CPL may be maintained even in the complex such that the probable mode of binding is an insertion of the point of the V (i.e. the propanediol moiety) into the receptor region of the ribosome.[23] However, there is still a major controversy on the active conformation of CPL in detail, especially on the presence of an acyclic ring formed by an intramolecular hydrogen bond between the two hydroxyl groups in the propanediol moiety as reviewed in ref. 2. The existence of an acyclic ring is an essential feature in such a proposal that CPL may be a structural analog of the aminoacyl-*t*RNA or puromycin and thus exhibit drug activity. Some studies[3,7,10] support this proposal, while others[4,12,13] have shown that the V-shaped conformation is stable even in the absence of the intramolecular hydrogen bond either in solution or in solid state. It is sterically impossible for the propanediol moiety in the D(−)-threo configuration to form an acyclic ring when the amino group is extended with respect to the phenyl ring.

Whatever the active conformation of CPL may be, the present study implies that CPLB may be inactive due to the different conformation in the propanediol moiety as well as the absence of the functionally important dichloroacetyl moiety. Furthermore, the present study indicates that the rigid, V-shaped conformation of CPL and its congeners is characteristically maintained by some intramolecular forces only in the presence of the dichloroacetyl moiety.

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Temperature Effect on the Configurational Properties of an *n*-Decane Chain in Solution

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Equilibrium and dynamical behaviors of an *n*-alkane poymer (decane) in solution hve been investigated by a molecuar dynamics simulation method. The polymer is assumed to be a chain of elements (CH_2) interconnected by bonds having a fixed bond length and bond angle, but esch bond of the polymer is allowed to execute hindered internal rotation The calculation explicitly considers the molecular natuer of solvent by including the intermolecular interactions between slovent-solvent molecules and chain element-solvent molecule. We present the results of calculations on (1) equilibrium properties (the solvent molecule-chain element pair correlation function, chain element-chain element pair correlation function, the mean square end-to-end distance and the mean square radius of gyration of the polymer) and (2) dynamic properties (four different autocorrelation functions ,namely, the autocorrelation functions for the end-to-end distance and the radius of gyration, and the velocity autocorrelation functions for the center of mass and the end point of the chain). We found that the physical properties of the polymer chain depends sensitively on temperature. Comparison of the present work with other authors' results is also presented.

1. Introduction

The behavior of chain molecules in solution has been the subject of considerable attention.[1-12] Chandler et al.[2] have reported the theoretical predictions that condensed-phase enviornment can shift the equilibrium between the gauche and trans forms of *n*-butane, and that the gauche population increases upon transfer from gas phase to aqueous solution. Jorgensene[3] has carried out the Monte Carlo (MC) simulation of *n*-butane in water, and found a similar fact as predicted by Pratt and Chandler,[2d] In the case of longer chain molecules, many computation results have been reported. Ceperley *et al.*[4] developed a dynamic MC technique which simulates the dynamics of a single polymer chain immersed in a solvent. Other MC results for the static and dynamic properties of condensed systems of polymers have been reported.[5-8]

Molecular dynamics (MD) simulation of chain molecules has been carred out by various authors.[9-14] Bishop *et al.*[9] have simulated polymer chains represented by beads linked by springs. Rapapport[10] simulated a freely linked polymer chain of hard spheres immersed in a solvent represented by hard spheres. Bruns and Bansal[11] have carried out a simulation of the dynamics of a nonamer chain immersed in solvent, the solute being nine beads connected by rigid rods. Lee *et al.*[12] have calculated the static and dynamic properties of a polymer chain immersed in solvent by using the model of beads connected by springs. The chain molecules of the above four groups[9-12] are freely-jointed chains having intramolecular interaction as well as the intermolecular interaction with solvent molecules.

Calculations using more realistic chain models are carried out by Weber *et al.*[13] and Ryckaert *et al.*[14] The former group simulated the chain molecules by flexible chains having the nature of bond stretching, bond-angle bending and bond rotation, and the latter group simulated by semi-rigid chains with fixed bond-length, fixed bond-angle and hindered