$P2_1/n$ (No. 14), $a = 10.979(6)$, $b = 14.897(5)$, $c = 16.606(4)$ Å, $\beta = 101.28(3)^\circ$, $V = 2663(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.417$ g cm^{-3}, crystal dimensions $0.36 \times 0.32 \times 0.18$ mm, $\mu = 30.70$ cm^{-1}, $T = 293$ K, final $R = 0.048$, $wR = 0.062$, and $S = 1.45$ for 307 parameters and 2158 unique observed reflections with $I > 3\sigma(I)$, $\Delta\rho_{max} = 0.58$ e Å^{-3}. Diffraction data for **2b** and **5b** were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) to $2\theta_{max} = 55^\circ$. The structures of **2b** and **5b** were solved by direct methods and heavy-atom Patterson methods, respectively, and expanded with Fourier techniques. The diallene moiety of **5b** was found to be disordered. All calculations were carried out with the teXsan crystallographic software package from the Molecular Structure Corporation. b) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101408. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] Crystal data for **8b**: $C_{32}H_{24}Br_2$, $M_r = 568.35$, monoclinic, space group $C2/c$ (No. 15), $a = 6.641(7)$, $b = 28.502(4)$, $c = 13.773(5)$ Å, $\beta = 96.66(5)^\circ$, $V = 2589(2)$ Å3, $Z = 4$, $\rho_{calcd} = 1.458$ g cm^{-3}, crystal dimensions $0.34 \times 0.06 \times 0.04$ mm, $\mu(Mo_{K\alpha}) = 31.58$ cm^{-1}, $T = 295$ K, $R = 0.057$, $wR = 0.075$, and $S = 1.67$ for 145 parameters and 969 unique observed reflections with $I > 3\sigma(I)$, $\Delta\rho_{max} = 0.68$ e Å^{-3}. Data collection and analysis were carried out in a similar way to those for **5b**. The phenyl groups were refined with two disordered positions.[10b]

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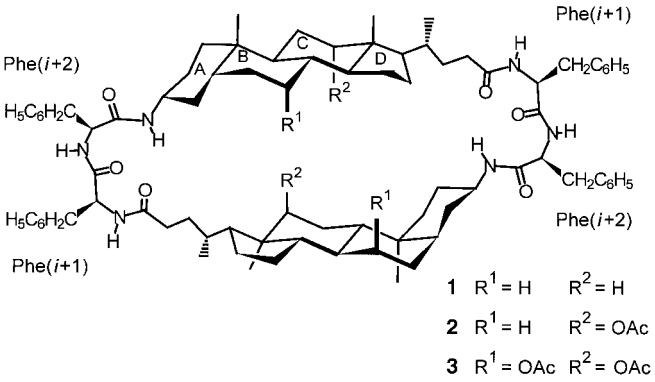
Crystal Structure of a Peptide–Steroid Macrocycle—Intramolecular Attraction between Steroids and Peptidic β(I) Turns**

Dieter Albert, Martin Feigel,* Jordi Benet-Buchholz, and Roland Boese

The concave surface of cholanic acids seems to be preorganized to bind molecular guests through weak interactions. Examples are the cholaphanes—synthesized by Davis, Bonar-Law, and co-workers from cholanic acid derivatives and aromatic spacers—which encapsulate carbohydrates and anions in solution.[1] Other researchers have used the hydroxyl groups on the α side of the steran residue to position covalently attached units such as peptides, carbohydrates, or polycyclic arenes.[2]

We intend to develop molecular hosts of designed characteristics by combining the rigid, concave surface of cholanic acids with the flexibility and functionality of amino acids.[3, 4] Analyzing the NMR spectra of compounds **1**–**3**, we found



1 $R^1 = H$ $R^2 = H$
2 $R^1 = H$ $R^2 = OAc$
3 $R^1 = OAc$ $R^2 = OAc$

that substitution of the cholanic surfaces by acetoxy groups influences the conformation of the peptide part.[4] The present work describes for the first time the solid-state structure of such a macrocycle (**1**) containing a steroid (lithocholic acid) and a dipeptide (Phe-Phe). The structure demonstrates that an optimal approach between the two steroidal surfaces in the molecule is achieved when the peptide parts fold to form two β(I) turns.

Compound **1** was obtained by cyclodimerization of the pentafluorophenol ester of bis(phenylalaninyl)-3-amidolithocholic acid.[4] Crystallization of **1** from chloroform yielded prisms which were suitable for X-ray diffraction. The structure was solved using the Patterson search method of Egert and Sheldrick;[5] the steran residue of lithocholic acid was used as a structural fragment. The macrocycle **1** adopts a compressed form of C_2 symmetry in the crystal. The two lithocholic acid units of the molecule are in van der Waals contact (Figure 1). The close contact between the α surface of

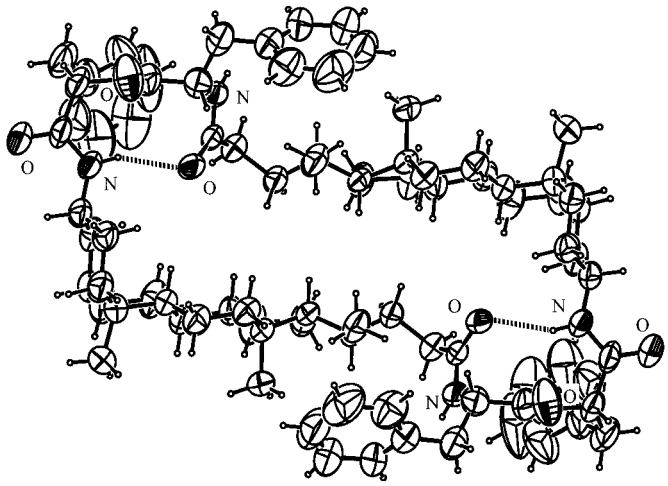


Figure 1. Structure of **1** in the crystal.

rings C and D and the branched side chain of the opposite lithocholic acid is particularly visible in Figure 1. The approach is achieved since the peptide parts of the molecule fold into β loops. The dihedral angles ϕ and ψ of the peptide parts (Phe($i+1$): $\phi/\psi = -75.7/-12.2$; Phe($i+2$): $\phi/\psi = -81.2/-3.5$) correspond to those found in a β(I) turn (residue($i+1$): $\phi/\psi = -60/-30$; residue($i+2$): $\phi/\psi = -90/0$).[6]

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The occurrence of phenylalanine in the $i+1$ and $i+2$ positions of the β turn is rather unusual.[7] The lipophilicity of the lithocholic acid residues apparently determines the geometry in the peptide part of **1**.

The crystal packing is influenced by an intermolecular van der Waals attraction between the lipophilic outer β surface of the lithocholic acids. They stack to form layers of steroids perpendicular to the crystallographic c axis. Three of the layers can be seen in Figure 2; the orientations of the

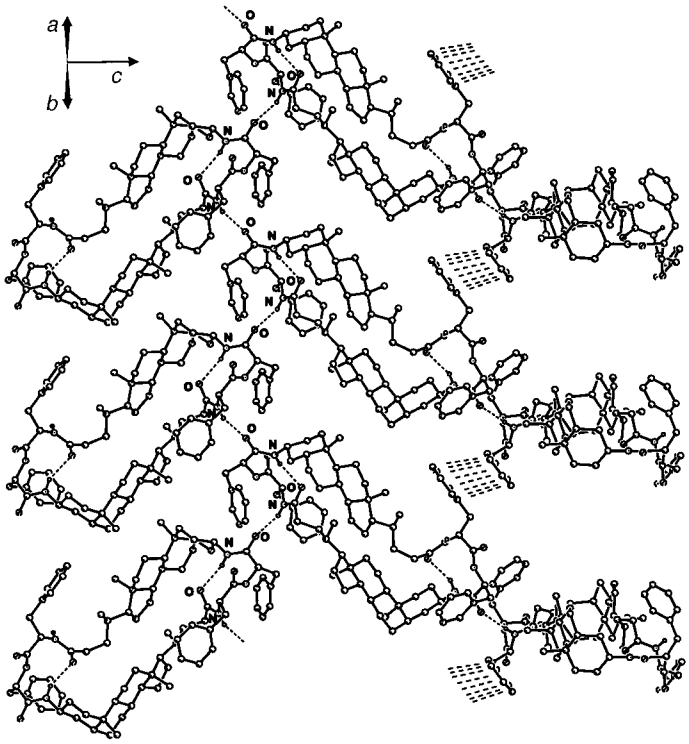

Figure 2. Formation of helical chains of hydrogen bonds between steroid layers in the crystal structure of **1**. The nitrogen and oxygen atoms within the chain of hydrogen bonds are marked. The π stacking between the aromatic side chains of Phe($i+1$) is indicated by dashed lines.

macrocycles in each layer differ by 120°, corresponding to the trigonal space group $P3_221$ of the crystal. The orientation is stabilized by hydrogen bonding between the NH protons of Phe($i+1$) in one layer and the carbonyl oxygen atoms of Phe($i+2$) in the adjacent layer (Table 1). The intermolecular hydrogen bonds together with the intramolecular hydrogen bonds of the β turns build helical chains of hydrogen bonds in which both types of interactions presumably stabilize each other (Figure 2).

The remaining free space in the crystal is occupied by chloroform and ethyl acetate molecules. Chloroform is found at two different positions. One of the molecules is relatively fixed and orientated so that its CH group comes in close contact to the carbonyl oxygen

Table 1. Geometrical parameters of the intra- and intermolecular hydrogen bonds.

Atoms	Distance [pm] H···O	C/N···O	Angle [°] C/N-H···O
NH(lithochol) O=C(lithochol)	203	303	155.6
NH(Phe($i+1$)) O=C(Phe($i+2$))	185	288	157.5
CH($CHCl_3$) O=C(Phe($i+1$))	234	328	145.0

atom of Phe($i+1$), which is not involved in other hydrogen bonds (Table 1). The NH proton of the corresponding amide bond (NH – Phe($i+2$)) does not contribute to any hydrogen bonding and is shielded from further contacts by the phenyl ring of Phe($i+2$). The second molecule of chloroform has two different orientations with occupation factors 0.5/0.5. Additional electron density is found in the crystal which can be explained by the presence of ethyl acetate with an occupation factor of 0.5. Four molecules of chloroform and one molecule of ethyl acetate per macrocycle **1** result as the total composition based on the symmetry of the crystal.

The chloroform and ethyl acetate molecules together with the phenyl groups of Phe($i+1$) are assembled in channels along the c axis of the crystal (Figure 3). High displacement factors of these structural elements indicate flexibility and perhaps mobility in the channels. The structure is also stabilized by π interaction between the aromatic side chains of the residues Phe($i+1$);[8] the phenyl rings of neighboring macrocycles are grouped "face to face" (see Figure 2).

Artificial β turns are normally synthesized to induce the conformation of an antiparallel β sheet in peptides or to orient side chains of amino acids within the loop region.[9] The system described here is structurally able to do both functions. We look forward to seeing whether similar macrocycles with longer peptide chains, with other amino acids, or even open chain compounds will adopt the β-turn structure observed in **1**. Furthermore, the combination of a strong lipophilic steroid with polar peptides will open up biochemical applications, for example the fixation of peptides in lipid membranes.

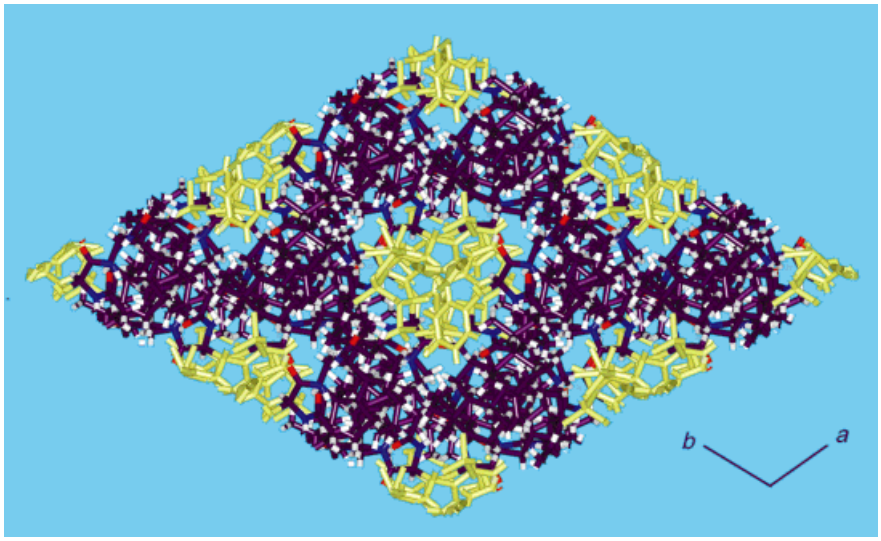

Figure 3. View along the crystallographic c axis onto four unit cells of the structure of **1**. The included solvent chloroform and ethyl acetate molecules as well as the aromatic side chains of Phe($i+1$) are colored yellow; they fill channels along the c axis.

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Experimental Section

X-ray structure determination of **1** ($C_{84}H_{114}N_6O_6$) at 220 K: The crystal contains chloroform and ethyl acetate and is stable at room temperature. Crystal size $0.24 \times 0.18 \times 0.17$ mm, Siemens SMART CCD area detector on a free axis platform, $Mo_{K\alpha}$ radiation, graphite monochromator. Cell dimensions from the positions of 5466 reflections: $a = 14.1464(1)$, $c = 42.8884(2)$ Å, $V = 7432.97(21)$ Å^3; trigonal, space group $P3_221$ (no. 154), $Z = 3$, $\rho_{calcd} = 1.062$ Mg m^{-3}, $\mu = 0.22$ mm^{-1}, empirical absorption correction based on redundant data (SADABS program, Siemens), max./min. transmission 1.000/0.816, R(merg) before/after correction 0.0633/0.0519, data collection $\Theta_{max} = 22.46^\circ$, detector distance 4.457 cm, half-sphere scan in ω with 0.3° spacing and four data sets of 636, 465, 636, and 465 pictures with $\phi = 0$, 88, and 180°, where more than 97% of the data are nominally recorded (data reduction with SAINT Program, V4.028, Siemens), decay correction (< 2%) by repetition of the measurements of the first 50 pictures at the end of the data sampling; of 49471 refections measured, 6471 were independent and 4174 observed ($I > 2\sigma(I)$); $R_{merg} = 0.0874$ (F^2). Structure solution with PATSEE[5] (no solution with direct methods) and refinement to F^2 (SHELXTL-Plus Ver. 97-1/Iris), 591 parameters, hydrogen atoms as riding groups with 1.2 or (for methyl groups) 1.5 times the isotropic displacement parameter of the corresponding carbon atom. $R = 0.0872$ ($I > 2\sigma(I)$), $wR2 = 0.2385$, GOF(F^2) = 1.068, $w^{-1} = \sigma^2(F_o^2) + (0.1074P)^2 + 4.41P$ with $P = [(\text{max. } F_o^2, 0) + 2F_c^2)]/3$, largest residual electron density 0.32 e Å^{-1}. Further details on the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-408718.

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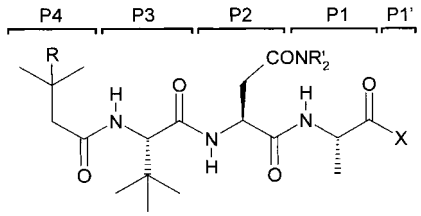
The Conformation of a Peptidyl Methyl Ketone Inhibitor Bound to the Human Cytomegalovirus Protease**

Steven R. LaPlante, Dale R. Cameron, Norman Aubry, Pierre R. Bonneau, Robert Déziel, Chantal Grand-Maître, William W. Ogilvie, and Stephen H. Kawai*

The transferred nuclear Overhauser effect (TRNOE) experiment represents a powerful NMR tool for the study of protein – ligand interactions.[1] Aided by computational chemistry, the method can provide valuable structural information concerning the conformation of a ligand when bound to a macromolecule. A key condition of the TRNOE method, however, is that the exchange between the free and complexed forms of the molecule to be investigated is rapid (faster than its spin-lattice relaxation rate) and reversible. In the present work, we provide the first structure of a peptidyl inhibitor bound to the human cytomegalovirus (HCMV) protease.[2] The use of the peptidyl methyl ketones MK1 and MK2 represents a novel approach to probing the structure of classical activated carbonyl inhibitors of serine proteases, which are themselves incompatible with the TRNOE method (Scheme 1). To date, such investigations of inhibitors of these enzymes have utilized, almost exclusively, peptide cleavage products or slowly cleaved substrates.[3]

There presently exists considerable interest in HCMV protease as a target for therapeutic agents against HCMV infection, which remains a serious clinical problem.[4] More-



MK1:	R = CH_3	R' = CH_3	X=CH_3
MK2:	R = H	R' = CH_3	X=CH_3
TFMK3:	R = CH_3	R' = CH_3	X=CF_3
PFEK4:	R = CH_3	R' = CH_3	X=CF_2F_3
AKA5:	R = CH_3	R'$_2$ = -$(CH_2)_4$-	X=C(O)N(H)CH_2(*p*-IC_6H_4)

Scheme 1. Various peptidyl inhibitors of HCMV protease. The numbers over the individual amino acids correspond to the notation of Schechter and Berger[10] for which a natural peptide substrate is cleaved between P1 and P1′.

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