Crystal Structure of a 1:1 Complex of Palmitic acid and Nicotinamide

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An equimolar mixture of palmitic acid (hexadecanoic acid) and nicotinamide (3-pyridinecarboxamide) in acetone yielded crystals of a 1:1 complex, C₂₂H₃₈N₂O₃. Palmitic acid forms a lipid bilayer and is stacked to form a lamellar structure. The alkyl chain of palmitic acid has an all-*trans* conformation. Nicotinamides form a dimer, which is intercalated into hydrophilic regions of the lamellar structure.

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Nicotinamide (NA) is mainly used to treat pellagra disease. It is known that normal saturated fatty acids (FA) of C₁₂ to C₁₈ form an equimolar complex (FA/NA) with NA.¹ The complex can improve hygroscopicity and remove the bitter taste of NA.² We determined the crystal structures of an equimolar complex (C₁₂/NA,³ C₁₇/NA⁴ and C₁₈/NA⁵). The common features of the complex were three types of hydrogen bonds, the conformation of FA and NA molecules and the formation of a lamellar structure. One type forms an equimolar FA/NA complex. Another type forms a dimer of the complex. The other type forms a hydrogen-bond sequence along with lamellar plane. These results lead us to speculate on the structural similarity of the complex from C₁₃/NA to C₁₆/NA with the complex reported in our previous papers. To confirm the speculation, we investigated the complex of palmitic acid and nicotinamide.

Crystals of an equimolar complex (Fig. 2) of C₁₆ and NA were grown by slow evaporation from an acetone solution at 35°C. A colorless plate-like crystal measuring 0.7 × 0.5 × 0.06 mm was used for X-ray analysis. Crystal and experimental data are given in Table 1, and the final atomic parameters for the non-H atoms are listed in Table 2. The structure was solved by direct

methods (SIR92)⁶ and refined by the full-matrix least squares method. All H-atoms, except for those of the carboxyl, amino and methyl groups, were refined using a riding model. The H-atoms of the carboxyl, amino and methyl groups were identified from a difference map and refined with an isotropic temperature factor. All calculations were performed using the CrystalStructure crystallographic software package.⁷

The alkyl chain of C₁₆ took an all-*trans* conformation, as can be seen in Fig. 2, and the hydrogen-bond distance observed between the N1 atom of the pyridine ring of NA and the O2 atom of C₁₆ is 2.699(6) Å, the angle of O2-H1...N1 is 178.1°. The O3 and N2 atoms of the amide group of NA form a hydrogen bond with the N2ⁱ and O3ⁱ atoms of the amide group of the other NA related by the symmetry operator of (i) -x, -y, -z - 1. The distance of O3...N2ⁱ (N2...O3ⁱ) is 2.948(5) Å and the angle of O3-H38...N2ⁱ is 172.2°. Because of these hydrogen bonds, the complex forms a dimer, as can be seen in Fig. 3. The

Fig. 1 Chemical structure of the title complex.

Fig. 2 ORTEP III drawing of the title compound with the atom-numbering scheme. The dotted line indicates a hydrogen bond. Displacement ellipsoids are drawn at the 50% probability level.

Table 1 Crystal and experimental data

Formula: C ₂₂ H ₃₈ N ₂ O ₃	
Formula weight: 378.55	
Crystal system: triclinic	
Space group: $P\bar{1}$	$Z = 2$
$a = 5.4461(9)$ Å	$\alpha = 90.61(2)^\circ$
$b = 41.627(7)$ Å	$\beta = 92.30(2)^\circ$
$c = 5.042(2)$ Å	$\gamma = 91.079(13)^\circ$
$V = 1141.9(6)$ Å ³	
$D_x = 1.101$ g/cm ³	
No. of reflections used = 3044	
$2\theta_{\max} = 136.0^\circ$ with Cu K_α	
$R = 0.0989$	$R_w = 0.0870$
$(\Delta/\sigma)_{\max} = 0.000$	
$(\Delta\rho)_{\max} = 0.37$ e Å ⁻³	
$(\Delta\rho)_{\min} = -0.39$ e Å ⁻³	
Measurement: Rigaku AFC7R	
Program system: CrystalStructure 3.7.0	
Structure determination: SIR92	
Refinement: full matrix	

CCDC 292804 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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Table 2 Atomic coordinates and equivalent thermal parameters for non-hydrogen atom

atom	x	y	z	$B_{eq}(\text{\AA}^2)$
O1	-0.2670(8)	0.13567(10)	0.0649(9)	5.67(12)
O2	-0.6119(7)	0.15759(9)	-0.0869(8)	4.88(11)
O3	-0.1947(7)	0.02815(9)	-0.3117(7)	3.99(10)
N1	-0.6407(9)	0.10725(11)	-0.4294(9)	3.91(12)
N2	-0.2213(8)	0.01590(10)	-0.7462(8)	3.61(11)
C1	-0.4127(11)	0.15721(13)	0.0681(12)	3.78(14)
C2	-0.4001(11)	0.18504(13)	0.2573(12)	4.43(16)
C3	-0.1507(10)	0.19288(12)	0.3861(12)	4.29(16)
C4	-0.1522(11)	0.22308(12)	0.5573(12)	4.39(16)
C5	0.0958(11)	0.23384(12)	0.6754(13)	4.45(16)
C6	0.0866(11)	0.26398(12)	0.8468(13)	4.44(16)
C7	0.3337(11)	0.27601(13)	0.9584(13)	4.67(17)
C8	0.3221(11)	0.30590(13)	1.1310(13)	4.63(16)
C9	0.5696(11)	0.31809(13)	1.2419(13)	4.90(17)
C10	0.5589(11)	0.34790(13)	1.4157(13)	4.90(17)
C11	0.8070(11)	0.35985(13)	1.5261(14)	5.21(18)
C12	0.7956(12)	0.38984(14)	1.6968(14)	5.38(19)
C13	1.0443(13)	0.40170(16)	1.8068(15)	5.9(2)
C14	1.0351(14)	0.43162(16)	1.9758(16)	6.6(2)
C15	1.2850(16)	0.44345(18)	2.0819(18)	8.7(3)
C16	1.2822(18)	0.47339(19)	2.253(2)	11.6(4)
C17	-0.4776(10)	0.08353(12)	-0.4072(11)	3.70(14)
C18	-0.4743(9)	0.05820(12)	-0.5822(10)	2.96(12)
C19	-0.6495(10)	0.05649(12)	-0.7887(11)	3.49(13)
C20	-0.8199(11)	0.08065(12)	-0.8097(12)	4.04(15)
C21	-0.8111(10)	0.10466(13)	-0.6267(12)	4.04(15)
C22	-0.2864(10)	0.03234(12)	-0.5358(10)	3.01(12)

$$B_{eq} = 8/3 \pi^2 [U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha]$$

O3 atom also forms a hydrogen bond with the N2ⁱⁱ atoms related by the symmetry operator of (ii) $x, y, z + 1$ and the N2 forms a hydrogen bond with the O3ⁱⁱⁱ atom related by the symmetry operator of (iii) $x, y, z - 1$. These hydrogen bonds (distance of N2...O3ⁱⁱⁱ is 2.911(5) Å and angle of N2-H37...O3ⁱⁱⁱ is 158.1°) form hydrogen-bond sequences along the c axis.

The structure of the title compound forms a lamellar structure in which NA molecules are intercalated in the hydrophilic regions of lipid bilayers composed of C₁₆ molecules (Fig. 3). In the lipid bilayers, the characteristics of the lateral packing of the hydrocarbon chains are usually described by subcells.⁸ The alkyl chains form a monoclinic subcell M_H with $a_s = 4.80$ Å, $b_s = 4.27$ Å, $c_s = 2.54$ Å, $\gamma_s = 113.1^\circ$. The amide group in NA is twisted out of the plane of the pyridine ring. The torsion angles N2-C22-C18-C19 and O3-C22-C18-C17 are 28.3(9) and 23(1)°, respectively.

The characteristics of the crystal structure of the title

Fig. 3 Intermolecular hydrogen bond (dashed lines) in the crystal structure of the title compound. Projection is along the a -axis. O2...N1: 2.699(6) Å, O3...N2ⁱ: 2.948(5) Å and N2...O3ⁱⁱⁱ: 2.911(5) Å with symmetry operators of (i) $-x, -y, -z - 1$ and (ii) $x, y, z + 1$. Subcell projected along the a_s -axis is shown by broken lines.

compound, such as the style of hydrogen bond, the conformation of the NA and FA molecules and subcell type of hydrocarbon chains, are very similar to these of the equimolar complex of NA and FA, reported previously.

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