Crystal Structure of a 2:1 Complex of Indomethacin and Lidocaine

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Crystals of a 2:1 complex, $(C_{19}H_{16}ClNO_4)_2 \cdot C_{14}H_{22}N_2O$, between indomethacin and lidocaine were grown by slow evaporation from an ethanol solution. Two different indomethacin (I and II) molecules showed different conformations. The proton of the carboxyl group of indomethacin II was transferred to an amino group of lidocaine. The intermolecular hydrogen bonds and CH/ π interactions were observed.

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Indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid) is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. Lidocaine (2-diethylamino-N-(2,6-dimethylphenyl)acetamide) is a common local anesthetic and antiarrhythmic drug. An injectable solution of lidocaine is used for epidural, conduction and infiltration anesthetics, and it may be applied as a liquid, jelly or spray to produce topical anesthesia. One of the authors has previously reported that the 9% lidocaine ointment is an effective agent for postherpetic neuralgia.¹

In the present study a topical medication containing indomethacin and lidocaine was examined, in order to develop a new and more effective analgesic agent. During the investigation, the formation of a crystal complex of indomethacin and lidocaine was observed.

An equimolar mixture of indomethacin and lidocaine in an ethanol solution yields crystals showing a 2:1 complex of indomethacin and lidocaine. A transparent colorless crystal measuring 0.2 × 0.2 × 0.17 mm was used for X-ray analysis. Crystal and experimental data are given in Table 1. The

structure was solved by the direct method (SIR92)² and refined by a full-matrix least squares procedure. All hydrogen atoms, except for those of the amide and carboxyl groups, were refined using a riding model. The hydrogen atoms of the amino group of lidocaine and the carboxy group of indomethacin were identified from a difference map. All calculations were performed using the CrystalStructure crystallographic software package.³

An ORTEP drawing of the title compound is shown in Fig. 2. The asymmetric unit is composed of one lidocaine and two

Fig. 1 Chemical structure of a 2:1 complex of indomethacin and lidocaine.

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Table 1 Crystal and experimental data

Formula: $C_{52}H_{54}N_4O_8Cl_2$
Formula weight = 949.93
Temperature: 93(1)K
Crystal system: triclinic
Space group: $P\bar{1}$ $Z = 2$
$a = 12.8479(2)\text{\AA}$ $\alpha = 94.9609(12)^\circ$
$b = 14.2054(3)\text{\AA}$ $\beta = 113.6968(11)^\circ$
$c = 15.2458(3)\text{\AA}$ $\gamma = 108.4726(12)^\circ$
$V = 2342.24(8)\text{\AA}^3$
$D_x = 1.347\text{ g/cm}^3$
No. of reflections used = 8463
$2\theta_{\max} = 136.5^\circ$ with Cu K_α
$R = 0.0380$
$(\Delta/\sigma)_{\max} = 0.000$
$(\Delta\rho)_{\max} = 0.46\text{ e}^-/\text{\AA}^3$
$(\Delta\rho)_{\min} = -0.28\text{ e}^-/\text{\AA}^3$
Measurement: Rigaku RAXIS-RAPID
Program system: CrystalStructure 3.7.0
Structure determination: SIR92
Refinement: full-matrix

CCDC 620023 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

Table 2 Hydrogen-bonding geometry(Å, °)

D-H...A	D...A	D-H	H...A	D-H...A
O103-H103...O204 #1	2.5069(19)	0.841	1.668	175.6
N1-H1...O203	2.730(2)	0.880	1.851	177.3
N2-H2...O1 #2	2.954(2)	0.930	2.030	172.3

#1: $-x, -y, -z + 1$, #2: $-x + 1, -y, -z + 1$ Table 3 CH/ π interactions(Å, °)

C-H	CgI	C...CgI	H...CgI	C-H...CgI
C117-H1171	1	3.898(2)	3.122	137.0
C117-H1172	2	3.523(2)	2.959	117.7

Cg is the centroid of rings in the indole system: Cg1 five-membered ring and Cg2 six-membered ring

Fig. 2 ORTEP view of the molecular structure of (a) lidocaine, (b) indomethacin I and (c) indomethacin II, showing the atom-labeling scheme, with the hydrogen atoms excluded. Thermal ellipsoids are drawn at the 50% probability level.

crystallographically independent indomethacin molecules (designated here as I and II). The proton of the carboxyl group of indomethacin II was transferred to an amino group of lidocaine, as shown in Fig. 3. Such proton transfer was observed in the crystal structure of lidocaine hydrochloride monohydrate.⁴ The two indomethacin molecules differ from

Fig. 3 Proton-transfer from a carboxy group of indomethacin II to an amino group of lidocaine. Dotted line shows a hydrogen bond.

each other in their conformation; the torsion angles C102-C103-C118-C119 and C202-C203-C218-C219 are $-91.4(2)^\circ$ and $50.1(3)^\circ$, respectively. These torsion angles also differ from that of γ -indomethacin ($100.1(2)^\circ$ and 99.9°)^{5,6} and of α -indomethacin ($90.4(7)^\circ$, $-93.9(7)^\circ$ and $-72.1(7)^\circ$).⁷ The intermolecular hydrogen bonds were observed, as shown in Table 2. The amide group (N1-H1) of the lidocaine cation formed a hydrogen bond with the carboxyl group (O203) of indomethacin II (anion form). The carboxyl group (O103-H103) of indomethacin I formed a hydrogen bond with the carbonyl group (O204) of indomethacin II. The amino group (N2-H2) formed a hydrogen bond with a carbonyl group (O1) of the adjacent lidocaine cation. The carbonyl group of a lidocaine cation is dimerized through N2-H2...O1ⁱ and O1...H2ⁱ-N2ⁱ hydrogen bonds, related by the symmetry operator of (i) $-x+1, -y, -z+1$, leading to a graph-set motif of $R_3^2(10)$. As well as hydrogen bonds, CH/ π interactions⁸ were observed, as shown in Table 3. The distance between the hydrogen atom (H1172) and the centroid of ring (Cg2) was 2.96 Å, and the distance between (H1171) and the centroid of ring (Cg1) was 3.12 Å. In summary, the intermolecular hydrogen bonds of type N-H...O and O-H...O and CH/ π interactions help to stabilize the crystal structure.

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