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CRYSTAL STRUCTURE OF CYTIDINE-SALICYLIC ACID COMPLEX

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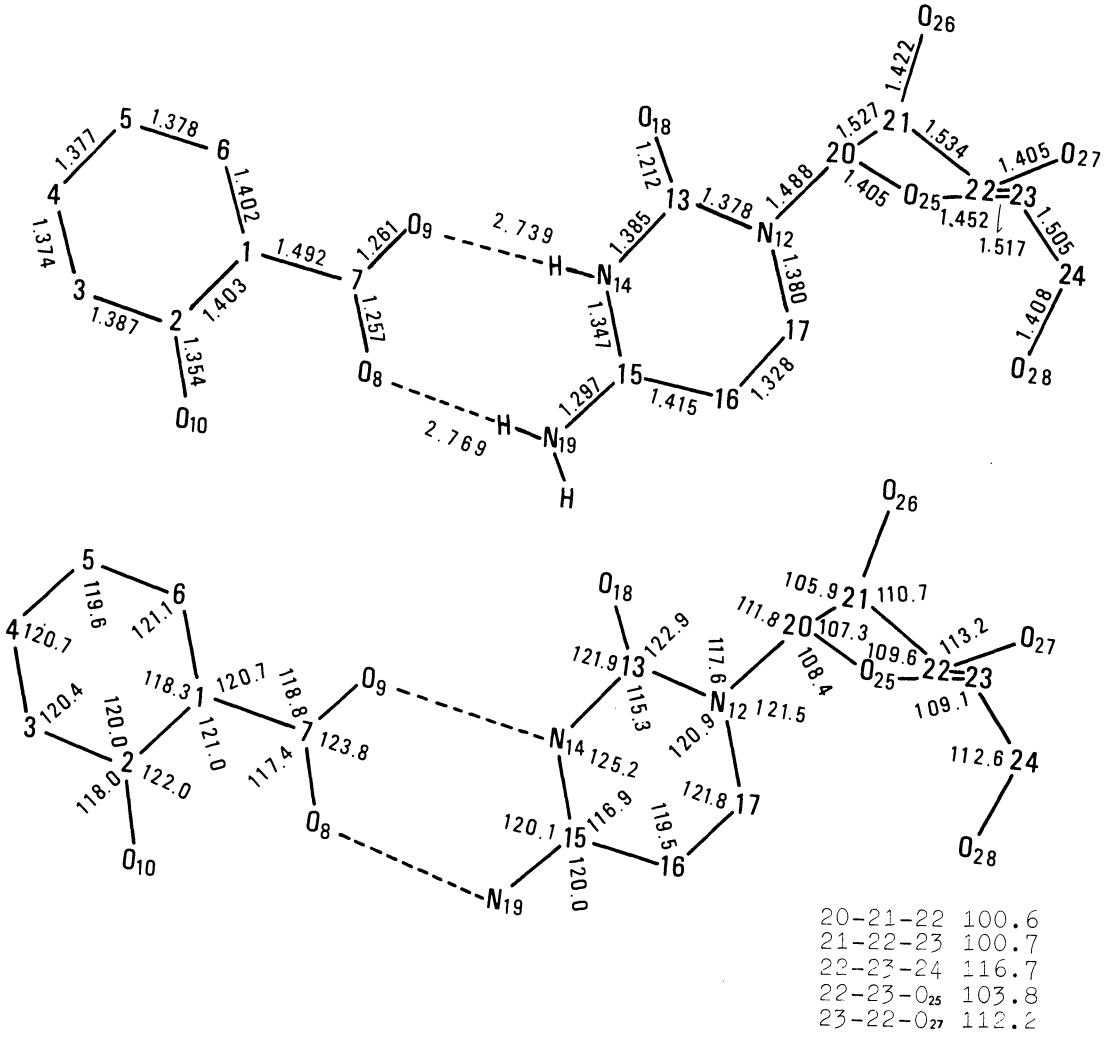
Crystal and molecular structure of cytidine-salicylic acid complex has been determined by X-ray diffraction methods and refined by block diagonal least-squares technique to the R-index of 4.7%. Hydrogen bonds in the complex are formed between the imidine and carboxyl groups.

Salicylic acid and cytidine, one of the representative nucleosides, have been found to form a complex in the crystalline state. Salicylic acid and its derivatives have long been known as pharmaceuticals because of their strong physiological activity. We have reported the complex forming ability of cytosine and adenine with organic acids wherein many of these acids can form complexes by means of hydrogen bonding and ionic forces[1-3]. However, complex forming ability of adenosine or cytidine with such acids was found to be fairly low. The present paper describes the crystal structure of the cytidine-salicylic acid complex which may be one of the best examples in this series for studying intermolecular hydrogen bonding schemes of nucleoside-organic acid molecules.

Equivalent moles of cytidine and the organic acid were dissolved in 90% aqueous ethanol. After standing for several days in a refrigerator, crystals were deposited from the solution. The complex formation was confirmed by means of a powder diffractometer in the same manner as described in the previous paper. Nicely formed parallelepiped complex crystals were then selected for single crystal analysis. The cell dimensions are $a = 9.246$, $b = 7.199$, $c = 7.141$ Å, $\alpha = 102.4$, $\beta = 114.8$, $\gamma = 73.5^{\circ}$; the crystals are triclinic and belong to the space group P1 or $P\bar{1}$. The density of the crystals measured by the floatation method in a mixture of tetrachloromethane and cyclohexane is 1.530g/cm^3 and its calculated

Fig. 2. Bond lengths and angles of cytidine-salicylic acid complex



Conspicuous intermolecular hydrogen bonds are formed between the imidine group in cytidine and the carboxyl group in salicylic acid. This hydrogen bonding scheme is the same as that in the cytosine-resorcylic acid (1:1) complex dihydrate[3] or the cytosine - N benzoylglycine complex monohydrate[2]. In these cases, the proton of the carboxyl group was transferred to the

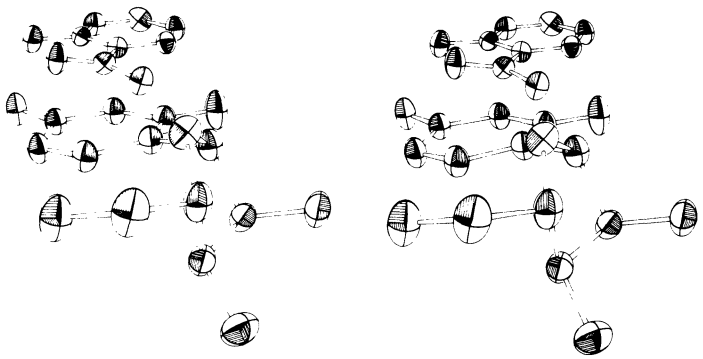
Table 1. Atomic parameters of cytidine-salicylic acid complex

Name	x/a	y/b	z/c
C 1	0.0024	1.0070	0.0082
C 2	-0.1202	1.1733	-0.0590
C 3	-0.2832	1.1648	-0.1335
C 4	-0.3256	0.9920	-0.1506
C 5	-0.2074	0.8260	-0.0888
C 6	-0.0449	0.8339	-0.0075
C 7	0.1786	1.0120	0.0878
O 8	0.2126	1.1608	0.0652
O 9	0.2843	0.8681	0.1721
O10	0.0851	1.3454	-0.0524
N12	0.8773	0.7078	0.4007
C13	0.7157	0.7011	0.3353
N14	0.6055	0.8780	0.2951
C15	0.6453	1.0506	0.3219
C16	0.8173	1.0510	0.4077
C17	0.9230	0.8833	0.4403
O18	0.6716	0.5513	0.3109
N19	0.5317	1.2061	0.2684
C20	0.9996	0.5193	0.4245
C21	1.0687	0.4632	0.6449
C22	1.2171	0.5575	0.7451
C23	1.2788	0.5128	0.5706
C24	1.3868	0.6383	0.5777
O25	1.1306	0.5400	0.3852
O26	1.1192	0.2565	0.6273
O27	1.3350	0.4782	0.9266
O28	1.3134	0.8384	0.5885

value is 1.539g/cm^3 if Z = 1. Therefore, the space group was uniquely determined as being P1 because the crystal contains the cytidine molecule having an asymmetric carbon. A total 1699 independent reflections were collected within 50° of 2θ value (MoKα) using the ω-2θ scanning technique.

Two sharpened (B=3.0 and 6.0) and a normal Patterson functions were calculated. In the case of B=3.0, interatomic vector peaks of salicylic acid and the basic part in the cytidine molecule were found, in which the intermolecular hydrogen bonding distances were in the appropriate range. From the first three dimensional Fourier map using the parameters derived from the Patterson map, the rest atoms, the sugar moiety in the cytidine molecule and the phenolic oxygen atom in salicylic acid could be recognized. Four cycles of the block-diagonal least-squares refinement reduced the R-index to 11.9%. The D-synthesis was then computed, and all hydrogen atoms were clearly found. Five more cycles of least-squares procedure using anisotropic temperature factors for the heavy atoms and isotropic for hydrogen atoms further reduced the R-index to 4.7%. The atomic parameters for heavy atoms are shown in Table 1. The bond distances are shown in Fig. 2 and the maximum standard deviations for carbon, nitrogen and oxygen atoms are 0.007, 0.005 and 0.005 Å respectively. In Fig. 1, the structure of the cytidine-salicylic acid complex is shown in stereoscopic perspective.

Fig. 1. Stereoscopic view of the cytidine-salicylic acid complex



imidine group forming a carboxylate anion and a cytosidyl cation. The hydrogen-bond distances are 2.739 and 2.769 Å. Hydrogen bondings in sugar moiety in usual nucleosides may be thought as playing an important role in forming these crystals. However, in this complex, somewhat long intermolecular hydrogen bonds are observed between the sugar hydroxy groups and the carboxylate anion in salicylic acid, i.e., 2.920, 3.000, and 3.051 Å for O(9)....HO(28), O(8)....HO(26), and O(9)....HO(27), respectively. Another weak hydrogen bonding distance is 3.019 Å for O(18)....HN(19). The intermolecular distance N(19)....O(26) is slightly short (3.065 Å) though they may not be hydrogen-bonded. As shown in Fig. 2, the bond lengths and angles are almost in the usual range of values and are similar to those found in the (1:1)-cytosine-resorcylic acid complex dihydrate[3] except for the sugar moiety.

From the results of this analysis, we expect that in some biological process the intermolecular interaction between cytidine and other acidic organic molecules probably is present in the form of the above mentioned hydrogen bonding scheme.

References

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3) to be published.

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