Studies on Intermolecular Complex Formation. IV. Crystal Structure of Cytosine-Resorcylic acid 2 : 1 Complex monohydrate

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The crystal and molecular structure of a cytosine and resorcylic acid complex monohydrate has been solved by the direct method. The molecular complex is formed by two moles of cytosine and one mole of resorcylic acid. The crystals are monoclinic, with a space group of $P2_1/n$, and with $a=8.335$, $b=20.605$, $c=10.159$ Å, and $\beta=95.5°$. The final R-factor for 1820 reflections is 0.100. Resorcylic acid is hydrogen-bonded to one of the cytosine molecules with one hydrogen bond, and to the two cytosine molecules with one hydrogen bond, and the two cytosine molecules are associated with three hydrogen bonds in a system similar to that of the guanine-cytosine hydrogen bond in the Watson-Crick model.

Recently the biological significance and drug activity of several molecular complexes have been investigated.[1-26] Since we surveyed a number of organic compounds interacting with nucleotide bases, some molecules with specific atomic constellations have been found to form complexes with cytosine and/or adenine.[25] Some of those complex structures have already been solved by means of single-crystal analysis. Herein we wish to describe the crystal structure of the resorcylic acid–cytosine monohydrate complex.

Experimental

Cytosine and resorcylic acid were dissolved in 70% aqueous ethanol at room temperature and crystallized as single crystals after the solution had been cooled in a refrigerator. The mass spectrometry of this complex revealed that both components were present. Preliminary oscillation and Weissenberg photographs showed that the crystals belong to the monoclinic system, space group of $P2_1/n$, and the density of the crystals was determined to be $1.34\,g\cdot cm^{-3}$ by the flotation method. The lattice parameters are $a=8.335$ (10), $b=20.605(18)$, $c=10.159(11)$ Å, and $\beta=95.5$ (1)°. The results of the elemental analysis and the calculation of the molecular weight from the cell constants and the measured density were compatible with a 2 : 1 molar ratio for cytosine and resorcylic acid with one water molecule.

Three-dimensional intensity data were collected on a Rigaku Denki auto-diffractometer up to a 2θ limit of 60°, using Mo Kα radiation with the $2\theta/\theta$ scanning mode at a scan speed of $2°\ min^{-1}$. The intensities were reduced to structure factors by correcting for the Lorentz-polarization factors using a program attached to this equipment. Because of the small size of the crystals, no corrections were made for absorption. The 1830 independent observed structure factors thus obtained were used for structure analysis.

Structure Analysis

The normalized structure factors, E, were calculated from the observed structure factors, F, which were put on an absolute scale by the use of Wilson's statistics.[27] A trial structure was obtained using the symbolic addition procedure. The reflections of 267 with $|E|$ values greater than 1.30 were obtained using the $\Sigma 2$ of Hauptman and Karle.[28] Three linear independent reflections (5,6,−6; 7,0,1; 0,5,2), each with a large number of interactions, were assigned to be +, three other reflections (1,15,5; 2,7,7; 7,1,2) were denoted by the symbols A, B, and C. After the symbolic addition procedure, the A, B, and C symbols are uniquely determined to be all −. A Fourier synthesis using these signs for the E-values showed over 38 large peaks. From a knowledge of the geometry of the molecules, the peaks corresponding to 27 atoms could easily be recognized. The initial structure factor calculations for the 27 atoms gave an R-factor of 0.38, with an isotropic temperature factor. After five cycles of block-diagonal least-squares refinements, the R-factor was reduced to 0.24. The remaining water molecules

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were found from the subsequent Fourier synthesis. Then difference synthesis was carried out in order to obtain the positions of the hydrogen atoms, which appeared satisfactorily on the map. The eight subsequent refinement cycles used the anisotropic temperature factor for C, N and O and the isotropic factor for H gave a final R-factor of 0.100 for all the observed reflections.

Table 1. Fractional atomic coordinates in cytosine–resorcylic acid (2:1) complex monohydrate

Atom	x/a	y/b	z/c
C (1)	−0.0718	0.2165	0.2923
C (2)	−0.1980	0.1835	0.2167
C (3)	−0.3507	0.1920	0.2570
C (4)	−0.3790	0.2311	0.3629
C (5)	−0.2545	0.2617	0.4284
C (6)	−0.1017	0.2573	0.3974
C (7)	−0.1633	0.1437	0.1010
O (8)	−0.0188	0.1361	0.0801
O (9)	−0.2803	0.1192	0.0307
O (10)	−0.4772	0.1602	0.1881
O (11)	0.0825	0.2100	0.2616
N (12)	0.4376	0.0077	−0.2265
C (13)	0.3088	−0.0174	−0.3041
N (14)	0.1579	−0.0070	−0.2691
C (15)	0.1375	0.0303	−0.1633
C (16)	0.2683	0.0580	−0.0844
C (17)	0.4158	0.0448	−0.1190
C (18)	0.3332	−0.0511	−0.4013
N (19)	−0.0107	0.0426	−0.1370
N (20)	−0.3622	−0.0960	−0.4579
C (21)	−0.2391	−0.0623	−0.3867
N (22)	−0.0884	−0.0719	−0.4261
C (23)	−0.0552	−0.1086	−0.5294
C (24)	−0.1874	−0.1435	−0.5995
C (25)	−0.3361	−0.1343	−0.5604
O (26)	−0.2616	−0.0274	−0.2936
N (27)	0.0901	−0.1135	−0.5596
W (28)	−0.2699	0.1634	−0.2403
H (4)	−0.486	0.238	0.383
H (5)	−0.247	0.282	0.510
H (6)	0.015	0.255	0.430
H (10)	−0.420	0.139	0.108
H (11)	0.078	0.188	0.200
A H (19)	−0.091	0.014	−0.166
B H (19)	−0.018	0.063	−0.054
H (16)	0.252	0.083	−0.017
H (17)	0.533	0.070	−0.098
H (12)	0.553	0.007	−0.323
A H (27)	0.171	−0.096	−0.499
B H (27)	0.112	−0.081	−0.591
H (24)	−0.176	−0.164	−0.676
H (25)	−0.436	−0.145	−0.606
H (20)	−0.466	−0.084	−0.429
H (22)	0.013	−0.058	−0.374
A W (28)	−0.243	0.195	−0.239
B W (28)	−0.271	0.159	−0.136

Results and Discussion

The final atomic parameters are given in Tables 1 and 2 and the corresponding structure factors, in Table 3. The bond lengths and angles are shown in Table 4, while Fig. 1 shows a diagram of the atomic notation. The crystal structure and hydrogen-bond system of the molecules are shown in Fig. 3, while a stereographic view is illustrated by the ORTEP plot in Fig. 2. Some important intermolecular atomic distances are listed in Table 5. The average estimated standard deviations for bond distances are: for C–C within 0.020 Å; for C–N and C–O within 0.013 Å; and for bond angles, 1.0° for all the heavy atoms.

Description of Crystal and Molecular Structure. As is shown in the stereographic plot (Fig. 2), two approximately coplanar cytosine (A and B) molecules are coupled to each other, with two NH···O (2.889, 2.778 Å) and one NH···N (2.815 Å) hydrogen bonds forming

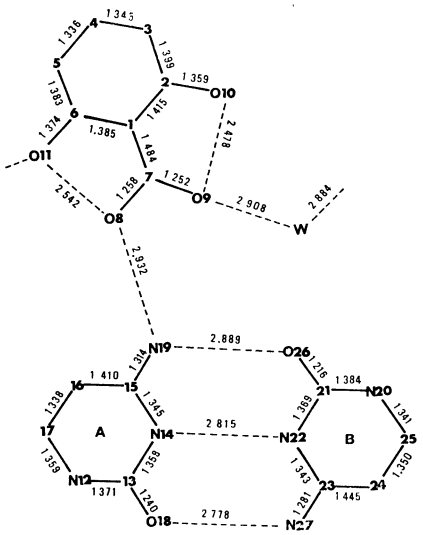

Fig. 1(a). Interatomic distances in cytosine-resorcylic acid (2 : 1) complex monohydrate.

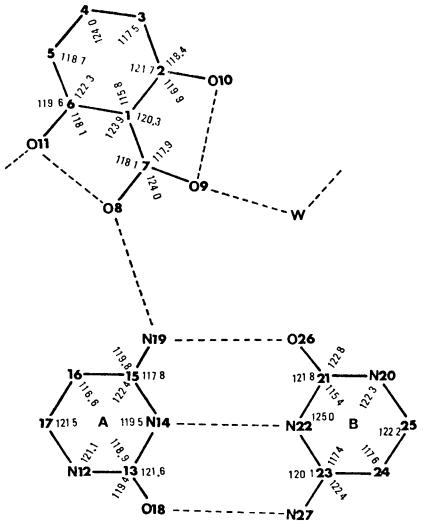

Fig. 1(b). Interbond angles in cytosine-resorcylic acid (2 : 1) complex monohydrate.

TABLE 2(a). ANISOTROPIC THERMAL PARAMETERS IN CYTOSINE-RESORCYLIC ACID (2:1) COMPLEX MONOHYDRATE
The thermal parameters are given in the form $T=\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+2B_{12}hk+2B_{13}hl+2B_{23}kl)]$.

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C (1)	0.01679	0.00145	0.00928	0.00104	0.00311	0.00006
C (2)	0.01258	0.00158	0.00565	0.00033	0.00259	−0.00021
C (3)	0.01630	0.00181	0.00854	0.00089	0.00124	0.00054
C (4)	0.02185	0.00304	0.01423	0.00260	0.00921	0.00176
C (5)	0.02685	0.00222	0.01003	−0.00030	0.00570	0.00051
C (6)	0.02183	0.00245	0.01016	−0.00050	0.00438	−0.00064
C (7)	0.01521	0.00142	0.00740	−0.00055	0.00170	0.00059
O (8)	0.01787	0.00286	0.00938	−0.00128	0.00298	−0.00145
O (9)	0.01753	0.00273	0.00888	−0.00133	−0.00007	−0.00074
O (10)	0.01716	0.00371	0.01327	0.00047	0.00128	0.00168
O (11)	0.01831	0.00263	0.01141	−0.00195	0.00269	−0.00141
N (12)	0.00677	0.00184	0.00666	−0.00018	0.00039	−0.00062
C (13)	0.00928	0.00148	0.00689	−0.00035	0.00125	−0.00032
N (14)	0.00636	0.00143	0.00626	−0.00029	0.00041	−0.00063
C (15)	0.00877	0.00180	0.00513	0.00026	0.00057	0.00004
C (16)	0.01011	0.00220	0.00684	0.00070	0.00175	−0.00051
C (17)	0.01218	0.00189	0.00755	−0.00057	−0.00192	−0.00069
C (18)	0.00709	0.00195	0.00588	−0.00044	0.00100	−0.00075
N (19)	0.00760	0.00228	0.00627	−0.00076	0.00028	−0.00039
N (20)	0.00609	0.00223	0.00783	−0.00125	0.00075	−0.00112
C (21)	0.00886	0.00174	0.00649	−0.00006	0.00114	0.00009
N (22)	0.00784	0.00168	0.00414	−0.00007	0.00028	−0.00071
C (23)	0.00839	0.00137	0.00496	0.00042	0.00102	0.00015
C (24)	0.01184	0.00152	0.00656	0.00032	0.00091	−0.00054
C (25)	0.01001	0.00157	0.00648	−0.00033	−0.00055	−0.00066
O (26)	0.00859	0.00252	0.00884	−0.00003	0.00128	−0.00150
N (27)	0.00817	0.00179	0.00682	−0.00023	0.00072	0.00005
W (28)	0.02303	0.00306	0.01034	0.00141	0.00380	−0.00026

TABLE 2(b). ISOTROPIC THERMAL PARAMETERS OF HYDROGEN IN CYTOSINE–RESORCYLIC ACID (2:1) COMPLEX MONOHYDRATE

Atom	B_{iso}	Atom	B_{iso}	Atom	B_{iso}
H (4)	5.77	B H (19)	4.20	H (24)	4.70
H (5)	4.59	H (16)	3.08	H (25)	2.96
H (6)	9.09	H (17)	4.14	H (20)	3.06
H (10)	4.46	H (12)	10.08	H (22)	5.01
H (11)	5.30	A H (27)	6.74	A W (28)	1.48
A H (19)	4.82	B H (27)	3.31	B W (28)	7.51

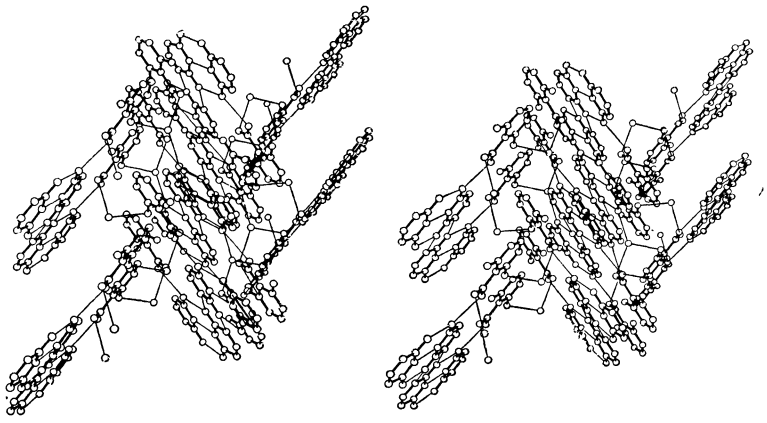

Fig. 2. Stereoscopic view of the packing and hydrogen bonding. Molecular bonds are drawn thick and hydrogen bonds thin.

TABLE 3. STRUCTURE FACTOR DATA (×10) FOR THE OBSERVED REFLECTIONS

L	FO	FC
K= 1, H= 0		
1	368	374
2	232	265
3	294	308
4	217	244
6	165	184
7	326	329
8	96	106
K= 2, H= 0		
1	642	639
2	145	168
3	91	90
4	315	332
5	160	149
6	64	84
8	73	33
9	117	115
10	82	38
11	111	82
K= 3, H= 0		
2	120	132
3	201	240
4	241	250
5	295	255
6	234	241
7	269	246
8	90	80
9	145	136
K= 4, H= 0		
1	545	592
2	1663	1642
3	463	440
5	203	203
8	153	178
9	97	113
K= 5, H= 0		
1	551	574
2	2596	2628
3	320	287
4	514	496
5	229	237
8	293	290
9	88	130
K= 6, H= 0		
1	644	644
2	1607	1590
3	597	602
4	595	583
5	409	407
7	110	79
9	94	79
K= 7, H= 0		
0	20	0
1	387	411
2	637	648
3	172	169
4	85	68
7	71	56
K= 8, H= 0		
1	347	310
2	441	447
3	90	87
4	119	196
6	63	32
7	103	100
8	136	157
9	182	196
11	86	88
K= 9, H= 0		
1	242	230
3	340	309
4	616	624
5	360	333
6	76	41
7	93	65
9	20	32
10	77	84
11	84	108
K= 10, H= 0		
1	84	82
2	384	370
3	450	449
4	957	948
6	152	144
10	125	154
K= 11, H= 0		
1	339	307
2	125	116
3	144	130
4	738	714
5	156	136
6	138	97
7	102	93
9	102	86
K= 12, H= 0		
1	79	72
2	237	240
3	271	286
4	135	193
5	154	161
10	19	12
K= 13, H= 0		
2	95	103
3	148	142
4	96	68
6	82	129
7	116	138
K= 14, H= 0		
2	82	111
5	90	102
6	162	230
7	181	172
10	83	77
K= 15, H= 0		
0	15	0
2	103	115
3	176	166
4	224	196
6	382	413
K= 16, H= 0		
1	236	242
2	137	141
5	83	109
6	205	220
K= 17, H= 0		
2	72	98
5	119	122
6	76	104
7	141	124
K= 18, H= 0		
4	109	88
K= 19, H= 0		
1	95	86
2	78	69
8	124	151
K= 20, H= 0		
1	77	82
2	15	38
5	112	102
6	83	95
9	18	28
K= 21, H= 0		
3	90	83
7	81	82
8	139	134
9	15	27
K= 22, H= 0		
5	104	62
K= 24, H= 0		
1	84	64
4	13	30
K= 25, H= 0		
1	103	78
K= 0, H= 1		
-7	336	364
-5	391	391
-3	851	802
1	867	874
3	675	665
5	271	297
7	143	141
9	205	201
11	91	77
K= 1, H= 1		
-12	88	60
-8	96	84
-7	332	311
-6	153	184
-5	413	388
-4	404	361
-2	225	215
0	343	357
1	70	55
2	845	844
3	173	178
6	85	73
7	137	138
9	160	172
K= 2, H= 1		
-11	111	99
-9	94	88
-7	142	150
-4	992	959
-3	105	84
-2	173	169
0	143	156
1	116	121
2	763	750
3	614	630
4	217	211
5	110	99
6	63	28
8	137	135
K= 3, H= 1		
-11	96	121
-9	85	107
-7	199	185
-6	391	408
-5	173	125
-3	263	251
-2	250	256
0	313	308
1	1064	1112
3	118	121
4	228	201
5	131	107
6	196	206
7	89	105
10	127	149
K= 4, H= 1		
-11	91	102
-9	143	147
-8	103	67
-7	317	296
-6	319	311
-5	74	93
-4	250	254
-3	130	155
-2	446	447
0	1009	1039
1	524	527
2	483	454
3	245	232
4	97	75
5	136	135
6	81	84
7	136	149
9	131	143
11	79	53
K= 5, H= 1		
-9	77	102
-8	81	88
-7	134	154
-6	189	190
-5	455	453
-4	386	392
0	306	281
1	1161	1137
2	530	522
3	442	445
4	160	147
5	106	114
7	123	133
K= 6, H= 1		
-7	71	61
-6	186	153
-5	358	324
-4	118	142
-3	245	224
-2	536	498
0	354	348
1	493	536
2	124	148
3	168	161
4	155	176
5	134	168
6	81	101
11	84	66
12	79	58
K= 7, H= 1		
-9	163	169
-5	374	367
-4	151	157
-3	163	196
-2	773	740
-2	637	740
2	236	220
3	320	299
4	522	514
5	222	253
6	65	112
7	192	183
8	186	183
K= 8, H= 1		
-11	84	64
-9	116	131
-8	176	222
-6	165	180
-5	364	306
-4	198	212
-3	223	217
-2	110	102
0	177	159
1	300	320
2	185	136
3	123	163
4	86	118
6	135	135
8	296	292
9	68	41
11	123	91
K= 9, H= 1		
-8	98	98
-7	84	87
-6	150	124
-5	199	175
-4	80	68
-3	242	273
0	288	289
2	160	177
4	381	391
5	226	217
7	86	83
8	95	62
K= 10, H= 1		
-9	135	149
-8	79	78
-6	89	57
-4	70	75
-3	713	743
-2	630	623
1	188	200
2	159	171
3	723	716
4	349	347
5	15	14
7	126	112
9	89	95
11	94	79
K= 11, H= 1		
-4	136	130
-3	215	198
-2	126	127
0	178	214
2	165	146
3	571	589
7	121	103
10	22	20
K= 12, H= 1		
-7	71	72
-5	124	113
-4	78	31
-3	435	444
0	261	248
1	134	149
2	64	70
3	90	72
5	67	44
6	421	454
K= 13, H= 1		
-10	119	115
-7	100	111
-4	145	167
-3	96	53
-2	84	88
0	188	157
1	119	77
3	86	130
4	182	155
5	203	209
6	286	262
8	17	14
12	83	66
K= 14, H= 1		
-5	157	194
-3	233	217
-2	192	174
-2	190	174
1	98	115
2	123	99
3	156	182
6	23	16
K= 15, H= 1		
-7	71	70
-5	98	106
0	135	129
5	456	454
6	180	202
11	108	97
12	90	45
K= 16, H= 1		
-5	196	199
-4	110	125
-3	82	88
-2	106	101
1	76	102
3	125	133
4	85	119
5	236	263
6	86	88
K= 17, H= 1		
-4	72	38
-3	187	182
0	101	99
2	136	151
3	210	201
4	211	217
5	173	207
6	89	49
11	92	62
K= 18, H= 1		
-2	98	65
1	165	188
2	115	111
3	78	40
4	292	277
5	105	97
7	96	120
K= 19, H= 1		
-6	87	57
1	94	106
3	123	131
4	164	153
7	109	99
K= 20, H= 1		
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0	105	89
3	109	104
7	107	131
8	127	141
K= 21, H= 1		
0	104	126
3	76	86
7	127	153
K= 22, H= 1		
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1	248	261
2	192	227
7	121	127
K= 23, H= 1		
2	169	188
5	10	43
K= 24, H= 1		
1	78	53
2	101	96
3	85	68
K= 25, H= 1		
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1	123	116
K= 26, H= 1		
3	108	74
4	12	19
K= 0, H= 2		
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-6	337	333
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2	379	424
4	94	57
8	106	54
10	280	311
K= 1, H= 2		
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-8	163	152
-7	206	163
-5	72	89
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-2	596	598
0	122	99
2	286	268
3	1164	1109
4	189	214
5	83	100
6	64	76
8	83	137
9	240	249
10	77	111
K= 2, H= 2		
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-11	78	58
-8	112	76
-7	128	115
-6	71	66
-5	246	229
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-3	486	467
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1	184	164
2	355	376
3	158	151
4	118	111
5	319	375
6	119	143
7	77	92
8	131	124
9	345	374
10	277	307
11	176	215
12	94	81
K= 3, H= 2		
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-8	126	89
-7	188	197
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-4	69	71
-2	193	178
0	198	178
1	281	264
2	270	249
3	591	578
4	295	273
5	430	420
6	117	151
8	175	166
9	292	300
10	145	147
11	238	268
K= 4, H= 2		
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-5	253	220
-4	208	219
-2	71	81
1	1075	1014
2	154	156
3	104	84
5	221	206
7	98	99
8	416	429
9	110	101
10	74	45
11	118	140
K= 5, H= 2		
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-7	97	76
-6	131	116
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-3	101	120
-2	184	133
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1	157	156
2	221	263
3	217	194
4	68	7
5	182	181
6	80	28
8	229	257
9	103	114
11	95	86
12	111	119
K= 6, H= 2		
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-9	103	61
-8	134	141
-5	88	94
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0	206	208
1	981	957
2	279	290
4	125	180
5	371	373
6	99	87
7	305	313
8	94	77
K= 7, H= 2		
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-3	410	404
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1	706	678
2	138	122
4	227	231
5	154	140
7	597	619
8	191	199
13	129	134
K= 8, H= 2		
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-9	117	117
-6	110	68
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1	453	436
2	203	190
5	235	228
6	268	252
7	196	170
8	190	198
9	51	41
11	82	54
13	106	112
K= 9, H= 2		
-9	77	36
-7	76	127
-4	122	122
-3	159	175
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1	354	367
2	142	116
3	141	154
4	195	208
6	483	501
7	148	163
8	156	155
K= 10, H= 2		
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-6	129	88
-5	135	107
-4	153	137
-3	126	70
-2	163	195
0	164	184
1	102	102
3	171	172
6	288	313
7	193	213
9	127	119
K= 11, H= 2		
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-5	107	95
-3	120	92
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1	101	87
2	140	161
3	254	271
5	245	235
6	156	187
8	98	99
K= 12, H= 2		
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-8	110	108
-7	101	110
-6	120	123
-3	75	65
-2	264	240
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1	93	57
5	529	559
7	102	88
12	109	57
K= 13, H= 2		
-8	136	129
-7	101	96
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1	121	109
3	108	92
4	241	196
5	284	249
6	297	274
7	124	143
K= 14, H= 2		
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2	108	116
4	388	414
5	17	24
6	94	87
8	17	39
9	138	122
10	23	16
K= 15, H= 2		
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-4	101	73
4	270	277
5	182	183
7	143	129
8	21	8
K= 16, H= 2		
-11	93	42
-7	88	93
-4	101	79
-3	234	248
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3	204	201
4	130	138
7	111	93
K= 17, H= 2		
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1	235	235
3	296	298
4	80	101
K= 18, H= 2		
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-6	155	154
-3	124	149
0	76	88
1	115	121
2	129	127
3	201	219
4	158	143
5	84	107
K= 19, H= 2		
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-5	104	104
-4	93	96
0	13	34
2	245	244
K= 20, H= 2		
-9	116	66
-3	90	61
2	131	148
3	174	164
7	102	60
K= 21, H= 2		
-5	109	113
2	110	126
K= 22, H= 2		
1	186	171
3	135	137
K= 23, H= 2		
-5	109	81
-3	95	105
1	130	109
K= 24, H= 2		
-4	97	110
0	140	116
2	89	105
3	91	81
K= 25, H= 2		
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0	107	106
1	94	76
K= 26, H= 2		
0	84	57
K= 0, H= 3		
-11	161	160
-7	260	277
-3	828	841
1	298	314
3	264	278
5	565	564
K= 1, H= 3		
-10	86	75
-9	119	84
-7	74	66
-4	254	195
-3	439	428
-2	376	356
0	385	418
2	615	616
3	67	40
5	106	108
8	76	84
9	94	118
K= 2, H= 3		
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-7	76	81
-6	90	53
-4	156	172
-3	308	287
-2	388	381
0	167	183
1	147	156
2	348	332
3	362	378
4	530	545
6	136	114
8	189	199
9	101	115
10	115	114
K= 3, H= 3		
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-10	147	146
-8	118	110
-6	134	84
-4	388	382
-3	205	206
-2	63	37
0	60	8
1	68	54
2	116	116
3	123	137
4	440	427
5	97	124
6	125	129
7	85	90
8	86	40
10	213	237
K= 4, H= 3		
-11	128	119
-8	106	73
-4	140	141
-2	475	452
0	67	82
1	249	269
2	249	248
3	240	235
4	392	411
5	78	78
6	206	202
8	106	119
11	76	54
K= 5, H= 3		
-9	173	179
-6	71	85
-4	114	113
-3	256	253
-2	14	32
0	419	385
1	240	250
2	240	263
3	508	504
4	253	275
7	187	216
8	80	97
10	144	146
K= 6, H= 3		
-11	106	98
-6	102	61
-5	515	515
-3	300	318
-2	180	200
1	390	411
2	452	458
3	170	148
4	215	218
5	191	211
6	182	179
10	82	71
11	130	150
K= 7, H= 3		
-9	127	138
-6	90	106
-5	144	165
-4	227	222
0	393	395
2	476	438
3	129	145
8	219	228
11	87	55
K= 8, H= 3		
-12	102	81
-9	174	167
-5	79	64
-4	164	178
-3	75	84
-2	98	79
0	68	85
1	197	197
2	339	309
3	74	89
6	109	105
7	94	122
8	138	124
K= 9, H= 3		
-9	168	129
-6	0	193
-5	98	89
-3	83	77
-2	141	158
0	97	70
1	305	274
4	93	67
6	78	103
8	220	202
K= 10, H= 3		
-8	101	105
-6	82	46
0	161	138
1	230	221
2	113	117
3	129	116
4	76	41
6	198	243
8	149	142
K= 11, H= 3		
-10	75	14
-7	235	242
-3	71	66
0	329	307
1	414	408
2	139	151
5	80	59
6	234	200
9	114	116
K= 12, H= 3		
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-10	76	19
-9	81	52
-6	190	201
-5	118	138
-3	157	146
-2	101	90
0	274	256
2	179	164
3	131	121
6	143	124
7	110	109
K= 13, H= 3		
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-3	71	93
0	271	283
1	15	36
6	229	227
8	87	99
K= 14, H= 3		
-7	162	104
-5	74	38
-1	115	82
2	79	38
6	190	177
K= 15, H= 3		
-7	83	77
-5	127	124
-1	88	133
3	84	57
6	98	107
8	99	104
K= 16, H= 3		
-7	108	96
-5	80	73
-2	110	107
-1	163	163
4	72	29
K= 17, H= 3		
-10	85	49
-4	86	86
-3	89	98
-2	200	191
4	256	224
K= 18, H= 3		
-9	95	57
-5	79	71
-4	74	55
-2	131	135
-1	77	38
2	86	61
3	96	79
4	136	136
K= 19, H= 3		
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-5	133	121
-1	19	37
4	102	99
K= 20, H= 3		
-10	146	119
-4	94	99
-3	115	117
4	110	102
5	90	83
K= 21, H= 3		
-9	83	33
-2	20	37
K= 22, H= 3		
-7	86	49
2	151	142
K= 23, H= 3		
-6	22	15
-4	81	106
7	16	19
K= 0, H= 4		
-10	186	224
-8	116	100
-6	68	90
-4	335	323
-2	225	193
0	88	74
2	342	389
4	324	324
6	121	94
K= 1, H= 4		
-11	80	111
-7	274	299
-5	86	52
-4	240	204
-1	899	852
1	107	98
3	415	416
4	67	63
5	111	157
6	100	88
K= 2, H= 4		
-10	86	81
-9	190	179
-8	176	145
-7	208	203
-6	78	112
-4	163	149
-3	454	435
-1	20	63
0	112	95
1	93	124
2	227	209
3	209	178
4	64	60
5	180	166
K= 3, H= 4		
-10	53	48
-9	156	183
-8	179	187
-7	197	183
-6	119	151
-5	115	107
-4	96	105
-1	387	362
0	144	137
1	190	217
3	238	219
4	222	261
5	291	282
6	125	138
K= 4, H= 4		
-9	129	110
-8	231	210
-7	126	125
-5	162	138
-4	15	56
-3	498	482
-1	306	297
0	177	186
1	120	57
3	212	237
4	77	83
5	110	126
6	8	35
7	89	42
11	79	63
K= 5, H= 4		
-10	102	59
-9	257	262
-8	69	49
-5	149	176
-4	167	130
-3	401	425
0	213	212
1	572	572
4	211	223
5	111	96
6	121	112
7	81	96
K= 6, H= 4		
-7	160	128
-6	158	189
-5	334	335
-3	381	390
-1	281	299
0	218	256
2	124	142
3	82	64
4	79	88
5	79	53
6	119	147
K= 7, H= 4		
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-8	80	59
-7	158	160
-4	84	118
-3	82	93
-1	132	175
0	131	108
1	282	268
2	129	122
3	89	148
7	169	164
10	89	74
K= 8, H= 4		
-11	107	80
-7	166	164
-4	106	131
-3	61	62
-1	98	70
0	104	97
1	371	356
2	128	151
4	82	87
7	108	129
K= 9, H= 4		
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-7	131	149
-6	230	215
-5	101	86
-3	101	72
-1	119	122
0	359	333
1	86	93
3	129	127
7	99	132
10	92	69
K= 10, H= 4		
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-6	225	218
-5	217	230
-4	212	230
-1	227	196
0	312	319
1	84	42
2	257	245
3	83	72
5	73	85
9	73	82
K= 11, H= 4		
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-10	86	49
-5	275	307
1	156	188
4	71	49
8	141	135
9	95	89
10	13	37
K= 12, H= 4		
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-5	92	86
-3	68	56
-1	158	161
3	90	60
8	73	25
9	153	152
K= 13, H= 4		
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-6	74	67
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1	118	121
2	131	128
3	72	91
8	77	92
K= 14, H= 4		
-5	143	153
-4	129	137
-3	96	109
2	169	171
3	78	94
9	105	90
K= 15, H= 4		
-7	89	109
-6	113	91
-4	138	124
-3	71	86
2	120	151
4	88	79
8	94	72
K= 16, H= 4		
-3	87	89
2	110	132
6	73	58
7	126	127
K= 17, H= 4		
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-1	95	94
1	94	65
3	87	82
6	98	80
7	76	79
K= 18, H= 4		
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-3	92	73
0	114	67
K= 19, H= 4		
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-3	116	136
6	10	37
K= 20, H= 4		
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K= 22, H= 4		
-1	118	107
0	77	51
5	112	119
K= 23, H= 4		
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6	11	38
K= 24, H= 4		
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K= 26, H= 4		
3	98	70
K= 0, H= 5		
-7	552	491
-5	158	170
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1	131	112
9	97	70
K= 1, H= 5		
-9	85	65
-8	467	495
-7	109	117
-6	68	64
-5	112	144
-4	150	152
-1	106	89
0	182	177
1	125	100
2	261	251
3	115	106
4	141	116
6	91	81
K= 2, H= 5		
-10	120	145
-9	151	119
-8	353	338
-7	105	98
-5	125	149
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-3	83	71
-1	309	307
3	165	176
4	109	109
5	76	70
6	103	108
8	97	75
K= 3, H= 5		
-10	251	243
-8	295	277
-5	184	185
-4	246	229
-3	127	129
-1	141	106
1	170	160
5	81	89
6	75	100
K= 4, H= 5		
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-9	209	206
-7	129	145
-6	135	154
-5	134	107
-4	122	142
-3	208	218
-1	196	208
0	325	315
1	144	94
3	92	78
5	106	109
K= 5, H= 5		
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-10	151	167
-9	127	77
-7	122	126
-6	241	245
-5	250	232
-3	278	286
-1	136	132
0	92	87
1	361	389
2	194	198
4	95	99
7	90	73
10	78	68
K= 6, H= 5		
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-7	81	57
-6	592	583
-5	299	312
-1	79	85
0	491	491
1	191	205
3	88	23
7	81	43
K= 7, H= 5		
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-7	152	135
-6	480	467
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0	82	75
1	268	259
3	79	35
4	142	134
7	75	67
10	85	76
K= 8, H= 5		
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-9	102	112
-6	96	106
-5	140	102
-1	104	92
1	89	79
K= 9, H= 5		
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-3	99	77
-1	72	101
0	86	90
1	114	108
2	135	126
3	121	98
4	135	145
5	69	72
K= 10, H= 5		
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-11	94	71
-7	94	112
-5	148	145
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-3	200	222
-1	107	130
2	204	227
3	131	146
5	126	135
8	20	28
11	109	77
K= 11, H= 5		
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-5	94	98
-4	475	479
-3	219	215
1	112	91
2	169	191
3	148	170
5	69	73
8	109	77
K= 12, H= 5		
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-1	137	151
2	202	233
3	97	112
K= 13, H= 5		
-9	101	55
-5	131	127
-3	96	110
0	72	43
2	141	144
9	80	71
K= 14, H= 5		
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-5	101	131
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0	76	48
9	104	89
K= 15, H= 5		
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-6	74	53
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-1	150	161
3	128	123
5	89	105
9	106	116
K= 16, H= 5		
-8	87	41
9	80	45
K= 17, H= 5		
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5	98	59
K= 18, H= 5		
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0	106	116
1	99	77
7	100	87
K= 19, H= 5		
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-6	131	114
7	105	70
K= 20, H= 5		
7	145	134
K= 21, H= 5		
0	188	215
1	108	75
5	12	8
6	18	40
K= 22, H= 5		
0	150	158
6	18	53
K= 25, H= 5		
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K= 0, H= 6		
-8	84	104
-4	210	164
0	77	80
2	158	164
4	106	84
K= 1, H= 6		
-9	92	66
-8	160	153
-4	40	33
-1	166	184
0	93	78
1	112	103
2	285	335
8	111	136
11	0	15
K= 2, H= 6		
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-7	88	65
-3	103	86
-1	253	254
1	79	90
2	123	130
5	108	130
K= 3, H= 6		
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-8	99	101
-7	14	39
-6	113	114
-1	191	220
0	157	155
1	321	325
2	94	84
3	87	111
4	147	141
5	91	82
7	167	167
K= 4, H= 6		
0	152	138
1	181	197
2	8	8
3	124	104
4	114	133
6	110	108
K= 5, H= 6		
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-6	101	103
-4	20	14
0	199	199
1	77	87
5	84	87
K= 6, H= 6		
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-6	154	148
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-1	162	122
0	290	320
1	107	64
2	73	39
3	124	114
6	80	84
7	134	114
8	76	52
K= 7, H= 6		
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-7	107	115
-6	136	147
-5	147	125
-3	102	112
0	262	253
3	189	198
5	80	80
6	88	114
K= 8, H= 6		
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-10	110	103
-7	124	110
-3	239	238
-1	161	126
0	99	82
1	126	88
6	139	134
7	115	110
K= 9, H= 6		
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-6	118	89
-3	83	84
3	152	177
4	96	117
5	179	165
10	89	53
K= 10, H= 6		
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-3	144	125
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0	111	101
3	205	182
K= 11, H= 6		
-10	92	49
-9	84	53
-5	132	102
-4	196	205
-3	109	124
-1	73	82
4	108	103
5	151	168
K= 12, H= 6		
-11	59	58
-8	49	33
-5	246	246
-4	117	109
-3	116	80
-1	145	142
4	149	137
6	88	81
K= 13, H= 6		
-11	112	95
-4	116	113
-3	94	81
2	74	66
5	157	170
K= 14, H= 6		
-8	125	101
-5	96	88
3	93	104
7	16	26
K= 15, H= 6		
-5	88	72
5	81	116
K= 16, H= 6		
-8	53	40
-5	123	84
-4	170	199
-3	195	207
K= 17, H= 6		
-4	222	225
2	88	98
3	79	79
5	10	42
7	100	81
K= 18, H= 6		
-7	99	65
-6	117	94
-5	85	64
-3	174	182
0	135	140
1	111	112
K= 21, H= 6		
-7	108	87
-1	100	120
K= 22, H= 6		
-5	116	87
-1	154	160
0	128	146
1	91	74
K= 23, H= 6		
2	8	39
K= 0, H= 7		
-5	426	404
1	796	786
K= 1, H= 7		
-6	89	83
-5	103	69
-3	97	114
0	127	120
1	335	324
2	504	504
3	122	144
4	101	105
8	114	124
K= 2, H= 7		
-5	141	156
0	150	138
1	258	270
2	91	61
4	161	173
K= 3, H= 7		
-8	118	96
-5	110	113
0	357	364
2	382	366
3	188	195
4	212	216
5	93	75
K= 4, H= 7		
-3	125	122
-1	123	147
0	210	203
1	160	182
2	112	94
3	401	441
4	225	233
6	108	102
K= 5, H= 7		
-9	56	39
-8	112	79
-7	227	185
-4	119	113
-3	252	267
-1	309	305
0	181	195
2	84	103
3	328	319
4	139	143
K= 6, H= 7		
-7	102	105
-6	95	60
-3	137	98

TABLE 3. (Continued)

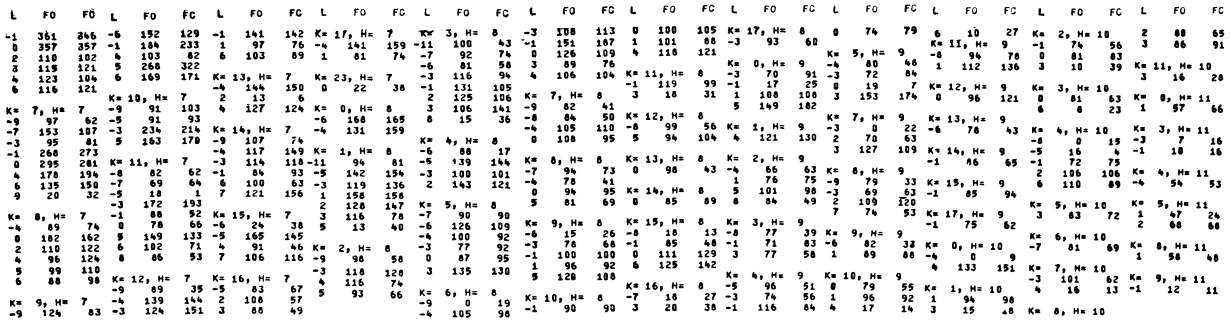


TABLE 4. INTERATOMIC BOND DISTANCES AND ANGLES IN CYTOSINE–RESORCYLIC ACID (2:1) COMPLEX MONOHYDRATE

C (1) - C (2)	1.415 Å	C (1) - C (2) - C (3)	121.7°
C (2) - C (3)	1.399	C (1) - C (2) - O (10)	119.9
C (3) - C (4)	1.345	C (3) - C (2) - O (10)	118.4
C (4) - C (5)	1.336	C (2) - C (1) - C (6)	115.8
C (5) - C (6)	1.383	C (6) - C (1) - C (7)	123.9
C (6) - C (1)	1.385	C (2) - C (1) - C (7)	120.3
C (1) - C (7)	1.484	C (1) - C (6) - C (5)	122.5
C (7) - O (8)	1.258	C (1) - C (6) - O (11)	118.1
C (7) - O (9)	1.252	C (5) - C (6) - O (11)	119.6
C (2) - O (10)	1.359	C (4) - C (5) - C (6)	118.7
C (6) - O (11)	1.374	C (3) - C (4) - C (5)	124.0
N (12) - C (13)	1.371	C (2) - C (3) - C (4)	117.5
C (13) - N (14)	1.357	C (1) - C (7) - O (9)	117.9
N (14) - C (15)	1.345	C (1) - C (7) - O (8)	118.1
C (15) - C (16)	1.410	O (8) - C (7) - O (9)	124.0
C (16) - C (17)	1.338	C (13) - N (12) - C (17)	121.1
C (17) - N (12)	1.359	N (12) - C (13) - N (14)	118.9
C (13) - O (18)	1.240	N (12) - C (13) - O (18)	119.4
C (15) - N (19)	1.341	N (14) - C (14) - O (18)	121.6
N (20) - C (21)	1.384	C (13) - N (14) - C (15)	119.5
C (21) - N (22)	1.369	N (14) - C (15) - C (16)	122.4
N (22) - C (23)	1.343	N (14) - C (15) - N (19)	117.8
C (23) - C (24)	1.445	C (16) - C (15) - N (19)	119.8
C (24) - C (25)	1.350	C (15) - C (16) - C (17)	116.6
C (25) - N (20)	1.341	C (16) - C (17) - N (12)	121.5
C (21) - O (26)	1.216	C (21) - N (20) - C (25)	122.3
C (23) - N (27)	1.281	N (20) - C (21) - N (22)	115.4
		N (20) - C (21) - O (26)	122.8
		N (22) - C (21) - O (26)	121.8
		C (21) - N (22) - O (26)	125.0
		N (22) - C (23) - C (24)	117.4
		N (22) - C (23) - N (27)	120.1
		C (24) - C (23) - N (27)	122.4
		C (23) - C (24) - C (25)	117.6
		C (24) - C (25) - N (20)	122.2

a pseudo-dimer, while to the amino group in one of the cytosines, A, the carboxylic acid group in resorcylic acid is bound by one hydrogen bond (2.932 Å). Further, these three molecules make a coplanar net-work. The other component, the water molecule, associates with the O(9) of the carboxyl and the O(11) of the phenolic groups of the neighboring resorcylic acid molecule in the crystal packing. These distances are 2.908 Å for O(9)···W and 2.884 Å for O(11)···W. There are two intramolecular hydrogen bonds at a distance of 2.478 for O(9)–O(10) and 2.542 Å for O(8)–O(11); these values agree well with the case of *o*-salicylic acid.[29,30] Although the amino groups of the two cytosine molecules, C(15)–N(19) of A and C(23)–N(27) of B, seem to have the same bond lengths, the values of the two molecules are significantly different; the values are 1.341 and 1.281 Å for A and B respectively. This significant shortening of the bond length in the B molecule can be attributed to the double-bond character in this specific portion. A few examples of the C=NH double bond lengths have been reported, *e.g.*, that in 1,3-dimethyl-4-imino-5-oxo-2-thione-imidazolidine is 1.25 Å.[31] The two cytosine molecules, A and B, are actually not identical, since B has no proton at N(22); A has a proton at the corresponding atom N(14), forming a cationic structure. This extra proton in the A molecule is the one which has migrated from the resorcylic acid proton. Furthermore, the bond lengths of the carboxyl groups are 1.258 Å for C(7)–O(8) and 1.252 Å for C(7)–O(9); these values correspond to the usual carboxyl acid anion structure observed in many aminoacids.[32] In the difference map, there are no hydrogen peaks around the carbonyl oxygen atoms. These facts indicate that the resorcylic component molecule is anionic. A similar phenomenon has been observed in the *N*-benzoyl glycine–cytosine complex, in which the proton from the acid moiety migrates to the base moiety. However, in the molecular complex of caffeine with 5-chlorosalcylic acid, the proton is retained in the acid moiety.[11] Thus far, no such anion-cation structure has been found for binding between a carboxylic acid and a basic compound. Interestingly, the cytosine B molecule is neutral and has no extra proton. Consequently, the actual nomenclature of this complex is cytosinyl-cation-cytosine-resorcylic acid anion-monohydrate.

The mean value of the C–N bonds in the cytosine-ring system is 1.359 Å which corresponds to those of

29) W. Cochran, *ibid.*, **6**, 260 (1953).
30) M. Sundaralingam and L. H. Jensen, *ibid.*, **18**, 1053 (1965).
31) T. Kinoshita, S. Sato, and C. Tamura, *Tetrahedron Lett.*, **1971**, 3695.
32) G. V. Gurskaya, "The Molecular Structure of Aminoacids (Translated from Russian)," Consultants Bureau, New York (1968).

Table 5. Intermolecular atomic distances, less than 3.7 Å between the molecules

x, y, z		C (18) .... O (26)	3.484
O (9) .... O (10)	2.478	$1-x, -y, -z$	
O (8) .... O (11)	2.542	O (17) .... C (17)	3.251
O (8) .... N (19)	2.932	$-x, -y, -1-z$	
O (8) .... W (28)	2.908	N (12) .... N (20)	3.687
N (14) .... N (22)	2.815	N (12) .... C (25)	3.443
N (18) .... N (27)	2.778	C (13) .... N (20)	3.422
N (19) .... O (26)	2.889	C (13) .... C (21)	3.542
$-x, -y, -z$		C (13) .... N (22)	3.647
C (2) .... N (22)	3.487	C (13) .... C (23)	3.658
C (2) .... C (23)	3.372	C (13) .... C (24)	3.576
C (2) .... N (27)	3.460	C (13) .... C (25)	4.432
C (1) .... C (13)	3.676	N (14) .... N (22)	3.495
C (1) .... N (14)	3.687	N (14) .... C (23)	3.203
C (1) .... C (18)	3.554	N (14) .... C (24)	3.394
C (6) .... C (13)	3.642	N (14) .... N (27)	3.574
C (6) .... C (18)	3.249	C (15) .... C (23)	3.522
C (4) .... N (27)	3.554	C (15) .... C (24)	3.407
C (3) .... C (23)	3.544	C (15) .... N (27)	3.664
C (3) .... N (27)	3.387	C (16) .... C (24)	3.668
C (7) .... C (13)	3.603	C (17) .... C (25)	3.747
C (7) .... N (14)	3.292	C (18) .... N (20)	3.371
C (7) .... C (15)	3.644	C (18) .... C (21)	3.223
O (9) .... N (14)	3.540	C (18) .... N (22)	3.602
O (9) .... C (15)	3.689	C (18) .... O (26)	3.496
O (8) .... N (12)	3.608	N (19) .... N (27)	3.417
O (8) .... C (13)	3.507	O (26) .... N (27)	3.620
O (8) .... N (14)	3.432	N (27) .... W (28)	2.832
O (8) .... C (15)	3.524	$-1-x, -y, -z$	
O (8) .... C (16)	3.693	O (11) .... N (20)	3.428
O (11) .... N (12)	3.495	$1/2+x, 1/2-y, 1/2+z$	
O (11) .... C (13)	3.421	C (2) .... W (28)	3.567
O (11) .... C (18)	3.268	C (3) .... O (11)	3.478
O (11) .... C (21)	3.503	C (3) .... W (28)	3.607
O (10) .... N (22)	3.299	O (10) .... W (28)	2.884
O (10) .... C (23)	3.455	$1/2+x, 1/2-y, -1/2+z$	
N (19) .... N (19)	3.280	O (9) .... C (4)	3.509
$1+x, y, z$		C (16) .... C (4)	3.722
N (12) .... N (20)	3.692	$-1/2+x, 1/2-y, 1/2+z$	
N (12) .... C (20)	3.582	C (4) .... O (9)	3.509
N (12) .... O (26)	2.758	C (4) .... C (16)	3.722
C (13) .... N (20)	3.661	$1/2+x, 1/2-y, -1/2+z$	
C (13) .... O (26)	3.578	O (11) .... C (4)	3.703
C (17) .... O (8)	3.216	O (11) .... C (16)	3.478
C (17) .... O (26)	3.675	W (28) .... C (2)	3.567
C (18) .... N (20)	2.813	W (28) .... C (3)	3.607
C (18) .... C (21)	3.561	W (28) .... O (10)	2.884
C (18) .... C (25)	3.742		

Table 6. Deviations of the atoms from the least-squares planes (Å)

Resorcilic acid		Cytosine (B)		Cytosine (A)	
C (1)	−0.004	N (12)	−0.001	N (20)	0.002
C (2)	−0.012	C (13)	0.013	C (21)	0.005
C (3)	−0.027	N (14)	−0.030	N (22)	−0.019
C (4)	−0.010	C (15)	−0.017	C (23)	0.010
C (5)	0.021	C (16)	0.005	C (24)	−0.012
C (6)	0.047	C (17)	−0.002	C (25)	0.005
C (7)	0.015	N (18)	0.010	O (26)	0.003
O (8)	−0.068	O (19)	0.022	N (27)	0.008
O (9)	0.108				
O (10)	−0.056				
O (11)	−0.015				

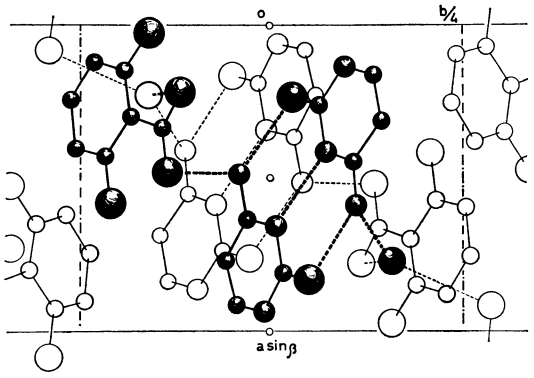


Fig. 3. The molecular packing and hydrogen bonding in cytosine–resorcylic acid (2 : 1) complex monohydrate viewed along the c-axis.

isocytosine,[33] thymine monohydrate,[34] uracil[35] barbituric acid,[36] and cytosine monohydrate[37] (1.354, 1.372, 1.361, 1.369 and 1.361 Å respectively), but which is slightly longer than those of the completely-conjugated systems of melamine,[34] pyrimidine[35] and purine[36] (1.343, 1.326, and 1.337 Å respectively). The bond lengths of C(16)–C(17), 1.338 Å, and C(24)–C(25), 1.350 Å, are clearly shorter than the fully-conjugated C=C double bond of 1.395 Å. The deviations of the atoms from each molecular plane are listed in Table 6; the inter-plane angles of the individual molecules are 7.23° for cytosine(A)–cytosine(B) and 5.14° for cytosine(B)–resorcylic acid.

A particularly interesting phenomenon in this analysis is the fact that the two cytosine molecules could form three hydrogen bonds in which they are bound to each other, with the formation of a pseudo-dimer of A and B. Such a hydrogen-bonding scheme resembles that of the guanine–cytosine three-hydrogen-bond system in the Watson-Crick model and its model complex.[2] Furthermore, it is reminiscent of the crystal structure of isocytosine[33] reported by McConell, in which tautomeric isomers of two cytosine molecules are bound by three hydrogen bonds. The present analysis of the complex is structurally different, but the

33) B. D. Sharma and J. F. McConnell, *Acta Crystallogr.*, **19**, 797 (1965).
34) R. Gerdil, *ibid.*, **14**, 333 (1961).
35) G. S. Parry, *ibid.*, **7**, 313 (1963).
36) W. Bolton, *ibid.*, **16**, 166 (1963).
37) G. A. Jeffrey and T. Kinoshita, *ibid.*, **16**, 20 (1963).
38) E. W. Hughs, *J. Amer. Chem. Soc.*, **63**, 1737 (1941).
39) P. J. Wheatley, *Acta Crystallogr.*, **13**, 80 (1960).
40) D. G. Watson, R. M. Sweet, and R. E. Marsh, *ibid.*, **19**, 573 (1965).
41) D. L. Barker and R. E. Marsh, *ibid.*, **17**, 1581 (1964).

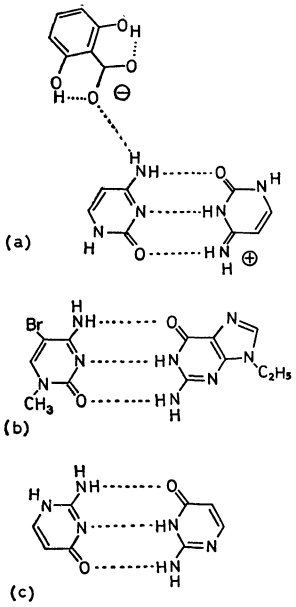
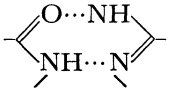


Fig. 4. Hydrogen bonding scheme of (a) present analysis, (b) 9-ethyl guanine[2] and (c) isocytosine[33].

combination scheme between these two molecules is very similar in manner when the proton is introduced from resorcylic acid, as is shown in Fig. 4. The crystal structures of cytosine and cytosine monohydrate have been determined to contain two hydrogen bonds which are of the  type; this has been established using NH···O and NH···N hydrogen bonds, as is shown in Figs. 5(a) and (b).[30] On the other hand, in crystals of cytosine-5-acetic acid (5-acetic-cytosine) and the

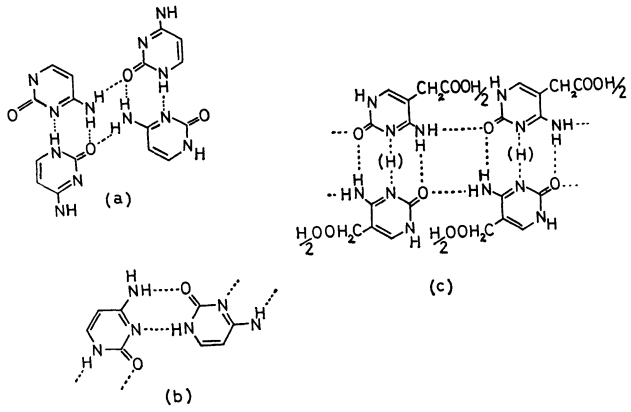


Fig. 5. Various hydrogen-bonding scheme in cytosine and its derivatives. (a) Cytosine[41] (b) cytosine monohydrate[37] (c) cytosine-5-acetic acid[42].

present complex which contain carboxylic acid moieties, the crystals form three hydrogen bonds (Fig. 5(c)).[42] These facts indicate that the change in the internal electronic states in the molecules is caused by a proton in the crystals involving a catalytic effect. The three-hydrogen-bond scheme resembles the Watson-Crick model between cytosine and guanine. In biological paths of RNA or DNA, the protonation of the bases may occur in many instances; thus, the cytosine–cytosine three-hydrogen-bond system might be said to be an interaction potentially important as a genetic proto-type in dynamic biological processes.

The authors are indebted to Miss Yuko Moriyama for her computational assistance.

42) R. E. Marsh, R. Bierstadt, and E. L. Eichhorn, *ibid.*, **15**, 310 (1962).