# RAMAN STUDY OF 6-AZACYTIDINE AND RELATED COMPOUNDS

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Raman spectra of 6-azacytidine (6-azaC) in the microcrystalline state and in various solutions ($H_2O$, $D_2O$, and DMSO) are measured for the first time. On the basis of the comparison with the measured Raman spectra of related compounds such as microcrystals of cytidine, cytosine, 5-azacytidine, and 6-azacytosine and solutions of cytidine, the main spectroscopic feature of the substitution of a CH group in the $6^{\text{th}}$ position of a pyrimidine base ring for an N atom is revealed as the absence of the low-frequency component of a characteristic doublet of cytidine in the region 1200–1300 $\text{cm}^{-1}$. Blue shifts of some Raman peaks in $D_2O$ solutions of 6-azaC and cytidine are observed. Apparently, they may be connected with the transformation of intramolecular H-bonds into D-bonds. In addition, improved X-ray data for 6-azaC single crystals are obtained.

## 1. Introduction

Anomalous nucleoside 6-azacytidine (6-azaC, 2-$\beta$-D-ribofuranosyl-5-$NH_2$-1,2,4-triazin-3(2H)-one) is a structural analog of canonical nucleoside cytidine. The only distinction between cytidine and 6-azaC consists in the replacement of a C-H group at the $6^{\text{th}}$ position of a pyrimidine ring by a nitrogen atom denoted as N* in Fig. 1. 6-azaC has a quite wide spectrum of biological properties that results in pharmacological primarily antitumor [1] and antiviral effects [2]. An efficient scheme of large-scale synthesis of 6-azaC was developed at Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine [3]. Toxic-pharmacological and preclinical systematic research of 6-azaC showed a low degree of metabolism with great efficiency. Investigations *in vivo* found that 6-azaC is present in biological fluids (blood, urine) in the unchanged form. This can indirectly indicate the safety of its use. It should be noted that the mechanism of its action is still not determined. The questions about where and how 6-azaC acts have no answer even today. In the previous authors' work, the spectrophotometric method showed that 6-azaC competes with ethidium bromide for DNA-binding places [4]. The comparison of the absorption spectra of 6-azaC and DNA water so-

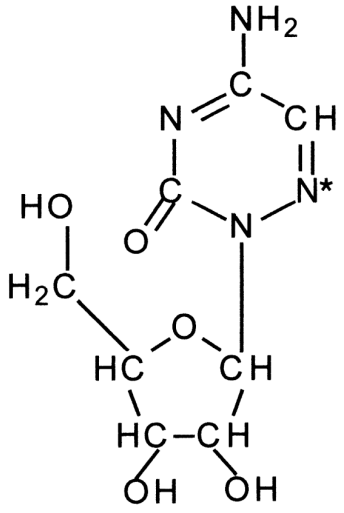


Fig. 1. Structural formula of 6-azacytidine

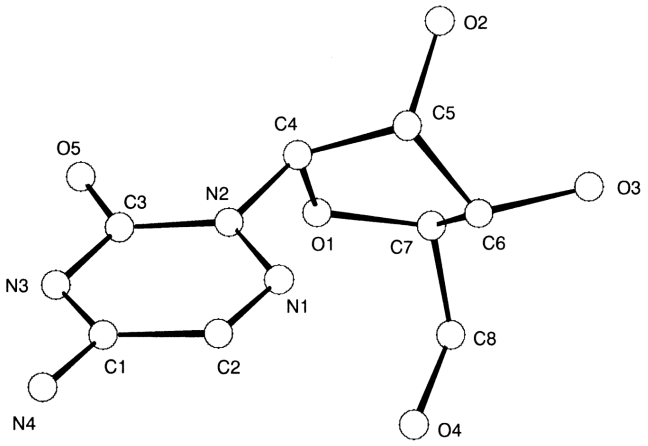


Fig. 2. Molecular structure of 6-azacytidine in the perspective view presented in the X-ray nomenclature (hydrogen atoms are not shown

lutions and their mixture shows the interaction between 6-azaC and DNA molecules. Available data indicates that the biological activities [5] of anomalous cytidines are connected with a special conformation of molecules of the nucleosides. Raman spectroscopy is used for the quantitative analytical determination of modified nucleosides and nucleotides in biological systems [6, 7]. The IR studies of synthesized 6-azaC were done in [8], but the Raman technique was applied only recently [9, 10]. In this paper, we present the Raman spectra of 6-azacytidine (6-azaC) in comparison with the spectra of related compounds (cytidine, cytosine, 5-azacytidine, and 6-azacytosine) in the microcrystalline form and in solutions.

## 2. Experimental

### *2.1. Materials and preparation of samples*

Anomalous nucleoside 6-azaC in the microcrystalline state was synthesized by the preparative method described in [3]. Solution samples were prepared by dissolving crystalline 6-azaC and cytidine in distilled deionized water, heavy water (99,9%), and DMSO.

### *2.2. Raman measurements*

An $Ar^+$ laser with 200 mW at 488 nm was used to obtain Raman spectra at room temperature with a Coderg T-800 triple monochromator with a photon counting system.

## 3. Results and Discussion

### *3.1. Crystal data*

The high purity and the structural perfection of 6-azaC microcrystals were confirmed by X-ray structure analysis: $C_8H_{12}N_4O_5$, $M = 244.21$, orthorhombic, space group $P2_12_12_1$ (N 19), $a = 6.9465(9)$, $b = 7.614(1)$, $c = 19.588(3)$ Å, $V = 1036.1(2)$ Å$^3$, $Z = 4$, $d_c = 1.565$ g·cm$^{-3}$, $\mu = 0.131$ mm$^{-1}$, $F(000) = 512$, crystal size ca. 0.19×0.22×0.27 mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the $\omega$ and $\varphi$ scanning mode. The cell parameters were obtained from the least-squares treatment of 2748 reflections in the $\theta$ range of 2.87–25.91°. The intensity data were collected within the range of $2.08 \leq \theta \leq 26.22°$ using Mo-$K_\alpha$ radiation ($\lambda = 0.71078$ Å). The intensities of 5181 reflections were collected (1236 unique reflections, $R_{\rm int} = 0.021$). Data were corrected for the Lorentz and polarization effects. The structure was resolved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using SHELXS97 and SHELXL97 programs [11, 12] and CRYSTALS program package [13]. Hydrogen atoms participating in hydrogen bonds were located in the difference Fourier maps and refined isotropically. The SADABS absorption correction was applied [14]. In the refinement, 1236 reflections (1083 reflections with $I \geq 3\sigma(I)$) were used. The convergence was obtained at $R_1 = 0.0247$ and $wR_2 = 0.0291$, GOF = 1.152 (174 parameters; the observed/variable ratio is 6.22; the largest and minimal peaks in the final difference map are 0.15 and –0.13 e/Å$^3$). In the refinement, the Chebyshev weighting scheme [15] was used (weighting coefficients are 0.845, 0.729, 0.679, 0.088, and 0.064). Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 759505.

The molecular structure of 6-azacytidine was determined by single-crystal X-ray diffraction. The perspective view of a 6-azacytidine molecule is given in Fig. 2. The 6-membered cycle C(1)C(2)N(1)N(2)C(3)N(3) is almost planar – the average deviations from the least square plane do not exceed 0.001 Å. At the same time, cycle C(4-7)O(1) is not planar (the maximum deviation from the least square plane is 0.234 Å) and has an envelop conformation: atoms

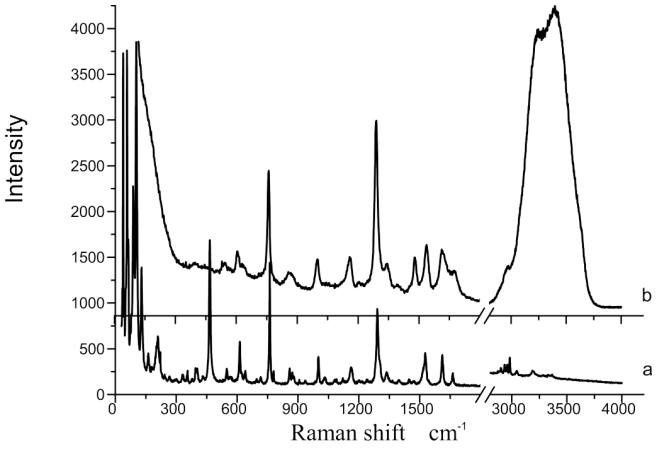


Fig. 3. Raman spectra of 6-azaC in the spectral range 30–3800 $cm^{-1}$ in the microcrystalline state (*a*) and in an $H_2O$ solution (*b*)

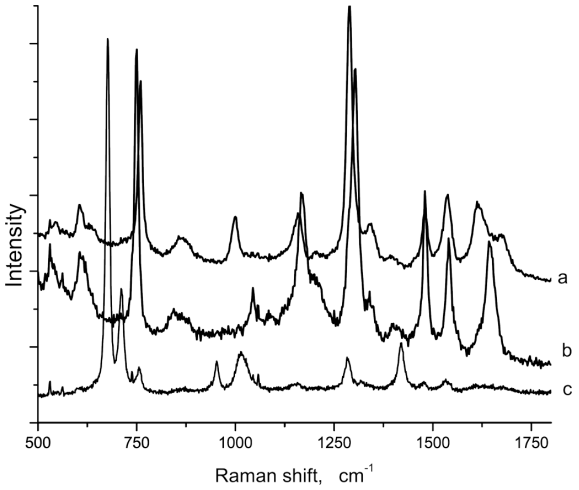


Fig. 4. Raman spectra of 6-aza in the spectral range 500–1800 $cm^{-1}$ dissolved in $H_2O$ (*a*), $D_2O$ (*b*), and DMSO (*c*)

C(4-7)O(1) are planar within 0.001 Å, and the "corner" C(5-7) forms a dihedral angle of 37.15° with this plane. N(2) and N(4) atoms have a trigonal-planar bond configuration (the sums of the bond angles are 359.9(1) and 358.7(2)°, respectively). In the solid state, molecules of 6-azacytidine are organized in nets by weak intermolecular hydrogen bonds [16]: O(3)–H...O(2) 2.758(2) Å (O(3)–H 0.85(3) Å, O(2)...H 1.94(2) Å, O(3)HO(2) 161°), N(4)–H...O(5) 2.835(2) Å (N(4)–H 1.98(3) Å, O(5)...H 0.89(2) Å, N(4)HO(5) 162(2)°), N(4)–H...O(3) 2.956(2) Å (N(4)–H 2.13(3) Å, O(3)...H 0.86(2) Å, N(4)HO(3) 159 (2)°), O(2)–H...O(4) 2.715(2) Å (O(2)–H 1.97(3) Å, O(4)...H 0.74(2) Å, O(2)HO(4) 177(2)°), O(4)–H...O(5) 2.823(2) Å (O(4)–H 1.97(3) Å, O(5)...H 0.90(2) Å, O(4)HO(5) 158(2)°).

### *3.2. Raman spectra*

The Raman spectra of 6-azaC in microcrystalline state and its $H_2O$ solution are shown in Fig. 3. The Raman peaks at wavenumbers $< 500$ $cm^{-1}$ in the spectrum of microcrystals obviously caused by lattice vibrations, because they disappear in the spectrum of a solution. In this paper, we are focusing at intramolecular vibrations, since the valuable properties of 6-azaC as a biologically active compound appear not in the crystalline state but in solutions, and the lattice vibrations of 6-azaC were already studied by IR spectroscopy in detail [8]. In the range over 500 $cm^{-1}$, these spectra are quite similar both by Raman peak positions and by the ratio of their intensities. The spectrum of a water solution is distorted by the overlapping with $H_2O$ Raman bands at 1600 and

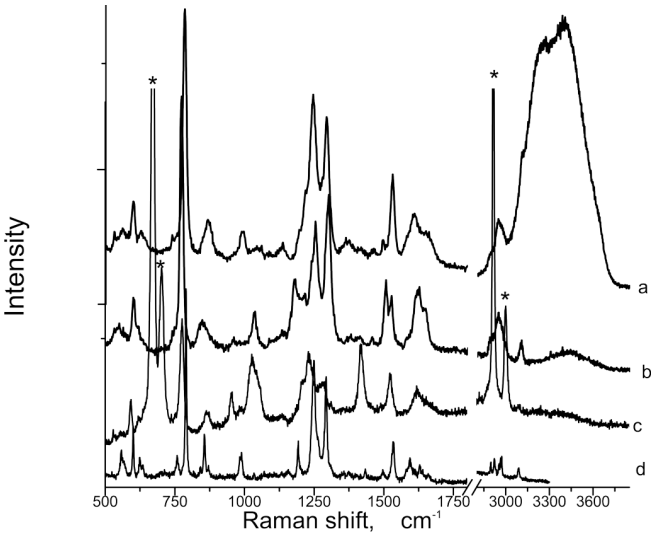


Fig. 5. Raman spectra of cytidine in the spectral range 500–3800 $cm^{-1}$ dissolved in $H_2O$ (*a*), $D_2O$ (*b*), DMSO (*c*) and in the microcrystalline state (*d*)

3200 $cm^{-1}$. For example, the group of peaks clearly visible in the microcrystalline spectrum between 2800 and 3000 $cm^{-1}$ which may be attributed to H-bonds appears as a shoulder at 2900 $cm^{-1}$ on the low-frequency slope of the OH-band in the $H_2O$ solution spectrum. In the spectrum of a $D_2O$ solution, this group is free of overlapping and looks like a broad band that is an envelope of the above group of peaks in the crystalline state. The similar peaks and envelope are present also in spectra of cytidine (Fig. 5).

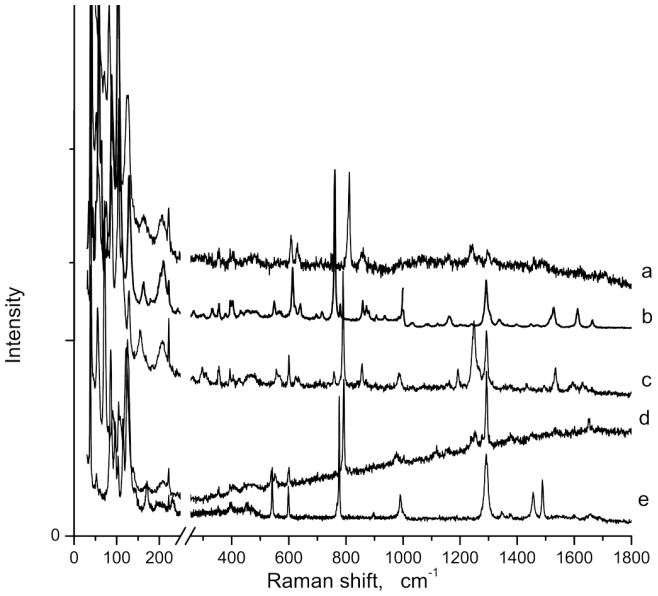


Fig. 6. Raman spectra of microcrystals in the spectral range 30–1800 $cm^{-1}$ 5-azaC (*a*), 6-azaC (*b*), cytidine (*c*), cytosine (*d*), and 6-azacytosine (*e*)

Figure 4 shows the Raman spectra of 6-azaC dissolved in $H_2O$, $D_2O$, and DMSO. The positions of Raman peaks for different solutions are distinct both from those of microcrystals and from one another. For example, some of Raman bands stay still, and another part has a little shift mostly to low frequencies on going from microcrystals to a $H_2O$ solution. In contrast to the $H_2O$ solution where all peaks are shifted to low frequencies relatively to the Raman spectrum of microcrystalline 6-azaC, some Raman peaks of the $D_2O$ solution of 6-azaC are shifted to high frequencies. As an example, let us look after the behavior of two most prominent Raman peaks of 6-azaC near 750 $cm^{-1}$ and 1290 $cm^{-1}$. In the spectrum of 6-azaC in the $H_2O$ solution, the first one is located at 758 $cm^{-1}$, whereas it appears at 748 $cm^{-1}$ in the spectrum of 6-azaC in the $D_2O$ solution with low-frequency shifts by 10 and 13 $cm^{-1}$ relatively to its positions in the $H_2O$ solution and the microcrystalline state, respectively (Table). This result is expected and usually explained by an increase of the reduced mass of the corresponding vibrational mode due to the substitution of a hydrogen atom by a deuterium atom as twice as heavy under assumption that the force constants do not change that results in a decrease of the vibration frequency. At the same time, the second peak at 1289 $cm^{-1}$ in the spectrum of the $H_2O$ solution of 6-azaC is shifted to 1302 $cm^{-1}$ in the $D_2O$ solution that means a high-frequency shift by 13 $cm^{-1}$ and 11 $cm^{-1}$ relatively to its position in the spectra of the $H_2O$ solution and microcrystals, respectively. Such blue-shift in the Raman spectra of dissolved compounds can occur due to the replacement of a solvent (in our case, $H_2O$ for $D_2O$) [17] or due to the deuteration of a solute molecule itself [18]. In both cases, the blue-shift is connected with the transformation of intermolecular or intramolecular H-bonds into D-bonds, respectively. NMR [19] and foregoing X-ray investigations showed the existence of strong H-bonds, including intramolecular ones, in the samples of microcrystalline 6-azaC. We are inclined to believe that, in our case, these shifts are caused by the deuteration of a nucleoside molecule itself.

The Raman spectra of 6-azaC and cytidine dissolved in DMSO manifest low-frequency shifts in respect to those in the microcrystalline state, as well as in water solutions, but generally of a bigger magnitude. A similar situation was observed under comparison of the Raman spectra of cytidine solutions in $H_2O$ and $D_2O$ (see Fig. 5, where the Raman peaks of DMSO are labeled as *). At the substitution $H_2O$ by $D_2O$, the peak at 784 $cm^{-1}$ in the spectrum of the cytidine water solution is shifted by 12 $cm^{-1}$ to low frequencies, in contrast to peaks at 1244 and 1292 $cm^{-1}$ which show blue shifts by 7 $cm^{-1}$ and 5 $cm^{-1}$, respectively. The Raman spectra (30–1800 $cm^{-1}$) of microcrystalline 6-azaC, 5-azaC, cytidine, cytosine, and 6-azacytosine are shown in Fig. 6. In the range of intramolecular vibrations 500-1800 $cm^{-1}$, the mentioned spectra are rather similar both by Raman peak positions and by the ratio of their intensities.

Nevertheless, the Raman spectra of microcrystalline 6-azaC and 5-azaC have an important distinction in the region 1200–1300 $cm^{-1}$, where only one strong peak is observed for 6-azaC at 1291 $cm^{-1}$ in contrast to the doublet at 1240–1298 $cm^{-1}$ for 5-azaC (Fig. 6,*a, b*), although both compounds are isomers and differ from each other only by a positions of the N atom in the base ring. The peaks at 1291 $cm^{-1}$ of 6-azaC and at 1298 $cm^{-1}$ of 5-azaC can be attributed to the valence vibrations of C(2)–N(3) [20]. In [21], the Raman peak at 1292 $cm^{-1}$ of neutral cytidine 5'-monophosphate is attributed to deformations of the sugar ring near the glycosidic bond. This disagrees with the observation of this peak in all studied compounds including those without a ribose ring, i.e., cytosine and 6-azacytosine. This vibration is present in all studied compounds, and the corresponding Raman peaks appear in the spectra both of microcrystals and solutions near 1290 $cm^{-1}$. Its frequency is not affected significantly by the replacement of C(5)H or C(6)H groups by an N atom. As for the

**Spectral positions of the Raman peaks of 6-azacytidine and related compounds**

| 6-azacytidine | | | | cytidine | | | | cytosine | | | 5-azacytidine | 6-azacytosine | Assigning |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Solid | Liquid | | | Solid | Liquid | | | Solid | Liquid | | Solid | Solid | |
| | $H_2O$ | $D_2O$ | DMSO | | $H_2O$ | $D_2O$ | DMSO | | $H_2O$ | $D_2O$ | | | |
| 57.6 | – | – | – | 51.3 | – | – | – | 54.5 | – | – | – | 52.2 | – |
| – | – | – | – | 73.2 | – | – | – | 70.9 | – | – | – | – | – |
| 88.6 | – | – | – | 87.4 | – | – | – | 80.1 | – | – | 82.3 | 85.8 | – |
| 549 | 544 | – | – | 555 | 560 | – | – | 551 | 546 | – | – | 541.9 | – |
| 614 | 606 | 608 | – | 600 | 600 | 600 | – | 600.7 | 592 | 594 | 608 | 598.3 | – |
| 761 | 758 | 748 | 756 | 790 | 784 | 772 | 777 | 792.1 | 786 | 778 | 811 | 776.6 | Breathing ring vibration |
| 859 | 864 | 844 | – | 856.3 | 868 | 848 | 867 | – | – | – | – | – | – |
| 1001 | 1000 | – | – | 987 | 990 | – | – | 980 | 967 | 986 | – | 990 | – |
| 1161 | 1158 | 1170 | – | 1158 | 1132 | – | – | 1153 | – | 1145 | – | – | – |
| – | – | – | – | 1249 | 1244 | 1251 | 1231 | 1252 | 1225 | 1204 | 1240 | – | C(5)–H and C(6)–H out of phase bending |
| 1291 | 1289 | 1302 | 1285 | 1292 | 1292 | 1297 | 1283 | 1292 | 1289 | 1290 | 1298 | 1291 | C(2)–N(3) stretching |
| 1336 | 1342 | 1341 | – | – | – | – | – | – | – | – | – | 1347 | – |
| – | 1480 | 1480 | – | 1495 | 1505 | 1505 | – | – | – | – | – | 1488 | – |
| 1528 | 1538 | 1540 | 1533 | 1534 | 1530 | 1523 | 1523 | 1530 | – | – | – | – | $NH_2$ deformation |
| 1612 | 1612 | 1646 | – | 1629 | 1606 | 1620 | – | – | – | 1612 | – | – | $NH_2$ deformation |
| – | – | – | – | – | – | – | – | 1650 | 1639 | 1646 | – | 1658 | C(5)=C(6) |
| 1664 | – | – | – | 1662 | – | – | – | – | – | – | – | – | C=O stretching |

low-frequency component of the mentioned doublet, it was assigned to C(5)–H and C(6)–H out-of-phase bending [22]. In principle, the replacement of CH group by an N atom in the $6^{th}$ or $5^{th}$ position of the pyrimidine ring of cytidine causes the disappearance of this vibrational mode but cannot explain the above distinction between the Raman spectra of 5- and 6-azaC. It is obvious that the locations of C(5)H and C(6)H groups at the base ring are nonequivalent. So, the replacement of a CH group by an N atom in the $6^{th}$ or $5^{th}$ position of the base ring will result in different changes (rearrangement) of the set of fundamental vibrational modes. For example, such a replacement in the $6^{th}$ position is accompanied by changing the N(1)–C(6)H bond by the N(1)–N(6) one. This can cause a significant shift of the low-frequency component of the cytidine doublet (at 1249–1292 $cm^{-1}$ in Fig. 6,*c*) and/or a change of its intensity. In the 5-azaC case, the replacement of a CH group by an N atom in the 5th position of the pyrimidine ring of cytidine does not influence noticeably the N(1)–C(6) bond.

Therefore, one may expect two Raman peaks at 1240 and 1298 $cm^{-1}$ for microcrystalline 5-azaC and only one peak for 6-azaC. This assumption is in agreement with the observation of the Raman spectra of 6-azacytosine (Fig. 6,*e*), where there is only one peak at 1291 $cm^{-1}$ in respect to the Raman spectrum of cytosine (Fig. 6,*d*) which has doublet at 1252–1292 $cm^{-1}$. Spectral positions and the attribution of noticeable Raman peaks of the studied compounds in the microcrystalline state and in various solutions are presented in the Table. For example, the above-mentioned intense narrow Raman peaks in the spectra of microcrystalline 6-azaC at 761 $cm^{-1}$ and similar peaks in the spectra of 6-azaC in $H_2O$ and $D_2O$ solutions at 758 $cm^{-1}$ and 748 $cm^{-1}$, respectively, can be attributed to the "breathing" mode of the pyrimidine ring, as it is well known for the corresponding peaks of cytidine at 789 $cm^{-1}$, 784 $cm^{-1}$ and 772 $cm^{-1}$ in the solid state and $H_2O$ and $D_2O$ solutions, respectively [20, 22]. The Raman peaks at 1291, 1289, and 1292 $cm^{-1}$ in spectra of 6-azaC in the microcrystalline state and dissolved in water and heavy water, respectively, can be attributed to the valence vibration of C(2)–N(3). The characteristic doublets of cytidine at 1249–1292 $cm^{-1}$, 1244–1292 $cm^{-1}$, 1251–1297 $cm^{-1}$ in the solid state and $H_2O$ and $D_2O$ solutions, respectively, in the Raman spectrum (Fig. 5) are similar by shape and the ratio of the intensities of components of a doublet at 1256–1293 $cm^{-1}$ in the spectrum of a deoxycytidine water solution [20]. Its high-frequency component at 1292 $cm^{-1}$ is attributed to C(2)–N(3) valence vibrations. The peaks at 1538 $cm^{-1}$ and 1612 $cm^{-1}$ in the spectrum of 6-azaC in an $H_2O$ solution (in the spectrum of cytidine in an $H_2O$ solution in Fig. 5 at 1530 $cm^{-1}$ and 1606 $cm^{-1}$, respectively) are related to $NH_2$ deformation vibrations. The wide band at 1670 $cm^{-1}$ (at 1658 $cm^{-1}$ in the spectrum of cytidine in Fig. 5) can be attributed to the valence vibration of C=O double bonds.

## 4. Conclusions

The replacement of a CH group by an N atom in the 6th position of the pyrimidine base ring results in the disappearance of a low-frequency component of the characteristic Raman doublet in the region 1200–1300 $cm^{-1}$ in spectra of 6-azaC and 6-azacytosine. This is apparently connected with the change of the N(1)–C(6)H bond by the N(1)–N(6) one in the pyrimidine ring. Raman peaks of the dissolved studied compounds are shifted to the low-frequency region except a certain peak in the spectra in $D_2O$, where a blue shift was observed as compared with the spectra of microcrystals. We suppose that it may be caused by a transformation of intramolecular H-bonds into D-bonds.

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ДОСЛІДЖЕННЯ 6-АЗАЦИТИДИНУ ТА СПОРІДНЕНИХ СПОЛУК МЕТОДОМ КРС

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Р е з ю м е

Спектри КРС мікрокристалічного 6-азацитидину та його розчинів у воді, важкій воді та ДМСО було виміряно вперше. Додатково отримано спектри КРС мікрокристалів споріднених сполук: цитидину, цитозину, 5-азацитидину, 6-азацитозину, а також розчинів цитидину. Основною спектроскопічною особливістю заміни CH групи на атом N у шостому положенні піримідинового кільця є відсутність низькочастотної компоненти характерного дублету у спектрі цитидину в діапазоні 1200–1300 $см^{-1}$. Блакитний зсув, що спостерігався для деяких ліній КРС 6-азацитидину та цитидину розчинених у важкій воді, може бути пов'язаний із заміною внутрішньомолекулярних водневих зв'язків дейтерованими. Також було отримано уточнені дані рентгеноструктурного аналізу для монокристала 6-азацитидину.