Crystal structure and vibrational spectra of salts of 1H-pyrazole-1-carboxamidine and its protonation route

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Abstract
Crystal structures of five salts of 1H-pyrazole-1-carboxamidine, PyCA, with various inorganic acids were determined, (HPyCA)Cl, (HPyCA)Cl·H2O, (HPyCA)Br, (HPyCA)2(I)I3, and (HPyCA)HSO4. Theoretical calculations of the protonation route of PyCA showed that the cationic form present in the studied crystals is energetically privileged. Tautomeric equilibrium constants indicated two isomers as the most stable neutral forms. Calculations for two other tautomers failed resulting in pyrazole and carbodiimid tautomer of cyanamide. Such decomposition is important in a view of guanylation reaction. Hydrogen bonding patterns were studied by means of the graph-set approach. Similarities of the patterns in different crystal structures were demonstrated by the algebraic relations between descriptors of the patterns. The strength of hydrogen bonding network in the crystals was assessed analyzing vibrational spectra. The bands were assigned on the basis of theoretical calculations for the complex [(HPyCA)2Cl4]2− ion and potential energy distribution analysis. The strength of hydrogen bonds was set in the following ascending series (HPyCA)2(I)I3 (4) < (HPyCA)Br (3) < (HPyCA)Cl (1) < (HPyCA)Cl·H2O (2) < (HPyCA)HSO4 (5).

Keywords Guanylation · Protonation route · Hydrogen bonding · Elementary graph-set descriptor · Vibrational spectroscopy · PED

Introduction
The 1H-pyrazole-1-carboxamidine, hereafter PyCA, has been a next-generation substrate for guanylation of amines after S-methylisothiouronium sulfate, cyanamide or 3,5-dimethyl-1-guanilpyrazole nitrate [1]. For instance, it was successfully used in the introduction of guanidinium group as the last step of synthetic procedure of zanamivir, an influenza A and B drug [2], or Boc protected PyCA was a guanylation agent in synthesis of dengue and West Nile virus protease inhibitors [3].

The 1H-pyrazole-1-carboxamidine is commercially available as a hydrochloride and is widely used in organic synthesis for years. It can be synthesized by mixing equimolar amount of pyrazole and cyanamide, and further crystallization from the reaction mixture [1]. This very simple one-step procedure and very simple isolation method of pure compound make the PyCA a low-cost reagent in organic synthesis. The (HPyCA)Cl has very good solubility in water or DMF and is stable even at basic conditions, i.e., 1 M water solution of 1 M Na2CO3 [1]. So, it was suggested that the guanylation mechanism proceeds with cationic form of 1H-pyrazole-1-carboxamidine and deprotonated form of respective amine. However, our preliminary search in Cambridge Structural Database revealed that crystal structure of PyCA or its salts have not been studied so far [4, 5].

Apart from pyrazole ring, a molecule of PyCA possesses three hydrogen atoms at the carboxyamidine residue forming NH2 and NH groups. It is worth noticing that a free nitrogen atom of the pyrazole ring may be theoretically faced to the NH2 or NH groups. Besides, the hydrogen atom of the NH group can be oriented in syn or anti position. In the first protonation step, the proton can be accepted either to the NH group or to the free nitrogen atom in the pyrazole ring. So, all these facts indicate that a few tautomers of neutral as well as cationic speciation forms of PyCA are expected in the solution. Here, we present theoretical investigation of the route of protonation of PyCA, which has an importance for

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| Chemical formula | \( \text{C}_4\text{H}_7\text{N}_4\cdot\text{Cl} \) | \( \text{C}_4\text{H}_7\text{N}_4\cdot\text{Cl} \cdot\text{H}_2\text{O} \) | \( \text{C}_4\text{H}_7\text{N}_4\cdot\text{Br} \) | \( 2(\text{C}_4\text{H}_7\text{N}_4)\cdot\text{I}_3\cdot\text{I} \) | \( \text{C}_4\text{H}_7\text{N}_4\cdot\text{HSO}_4 \) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| \( M_r \)      | 146.59          | 164.60          | 191.05          | 729.87          | 208.20          |
| Crystal system, space group | Monoclinic, \( P2_1/n \) | Triclinic, \( P–1 \) | Monoclinic, \( P2_1/c \) | Triclinic, \( P–1 \) | Monoclinic, \( P2_1/c \) |
| \( a, b, c (\text{Å}) \) | 4.8201(3), 14.0874(14), 9.8888(10) | 4.8942(5), 9.9827(10), 9.4374(12) | 4.8597(2), 9.4774(4), 15.2411(6) | 7.3359(3), 10.6942(4), 12.9130(5) | 10.6853(7), 9.6487(6), 8.1609(6) |
| \( \alpha, \beta, \gamma (°) \) | 90, 92.566(6), 90 | 66.408(11), 82.383(9), 81.94(28) | 90, 90.576(4), 90 | 72.536(3), 75.929(3), 85.996(3) | 90, 94.293(6), 90 |
| \( V (\text{Å}^3) \) | 670.80(10) | 385.81(8) | 701.93(5) | 937.35(7) | 839.03(10) |
| \( Z \) | 4 | 2 | 4 | 2 | 4 |
| \( \mu (\text{mm}^{-1}) \) | 0.48 | 0.44 | 5.77 | 6.65 | 0.38 |
| Crystal size (mm) | 0.45 \( \times \) 0.25 \( \times \) 0.09 | 0.63 \( \times \) 0.20 \( \times \) 0.08 | 0.61 \( \times \) 0.48 \( \times \) 0.39 | 0.48 \( \times \) 0.13 \( \times \) 0.05 | 0.42 \( \times \) 0.35 \( \times \) 0.08 |
| \( T_{\text{min}}, T_{\text{max}} \) | 0.894, 0.972 | 0.850, 0.969 | 0.143, 0.247 | 0.182, 0.767 | 0.868, 0.971 |
| No. of measured, independent and observed \([I > 2\sigma(I)]\) reflections | 4156, 1414, 1059 | 2936, 1621, 1313 | 6248, 1476, 1218 | 7975, 3891, 3112 | 3865, 1850, 1571 |
| \( R_{\text{int}} \) | 0.027 | 0.022 | 0.037 | 0.024 | 0.017 |
| (sin \( \theta/\lambda_{\text{max}} \) (Å\(^{-1}\)) | 0.633 | 0.633 | 0.633 | 0.633 | 0.649 |
| \( R[F^2 > 2\sigma(F^2)], wR(F^2), S \) | 0.043, 0.109, 1.03 | 0.052, 0.161, 1.10 | 0.036, 0.094, 1.03 | 0.033, 0.069, 1.01 | 0.035, 0.090, 1.07 |
| No. of reflections and parameters | 1414, 82 | 1621, 97 | 1476, 82 | 3891, 181 | 1850, 120 |
| \( \Delta f_{\text{max}}, \Delta f_{\text{min}} \) (e Å\(^{-3}\)) | 0.19, −0.22 | 0.55, −0.28 | 0.90, −0.53 | 0.66, −0.82 | 0.18, −0.37 |
understanding guanylation reaction. Crystal structures of new PyCA salts with inorganic acids are described. Hydrogen bonding networks are analyzed by topological approach and graph-set descriptors [6, 7]. The compounds are also characterized by infra-red and Raman spectra. The bands are assigned with the help of theoretical simulations and potential energy distribution (PED) analysis.

Materials and methods

Synthesis

The starting compounds, (HPyCA)Cl (ArkPharm Inc., 97+ %), hydrofluoric acid (Aldrich, ≥ 57 wt % in H2O), hydrobromic acid (Aldrich, ≥ 48 wt % in H2O), hydroiodic acid (Aldrich, 57 wt % in H2O, 99.95 %, no stabilizer), and sulfuric acid (Aldrich, 95.0–98.0 wt % in H2O, 99.95 %) were used as supplied. The (HPyCA)Cl was re-crystallized from 3 ml of methanol. In each synthesis, the (HPyCA)Cl (1 mmol, 0.1466 g) was dissolved in 3 ml of methanol and then respective acid was added: 1 ml HF, 1.5 ml HBr, 1 ml HI, and 1 ml H2SO4. The crystals of (HPyCA)Br (3) and (HPyCA)HSO4 (5) were obtained after 1 to 5 days by slow evaporation of the mixture in air at room temperature. The crystals of (HPyCA)2(I)I3 (4) were formed after 2 months, whereas (HPyCA)Cl·H2O (2) was obtained instead of fluoride salt.

Single crystal x-ray diffraction studies

X-ray diffraction data were collected on an Oxford Diffraction four-circle single crystal diffractometer equipped with a CCD detector using graphite-monochromatized MoKα radiation (λ = 0.71073 Å). The raw data were treated with the Crysalis Data Reduction Program (version 1.171.38.43). The intensities of the reflection were corrected for Lorentz and polarization effects. The crystal structures were solved by direct methods [8] and refined by full-matrix least-squares method using SHELXL-2017 program [9]. Non-hydrogen atoms were refined using anisotropic displacement parameters. All H-atoms were visible on the Fourier difference maps, but placed by geometry and allowed to refine “riding on” the parent atom (with Uiso = 1.2 Ueq for sp2-carbon atoms, and Uiso = 1.5 Ueq for other atoms). Visualizations of the structure were made using Diamond 3.2 k [10]. Low temperature X-ray diffraction experiments were carried out using Oxford Cryosystems device in the range of 295–100 K with temperature step ΔT = 10 K, but no phase transition was observed for all the crystals. Crystal data and refinement details are presented in Table 1.

Spectroscopic measurements

Room temperature FT-IR spectra in the 4000–400 cm−1 range were measured on the Bruker IFS-88 spectrometer with 2 cm−1 resolution. Nujol and fluorolube mull techniques have been used in the measurements. Nd:YAG laser (1064 nm) was used to collect room temperature FT-Raman spectra, which were

| Table 2 | Total energy (Hartree), zero-point energy plus thermal corrections (Ethermal, kcal/mol) and entropy (cal/molK) for the neutral and protonated forms of 1H-pyrazole-1-carboxamidine |
|---------|-------------------------------------------------------------------------------------------------------------|
|          | E_total | E_thermal | Entropy |
| Carbodiimid + pyrazol = 3ab4a | −45.26 | 1.54·10^4 |
| Carbodiimid + pyrazol = 3ab4b | −38.49 | 1.26·10^4 |
| Carbodiimid + pyrazol = 3ab4c | −21.55 | 1.43·10^4 |
| Carbodiimid + pyrazol = 3ab4d | −7.77 | 1.12·10^2 |
| Carbodiimid + pyrazol = 3ab4e | −979.21 | 1.54·10^1 |
| Carbodiimid + pyrazol = 3ab4f | −925.26 | 2.84·10^9 |
| Carbodiimid + pyrazol = 3ab4g | −887.32 | 1.26·10^16 |
| Carbodiimid + pyrazol = 3ab4h | −871.31 | 8.03·10^16 |
| Carbodiimid + pyrazol = 3ab4i | −863.06 | 2.24·10^20 |
| Carbodiimid + pyrazol = 3ab4j | −53.96 | 2.84·10^9 |
| Carbodiimid + pyrazol = 3ab4k | −91.90 | 1.26·10^16 |
| Carbodiimid + pyrazol = 3ab4l | −107.90 | 8.03·10^16 |
| Carbodiimid + pyrazol = 3ab4m | −116.15 | 2.24·10^20 |
| Carbodiimid + pyrazol = 3ab4n | −439.32 | 23ab4ab^+ = 23ab4ab^− |

| Table 3 | Gibbs free energy (kJ/mol) and tautomeric equilibrium constant (K_T) for tautomeric equilibria of the neutral and protonated forms of 1H-pyrazole-1-carboxamidine |
|---------|-------------------------------------------------------------------------------------------------------------|
|          | ∆G  | K_T |
| Carbodiimid + pyrazol = 3ab4a | −45.26 | 1.54·10^4 |
| Carbodiimid + pyrazol = 3ab4b | −38.49 | 1.26·10^4 |
| Carbodiimid + pyrazol = 3ab4c | −21.55 | 1.43·10^4 |
| Carbodiimid + pyrazol = 3ab4d | −7.77 | 1.12·10^2 |
| Carbodiimid + pyrazol = 3ab4e | −979.21 | 1.54·10^1 |
| Carbodiimid + pyrazol = 3ab4f | −925.26 | 2.84·10^9 |
| Carbodiimid + pyrazol = 3ab4g | −887.32 | 1.26·10^16 |
| Carbodiimid + pyrazol = 3ab4h | −871.31 | 8.03·10^16 |
| Carbodiimid + pyrazol = 3ab4i | −863.06 | 2.24·10^20 |
| Carbodiimid + pyrazol = 3ab4j | −53.96 | 2.84·10^9 |
| Carbodiimid + pyrazol = 3ab4k | −91.90 | 1.26·10^16 |
| Carbodiimid + pyrazol = 3ab4l | −107.90 | 8.03·10^16 |
| Carbodiimid + pyrazol = 3ab4m | −116.15 | 2.24·10^20 |
| Carbodiimid + pyrazol = 3ab4n | −439.32 | 23ab4ab^+ = 23ab4ab^− |
Table 4  Theoretical frequencies for the ([(HPyCA)\textsubscript{2}Cl\textsubscript{4}]\textsuperscript{-} ion scaled by \(\nu_{Sc} = 0.9614 \cdot \nu_{Calc} + 17.8\) equation (\(\nu_{Sc}\)), mode symmetry (S), experimental frequencies taken from infrared (\(\nu_{Exp, IR}\)) and Raman (\(\nu_{Exp, R}\)) spectra for (HPyCA)\textsubscript{2}Cl\textsubscript{4} (1) compound, PED (%) and assignment of the experimental bands. Frequencies in cm\textsuperscript{-1}.

| \(\nu_{Sc}\) | S  | \(\nu_{Exp, IR}\) | \(\nu_{Exp, R}\) | PED (%) | Assignment          |
|------------|----|------------------|------------------|---------|---------------------|
| 3443       | \(A_g\) | s1(96)            |                   |         | \(\nu_{NH(3b)}\)  |
| 3432       | \(A_u\) | 3379 s97          | 3227             |         | \(\nu_{NH(3b)}\)  |
| 3156       | \(A_g\) | 3134 s96          |                   |         | \(\nu_{NH(3b)}\)  |
| 3116       | \(A_u\) | 3128 s96          |                   |         | \(\nu_{NH(3b)}\)  |
| 3116       | \(A_g\) | 3100 s96          |                   |         | \(\nu_{NH(3b)}\)  |
| 3106       | \(A_u\) | 3102 s96          |                   |         | \(\nu_{NH(3b)}\)  |
| 3026       | \(A_g\) | 3024 s98          |                   |         | \(\nu_{NH(3b)}\)  |
| 3025       | \(A_u\) | s10(87)            |                   |         | \(\nu_{NH(3b)}\)  |
| 2998       | \(A_g\) | s11(91)            |                   |         | \(\nu_{NH(3b)}\)  |
| 2997       | \(A_u\) | s12(92)            |                   |         | \(\nu_{NH(3b)}\)  |
| 2825       | \(A_g\) | s13(87)            |                   |         | \(\nu_{NH(3b)}\)  |
| 2821       | \(A_u\) | 2753 s14(88)       | 2346 1806 1768    |         |                     |
| 1705       | \(A_g\) | 1634 s15(62)       |                   |         | \(\nu_{CN(gua)}\) |
| 1703       | \(A_u\) | 1702 s16(62)       |                   |         | \(\nu_{CN(gua)}\) |
| 1613       | \(A_g\) | 1669 s17(88)       |                   |         | \(\delta_{NH_2}\) |
| 1611       | \(A_u\) | 1570 s18(80)       |                   |         | \(\delta_{NH_2}\) |
| 1537       | \(A_g\) | 1538 s20(53)       |                   |         | \(\nu_{CC + VCN}\) |
| 1529       | \(A_u\) | s21(51)            |                   |         | \(\nu_{CC + VCN}\) |
| 1523       | \(A_g\) | s22(44) s36(13) s38(12) | \(\nu_{CN(gua)}\) |         | \(\delta_{NH_2}\) |
| 1506       | \(A_u\) | s23(64) s22(13) s15(10) | \(\nu_{CN(gua)}\) |         | \(\delta_{NH_2}\) |
| 1504       | \(A_g\) | s24(58)s16(11)     |                   |         | \(\delta_{NH_2}\) |
| 1408       | \(A_u\) | 1408 s31(23) s25(17) s28(12) s41(10) | \(\nu_{CN(gua)}\) |         | \(\delta_{NH_2}\) |
| 1400       | \(A_g\) | 1408 s26(19) s33(14) s40(11) s32(10) s62(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CC + VCN}\) |
| 1309       | \(A_u\) | 1309 s29(57)       |                   |         | \(\nu_{CN(gua)}\) |
| 1309       | \(A_g\) | 1311 s30(51)       |                   |         | \(\nu_{CN(gua)}\) |
| 1231       | \(A_u\) | 1233 s31(54) s25(13) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1230       | \(A_g\) | 1231 s32(57) s27(11) s33(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1221       | \(A_u\) | 1222 s33(30) s21(13) s44(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1218       | \(A_g\) | 1217 s34(36) s25(34) s36(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1140       | \(A_u\) | s35(50)            |                   |         | \(\nu_{CN(gua)}\) |
| 1139       | \(A_g\) | 1128 s36(34) s20(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1127       | \(A_u\) | 1127 s37(57) s40(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1091       | \(A_g\) | 1089 s38(61) s22(14) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1090       | \(A_u\) | 1090 s39(15) s36(13) s22(12) s34(11) s20(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1043       | \(A_g\) | 1043 s40(23) s35(14) s21(10) s27(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 1042       | \(A_u\) | 1042 s41(52) s28(22) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 945        | \(A_g\) | 945 s42(51) s26(31) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 943        | \(A_u\) | 943 s43(52) s41(19) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 940        | \(A_g\) | 940 s44(54) s71(11) s42(10) | \(\nu_{CN(gua)}\) |         | \(\nu_{CN(gua)}\) |
| 927        | \(A_u\) | 927 s45(81)        |                   |         | \(\nu_{CN(gua)}\) |
| 892        | \(A_g\) | 892 s46(84)        |                   |         | \(\nu_{CN(gua)}\) |
| 892        | \(A_u\) | 892 s47(88)        |                   |         | \(\nu_{CN(gua)}\) |
| 859        | \(A_g\) | 859 s48(82)        |                   |         | \(\nu_{CN(gua)}\) |
| 855        | \(A_u\) | 855 s49(87)        |                   |         | \(\nu_{CN(gua)}\) |
| 826        | \(A_g\) | 826 s50(89)        |                   |         | \(\nu_{CN(gua)}\) |
| 824        | \(A_u\) | 824 s51(52)        |                   |         | \(\nu_{CN(gua)}\) |
| 781        | \(A_g\) | 781 s52(30)        |                   |         | \(\nu_{CN(gua)}\) |
| 780        | \(A_u\) | 780 s53(16)        |                   |         | \(\nu_{CN(gua)}\) |
| 726        | \(A_g\) | 726 s54(88)        |                   |         | \(\nu_{CN(gua)}\) |
| 724        | \(A_u\) | 724 s55(88)        |                   |         | \(\nu_{CN(gua)}\) |

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measured in the 3600–80 cm⁻¹ range with 2 cm⁻¹ resolution using Bruker IFS-88 instrument with FRA-106 attachment. Raman spectrum for (HPyCA)(I)I₃ was recorded using a Renishaw InVia Raman spectrometer equipped with a confocal DM 2500 Leica optical microscope.

Computational details

All the computations were performed with the Gaussian 16 program [11]. The calculations were carried out using density-functional theory (DFT) and hybrid Becke’s three-parameter and the Lee–Yang–Parr correlation functionals (B3LYP) [12–15] with Grimme’s correction for dispersion with Becke–Johnson damping [16]. The 6-311G(d,p) basis set was used, because it gives satisfactory results for vibrational and thermochemical data with respect to the computational costs [17]. For all the neutral and protonated forms of the PyCA, the minima were found for the singlet electronic state. Calculated total energy, zero-point energy (ZPE) plus thermal corrections and entropy are listed in Table 2, whereas Gibbs free energy and tautomer equilibrium constant for tautomeric equilibria of the neutral and protonated forms of 1H-pyrazole-1-carboxamidine are shown in Table 3.

Vibrational frequencies were calculated for protonated form of 1H-Pyrazole-1-carboxamidine, i.e., HPyCA⁺ ion. Since the HPyCA⁺ ion is involved in hydrogen bonding network in the studied crystal structures, the calculations were also carried out for the centrosymmetric [(HPyCA)₂Cl₄]²⁻ ionic system present in the crystal structure of (HPyCA)Cl (1). The positions of all the atoms were taken from crystallographic data, and a constrain with C₁ point group symmetry for geometry parameters was applied. Additionally, positions of four chloride anions were frozen in order to prevent the ions from escaping to infinity. Frequency of normal modes was...
| ν<sub>exp, IR</sub>(2) | ν<sub>exp, R</sub>(2) | ν<sub>exp, IR</sub>(3) | ν<sub>exp, R</sub>(3) | ν<sub>exp, IR</sub>(4) | ν<sub>exp, R</sub>(5) | Assignment |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|------------|
| 3380            | 3376            | 3346            | 3363            | 3151            | νNH             |            |
| 3235            | 3132            | 3125            | 3129            | 3132            | νNH             |            |
| 3128            | 3125            | 3109            | 3111            | 3139            | γCH             |            |
| 3101            | 3099            | 3052            | 3111            | 3139            | γCH             |            |
| 3117            | 3123            | 3109            | 3111            | 3121            | γCH             |            |
| 3023            | 3063            | 3060            | 3083            | 3121            | γCH             |            |
| 2753            | 2778            | 2562            | 2453            | 2326            | γCH             |            |
| 2646            | 2644            | 2330            | 2194            | 1836            | γCH             |            |
| 2342            | 2330            | 2194            | 1844            | 1805            | ν<sub>as</sub>CN<sub>(gua)</sub> |            |
| 2249            | 2194            | 1801            | 1633            | 1662            | ν<sub>as</sub>CN<sub>(gua)</sub> |            |
| 1843            | 1625            | 1619            | 1635            | 1700            | ν<sub>as</sub>CN<sub>(gua)</sub> |            |
| 1805            | 1625            | 1619            | 1635            | 1700            | ν<sub>as</sub>CN<sub>(gua)</sub> |            |
| 1633            | 1625            | 1619            | 1635            | 1700            | ν<sub>as</sub>CN<sub>(gua)</sub> |            |
| 1568            | 1558            | 1567            | 1556            | 1568            | δ<sub>NH<sub>2</sub> |            |
| 1537            | 1538            | 1538            | 1532            | 1529            | γCN             |            |
| 1407            | 1413            | 1408            | 1416            | 1407            | γCN             |            |
| 1397            | 1395            | 1391            | 1391            | 1392            | γCC + νCN       |            |
| 1309            | 1309            | 1309            | 1309            | 1308            | γCC             |            |
| 1221            | 1220            | 1227            | 1223            | 1229            | νCN + νCC       |            |
| 1128            | 1129            | 1112            | 1105            | 1130            | ρNH<sub>2</sub> |            |
| 1099            | 1097            | 1045            | 1041            | 1023            | δCH             |            |
| 1055            | 1050            | 1050            | 1050            | 1055            | ν<sub>as</sub>NC |            |
| 941             | 944             | 944             | 942             | 936             | γCH             |            |
| 927             | 928             | 928             | 928             | 919             | γCH             |            |
| 868             | 873             | 863             | 857             | 885             | γCH             |            |
| 735             | 730             | 758             | 723             | 723             | γCH             |            |

Note: The table lists experimental frequencies (ν<sub>exp</sub>) taken from infrared (IR) and Raman (R) spectra for (HPyCA)Cl·H<sub>2</sub>O (2), (HPyCA)Br (3), (HPyCA)<sub>2</sub>(I)I<sub>3</sub> (4), (HPyCA)HSO<sub>4</sub> (5) and assignment of the experimental bands. Frequencies in cm<sup>-1</sup>.
scaled using scaling equation $\nu_{sc} = 0.9614 \cdot \nu_{calc} + 17.8$ [17]. Juxtaposition of experimental and calculated frequencies for HPyCA$^+$ ion and [(HPyCA)$_2$Cl$_4$]$^{2-}$ ionic system and assignment of the bands are presented in the Tables 4 and 5, and in Supplementary Information.

Results and discussion

Protonation of 1H-pyrazole-1-carboxamidine

Theoretically, the neutral molecule of 1H-pyrazole-1-carboxamidine has as many as eight tautomers (Scheme 1). In this work, the tautomers are named after the labels of hydrogen atoms connected to the nitrogen atoms. This labeling scheme is inherited from crystallographic data (Fig. 1). For instance, the 3ab4a abbreviation means that two hydrogen atoms are bound to the N3 atom in $a$ and $b$ positions, one H-atom is connected to the N4 atom in $a$ position, but aromatic N2 atom is free, because its label does not occur in the abbreviation. A protonation route for the PyCA is presented in Scheme 1.

Table 2 shows that the most stable geometry is observed for 3ab4a form. However, calculations for the 23b4a, 23b4b, and 23a4b isomers failed revealing their instability. In the case of 23a4b isomer, a hydrogen atom bound to pyrazole N2 atom moved to the 3b position during geometry optimization. As a result, another isomer was formed, 3ab4b, which is the second most stable tautomer of PyCA neutral molecule. Surprisingly, there is one stable tautomer where the hydrogen atom is attached to the N2 atom, 23a4a, although it is featured by the highest energy (Table 2). The 23a4a form is probably a zwitterion consisting of a positively charged pyrazole and a negatively charged carboxamidine residue. It is worth noting that possible hopping of the hydrogen atom from N2 atom to 3b position in 23a4a results in the most stable 3ab4a form. Such proton transfer proceeds by analogy to the transformation between 23a4b and 3ab4b isomers, and it is very likely due to low $\Delta G$ for tautomerization to the energetically privileged 3ab4a form.

The calculations also revealed decomposition of both 23b4a and 23b4b isomers into pyrazole and cyanamide (its carbodiimid tautomer) during optimization of their structure. These results indicate strongly unfavorable binding of two hydrogen atoms to the N2 atom and at 3b site. Therefore, free energy for formation of PyCA from pyrazole and carbodiimid was calculated for five stable species. The only three isomers are featured by negative $\Delta G$ and the value for 23a4a relatively highly positive (Table 3). The tautomeric equilibrium constants clearly reveal that the main neutral form of PyCA is 3ab4a which stays in quite relevant equilibrium with 3ab4b tautomer.
The first protonation step theoretically gives five products. All these reactions are featured by large negative free energy. However, they differ from each other as much as one cationic form $3ab4ab^+$ is a dominant product at the first protonation step. The tautomeric equilibrium constants for the cations indicate that approximately only one molecule of the second energetically stable $23ab4ab^+$ ion may appear over a billion $3ab4ab^+$ ions. Besides, a molecule of the highest unfavorable $23ab4b^+$ tautomer can be found in the surroundings of 1 mmol of $3ab4ab^+$ ions. So, the latter is reasonably expected in solution as well as in a crystalline product obtained from acidic conditions.

The protonation route of PyCA eventually ends at the second stage leading to the formation of the $23ab4ab^{2+}$ ion. Here, all the proton acceptors are occupied. Since the protonation free energy is negative, formation of the $23ab4ab^{2+}$ ion bearing compound is also probable. However, it is worth noticing that the value of $\Delta G$ is twice lower than in the first protonation stage. So, any effort to obtain a crystalline product containing $23ab4ab^{2+}$ cation requires a strongly acidic condition.
Role of pyrazole and carboxamidine residue in formation of hydrogen bonding patterns

All the presented salts of 1H-pyrazole-1-carboxamidine crystallize in centrosymmetric space groups of monoclinic or triclinic symmetry (Table 1). The common feature of the studied compounds is the presence of the same cationic form of HPyCA⁺ ion, labeled as 3ab4ab⁺ in the former theoretical section, which is the most energetically privileged tautomer among all the HPyCA⁺ cations. Since the N2 atom of pyrazole ring is not protonated, it may play an acceptor role in a hydrogen bonding network. In the crystal structures of (HPyCA)Cl (1), (HPyCA)Cl·H2O (2), and (HPyCA)Br (3), two HPyCA⁺ are complementary arranged around the inversion center. The ions are connected to each other by two N3–H3B···N2 hydrogen bonds forming a ring pattern, R²(10) (Fig. 2a).

Interestingly, it is the only characteristic motif created by the N2 atom in the studied crystal structures. Two NH₂ groups of the carboxamidine residue and two anions create another ring pattern R²(4)(8), which is composed similarly to the R²(10) ring around the inversion center (Fig. 2b). This pattern occurs in the crystal structure of bisulfate and two chloride salts.

Figure 2c–f shows also small rings arranged in an ascending order R¹(6) < R²(8) < R³(8). Formation of these patterns can be expressed by the sum of the elementary graph-set descriptors, Eₐ(n), which were originally invented for description of atomic pathways in each independent molecule [6,7]. A juxtaposition of the molecules and formation of hydrogen bonding patterns are represented by the algebraic equation of elementary graph-set descriptors. Thus, the aforementioned rings are created as follows:

\[
E^0_2(5)_{HNCNH} + E^1_0(1)_{Cl/I} = R^1_2(6) \text{ (HPyCA)Cl (1) and (HPyCA)Br (3)}
\]

\[
E^0_2(5)_{HNCNH} + E^2_0(3)_{OSO} = R^2_2(8) \text{ (HPyCA)HSO₄ (5)}
\]

\[
E^0_2(5)_{HNCNH} + E^1_0(1)_{Cl} + E^1_1(2)_{HO} = R^3_3(8) \text{ (HPyCA)Cl·H₂O (2)}
\]

The first one occurs in the chloride salt (1) and bases on the bifurcated hydrogen bonding interaction of one chloride anion. The same two rings are found in (HPyCA)₂[I]₁ (4) and they are arranged in the pseudo centrosymmetric binary system. So, one iodide anion takes part in as many as four hydrogen bonds and such surrounding of the anion is not present in the other studied crystal structures. In the bisulfate salt (5), the ring pattern is naturally enlarged due to two oxygen atoms are involved in hydrogen bonding network. Therefore, the simplest ring R²(6) is expanded by the S–O two-atomic pathway, which can be expressed by the elementary graph-set E₀(2)SO.

Using algebraic approach, a relation between two patterns found in chloride and bisulfate is written as R²(6) + E₁(2) = R²(8). Similarly, the ring R³(8) present in (HPyCA)Cl·H₂O (2) results from expansion of the simplest R¹(6) pattern by the O–H pathway R²(6) + E₁(2) = R³(8).

Apart from the rings, the chain patterns have got high importance in a view of propagation of the crystal structure and of the crystal growth. In (HPyCA)HSO₄ (5), (HPyCA)Cl·H₂O (2), and (HPyCA)Cl (1), very short chain patterns containing only four atoms are found, C¹(4) or C¹(2). The former is
created by the only one symmetry independent O1–H10···O4 hydrogen bond and exists in the crystal structure of (HPyCA)HSO4 (5) (Fig. 3a). The latter C12(4) chain is observed in (HPyCA)Cl·H2O (2) and it runs through the Cl− anions and water molecules. In the case of (HPyCA)Br (3) and (HPyCA)Cl (1), the C12(4) chain is constructed by the NH2 group and anions. So, the organic cations are involved in stabilization of the hydrogen bonding network in the crystal structure of bromide and chloride salts, but interestingly the HPyCA+ ions are completely omitted in those short chains in bisulfate and hydrated chloride salts. Such architecture of the network is probably connected to the high tendency of the bisulfate anions to associate with each other, as a data mining of Cambridge Structural Database reveals a lot of crystal structures containing the (HSO4–)n chains [4, 5]. A branched molecular structure of the HSO4− ion may also be important in this question.

Figure 3 shows that the chain patterns are connected to each other by the HPyCA+ associated in dimers forming aforementioned R22(10) or R24(8) rings. So, one can infer that the rings play a supporting role in stabilization of the crystal structures. However, their role cannot be regarded as secondary, as creation of the dimers allows crystal growth along orthogonal direction to the chains.

Vibrational characteristics

Geometry data taken from crystal structure analysis show weak nature of N/O–H donor hydrogen bonds in the studied compounds except one O–H···O interaction. The shortest donor–acceptor distance is observed for the O–H···O hydrogen bond, 2.5969(19) Å (Table S1), formed by the adjacent bisulfate anions in (HPyCA)HSO4 (5). According to earlier Novak’s work, the band associated with the stretching vibration of hydroxyl group νOH is seen at 2453 cm−1 [18]. This value correlates very well with a dependence of OH stretching frequency on O···O distance and indicates medium-strong feature of O–H···O hydrogen bond in the (HPyCA)HSO4 crystal. A medium hydrogen bond of the N–H···O type is created in (HPyCA)Cl·H2O (2). Since the N···O distance is 2.800(3) Å, the νNH band is observed in higher frequency region than νOH in the bisulfate salt, 3136 cm−1 (Fig. 4). Geometry data for the other N–H···donor hydrogen bonds indicate their weak nature, and therefore, the respective νNH bands are expected near the νCH ones. So, theoretical calculations have been carried out for the HPyCA+ ion and potential energy distribution analysis was performed (Table S2). However, such kind of calculations can provide artificial results; theoretical frequencies of normal modes were also determined for the complex [(HPyCA)2Cl4]2− ionic system with C1 point group symmetry constrain for geometry parameters. Generally, Table 4 shows good agreement of the theoretical and experimental frequencies and PED analysis reveals a character of each mode.

According to the crystallographic data, the HPyCA+ ions are arranged in pairs and connected to each other by two relatively long N3–H3B···N2 hydrogen bonds, 3.028(3) Å.
Although it is the shortest hydrogen bonding interaction in (HPyCA)Cl (1), the N–H···N angle is significantly lower than 180 deg indicating very low strength in this intermolecular interaction. Calculations of theoretical frequencies for the [(HPyCA)2Cl4]2– anions suggest that the N–H···N hydrogen bond is the weakest one in the crystal structure of (HPyCA)Cl (1). Both N3–H3A···Cl1 and N4–H4A···Cl1 have similar geometry, albeit longer N···Cl distance is observed than for N3···N1, which is probably connected to a different radius for nitrogen atom and chloride anion. Those two N–H···Cl hydrogen bonds are expectedly coupled resulting in the symmetric and antisymmetric $\nu$NH2(3a+4b) modes. Accordingly, two well-shaped bands seen in the infrared spectrum at 3321 and 3030 cm$^{-1}$ are assigned. Interestingly, the Raman component of the latter band is probably observed at 3024 cm$^{-1}$.

A series of relatively broad bands are observed in the infrared spectra in the range of 2000–3600 cm$^{-1}$. They lie at a little bit higher frequency region in the spectrum of the bromide salt suggesting weaker nature hydrogen bonding network in (HPyCA)Br (3). Although one may expect lower strength of intermolecular interactions for (HPyCA)$_2$(I)$_3$ (4) according to well-known tendency among the halides, the aforementioned $\nu$NH bands for 4 appear at approximately the same position as for bromide. Such somewhat unusual result can be associated with two speciation forms of iodide or a multitude of intermolecular interactions (Table S1). In the case of (HPyCA)Cl·H2O (2), both infra-red and Raman spectra have got almost the same shape as (HPyCA)Cl (1). However, a few bands covered in the $\nu$NH/$\nu$OH region result in noticeably broader absorption, especially in the lower frequency part. Taking into account geometry parameters for the N3–H3A···O1 hydrogen bond (Table S1), the maximum of the $\nu$OH band is expected below 3000 cm$^{-1}$. So, the strength of hydrogen bonding network in the hydrated chloride salt appears to be higher than anhydrous chloride.

Apart from stretching modes, several bands associated with the bending vibration of the NH2 groups are seen in the spectra. The bands attributed to the in-plane bending modes, $\delta$NH2, occur near the $\nu$CN bands at 1669 and 1537 cm$^{-1}$ in the infrared spectrum of (HPyCA)Cl (1), whereas rocking vibrations are observed at 1127 and 1099 cm$^{-1}$. The position of these bands does not differ so much for the other studied salts of PyCA. So, a strength of hydrogen bonds can be assessed on the basis of the stretching vibrations in the following ascending series: (HPyCA)$_2$(I)$_3$ (4) < (HPyCA)Br (3) < (HPyCA)Cl (1) < (HPyCA)Cl·H2O (2) < (HPyCA)HSO4 (5).

Among all the studied compounds, the internal vibrations of the anion can be observed in the (HPyCA)$_2$(I)$_3$ (4) and...
The (HPyCA)Cl (1) was used to obtain four new salts of 1H-pyrazole-1-carboxamidine with various inorganic acids. The simplicity of synthetic procedure of presented compounds can be optionally used in organic synthesis wherever other salt than commercially available (HPyCA)Cl (1) is required. Since the literature data as well as Cambridge Structural Database do not contain any structural data about the salts of PyCA, five crystal structures were determined by means of single-crystal X-ray diffraction and presented here. The topological analysis with algebraic approach on the graph-set descriptors of hydrogen bonding patterns showed similarities in formation of particular patterns regardless of the counterion present in the structure. This fact was also confirmed by vibrational spectroscopy, where some differences in the infra-red spectra were observed in the high frequency region for νNH modes. In all the studied compounds, the HPyCA+ possesses protonated carboxamidine group, whereas the nitrogen atom of pyrazole ring is deprotonated. Theoretical calculations on the protonation route of PyCA revealed that aforementioned speciation cationic form of 1H-pyrazole-1-carboxamidine is the only favored one. Besides, these calculations showed two relatively numerous stable neutral forms and also two other tautomers that are unstable. The molecules decomposed into pyrazole and carbodiimid tautomer of cyanamide. This result seems only seemingly insignificant, but it shows possible mechanism of guanylation by PyCA which is important step in synthesis of some biological active compounds including antiviral drugs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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