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Formyl-L-arginine monohydrate ☆

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Abstract

A new compound N^{α}-formyl-L-arginine $^{+}(H_2N)_2CNH(CH_2)_3CH(HN(HCO))COO^{-}$ with zwitter-ionic structure has been found out in the system L-arginine + HCOOH + H_2O. The title compound crystallizes in monoclinic system (space group $P2_1$) as monohydrate. Crystal structure has been determined by single crystal X-ray diffraction method and FTIR ATR, FT Raman spectra are reported. Dehydration process has been studied.

Keywords: Formyl-L-arginine; Crystal structure; Vibrational spectra

1. Introduction

In the system L-Arg + $H_2C_2O_4$ + H_2O, where L-Arg is L-arginine and $H_2C_2O_4$ is oxalic acid, in addition to salts with various compositions, a compound with non-salt nature N^{α}-oxalyl-L-arginine (NOLA) was discovered [1]. The crystal NOLA has been found out as a result of long standing of the mother solution at 35 °C during crystal growth of L-arginine oxalate. In the molecule of NOLA guanidyl group is protonated due to deprotonation of oxalyl group, while carboxyl group remains neutral. So, NOLA has a zwitter-ionic structure: $^{+}(H_2N)_2CNH(CH_2)_3CH(NHC_2O_3^{\,-})COOH$. Similar compound has been found out by us in the system L-Arg + HCOOH + H_2O.

From this system a salt L-Arg·HCOOH with monoclinic symmetry has been obtained [2]. In Ref. [3] another form of L-Arg·HCOOH with orthorhombic symmetry was obtained. Earlier in Ref. [4] the salt L-Arg·HCOOH has been obtained in form of powder. During crystal growth of L-Arg·HCOOH a new compound N^{α}-formyl-L-arginine (NFLA) has been discovered [5]. The present work deals with investigation of this compound by X-ray diffraction and vibrational spectroscopic methods.

2. Experimental

The starting reagents were L-arginine (Sigma Chem. Co.) and formic acid (MERCK 98–100% GR). X-ray diffraction data for the structure analysis were collected by a CAD-4 Enraf Nonius diffractometer. For the structure solution and refinement we used the programs SHELXS 97 and SHELXL 97 [6,7]. Fourier transform Raman spectra were registered by a NXP FT-Raman Module of a Nicolet 5700 spectrometer (number of scans 512, resolution 4 cm^{-1}). The same spectrometer was used for measuring IR spectra with nujol (4000–400 cm^{-1}, number of scans 32, resolution 2 cm^{-1}). Attenuated total reflection Fourier transform infrared spectra (FTIR ATR) were registered by the aid of a Nicolet “Nexus” FT-IR spectrometer with ZnSe prism (4000–650 cm^{-1}, number of scans 16, resolution 4 cm^{-1}).

☆ CCDC 609291 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033).

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For the study of thermal properties we employed a Paulik–Paulik–Erdey Derivatograph (MOM, Hungary) and also a Boëtius type microscope with heating table.

3. Results and discussion

3.1. Formation of N^{α}-formyl-L-arginine

N^{α}-Formyl-L-arginine (NFLA) is formed in aqueous solution containing L-arginine and formic acid in mole ratio 1:2 at a temperature above 30 °C. It was discovered during crystal growth of L-Arg·HCOOH and can be formed according to the following scheme:

$$^{+}(H_2N)_2CNH(CH_2)_3CH(NH_2)COO^{-} + HCOOH \rightarrow {}^{+}(H_2N)_2CNH(CH_2)_3CH(HN(HCO))COO^{-} + H_2O$$

Crystals formed at 38 °C proved to be monohydrate (NFLA·H_2O). Recrystallization at room temperature results in the same phase. At 60 °C anhydrous NFLA in powder form can be obtained from solution (see Section 3.4). In contrast to oxalyl-L-arginine [1], formyl-L-arginine monohydrate has very high solubility. It is possible to obtain NFLA·H_2O in form of bulk crystals. Due to presence of optically active L-arginine moiety NFLA·H_2O crystallizes in non-centrosymmetric group (space group $P2_1$) and displays second harmonic generation signal of a Nd:YAG laser [5].

Table 1
Crystal data and structure refinement for N^{α}-formyl-L-arginine monohydrate

Identification code	NFLA·H_2O
Empirical formula	$C_7H_{16}N_4O_4$
Formula weight	220.24
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	$a = 7.3099(15)$ Å, $\alpha = 90°$; $b = 8.8550(18)$ Å, $\beta = 94.93(3)°$; $c = 8.3716(17)$ Å, $\gamma = 90°$
Volume (Å^3)	539.88(19)
Z	2
Density (calculated) (Mg/m^3)	1.355
Absorption coefficient (mm^{-1})	0.111
$F(000)$	236
Crystal size (mm^3)	$0.14 \times 0.17 \times 0.22$
Theta range for data collection	2.44–29.96°.
Index ranges	$0 \leqslant h \leqslant 10$, $-12 \leqslant k \leqslant 12$, $-11 \leqslant l \leqslant 11$
Reflections collected	3358
Independent reflections	3141 [$R_{\text{int}} = 0.0119$]
Completeness to theta = 29.96°	100.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3141/1/200
Goodness-of-fit on F^2	1.032
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0340$, $wR2 = 0.0823$
R indices (all data)	$R1 = 0.0409$, $wR2 = 0.0864$
Largest diff. peak and hole	0.205 and −0.151 e Å^{-3}

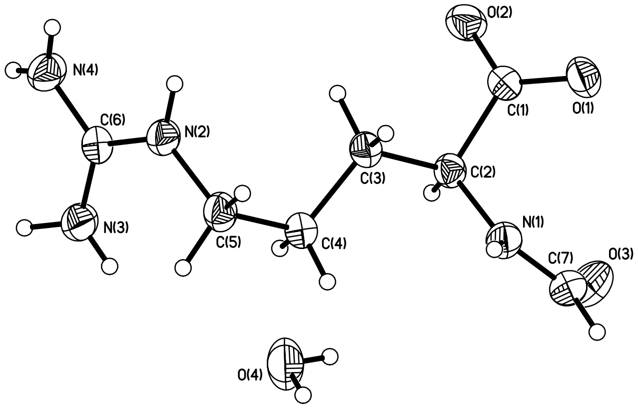

Fig. 1. Independent part of unit cell of N^{α}-formyl-L-arginine monohydrate (NFLA·H_2O) and atomic numbering scheme.

3.2. Crystal and molecular structure

Formyl-L-arginine crystallizes in monoclinic system. Crystallographic data and details of structure refinement are listed in Table 1. Independent part of unit cell contains one formyl-arginine molecule and a water molecule (Fig. 1). As in case of NOLA the molecule of formyl-L-arginine has zwitter-ionic structure. However, here protonation of guanidyl group occurs due to carboxyl group of L-arginine moiety, in contrast to NOLA, where protonation of guanidyl group occurs due to oxalyl group. So, the molecule of NOLA can be compared with doubly charged L-Arg^{2+} cation, while NFLA can be compared with singly charged L-Arg^{+} cation. Intramolecular bond

Table 2
Bond lengths [Å] and angles [°] for N^{α}-formyl-L-arginine monohydrate

C(1)–O(1)	1.2578(16)	C(6)–N(2)–C(5)	125.1(1)
C(1)–O(2)	1.2519(16)	O(2)–C(1)–O(1)	124.8(1)
C(7)–O(3)	1.232(2)	O(2)–C(1)–C(2)	116.5(1)
N(1)–C(7)	1.316(2)	O(1)–C(1)–C(2)	118.8(1)
C(2)–N(1)	1.457(2)	N(1)–C(2)–C(3)	109.7(1)
C(5)–N(2)	1.459(2)	C(3)–C(2)–C(1)	110.3(1)
C(6)–N(2)	1.325(2)	N(1)–C(2)–C(1)	112.2(1)
C(6)–N(3)	1.326(2)	C(4)–C(3)–C(2)	112.6(1)
C(6)–N(4)	1.332(2)	C(5)–C(4)–C(3)	112.9(1)
C(1)–C(2)	1.540(2)	N(2)–C(5)–C(4)	113.3(1)
C(2)–C(3)	1.529(2)	N(2)–C(6)–N(3)	122.7(1)
C(3)–C(4)	1.529(2)	N(2)–C(6)–N(4)	118.1(1)
C(4)–C(5)	1.521(2)	N(3)–C(6)–N(4)	119.3(1)
C(7)–N(1)–C(2)	124.8(1)	O(3)–C(7)–N(1)	126.1(1)

Table 3
Hydrogen bonds parameters (Å, °) in the structure of N^{α}-formyl-L-arginine monohydrate (NFLA·H_2O)

D–H	d(D–H)	d(H···A)	⟨DHA	d(D···A)	A
N1–H2	0.87(3)	2.13(3)	151(2)	2.919(2)	O1 [$-x, y-1/2, -z+1$]
N2–H10	0.86(2)	2.00(2)	170(2)	2.856(2)	O2 [$-x, y-1/2, -z$]
N3–H11	0.81(2)	2.20(2)	164(2)	2.980(2)	O3 [$-x+1, y-1/2, -z+1$]
N3–H12	0.92(2)	1.98(2)	170(2)	2.887(2)	O2 [$-x+1, y-1/2, -z$]
N4–H13	0.83(2)	2.09(2)	168(2)	2.903(2)	O1 [$-x, y-1/2, -z$]
N4–H14	0.82(2)	2.05(2)	162(2)	2.841(2)	O4 [$-x+1, y+1/2, -z$]
O4–H15	0.89(3)	1.91(3)	174(2)	2.802(2)	O3 [$x, y-1, z$]
O4–H16	0.78(3)	2.09(3)	167(3)	2.854(2)	O1 [$-x, y-1/2, -z+1$]

lengths and angles are given in Table 2. Bond lengths C(1)–O(1) (1.258 Å), C(1)–O(2) (1.252 Å) and O(1)–C(1)–O(2) angle (125°) are characteristic for carboxylate group (compare with respective values of L-Arg·HNO_3·0.5H_2O [8] and L-Arg·$HClO_3$ and L-Arg·$HBrO_3$ [9]). In formyl group C(7)–O(3) bond length is equal to 1.232 Å. C–C distances are also typical. C–N bond lengths in guanidyl group have expected values, while N–C(6)–N angles indicate that guanidyl group slightly deviates from expected planarity. Bond length C(2)–N(1) (1.457 Å) is somewhat shorter than the respective value C(2)–NH_3^+ (ca. 1.500 Å) of L-Arg^+ cation and is close to the respective value of NOLA (1.452 Å). Torsion angles: O1C1C2N1(φ^1) (−6.3(2)°), N1C2C3C4(χ^1) (−65.0(1)°), C2C3C4C5(χ^2) (176.4(1)°), C3C4C5N2(χ^3) (61.6(1)°), C6N2C5C4(χ^4) (85.0(2)°), C5N2C6N4(χ^5) (175.1(1)°) determine the conformation of L-arginine moiety, while the C2N1C7O3 (−2.7(2)°) angle that of formyl moiety. Hydrogen bonds parameters are given in Table 3. All active hydrogen atoms are involved in hydrogen bonds (Fig. 2). Oxygen atom O(1) forms three hydrogen bonds, while each of O(2) and O(3) form two hydrogen bonds. Water molecule binds together three neighboring molecules forming two hydrogen bonds as a donor (O4–H15···O3 and O4–H16···O1) and one hydrogen bond as an acceptor (N4–H14···O4). Conformation

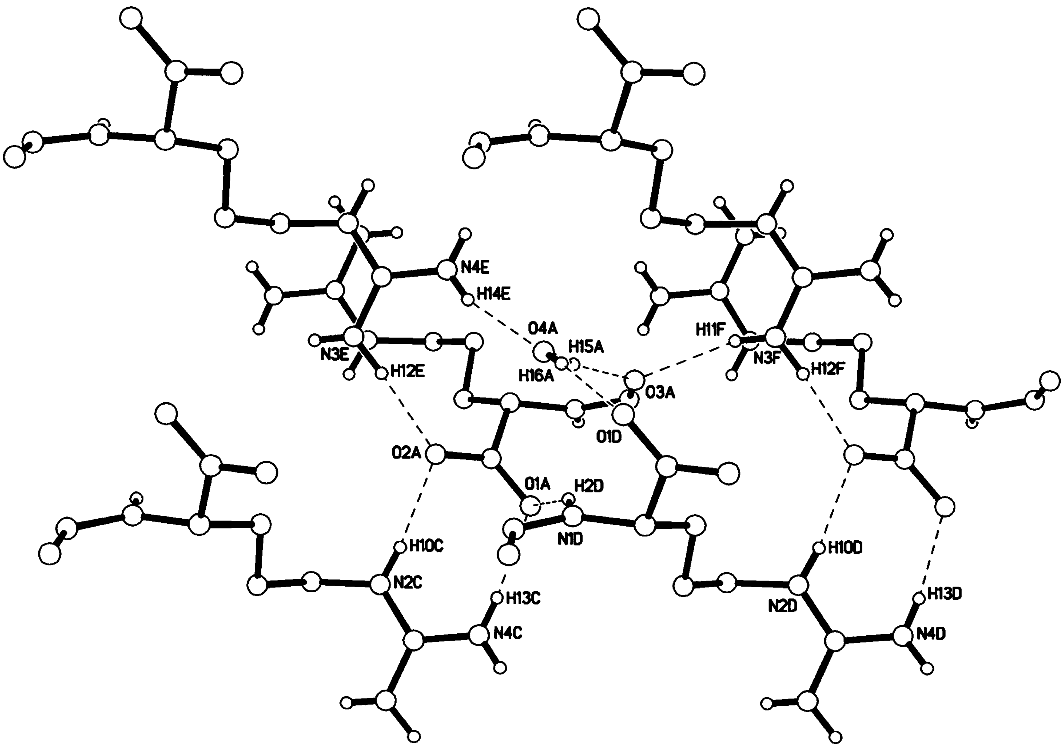

Fig. 2. Hydrogen bonding scheme in the structure of NFLA·H_2O.

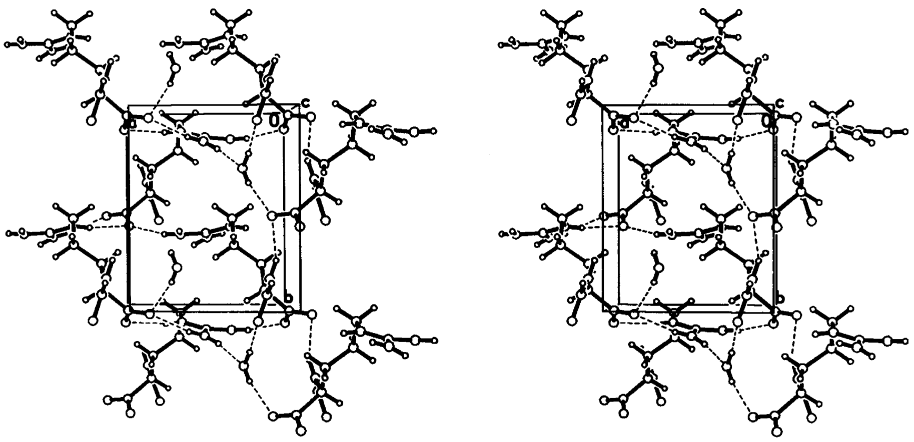

Fig. 3. A stereoscopic view of packing in the crystal structure of NFLA·H_2O.

and hydrogen bonds scheme of the NFLA molecule can be seen from stereoscopic view of packing in the crystal structure shown in Fig. 3. As can be seen from Table 3 and Fig. 2 nitrogen atoms N(2) and N(4) form hydrogen bonds N(2)–H···O(2) and N(4)–H···O(1) with oxygen atoms O(1) and O(2) of the same neighboring molecule. Such type of hydrogen bond is designated as type B in Ref. [10].

3.3. FTIR ATR and raman spectra

FTIR and FT Raman spectra are shown in Figs. 4 and 5. Wavenumbers with tentative assignment of some characteristic bands are collected in Table 4. Absorption bands in the high-frequency region (3500–2800 cm^{-1}) are related to stretching vibrations of O–H, N–H and C–H bonds. In the Raman spectrum, strong characteristic

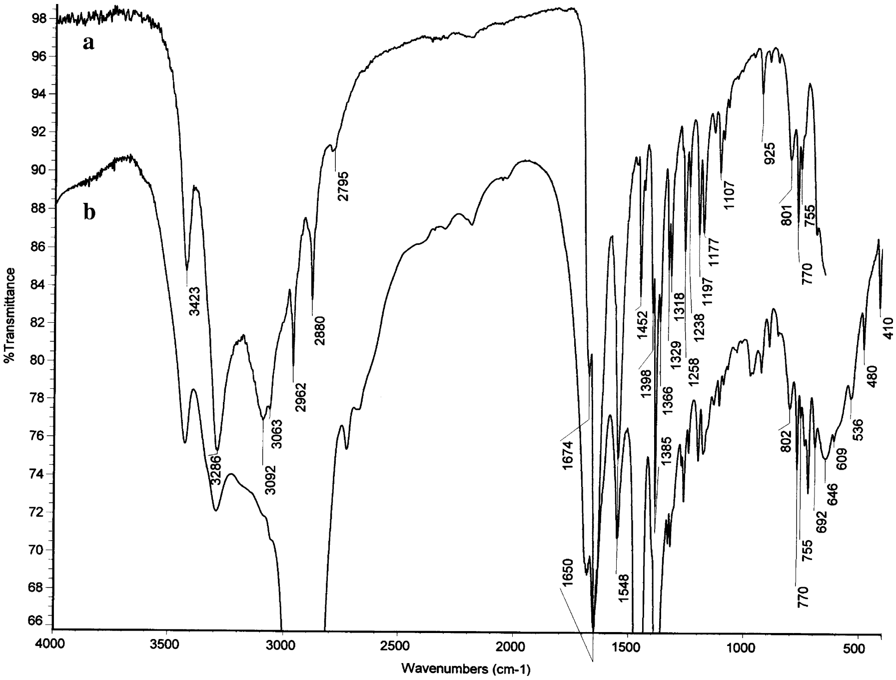

Fig. 4. FTIR spectra of NFLA·H_2O [ATR (a), in nujol (b)].

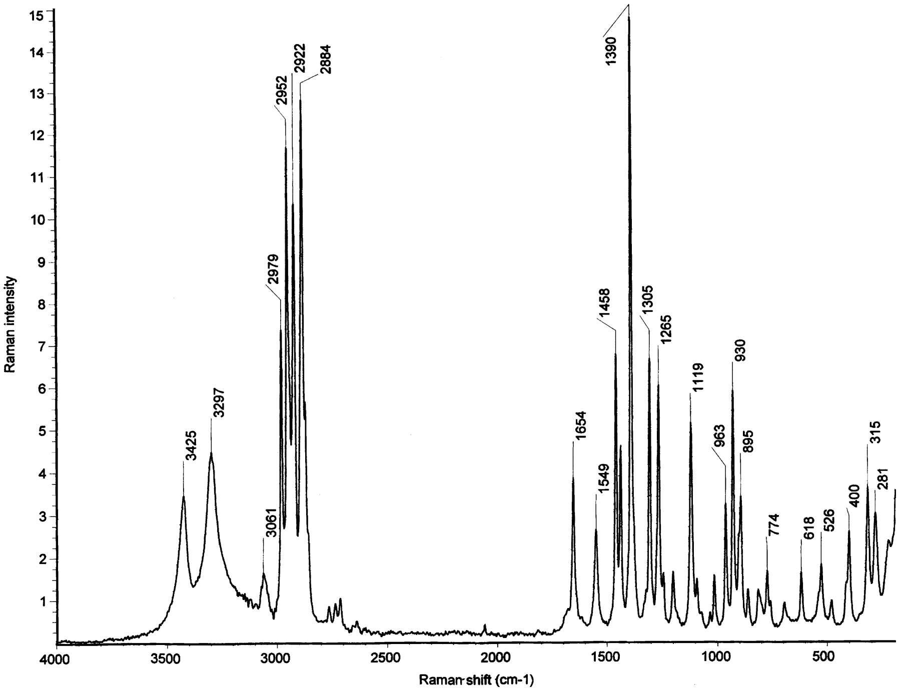

Fig. 5. FT Raman spectrum of NFLA·H_2O.

Table 4
Wavenumbers (cm^{-1}) of IR absorption peaks and Raman lines in the spectra of NFLA·H_2O

IR	Raman	Assignment
3423	3425	H_2O stretching
3286	3297	N–H stretching of NH and NH_2 groups
3092; 3063	3061	N–H stretching of NH and NH_2 groups
2962	2979; 2952; 2922	C–H stretching of CH_2 groups
2880	2884; 2871	C–H stretching of CH groups
2795	2765; 2736; 2713	Overtones
2195		Combinational
1674	1678	C═O stretching of formyl group
1650	1654	Asymmetric stretching of COO^- group
1548	1549	Deformation of NH_2 groups
1464; 1452	1458	Deformation of CH_2 groups
1434	1437	Deformation of CH_2 groups
1398;1385	1390	Symmetric stretching of COO^- group
1366		
1329		Wagging of CH_2 groups
1318	1305	Twisting vibration of CH_2 groups
1269	1265	Twisting vibration of CH_2 groups
1258		
1238	1244	
1197	1200	C–N stretching of C–NHCHO group
1177	1169	Wagging of NH_2 groups
1131	1119	Rocking of CH_2 groups
1107		
1090	1093	
1070	1073; 1034; 1015	Stretching of C–N bonds
960	963	
925	930	
891	895	Stretching of C–C bonds
855	862	Stretching of C–C bonds
801	815	
770	774	Deformation of COO^- group
755; 739	759	
692	695	Deformation of COO^- group
646		
609	618	Libration of H_2O
536	526	Libration of H_2O
480	479	Rocking of COO^- group
410	413; 400	
	315	
	281	
	221	

peaks at 2884, 2919, 2950, 2976 cm^{-1} are related to stretching vibrations of C–H bonds, hence narrow bands at 2880 and 2962 cm^{-1} in the IR spectrum are related to C–H bonds as well. We assign absorption band at 3423 cm^{-1} (corresponding Raman-line is at 3425 cm^{-1}) to stretching vibration ν(O–H) of water molecule. From the correlation of ν(O–H) vs. R(O···O) [11] one can estimate ν(O–H) ca. 3400 cm^{-1} for 2.802 and 2.854 Å (O4···O3 and O4···O1, respectively), which is in good agreement with observed value 3423 cm^{-1}. Other bands (3063, 3092, 3286 cm^{-1}) are related to stretching vibrations of N–H bonds of NH_2 and N–H groups. Deformation vibrations of water molecule, NH_2 group and also asymmetric stretching vibrations of carboxylate and formyl groups are in the 1700–1500 cm^{-1} region. The peak at 1674 cm^{-1}, which probably corresponds to ν(C═O) of formyl group, is shifted towards low-frequency region due to two formed hydrogen bonds. A strong band at 1385 cm^{-1}, which has a Raman-counter part at 1390 cm^{-1}, can be assign to symmetric stretching vibration of carboxylate group. Absorption band in the 500–700 cm^{-1} region (measured in nujol) may be assigned to libration vibrations of water molecule and deformation vibrations of carboxylate group.

3.4. Dehydration of NFLA·H_2O

Thermogravimetric (TG), derivative thermogravimetric (DTG) and differential thermoanalytical (DTA) curves are shown in Fig. 6. The first loss of mass having endothermic character occurs near 110 °C. Apparently, this process is caused by dehydration. However, the loss of mass (6.6%) is less than 8.18% expected for one water molecule. Respective quantity is equal to $n = 0.8$. The second loss of mass also having endothermic character occurs near 175 °C. For elucidation of the nature of these processes, we heated NFLA·H_2O at 125 °C and 190 °C. Registered IR spectra of obtained specimens are shown in Figs. 7(a and b). Comparison of these spectra shows their great similarity. The main distinction is the presence of a band at 3284 cm^{-1} which disappears at complete dehydration. So one can suppose that at partially dehydration a compound with definite composition (5NFLA·H_2O) is formed and the band at 3284 cm^{-1}

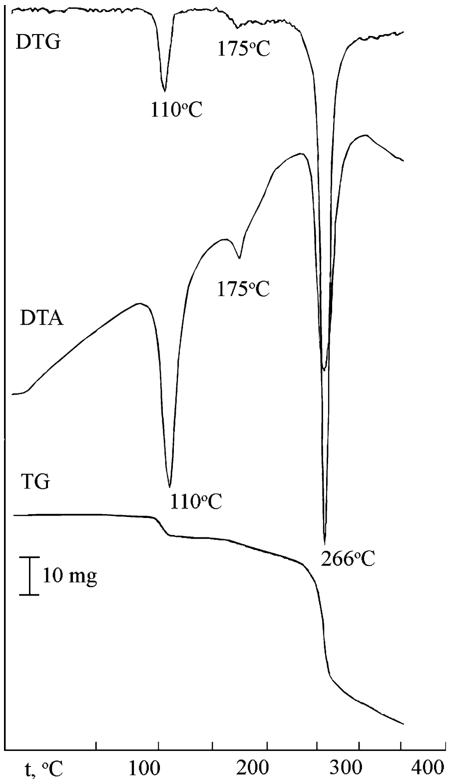

Fig. 6. Thermogravimetric (TG), derivative thermogravimetric (DTG) and differential thermoanalytical (DTA) curves of NFLA·H_2O.

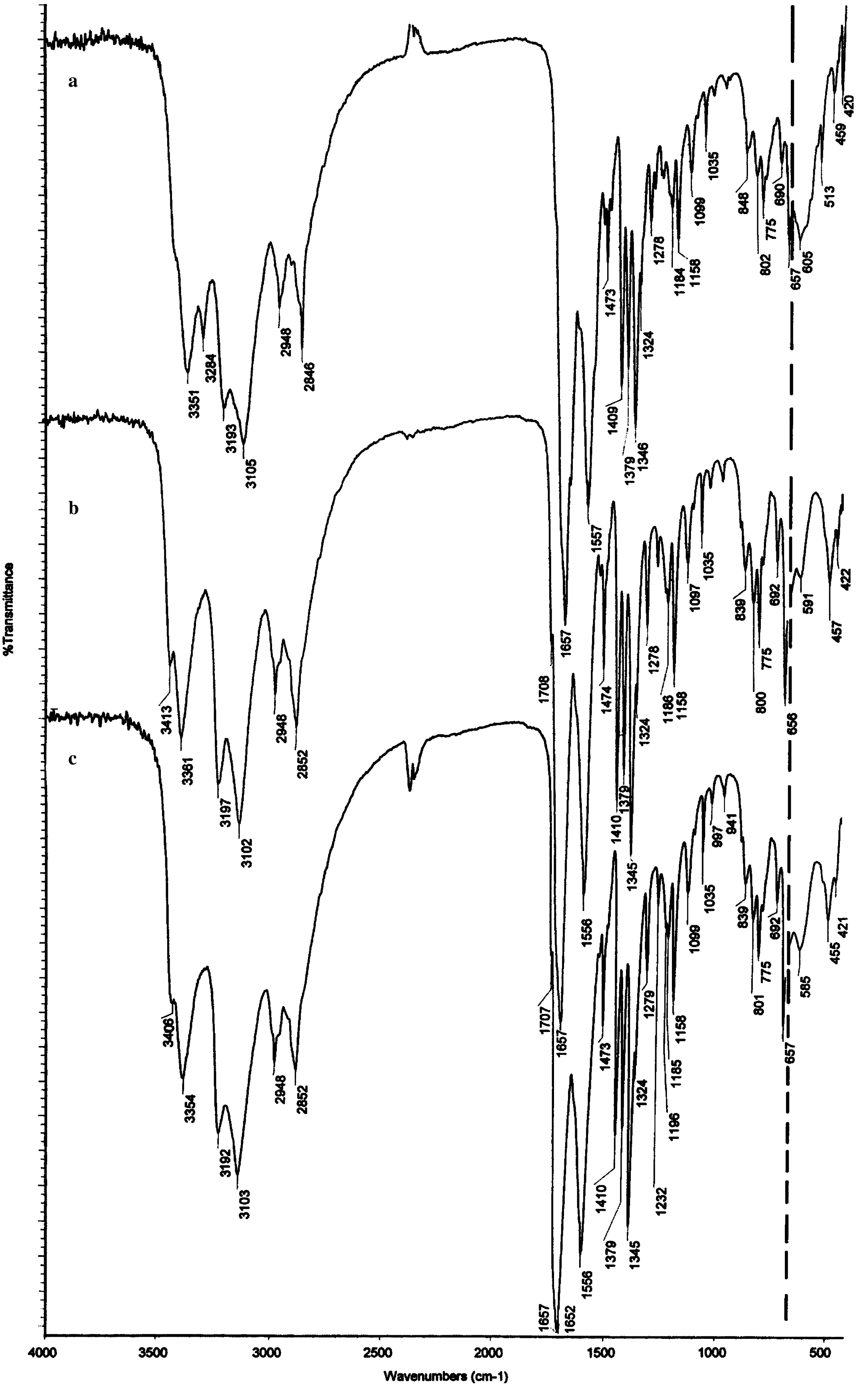

Fig. 7. ATR-IR spectra of NFLA·H_2O heated at 125 °C (a) and 190 °C (b) and specimen obtained from solution at 60 °C (c) [spectra in the 650–400 cm^{-1} region are measured in nujol].

corresponds to stretching vibration of water molecule. It is possible to notice also changes in the region of libration vibrations of water molecule. We tried to obtain anhydrous NFLA from water solution at higher temperature and have succeeded to obtain anhydrous NFLA at 60 °C in form of white powder. IR spectrum (Fig. 7c) of this specimen completely coincides with spectrum of anhydrous NFLA obtained by dehydration at 190 °C. This spectrum contains a shoulder at 1707 cm^{-1}, which we assign to $\nu(C{=}O)$ of formyl group. We recrystallized from water solution at room temperature specimens obtained by heating at 125 °C and 190 °C, as well obtained from solution at 60 °C. In all cases recrystallized specimens proved to be NFLA·H_2O by IR spectra. This shows that the process at 175 °C is caused by complete dehydration and not by decomposition of NFLA molecule. Decomposition of the NFLA molecule occurs near 266 °C.

4. Conclusions

A new L-arginine derivative with non-salt nature, namely, N^{α}-formyl-L-arginine monohydrate (NFLA·H_2O) has been obtained and studied by single crystal X-ray diffraction and vibrational spectroscopic methods. Anhydrous NFLA in form of powder has been obtained by dehydration of NFLA·H_2O at 190 °C and also from aqueous solution at 60 °C.

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