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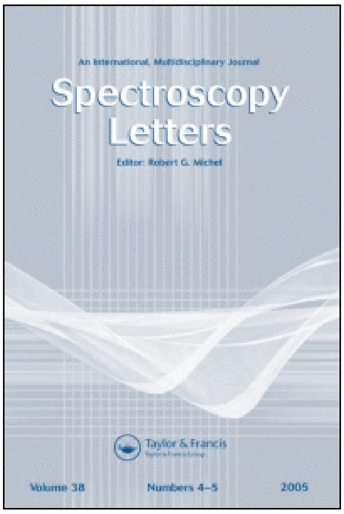

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Theoretical and Experimental Study of the Conformation and Vibrational Frequencies of N-Acetyl-L-alanine and N-Acetyl-L-alaninate

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ABSTRACT

The vibrational frequencies of N-acetyl-L-alanine (NAAL), its potassium salt (NAALK) and its free anionic form ($NAAL^-$) are calculated using density functional theory (B3LYP) combined with the 6-311 + + G(d,p) basis set. The experimental Raman spectrum of solid NAALK and the scaling factors for calculated values are discussed as well. The three species are characterized by intramolecular NH...O

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hydrogen bonds leading to the formation of a five-membered ring. As indicated by the intramolecular (N)H...O distances and by the ν(NH) frequencies, the strength of the intramolecular hydrogen bond is ordered as follows: NAAL$^-$ < NAALK < NAAL$^-$. Owing to their difference in the coupling with other vibrational modes, the in-plane and out-of-plane vibrations do not reflect the strength of the hydrogen bond.

Key Words: N-acetyl-L-alanine; N-acetylalaninate; DFT calculations; Conformation; Raman spectrum; Intramolecular hydrogen bond.

INTRODUCTION

The conformation of dipeptides has been well documented by many experimental[1–9] and theoretical[10–16] studies. It emerges from these studies that the most stable conformation of the dipetides is characterized by C=O...HN intramolecular hydrogen bonds leading to the formation of a five-membered ring (C5 conformation) or a seven-membered ring (C7 conformation). Amino acids and N-protected amino acids may also be stabilized by intramolecular hydrogen bonds.[17–19] Simple amino acids such as glycine, α-alanine, and proline exist in the gas phase in the non-ionized forms.[20–22] In low-temperature matrices, glycine, α-alanine and valine are also present in the neutral forms.[23–25] Simple peptides[26] are zwitterions at physiological pH and they are ideal model systems for exploring the influence of negatively or positively charged groups on the peptide's structural and vibrational properties. While the zwitterionic form of the simplest aminoacid glycine is not a minimum in vacuo, it is well known that this tautomeric form predominates in crystalline or aqueous media.[27] In a recent work,[28] we have shown using the experimental infrared spectra and ab initio calculations (density functional theory (DFT-B3LYP)) that the *trans* conformer of N-acetyl-L-alanine (NAAL), where the NH bond and the C=O bond of the acetyl group are in *trans* position, is stabilized by an intramolecular NH...O hydrogen bond leading to the formation of a five-membered ring. As shown in recent works,[29–31] vibrational spectroscopy appears to be an excellent method to investigate the structure of aminoacids in solution. It must also be mentioned that the K$^+$ cations can induce conformational changes when they bind to aminoacids.[32,33] It seemed therefore interesting to us to investigate the conformation and the strength of the intramolecular hydrogen bond in the potassium salt of NAAL (NAALK) and in the deprotonated form of NAAL (NAAL$^-$). The experimental Raman spectrum of solid NAALK at room temperature is discussed as well.

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EXPERIMENTAL AND THEORETICAL METHODS

Experimental Methods

The Raman spectrum of solid NAALK has been recorded at room temperature on the FTS Bruker 66 spectrophotometer equipped with the FRA-106 Raman module (resolution = 2 cm^{-1}; source = YAG Laser operating at 1.06 μm with a power of 200 mW; detector = cooled-Ge). The spectrum resulted from 1000 accumulations.

The K salt of NAAL was prepared from the evaporation of an equimolecular solution of NAAK and KOH. NAAL purchased from Sigma has been used without further purification and kept in an excicator at temperature lower than 0°.

Theoretical Methods

In a first step, the geometries of NAAL, NAALK and $NAAL^-$ were optimized using the DFT with the hybrid B3LYP exchange correlation functional[34,35] and the 6-311 + + G(d,p) basis set. This level was choosen because calculations without diffuse and polarization functions for the heavy and hydrogen atoms may be inadequate for ion-molecule complexes.[32,33] The Gaussian 98 package was used for the calculations.[36] The harmonic vibrational frequencies and eigenvectors were subsequently calculated using the analytical second derivatives. Then the force constant matrices obtained in the Cartesian coordinates were transformed to the internal coordinates. The matrices of the potential energy distribution (PED) were calculated. The PED elements provide a measure of each internal coordinate's contribution to the normal coordinate. The nonredudant set of 48 symmetrized internal coordinates for NAAL and NAALK and 45 internal coordinates for $NAAL^-$has been derived using the GAR2PED program.[37]

RESULTS AND DISCUSSION

Optimized Geometries

The B3LYP/6-311 + + G(d,p) optimized structures of NAAL, its K salt and deprotonated form are shown in Figure 1. Earlier calculations carried out at the B3LYP/6-311G(d,p) level have shown that the *trans* configuration is more stable by 23 kJ mol^{-1} than the *cis* one.[28] At the 6-311 + + G(d,p) level used in the present work, the *trans* form is calculated

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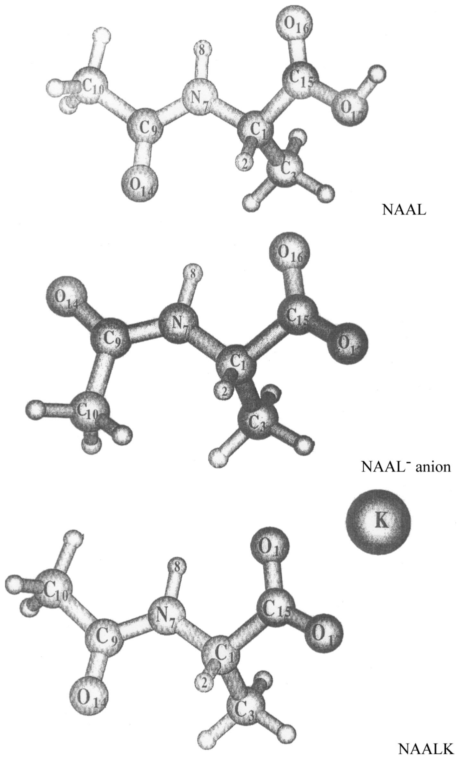

Figure 1. B3LYP/6-311 + + G(d,p) optimized structures of NAAL, NAAL$^-$ and NAALK. NAAL and NAALK are in the *trans* conformation and NAAL$^-$ in the *cis* conformation.

to be more stable by 20 kJ mol^{-1}. This small difference may be due to the use of diffuse functions for the heavy and hydrogen atoms. Our results are in line with the fact that the H8...O16 distance calculated at the present level is longer than the distance of 2.244 Å calculated at the 6-311G(d,p) level. The strength of the intramolecular hydrogen bond appears as a determinant factor in the stabilization of the *trans* conformation of neutral NAAL. In the carboxylate salt, the *trans* structure also appears as the most stable one. In this salt, the K$^+$ ion is coordinated to the COO$^-$ group, the two O...K$^+$ distances being approximately equal (2.534 and 2.522 Å). In NAAL$^-$, the *cis* conformation appears as the only stable structure, lying about 34 kJ mol^{-1} below the corresponding *trans*-conformer. As illustrated in Figure 2, if the anion is in the *trans* conformation, the NH proton is transferred to one of the oxygen atom of the carboxylate group. This

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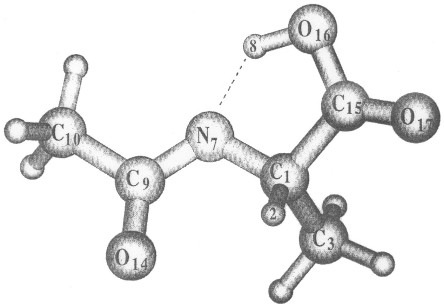

Figure 2. B3LYP/6-311 + + G(d,p) optimized geometry of *trans*-NAAL$^-$.

N$^-$-anionic form is stabilized by a OH...N intramolecular hydrogen bond, where the N...H distance is equal to 1.621 Å and the OH distance of 1.030 Å is strongly elongated with respect to the OH distance of 0.969 Å predicted in *trans*-NAAL. This structure will no more discussed hereafter.

Table 1 reports relevant geometrical parameters for NAAL, NAALK and NAAL$^-$. In the three species, theN atom is nearly sp^2 hybridized, the

Table 1. B3LYP/6-311 + + G(d,p) optimized geometries in *trans*-NAAL, *trans*-NAALK and *cis*-NAAL$^-$.[a]

Geometrical parameter	*trans*-NAAL	*trans*-NAALK	*cis*-NAAL$^-$
R(OH)	0.969		
R(C15═O16)	1.207	1.269	1.254
R(C15═O17)	1.348	1.260	1.248
R(C1C15)	1.519	1.540	1.584
R(C1N7)	1.452	1.457	1.463
R(N7H8)	1.010	1.012	1.022
R(H8...O16)	2.269	2.121	2.027
R(N7C9)	1.365	1.357	1.347
R(C9═O14)	1.223	1.226	1.236
∠N7C1C15	108.0	109.0	108.4
∠N7H8O16	116.8	114.2	110.8
∠C9N7H8	120.8	121.2	118.2
∠C9N7C1	121.7	123.4	130.4
τ(N7C1C15O16)	− 10.8	− 7.3	− 8.3
R(O16...K)		2.543	
R(O17...K)		2.522	

[a] See Figure 1 for atom numbering. Distances are given in Å and bond angles in degrees.

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sum of the angles around this atom being 359.2°, 358.8° and 359.4°, respectively. As shown by the values of the N7C1C15O16 dihedral angles which range between $-7.3°$ and $-10.8°$, the five-membered ring is nearly planar. The intramolecular H8...O16 distance is markedly shorter, by 0.242 Å in NAAL$^-$ than in NAAL. This suggests that the strength of the intramolecular hydrogen bond increases in the order NAAL < NAALK < NAAL$^-$. This increase parallels a larger elongation of the N7H8 bond, a decrease of the N7H8O16 angle and an increase of the C1N7 and C1C15 distances.

The intramolecular NH...O hydrogen bond is expected to be stronger when the O atom is negatively charged. However, no correlation could be found between the intramolecular distances and the Mulliken charges on the O16 atom which are equal to -0.300 e in NAAL, -0.538 e in NAALK and -0.476 e in NAAL$^-$.

Calculated and Experimental Raman Frequencies of NAALK

The Raman spectrum of solid NAALK is shown in Figure 3. The calculated harmonic frequencies and the experimental Raman frequencies are listed in Table 2 which also reports the potential energy distribution along with the scaling factor defined as the ratio of the experimental to the theoretical frequencies. The methyl group implanted on the C1 atom is labeled CH3 and the methyl group implanted on the C10 atom CH3′. The carboxylate group is indicated by COO$^-$. We must notice that we compare here theoretical frequencies in the gas phase and experimental frequencies in the solid state. In NAAL, the theoretical and experimental frequencies

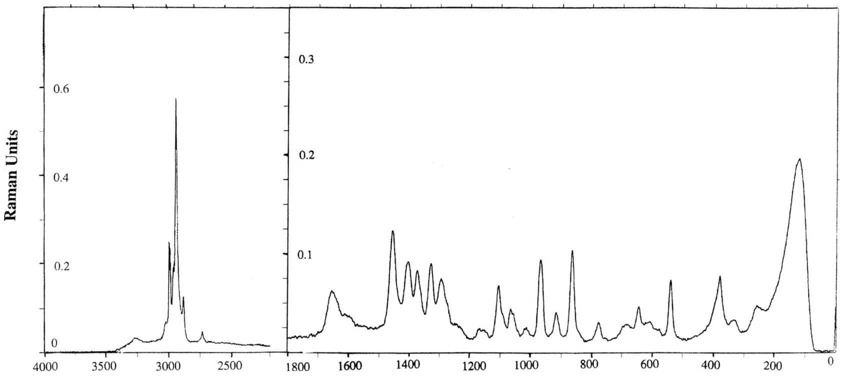

Figure 3. Raman spectrum of solid NAALK recorded at room temperature.

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Table 2. Experimental and calculated frequencies (cm^{-1}) in *trans*-NAALK, scale factor (SF), assignment, and potential energy distribution ($\geq$ 10%).[a]

ν^{exp}	ν^{calc}	SF	Assignment and PED
3253	3578	0.909	νNH (98)
2891	3124	0.954	ν^{as}CH$_3$ (100)
	3113	0.958	ν^{as}CH$_3$′ (91)
2942	3051	0.943	νC1H2 (92)
2882	3039	0.948	ν^{s}CH3′ (99)
	3030	0.949	ν^{s}CH3 (95)
2734			2 × 1375
1665	1721	0.967	νC9═O14 (62) − lin1 (17)
~ 1590	1600	0.994	ν^{as}COO^{-} (80)
n.o	1522	0.985	δN7H8 (33) − νN7C9 (23)
1470	1503	0.978	δ^{as}CH3 (90)
	1493	0.984	δ^{as}CH3
1454	1480	0.982	δ^{as}CH3′ (55) + δNH (12) + δ^{as}CH3 (11)
	1473	0.987	δ^{as}CH3′ (84)
1403	1425	0.985	δ^{s}COO^{-} (40) − δ^{s}CH3 (16) + δCOO^{-} (10)
1375	1395	0.993	δ^{s}CH3′ (80)
1328	1383	0.960	δ^{s}CH3 (70)
1295	1357	0.954	δC1H2 (66)
1280	1308	0.979	δC1H2 (30)
1230	1245	0.988	δNH (31) − δC1H2 (16) + νN7C9 (11)
1160	170	0.991	δC1H2 (38) + lin1 (13) + rCH3 (10)
1106	1109	0.997	lin1 (26) γC9N7H8 (18) + νC1C3 (15) + t (13) + rCH3 (12)
1070	1084	0.987	rCH3 (26) − lin1 (22) − δC1H2 (10)
1013	1054	0.961	γN7C9═O14 (63) + γC9N7H8 (10) + rCH3 (10)
969	1009	0.960	rCH3 (36) + rCH3′ (13) − γC9N7H8 (11)
932	977	0.953	Lin1 (26) + νC9C10 (23) − δNH (16)
n.o	921		Lin1 (42)
866	873	0.992	Lin1 (27) + δCOO^{-} (12) + $\boldsymbol{\nu}$C1C15 (10)
776	777	0.999	γCOO^{-} (29) + tN7C9 (19) + γC9N7H8 (16)
681	683	0.997	tN7C9 (24) − lin1 (18) − 10C9═O14 (11)
642	666	0.964	tN7C9 (57) + γC9N7H8 (22) − γC10C9═O14 (16)
607	615	0.987	γC9N7H8 (63)
540	563	0.959	γC9N7H8 (66) + tN7C9 (22)
n.o	536		tN7C9 (21) + γC9C10═O14 (16) + δC10C9═O14 (12) + γC9N7H8 (12)

(*continued*)

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Table 2. Continued.

v^{exp}	v^{calc}	SF	Assignment and PED
n.o	421		Lin1 (52) + tN7C9 (18) + γC9N7H8 (16)
380	378	1.005	skeletal + torsion modes
335	350	0.957	skeletal + torsion modes
259	262	0.970	skeletal and torsion modes
n.ob	241		skeletal and torsion modes
n.o[b]	207		skeletal and torsion modes
n.o[b]	180		skeletal and torsion modes
122	125	0.976	

[a] n.o = not observed, v = stretching, δ = deformation; γ = out-of-plane deformation; r = rocking; tN7C9 = torsion around the N7C9 bond; lin1 = linear bending of the C9N7C1C15 skeleton; tN7C9 = torsion around the N7C9 bond. The contributions of the torsion around the C1N7 bond and of the linear bend C9N7C1C15 are lower than 10%.

[b] Overlapping with the broad band observed at 122 cm^{-1}.

are markedly different owing to strong intermolecular hydrogen bonds between the OH and C9═O14 groups.[38] In solid NAALK, only weak van der Waals interactions are likely to exist. This will be further discussed in Section 3.

The v^{as}CH3 and v^{as}CH3′ vibrations are predicted at sligthly different frequencies, namely 3124 and 3113 cm^{-1}, but only one band could be observed in the Raman spectrum. The same remark also holds for the v^{s}CH3 and ^{s}CH3′ vibrations. A splitting of the degenerate vibrations δ^{as}CH3 and δ^{as}CH3′ vibrations is theoretically predicted. Their frequency differences is however too small to be observed experimentally. The rocking vibrations of the CH3 group appear to be strongly mixed with other modes. Their main components are observed at 1070 and 969 cm^{-1}.

The v^{as} and v^{s} vibrations of the COO^{-} group are observed at 1590 and 1403 cm^{-1}, respectively, in good agreement with Raman data on crystalline DL−α-alanine where the two modes are observed at 1600 and 1418 cm^{-1}, respectively.[39] Our calculations indicate further that the in-plane and out-of-plane vibrations of the COO^{-} are strongly coupled with other vibrations. The band observed at 866 cm^{-1} contributes by only 12% to the $\delta(COO^{-})$ vibration and the band observed at 776 cm^{-1} by 20% to the γCOO^{-} vibration. In the gas-phase zwitterion of L-alanine, ab initio calculations performed with the 6-31G(d) basis set have shown that the modes predicted at 922 and 850 cm^{-1} contribute both to the δCOO^{-} vibration and that the mode calculated at 775 cm^{-1} can be assigned to

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Table 3. B3LYP/6-311 + + G(d,p) calculated frequencies (cm^{-1}) of relevant vibrational modes, assignment, and PED in *trans*-NAAL and *cis*-NAAL$^-$.[a]

trans-NAAL		*cis*-NAAL$^-$	
ν^{calc}	PED	ν^{calc}	PED
3609	νNH (96)	3442	νNH (90)
3057	νC1H2 (89)	3022	νC1H2
		1700	$\nu^{as}COO^-$ (55) − νC9═014 (23)
1733	νC9═O14 (50) − lin1 (27) + δC1N7C1 (11)	1681	νC9═O14 (40) − $\nu^{as}COO^-$ (38) − νN7C9 (10)
1535	δC9N7H8 (39) − νN7C9 (20)	1442	νC9H7 (27) − δC9N7H8 (24)
1254	δC9N7H8 (27) + ν(C9═O14 (14)		
1056	δC1N7C9 (66) + γC9N7H8 (10)		
750	tN7C9 (25) + γC9N7H8 (11) − γO16C1O17 (25)	786	tN7C9 (32) + γC9N7H8 (28)
		665	δC9N7H8 (23) + δCOO^- (23)
519	γC9N7H8 (16) − γN7C9═O14 (14)		
494	γC9N7H8 (63) + tN7C9 (10)		

[a]See footnotes below Table 2.

both δCOO^- and γCOO^- vibrations.[40] No PED data are available for this gas-phase zwitterion.

The vibrations involving the H8N7C9═O14 skeleton present some similarities with the amide vibrations. The band observed at 1665 cm^{-1} has a predominant νC9═O14 character (amide I vibration). The vibration predicted at 1522 cm^{-1} (not observed in the Raman spectrum) involves mainly the δNH vibration coupled with the νN7C9 vibration (amide II vibration). The band observed at 1230 cm^{-1} with a very weak Raman intensity can be ascribed to a mixed δNH + νN7C9 vibration (amide III vibration). The modes predicted at 607 and 540 cm^{-1} have a predominant γNH character (amide V vibration). The amide IV vibration which involves mainly an in-plane deformation of the C═O group contributes by less than 10% to all the modes predicted between 1000 and 300 cm^{-1}.

We wish now to comment on the scaling factors summarized in Table 2. The average scaling factor for the vibrations between 1700 and 120 cm^{-1} is 0.979. This value indicates that that the the comparison between the theoretical frequencies and the frequencies observed in the solid state is valuable, at least in the present case. It must be mentioned that the scaling factors for the νCH3, νCH3′ and νCH vibrations are lower and range between 0.948 and 0.958. This can be accounted for by the larger anharmonicity (X) of the latter vibrations which is of the

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order of 60 cm^{-1}.[a] The harmonic frequencies (ν^e) can be obtained from the second-order perturbation theory by the following equation:

$$\nu^e = \nu^{exp} + 2X$$

When the experimental frequencies are corrected for anharmonicities, an average scaling factor of 0.982 is obtained in this way for the ν(CH3), ν(CH3′) and ν(CH) vibrations. This factor is similar to the average factor of 0.979 calculated for the other vibrational modes. We must also notice that the scaling factor for the vibration is markedly lower (0.909). This can be accounted for not only by the larger anharmonicity of this vibration which is equal to 70–75 cm^{-1} for free NH bonds but also by its sligth increase resulting from hydrogen bond formation.[45] It is also worth mentioning that the out-of-plane deformation mode of the NH vibration is also characterized by a large anharmonicity. However, as shown by the data of Table 2, several modes contribute to this vibration and their scaling factors do not markedly differ from the average scaling factor.

Comparison Between the Calculated Frequencies in NAAL, NAALK, and NAAL$^-$

Table 3 lists the calculated frequencies of selected vibrational modes in *trans*-NAAL and *cis*-NAAL$^-$ along with the PED of the considered modes.[b] All the vibrational data can be obtained from the authors, on request. The B3LYP/6-311G(d,p) frequencies in *trans*-NAAL have been reported in an earlier work.[28] They are slightly higher, by about 5 cm^{-1}, than the B3LYP/6-311 + + G(d,p) ones. A greater departure can be noticed for the νC9═O14 frequency which is predicted to be 20 cm^{-1} lower when diffuse functions are added to the basis set.

The νC1H2 vibration seems to be very sensitive with respect to the existing form; this mode is indeed predicted at 3057 cm^{-1} in NAAL, at 3051 cm^{-1} in NAALK and at 3022 cm^{-1} in NAAL$^-$. This difference can mainly be accounted for by the different conformations of NAAL and NAAL$^-$ that are characterized by *trans* and *cis* conformation, respectively. Our present calculations show indeed that the νC1H2 vibration in *cis*-NAAL is expected at 3081 cm^{-1}, leading to a difference of about 30 cm^{-1} between the *cis*- and *trans* conformer. This difference is similar to the one calculated in *trans*-NAAL and in *cis*-NAAL$^-$. Marked differences of the frequencies of the stretching and rocking vibrations of the CH3 goup are also predicted for both conformers.[b]

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[a] For recent references see: Refs. [41–44].

[b] All the vibrational data can be obtained from the authors, on request.

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The three species investigated in the present work are characterized by intramolecular NH...O hydrogen bonds. The vibrations involving the NH group usually reflect the strength of the molecular interactions. How lower the (NH) frequencies, how stronger the hydrogen bonds. A comparison of the data of Tables 2 and 3 indicates that the frequency of the ν(NH) vibration which is, as indicated by the PED, a strongly localized mode decreases is ordered as follows: NAAL (3609 cm^{-1}), NAALK (3578 cm^{-1}), NAAL^{-} (3442 cm^{-1}) in agreement with the shortening of the (N)H...O intramolecular distances. Hydrogen bond formation usually results in an increase of the in-plane and out-of-plane deformation modes. The data of Tables 2 and 3 indicate, however, that these modes are strongly mixed. The main components of the in-plane δC9N7H8 vibration are predicted at 1522 cm^{-1} in NAAL, 1535 cm^{-1} in NAALK and at 1442 and 665 cm^{-1} in NAAL^{-}. The modes at 666, 615 and 563 cm^{-1} in NAAL involve an important γC9N7H8 contribution. The same remark also holds for the 750, 519 and 494 cm^{-1} modes in NAALK and for the mode at 786 cm^{-1} in NAAL^{-}. In the three species, the γC9N7H8 vibration is strongly mixed with other vibrations and as a consequence it does not reflect the strength of the intramolecular bond. This behavior is in contrast with the one observed for the great majority of hydrogen-bonded species where empirical correlations have been found between the νNH and γNH frequencies.[46]

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