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# Spectroscopy and crystal structure of anabasine salts

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#### Abstract

The anabasinium hydrochloride, hydriodide and perchlorate were characterized by IR and NMR spectroscopy as well as by X-ray diffraction. Anabasinium hydrochloride crystallizes with three independent ionic pairs in the asymmetric part of the orthorhombic unit cell, while anabasinium hydriodide and perchlorate crystals, being isostructural, are hexagonal and contain only one symmetry independent ionic pair. Despite these differences in the crystal data, both types of crystals display very similar helical solid-state patterns. The reported results combined with the CSD searches indicate an inherent tendency of anabasinium salts to crystallize with multiple asymmetric units, and to form folded arrangements in crystals. In the solid state the anabasinium cations predominantly adopt either synperiplanar or antiperiplanar conformations with respect to the mutual orientation of  $C^*$ –H and pyridine C–C(N) bonds, with deformations towards, respectively, (+) synclinal or (+) anticlinal rotamers.

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#### 1. Introduction

(S)-(-)-Anabasine (I) is a minor alkaloid in many nicotine-producing species [1,2], for example *Nicotiana tabacum* [3,4]. It was also found in *Solanum carolinense* (*Solanacae*) [5] and in *Priestleya elliptica* (*Leguminsae*) [6].

This alkaloid was preferentially found in extracts of *Nicotiana glauca Graham* known as wild tree tobacco [7,8], however for the first time it was isolated from *Anabasis aphylla* in which it is the main constituent [9,10]. More recently, (S)-(-)-anabasine has also been reported from animal sources, e.g., in two species of hoplonemertine worms surveyed [11], in the poison gland of the ants *Messor ebeninus* [12], *M. bouvieri* [13], and as a minor component in *M. capensis* [14], *M. sanctus, Aphaenogaster miamiana* [15], and *A. rudis, A. subterranea* where it coexists with anabaseine [15,16].

Recent pharmacological studies have demonstrated that naturally occurring tobacco alkaloids like (S)-(-)-nicotine and **I** and also their analogues [17] may have beneficial effects in treatment of age-related neurodegenerative diseases such as Parkinson's disease [18,19], Alzheimer's disease [18,20–23] and also in Turrette's syndrom [24,25].

Anabasine hydrochloride (hereafter  $IH^+[CI^-]$ ) is commercially available in Russia as medicine *Gamibasinum*, that is used in the nicotine replacement therapy as an antismoking agent [26].

Potential therapeutic activity of above-mentioned alkaloids is based on the interaction of their protonated forms with central neuronal nicotinic acetylocholine receptors (nACHR) that are differently expressed in many regions of CNS (central nervous system) and PNS (peripheral nervous system) [27]. Salts of pharmaceutical candidate molecules are often prepared in order to improve the physical properties of the molecule such as solubility, hydroscopicity and crystallinity [28].

Recently, thermochemical and thermodynamic properties of anabasine hydrochloride and its derivatives were studied [29,30]. A search through the Cambridge

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Crystallographic Data Base [31] has revealed that the X-ray data for anabasine, its derivatives and salts are limited to only two O,O'-alkilophosphorothioate salts [32]. The present paper reports the results obtained in studying spectroscopy (NMR, IR, MS) and the crystal structures of anabasine hydrochloride (IH<sup>+</sup>[CI<sup>-</sup>]), hydriodide (IH<sup>+</sup>[I<sup>-</sup>]) and perchlorate (IH<sup>+</sup>[CIO<sub>4</sub><sup>-</sup>]). Fig. 1.

#### 2. Experimental

### 2.1. General techniques

The IR spectra were recorded using FT-IR Bruker IFS 113 V spectrometer (KBr pellets, film). Mass spectra (EI) were taken on an AMD 402 spectrometer at standard parameters. The NMR were obtained on a Varian Gemini 300 spectrometer at 300 MHz and at ambient temperature, using ~0.5 M solutions in CD<sub>3</sub>OD, TMS as internal reference. The NMR assignments were made by first-order analysis of <sup>1</sup>H resonances and aided by DEPT, <sup>13</sup>C–<sup>1</sup>H-HETCOR, <sup>1</sup>H–<sup>1</sup>H- COSY and <sup>1</sup>H–<sup>1</sup>H- NOESY spectra. Melting points were determined on Melt-Temp II apparatus (Laboratory Devices Inc.) Elemental analysis was carried out by means of a Perkin-Elmer 2400 CHN automatic device.

# 2.2. Anabasine hydrochloride (IH<sup>+</sup>[Cl<sup>-</sup>])

(S)-(-)-Anabasine (0.81 g, 5 mM) was dissolved in acetone (10 cm<sup>3</sup>) and ammonium chloride (0.27 g, 5 mM + 10% excess) dissolved in acetone (10 cm<sup>3</sup>) was added, and gently warmed for 12 h to remove ammonia that evolved. A white crystallic powder was precipitated. Recrystallization from acetone gave 0.40 g (yield 40%) of transparent crystals, mp. 194–195 °C (lit. 194–195 °C [33]) MS m/z: 162 (M<sup>+</sup>, 30.80), 161 (17.25), 147 (3.65), 133 (38.97), 119 (32.64), 106 (39.84), 105 (47.47), 84 (100), 80 (25.59), 51 (16.00).

 $C_{10}H_{14}N_2HCl$  (198.45): Anal. Calcd.: C: 60.47; H: 7.55; N: 14.10; found: C: 60.45; H: 7.56; N: 14.08%.

NMR see Tables 2 and 3, IR see Fig. 2.

# 2.3. Anabasine hydriodide $(IH^+[I^-])$

(S)-(-)-Anabasine (0.81 g, 5 mM) was dissolved in acetone (5 cm<sup>3</sup>) and ammonium iodide (0.71 g, 5 mM)



Fig. 1. Atom numbering in (S)-(-)-anabasine salts.

dissolved in acetone  $(10 \text{ cm}^3)$  was added, and stirred at 0 °C for 5 h to remove ammonia that evolved. A brown crystallic powder was precipitated. Recrystallization from acetone gave 0.65 g (Yield 45%) of brown, transparent crystals, mp. 252–253 °C (lit. 252–253 °C [34–36]) MS *m*/*z*: 162 (M<sup>+</sup>, 33.17), 161 (23.02), 147 (4.71), 133 (45.43), 128 (100), 127 (51.18), 119 (36.56), 106 (46.76), 105 (53.06), 84 (84.73), 80 (20.09), 51 (13.52).

 $C_{10}H_{14}N_2HI$  (289.90): Anal. Calcd.: C: 41.38; H: 5.17; N: 9.65; found: C: 41.39; H: 5.21; N: 9.66%

NMR see Tables 2 and 3, IR see Fig. 2.

## 2.4. Anabasine perchlorate (IH<sup>+</sup>[ClO<sub>4</sub>])

(S)-(-)-Anabasine (0.81 g, 5 mM) was dissolved in methanol and (10 cm<sup>3</sup>) and HClO<sub>4</sub>/MeOH mixture (1:6, v/v) to pH 7 was added. A pale yellow crystallic powder was precipitated. Recrystallization from ethanol gave 0.46 g (yield 35%) of transparent crystals, mp. 245–246 °C (lit. 245–246 °C [37]), MS m/z: 162(M<sup>+</sup>, 59.10), 161 (34.71), 147 (5.02), 133 (52.55), 119 (36.96), 106 (39.28), 105 (48.65), 84(100), 80 (20.86), 52 (5.97).

 $C_{10}H_{14}N_2HClO_4$  (262.05): Anal. Calcd.: C: 45.79; H: 5.72; N: 10.68; found: C: 45.42; H: 5.55; N: 10.55%

NMR see Tables 2 and 3, IR see Fig. 2.

## 2.5. X-ray crystal structure determination

Single crystals were obtained by slow evaporation of saturated acetone and ethanol solutions. Transparent crystals of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  were selected for the X-ray investigations. In the preliminary course of X-ray investigations it became obvious that crystals of anabasinium iodide and perchlorate are isomorphic. Therefore, the X-ray analysis has been completed only for hydrochloride  $\mathbf{H}^{+}[\mathbf{C}\mathbf{I}^{-}]$  and iodide  $\mathbf{H}^{+}[\mathbf{I}^{-}]$  crystals. The intensity data were measured with a KM4CCD k-geometry diffractometer [38] equipped with graphite monochromated Mo K $\alpha$ radiation ( $\lambda = 0.71073$  Å) at 295 K. The structures were solved by direct methods using SHELXS-86 [39] and refined by least-squares techniques with SHELXL-97 [40]. The intensity data were corrected for Lp effects as well as for absorption [41]. Anisotropic thermal parameters were employed for non-hydrogen atoms. The positions of the hydrogen atoms bonded to carbon atoms were calculated geometrically while those attached to the piperidine nitrogens were located on difference Fourier maps. The hydrogen-atom positions were refined using a riding model with isotropic temperature factors 20% higher than the isotropic equivalent for the atom to which the H-atom was bonded. The absolute structure of the crystals was established on the basis of the Flack parameter [42]. Siemens computer graphics program [43] was used to prepare drawings. The relevant crystal data collection and refinement parameters are listed in Table 1 and selected torsion angles are reported in Table 4. Atomic coordinates, anisotropic displacement parameters and tables of all bond distances

Table 1 Crystal data and experimental details for  $IH^+[CI^-]$  and  $IH^+[I^-]$ 

Crystal data	IH <sup>+</sup> [Cl <sup>-</sup> ]	IH⁺[I <sup>−</sup> ]
Chemical formula	C <sub>10</sub> H <sub>15</sub> ClN <sub>2</sub>	C <sub>10</sub> H <sub>15</sub> IN <sub>2</sub>
$M_{ m r}$	198.69 290.14	
Cell setting, space group	Orthorhombic, $P2_12_12_1$	Hexagonal, P61
Temperature (K)	295 (2)	295 (2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	5.5466 (3), 17.3188 (10), 33.209 (2)	7.8877 (3), 7.8877 (3), 32.2306 (13)
$\alpha, \beta, \gamma$ (°)	90.00, 90.00, 90.00	90.00, 90.00, 120.00
$V(Å^3)$	3190.1 (3)	1736.60 (12)
Z	12	6
$D_{\rm x} ({\rm Mg}\;{\rm m}^{-3})$	1.241	1.665
Radiation type	Μο Κα	Μο Κα
No. of reflections for cell parameters	3042	7656
$\mu (\mathrm{mm}^{-1})$	0.32	2.73
Crystal form, colour	Plate, colourless	Pyramidal, orange
Crystal size (mm)	$0.40 \times 0.20 \times 0.05$	$0.40 \times 0.35 \times 0.25$
Data collection		
Diffractometer	Kuma KM4CCD k-geometry diffractometer	Kuma KM4CCD κ-geometry diffractometer
Data collection method	ω scans	$\omega$ scans
Absorption correction	Analytical	Numerical
T <sub>min</sub>	0.884	0.477
T <sub>max</sub>	0.984	0.722
No. of measured, independent and observed reflections	25377, 5661, 3678	15900, 2527, 2437
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R <sub>int</sub>	0.091	0.026
$\theta_{\rm max}$ (°)	25.1	27.1
Range of $h, k, l$	$-4 \rightarrow h \rightarrow 6$	$-10 \rightarrow h \rightarrow 10$
	$-20 \rightarrow k \rightarrow 20$	$-10 \rightarrow k \rightarrow 5$
	$-35 \rightarrow l \rightarrow 39$	$-41 \rightarrow l \rightarrow 41$
Refinement		
Refinement on	$F^2$	$F^2$
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.070, 0.089, 1.04	0.022, 0.044, 1.08
No. of reflections	5661 reflections	2527 reflections
No. of parameters	352	120
H-atom treatment	Riding	Riding
Weighting scheme	Calculated $w = 1/[\sigma^2(F_2^2) + (0.0216P)^2]$ where	Calculated $w = 1/[\sigma^2(F_a^2) + (0.0212P)^2 + 0.4579P]$
0 0	$P = (F_{2}^{2} + 2F_{2}^{2})/3$	where $P = (F_{2}^{2} + 2F_{2}^{2})/3$
$(\Delta/\sigma)_{\rm max}$	0.001	0.001
$\Delta \rho_{\rm max}, \Delta \rho_{\rm min}$ (e Å <sup>-3</sup> )	0.29, -0.19	0.25, -0.52
Flack parameter	0.00 (8)	-0.01 (2)

and angles have been deposited at the Cambridge Crystallographic Data Centre (deposition numbers CCDC 299809 and 299810).

### 3. Results and discussion

Protonation of (S)-(-)-anabasine results in the formation of an ammonium bond  $R_2NH_2^+$ , which presence is readily seen in the IR spectra of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$ . Salts of (S)-(-)-anabasine show the characteristic, very intense, broad absorption band  $v(R_2NH_2^+)$  in the region of 2950–2380 cm<sup>-1</sup>. In the region of 3450– 3280 cm<sup>-1</sup> ( $v_{N-H}$ ), there is only one, very weak absorption band at 3432, 3431 and 3454 cm<sup>-1</sup> for  $IH^+[CI^-]$ ,  $IH^+[I^-]$ and  $IH^+[CIO_4^-]$ , respectively, in contrast to two, intense absorption bands at 3386 and 3280 cm<sup>-1</sup> in the IR spectra of I.

Some further features of the IR spectra of  $IH^+[ClO_4^-]$  were observed in the region of 1150–1011 cm<sup>-1</sup> on the

high-frequency side of the broad  $\text{ClO}_4^-$  band. The single band derived from ( $v_{\text{Cl}-\text{O}}$ ) of the group is situated in its normal position at 1104 cm<sup>-1</sup>. Fig. 2 shows the IR spectra of (*S*)-(-)-anabasine with corresponding spectra of its salts.

# 3.1. <sup>13</sup>C NMR and <sup>1</sup>H NMR of I and its salts

The NMR spectra of the compounds  $IH^+[CI^-]$ ,  $IH^+[I^-]$ and  $IH^+[CIO_4^-]$  confirm the structure of (S)-(-)-anabasine salts in solution. In <sup>13</sup>C NMR spectra of  $IH^+[CI^-]$ ,  $IH^+[I^-]$ and  $IH^+[CIO_4^-]$  the chemical shifts of the carbon atoms are similar to those assigned for I except for the carbon atoms in piperidine moiety. On the basis of comparison of the NMR spectra of the salts studied and the free base it was possible to calculate the protonation effect. The chemical shift changes resulting from protonation were determined by substructing the chemical shifts of the individual carbon atoms of I from those of the corresponding atoms of the

Table 2 <sup>13</sup>C NMR data of (S)-(-)-anabasine and its salts in CD<sub>3</sub>OD

Carbon atom	DEPT	I $\delta_{\rm C}$ (ppm)	IH <sup>+</sup> [Cl <sup>-</sup> ] $\delta_{\rm C}$ (ppm)	$\mathbf{IH^+[I^-]} \ \delta_{\mathbf{C}} \ (ppm)$	$\rm IH^+[ClO_4^-] \ \delta_C \ (ppm)$
2'	СН	149.00	149.60	149.51	149.14
			+0.73	+0.51	+0.14
3'	С	142.14	134.71	134.61	134.70
			-7.43	-7.53	-7.44
4'	СН	136.66	137.14	137.10	137.32
			+0.48	+0.44	+0.66
5'	CH	125.31	125.61	125.68	125.87
			+0.30	+0.37	+0.56
6'	CH	148.87	149.60	151.04	150.82
			+0.73	+2.17	+1.95
2	СН	60.61	59.60	59.49	59.53
			-1.01	-1.12	-1.08
3	$CH_2$	35.10	31.01	30.93	30.83
			-4.09	-4.17	-4.27
4	$CH_2$	26.12	22.99	23.13	23.16
			-3.13	-2.99	-2.96
5	$CH_2$	26.32	23.85	23.75	23.73
			-2.48	-2.58	-2.60
6	$CH_2$	48.26	46.94	46.97	46.99
	2		-1.32	-1.29	-1.27

Atom numbering is shown in Fig. 1. Numbers given in italics represent the protonation effect. (-), upfield shift, (+), - downfield shift. Protonation effects were calculated by subtracting the chemical shifts of individual carbon atoms of free bases from the values of the chemical shifts of the corresponding carbon atoms in the corresponding salts.

Table 3 <sup>1</sup>H NMR chemical shifts of (S)-(-)-anabasine and its salts in CD<sub>3</sub>OD

H atoms	Compound							
	I		IH <sup>+</sup> [Cl <sup>-</sup> ]				$IH^+[ClO_4^-]$	
	$\delta_{\mathrm{H}}$	J (Hz)	$\delta_{ m H}$	J (Hz)	$\delta_{\mathrm{H}}$	J (Hz)	$\delta_{\mathrm{H}}$	J (Hz)
H-2′	8.54	2.2	8.75		8.73	1.9	8.69	1.6
	d		bs		d		bd	
H-4′	7.86	7.9, 2.2, 1.6	8.12	7.9, 1.6, 1.6	8.07	7.9, 1.9, 1.9	8.02	8.2, 1.9, 1.6
	dt		dt		dt		dt	
H-5′	7.40	7.9, 4.9, 0.5	7.55	7.9, 4.9	7.57	7.9, 4.9, 0.5	7.59	7.9, 4.9, 0.5
	ddd		dd		ddd		ddd	
H-6′	8.42	4.9, 1.6	8.60	4.12	8.61	4.9, 1.6	8.63	3.6
	dd		bd		dd		bd	
H-2 <sub>ax</sub>	3.68	10.7, 2.7	4.44	10.2, 4.9	4.52	11.2, 4.1	4.44	11.8, 3.3
	dd		dd		dd		dd	
H-3	$1.82^{*}$		1.96*		1.97*		2.05*	
	${ m m}$ 1.60 $^{*}$		m		m		m	
Н-4	m 1.93*		1.96*		1 97*		2.05*	
11 4	n.95		n.90		1.97 m		2.05 m	
	$1.60^{*}$				III		III	
н	m 1.60 <sup>*</sup>		1.06*		1.07*		2.05*	
11-5	1.00 m		1.90 m		1.97 m		2.05 m	
	111		111		111		1.84*	
							1.04 m	
H-6 <sub>eq</sub>	3.15*	14.0. 2.7. 2.5	3.52 <sup>*</sup> m	12.1	3.52*	12.4. 2.2. 1.9	3.52*	11.3. 2.2
	dt	,,	d		dt	,,	dd	
H-6 <sub>ax</sub>	$2.78^{*}$	14.6, 5.5, 3.3	3.27*	11.5, 8.24, 3.2, 1.6	2.30*	12.7, 11.2, 3.3, 1.6	3.26*	14.5, 3.3, 1.6
	ddd		dddd		dddd		ddd	

(a) as seen in the spectrum, m, multiplet; s, singlet; dd, doublet of doublets; ddd, doublet of doublet of doublets; bs, broad singlet; dddd, doublet of triplets; bd, broad doublet, Atom numbering is shown in Fig. 1.

\*  $\delta_{\rm H}$  values extracted from  ${}^{13}\text{C}{}^{-1}\text{H}$  and  ${}^{1}\text{H}{}^{-1}\text{H}$  COSY spectra.





Table 4 Selected torsion angles (°) for anabasine derivatives

(a) Defining the conformation	of the piperidine rings in the rep	orted crystal structures		
	IH <sup>+</sup> [Cl <sup>-</sup> ] (molecule 1)	IH <sup>+</sup> [Cl <sup>-</sup> ] (molecule 2)	IH <sup>+</sup> [Cl <sup>-</sup> ] (molecule 3)	IH <sup>+</sup> [I <sup>−</sup> ]
C12-C7-N8-C9	58.9 (5)	57.1 (5)	58.3 (5)	56.5 (3)
C7-N8-C9-C10	-58.6 (5)	-56.5 (5)	-56.4 (5)	-57.3 (4)
N8-C9-C10-C11	55.0 (5)	54.3 (5)	53.6 (5)	56.8 (4)
C9-C10-C11-C12	-53.6 (5)	-54.5 (6)	-53.6 (5)	-57.2 (4)
C10-C11-C12-C7	55.3 (5)	55.8 (6)	56.0 (5)	57.7 (4)
N8-C7-C12-C11	-56.8 (4)	-56.1 (5)	-57.9 (4)	-56.1 (3)
(b) Defining four types of anal	basine conformers present in its v	various crystal structures		
	C4-C3-C7-N8	C2-C3-C7-N8	C4-C3-C7-C12	C2- 3 - C7 - C12
Conformer A				
$\mathbf{IH}^{+}[\mathbf{CI}^{-}]$ (molecule 1)	-61.6(5)	120.7(4)	59.9(5)	-117.8(4)
$\mathbf{IH}^{+}[\mathbf{CI}^{-}]$ (molecule 2)	-59.0(6)	123.9(4)	64.8(6)	-112.4(5)
$\mathbf{IH}^{+}[\mathbf{Cl}^{-}]$ (molecule 3)	-53.1(6)	127.8(4)	69.7(5)	-109.4(5)
MeAbZnBr [45] (molecule 1)	-44.9(9)	139.5(6)	78.4(8)	-97.2(7)
MeAbZnBr [45] (molecule 2)	-53.8(8)	130.3(6)	66.0(8)	-109.9(8)
KOKFEV [32] (molecule 1)	-60.4	120.6	62.0	-117.1
Conformer B				
KOKFIZ [32] (molecule 1)	-35.5	147.5	87.8	-89.2
KOKFIZ [32] (molecule 2)	-37.1	148.4	90.2	-84.2
Conformer C				
KOKFEV [32] (molecule 2)	131.6	-53.1	-106.1	69.2
KOKFIZ [32] (molecule 3)	126.6	-57.8	-119.1	56.5
KOKFIZ [32] (molecule 4)	133.8	-52.9	-105.0	68.4
Conformer D				
IH <sup>+</sup> [I <sup>-</sup> ]	82.1(3)	-98.7(3)	-154.4(3)	24.8(4)

Standard deviations, given in parentheses, are available only for structures  $IH^+[CI^-]$  and  $IH^+[I^-]$ , presented in this paper.

compounds  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$ . <sup>13</sup>C chemical shifts of (S)-(-)-anabasine and its salts are shown in Table 2.

The chemical shifts on the sp<sup>2</sup> carbon atoms of aromatic ring of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  correlate well

with the shifts of the corresponding carbon atoms of the free base. The protonation effects for carbon atoms C-2', C-4', C-5' and C-6' is positive, whereas for C-3' and carbon atoms in pyridyl ring is negative. Due to the protonation at C-3' upfield shift by approximately -7.4 ppm is observed,

which is the greatest value of protonation effect for all salts of anabasine.

For the adjacent carbon atoms to the protonated nitrogen atom N-1 in piperidyl ring the negative  $\alpha$ -effect is observed. For compounds IH<sup>+</sup>[Cl<sup>-</sup>], IH<sup>+</sup>[I<sup>-</sup>] and IH<sup>+</sup>[ClO<sub>4</sub><sup>-</sup>] this effect at C-2 is equal to -1.01, -1.12, -1.08 ppm, respectively, whereas at C-6 it amounts -1.32, -1.29 and -1.27 ppm, respectively.

For the methylene carbon atoms at the  $\beta$ -position to N-1 atom, the protonation effect at C-3 is greater than  $\gamma$ -effect at C-4 but that observed at C-5 is lower. The greatest  $\beta$ -effect is observed at C-3 for IH<sup>+</sup>[CIO<sub>4</sub><sup>-</sup>] (-4.27 ppm), whereas the lowest value (-2.48 ppm) is found in spectrum of IH<sup>+</sup>[CI<sup>-</sup>]. The average value of  $\gamma$ -effect amounts -3.02 ppm in compounds IH<sup>+</sup>[CI<sup>-</sup>], IH<sup>+</sup>[I<sup>-</sup>] and IH<sup>+</sup>[CIO<sub>4</sub><sup>-</sup>] (see Table 2).

The assignments of the <sup>1</sup>H NMR signals to particular protons was achieved by one and two-dimensional spectra, mainly <sup>1</sup>H–<sup>13</sup>C -HETCOR and <sup>1</sup>H–<sup>1</sup>H -COSY. The signals in the <sup>1</sup>H NMR spectra of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  were assigned by comparing them with the spectra of (S)-(–)-anabasine.

The <sup>1</sup>H NMR spectra of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  in CD<sub>3</sub>OD is quite similar to that of I, the differences being a logical consequence of a protonation. Although some similarity between the value of chemical shifts in pyridyl ring of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  is observed, there are some changes in piperidine ring.

Due to the protonation, the <sup>1</sup>H shielding effect on protons H-2<sub>ax</sub> and H-6<sub>eq</sub> at the  $\alpha$  position to the piperidine nitrogen atom is observed. The chemical shift of H-2<sub>ax</sub> (doublet of doublets) amounts  $\delta_{\rm H} = 4.52$  ppm for IH<sup>+</sup>[I<sup>-</sup>] and  $\delta_{\rm H} = 4.44$  ppm for IH<sup>+</sup>[Cl<sup>-</sup>] and IH<sup>+</sup>[ClO<sub>4</sub><sup>-</sup>]. The signals attributed to the proton H-6<sub>eq</sub> occur at  $\delta_{\rm H} = 3.52$  ppm in the <sup>1</sup>H NMR spectra of all salts.

Although the signal of proton H-6<sub>eq</sub> in spectrum of  $IH^+[CI^-]$  has *geminal* coupling constant  $J_{H-H} = 12.1$  Hz, the signal at  $\delta_H = 3.27$  ppm is assigned as *axial*, on account of the observable correlation of that proton with H-2<sub>ax</sub> in two-dimensional spectrum  ${}^1H^{-1}H$  NOESY. Assignment of chemical shift  $\delta_H = 3.27$  ppm to H-6<sub>ax</sub> is true to the original assignment based on the  ${}^1H$  NMR spectra of  $IH^+[CI^-]$  taken in D<sub>2</sub>O at observation frequency of 100 MHz [44].

Although some protons are involved in higher order spectra, 17, 13, 18 and 15 coupling constants were successfully determined directly from the <sup>1</sup>H NMR spectra of I, IH<sup>+</sup>[Cl<sup>-</sup>], IH<sup>+</sup>[I<sup>-</sup>] and IH<sup>+</sup>[ClO<sub>4</sub><sup>-</sup>], respectively. We noticed that both; axial and equatorial protons of C-6 carbon atom in spectrum of (*S*)-(–)-anabasine and its salts IH<sup>+</sup>[Cl<sup>-</sup>], IH<sup>+</sup>[I<sup>-</sup>] and IH<sup>+</sup>[ClO<sub>4</sub><sup>-</sup>] have a large coupling constant in the range of  $J_{H-H} = 11-15$  Hz.

Analysis of <sup>1</sup>H-<sup>1</sup>H NOESY spectra of  $IH^+[CI^-]$ ,  $IH^+[I^-]$ and  $IH^+[CIO_4^-]$  allowed to find the <sup>1</sup>H-<sup>1</sup>H correlation. Apart from the H-2<sub>ax</sub>-H-6<sub>ax</sub> correlation mentioned for compound  $IH^+[CI^-]$ , we noticed in spectra of all salts also the presence of  $H-2_{ax}-H-2'$  correlation. Correlation between protons  $H-2_{ax}$  and H-4' is seen only in spectra of  $IH^+[CI^-]$  and  $IH^+[I^-]$ .

On the basis of NMR data we can determine the precise conformation of piperidine ring of  $IH^+[CI^-]$ ,  $IH^+[I^-]$  and  $IH^+[CIO_4^-]$  in solution. In all compounds this ring retains from the parent molecule a *chair* conformation, while free rotation around the C<sup>\*</sup>-C(sp<sup>2</sup>) bond leads to existence of several possible conformers of (*S*)-(-)-anabasine and its salts in solution.

# 3.2. Crystal structure of $IH^+[Cl^-]$ and $IH^+[I^-]$

#### 3.2.1. Conformation of anabasinium cations

Anabasine hydrochloride ( $\mathbf{IH}^{+}[\mathbf{Cl}^{-}]$ ) crystallizes with three distinct cations and anions in the asymmetric part of the orthorhombic unit cell. The anabasinium cations are all protonated at the piperidine nitrogen and are very similar in conformation. The ellipsoid plot for one of the three cations is shown in Fig. 3a. In contrast, crystals of anabasinium iodide  $(\mathbf{IH}^+[\mathbf{I}^-])$  as well as the isomorphic crystals of anabasinium perchlorate ( $\mathbf{IH}^+[\mathbf{ClO}_4^-]$ ) possess  $P6_1$  symmetry and contain only one ionic pair in the asymmetric part of the unit cell. The ellipsoid plot for the anabasinium cation in  $\mathbf{IH}^+[\mathbf{I}^-]$  is displayed in Fig. 3b. In all four anabasinium cations the pyridine rings are planar to within 0.008 Å (mean deviation from the plane) and the piperidine rings adopt the *chair* conformations (Table 4a). The pyridine rings are equatorial. The most general description of the conformation of the anabasinium cation is the mutual orientation of the pyridine and piperidine rings. This can be described by the values of the torsion angles around the  $C^*-C(sp^2)$  bond joining the two rings, that are listed in Table 4. In all three independent anabasinium cations present in the IH<sup>+</sup>[Cl<sup>-</sup>] crystals, the values of the torsion angles around this bond



Fig. 3. Perspective view and atom numbering scheme of (a) one of the three crystallographically independent, but conformationally similar anabasinium cations found in the crystal structure of  $IH^+[CI^-]$ , (b) present in the crystal structure of  $IH^+[I^-]$ . Thermal ellipsoids which are drawn at 40% probability illustrate the displacements of atoms at 295 K.

indicate the synperiplanar orientation of the C<sup>\*</sup>-H bond with respect to the pyridine C-C(N) bond (Fig. 4, conformer A). Similar synperiplanar conformation has been previously observed by us in the two 1-N-methylanabasine units, which, by acting as monodentate ligands, formed a tetrahedral complex with ZnBr<sub>2</sub> [45]. The same type of conformer is also present in the crystal structure of anabasinium O, O'-diethylphosphorothioate [32], deposited in the CSD [31] as KOKFEV (strictly speaking this conformation is displayed by one of the two conformers that are present in the independent part of the unit cell). Somewhat similar conformation is adopted by two out of four symmetry independent anabasinium cations that are present in the crystal structure of anabasinium O,O'-diisopropylphosphorothioate [32], (KOKFIZ). However, in this conformation the C<sup>\*</sup>-H and C(sp<sup>2</sup>)-C(N) bonds are close to (+) synclinal orientation (Fig. 4, conformer B). As a result, the  $C^*$ -C(piperidine) bond is situated perpendicular to the pyridine plane. The remaining three anabasinium cations present in the crystal structures of KOKFEV and KOKFIZ adopt a conformation that differs from A by the rotation of 180° around the  $C^*-C(sp^2)$  bond (Fig. 4, conformer C) and hence can be described as antiperiplanar. Consequently, in this conformation, the C<sup>\*</sup>-H bond eclipses the other pyridine  $C(sp^2)-C(sp^2)$  bond, i.e. the bond that is distal to the pyridine nitrogen. Summarizing, the 11 anabazinium cations for which the X-ray structure is known, adopt three types of conformation, depicted in Fig. 4 as A, B and C. The three conformations differ in the N(pyridine)...N(piperidine) intramolecular contact which is the shortest in the C conformer (the corresponding values being in the range 4.295 to 4.366 Å), reaches the highest value for the **B** rotamer (4.820 and 4.865 Å) and adopts intermediate values in the investigated hydrochloride  $IH^+[CI^-]$  (4.700(5) to 4.730(5) Å). In this context the conformation of anabasinium cation displayed in its iodide salt  $\mathbf{IH}^{+}[\mathbf{I}^{-}]$  is unique. In this cation the orientation of the  $C^*$ -H bond with respect to the  $C(sp^2)$ -C(N) bond is nearly anticlinal (Fig. 4, conformer **D**). This situates the  $C^*-N$ 



Fig. 4. Conformational rotamers of anabasine observed in the crystals of its derivatives and salts. Conformers A and D are present in  $IH^+[CI^-]$  and  $IH^+[I^-]$ , respectively.

bond perpendicular to the pyridine plane. The intramolecular N···N contact in the crystal structure of  $\mathbf{IH}^+[\mathbf{I}^-]$ amounts to 4.557(3) Å. The conformational uniqueness of  $\mathbf{IH}^+$  in the solid state can be correlated with exceptional inter-cation hydrogen-bond interactions observed in this crystal structure and absent in other anabasinium salts (vide infra).

#### 3.2.2. Crystal packing

The hydrochloride salt of anabasine of  $IH^+[Cl^-]$  crystallizes with three independent ionic pairs in the asymmetric part of the unit cell (space group  $P2_12_12_1$ , z = 12, z' = 3), while the iodide salt crystals of  $IH^+[I^-]$  are hexagonal (space group  $P6_1$ ) and contain only one ionic pair in the asymmetric part of the unit cell. Judging exclusively from the crystal data it would seem reasonable to conclude that the two crystal structures differ considerably in packing. This, however, is not the case. The unit cell parameter along the *c*-direction is very similar in the two structures and the helical arrangement of cationic and anionic species in of **IH<sup>+</sup>[CI<sup>-</sup>]** resembles the helical arrangement around the six -fold screw axis as in the crystal structure of  $\mathbf{IH}^{+}[\mathbf{I}^{-}]$ , as illustrated in. Fig. 5a and b, respectively. This observation indicates that anabasinium cations display a tendency to arrange themselves in a crystal in a helical manner, and provides an explanation for the presence of three independent ionic pairs in the crystal structure of **IH**<sup>+</sup>[**CI**<sup>-</sup>]. Presumably the helical arrangement around the six-fold screw axis leads to the formation of substantial structural voids that are too big for chloride anions, but can easily be filled by the iodides. This supposition gains an additional support from our finding that the perchlorate salt of anabasine  $(IH^+[CIO_4^-])$  forms crystals isomorphic with the crystals of  $\mathbf{IH}^{+}[\mathbf{I}^{-}]$ . Of the two other crystal structures of anabasine salts reported in the literature [32], one crystallizes with four, and the other with two ionic pairs



Fig. 5. a and b. Helical arrangement of ionic pairs in the crystal structures of  $\mathbf{IH}^+[\mathbf{CI}^-]$  and  $\mathbf{IH}^+[\mathbf{I}^-]$  along the c-direction (view down the *x*-axis).

Table 5 Hydrogen bond parameters for  $\mathbf{IH}^{+}[\mathbf{CI}^{-}]$  and  $\mathbf{IH}^{+}[\mathbf{I}^{-}]$ 

	D–H (Å)	$D{\cdots}A\;(\mathring{A})$	$H{\cdots}A\;(\mathring{A})$	$D–H\cdot\cdot\cdot A\;(^\circ)$	Symmetry operations on A
IH <sup>+</sup> [Cl <sup>-</sup> ]					
N48—H481 ··· Cl1	1.02	3.150(4)	2.16	165	1+x, y, z
N48—H482 · · · Cl1	1.08	3.088(4)	2.10	151	<i>x</i> , <i>y</i> , <i>z</i>
C44–H441 · · · Cl1	0.93	3.720(4)	2.85	156	1+x, y, z
N8–H81 · · · Cl2	1.06	3.232(4)	2.18	171	-1+x, y, z
$N8-H82\cdots Cl2$	1.04	3.103(4)	2.09	162	x, y, z
$C4-H4\cdots Cl2$	0.93	3.610(5)	2.75	154	-1+x, y, z
C30–H301 · · · Cl2	0.97	3.762(4)	2.83	162	-1+x, y, z
N28–H281 · · · Cl3	1.11	3.152(4)	2.08	161	-1+x, y, z
N28–H282 · · · Cl3	1.07	3.105(4)	2.08	159	x, y, z
$C24-H24\cdots Cl3$	0.93	3.673(5)	2.81	155	-1+x, y, z
$\mathbf{IH}^{+}[\mathbf{I}^{-}]$					
N8–H81 · · · I1	0.98	3.503(2)	2.52	178	1+x, 1+y, z
$C7-H7\cdots I1$	0.96	3.896(3)	2.94	171	<i>x</i> , <i>y</i> , <i>z</i>
$N8-H82\cdots N1$	0.94	2.831(4)	1.92	165	y, 1-x+y, 0.17+z

Those involving C-H groups have been written in italic.

in the asymmetric part of the unit cell. However, unlike in the investigated crystal structures of  $IH^+[Cl^-]$  and  $IH^+[I^-]$ , in which the molecules in the crystal do not substantially differ in conformation, in the structures reported in the literature substantial conformational disparity is observed (vide supra). The predominance of structures with high Z' values observed in crystals of anabasinium salts brings about the question of factors that, either in combination or separately, contribute to such incidence. It seems that in the case of anabasinium salts the important factors influencing the formation of multiple asymmetric units are: the ability of the cations to adopt different, though close in energy, conformational rotamers, crystal and molecular chirality, and the occurrence of strong intermolecular interactions combined with the close packing requirements. Obviously, in the investigated crystal structures, besides the electrostatic attractions between the cationic and anionic species, formation of strong charge assisted hydrogen bonds of the N–H···X (X = Cl, I) type takes place. Geometrical parameters describing hydrogen bond interactions in both investigated crystals are listed in Table 5. However, while in  $\mathbf{IH}^+[\mathbf{CI}^-]$  the piperidine >  $\mathbf{NH}_2^+$  group utilizes both hydrogens in hydrogen bond interactions with chloride anions forming the  $Cl^- \cdots H - N - H \cdots Cl^-$  chains, in  $\mathbf{IH}^{+}[\mathbf{I}^{-}]$  crystals the equatorially oriented piperidinium hydrogen is involved in hydrogen bond interactions with the pyridine nitrogen acting as an acceptor (Table 5). Such direct hydrogen bond between anabasinium cations has not been reported previously [31] and therefore might be considered as the major factor responsible for the unprecedented anticlinal conformation of IH<sup>+</sup>.

#### 4. Conclusions

Anabasine salts display an inherent tendency to crystallize with multiple asymmetric units and to arrange themselves in the crystal in a helical manner. This may be a result of the presence of strong intermolecular interactions combined with the crystal and molecular chirality, as well as conformational flexibility of the anabasinium cations.

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