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Conformational analysis of 5-piperidinevaleric acid, 5-(*N*-methylpiperidine)valerate and their hydrogen halides by MO calculations, X-ray diffraction and FTIR spectroscopy

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Abstract

The most stable conformers of 5-(piperidine)valeric acid (**1**), 5-(*N*-methylpiperidine)valerate (**2**) and their hydrogen halides (**3** and **4**) were analyzed by the semiempirical PM3 method and selected compounds by the B3LYP/6-31G(d,p) method. As some of the investigated compounds are charged and the others can be neutral, some have acidic proton, others do not. They are capable of forming ionic bonds (via Coulombic attraction between the oppositely charged groups) or of forming the various types of hydrogen bonded conformers. As a result these compounds are ideally suited to study the importance of electrostatic interactions and hydrogen bonding on the relative stabilities of conformers. In the case of compounds containing *N*-methylpiperidine unit, for a particular conformer, the intramolecular attractive electrostatic interactions between the charged group play key roles in their relative stability in the gas phase. The electrostatic interaction of the X^- ion with the positively charged nitrogen atom decreases their proton-acceptor properties and COOH$\cdots X^-$ hydrogen bonds are present in all hydrogen halides (**3**). 5-Piperidine valeric acid with HF forms a molecular complex, while with HCl, HBr and HI an ion pair, according to the B3LYP calculations. The PM3 calculations predict a molecular complex also with HCl. The crystal structure of 5-(piperidine)valeric acid hydrogen bromide (**4HBr**), space group of crystals $P2_1/n$ with $a = 6.204(1)$, $b = 32.777(7)$, $c = 6.416(1)$ Å, $\beta = 106.21(3)°$, $Z = 4$ and $R = 0.0685$ was characterised by X-ray crystallography methods. Br^- ion forms two types of hydrogen bonds: Br$\cdots$N(1), 3.247(14) Å, and O(1) $\cdots$Br, 3.118(11) Å. Moreover, C–H$\cdots$Br short contacts, which can be recognized as weak hydrogen bonds, exist in the crystal. The FTIR spectrum of **1** in the solid state shows an intense broad absorption in the 1600–400 cm^{-1} region typical for a very short NHO hydrogen bonds. In solution the hydrogen bond seems to be longer. The bands of νC=O at 1708 cm^{-1} and $\nu_{as}COO^-$ at 1615 cm^{-1} in CD_3CN solution show that OH$\cdots$N $\rightleftharpoons$ O$^-\cdots$HN$^+$ equilibrium exists. Ab initio calculations predict molecular structures of three most stable conformers of **1** in the gas phase.

Keywords: 5-(Piperidine)valeric acid; Conformation; PM3; B3LYP calculations; X-ray diffraction; FTIR

1. Introduction

Theoretical calculations were used successfully to analyze the relative energies and geometries of the conformers of a fairly large number of amino acids [1]. In the gas phase amino acids are known to exist as

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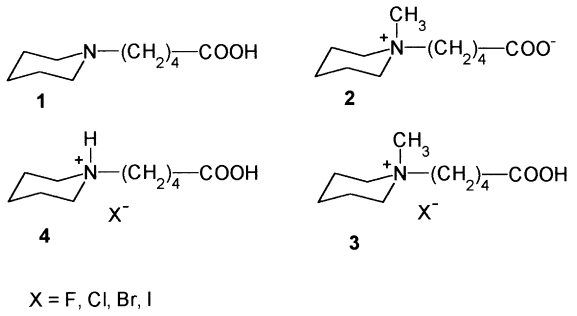

Scheme 1.

neutral molecules, while zwitterionic forms dominate in crystalline or aqueous media [1–6]. For each neutral and zwitterionic species these are a large number of possible conformers. In the case of *N*,*N*-dimethylglycine five of the most stable conformers were analyzed by ab initio calculations [1]. Amino acids form crystalline acid and alkaline salts, however, they were much less systematic studied [6]. It is concluded, that for a particular conformers the relative strength and number of possible H-bonds that can be formed and not necessarily the magnitude of the dipole moment play key roles in relative stability of amino acid conformers in the gas phase. In the case of zwitterionic species (amino acids and betaines) the electrostatic compensation of charges between the oppositely charged nitrogen atom and carboxylate group and H-bonding determine their relative stability [7].

N-Alkylated amino acids play important role in a biological chemistry [8–15]. The incorporation of *N*-alkylated amino acids, in place of natural amino acids, into proteins is known to have dramatic effects on the bioactive conformation of such mutant proteins. The study of the activity of such mutant proteins reveals the importance of H-bonds on the activity of proteins in general [16–25]. *N*-alkylation of amino acids is known also to increase the population of the neutral tautomers in solution [26]. Knowledge of the most stable conformers of the individual *N*-alkylated amino acids and the factors that contribute to their stability is essential in order to understand fully the biological consequences of their incorporation into proteins.

In this article, the relative energies and optimized geometries of the 5-piperidinevaleric acid (**1**), 5-(*N*-methylpiperidine)valerate (piperidine betaine) (**2**) and their hydrogen halides (**3** and **4**) (Scheme 1) are obtained from PM3, ab initio calculations and X-ray diffraction. From these results, the influence of the methylene groups separating the positively charged nitrogen atom from the COO group, effects of electrostatic interactions, H-bonds and protonation on the relative energies of the conformers are discussed.

Recently Feeder and Jones [27] have determined the crystal structures of five ω-phthalimidoalkanocarboxylic acids ($C_8H_4O_2N-(CH_2)_nCOOH$, $n = 1–5$) and demonstrated that hydrogen bonds vary with n. Four ω-piperidinealkanocarboxylic acid ($C_5H_{10}N-(CH_2)_nCOOH$, $n = 1–4$) were investigated in solution by Zundel et al. [28–30] and intramolecular hydrogen bonds were postulated.

2. Experimental

The general synthesis of *N*-(4-carboxybutyl)piperidinium bromide (**4HBr**) and its *N*-methyl derivative (**3HBr**) is quaternization of piperidine or *N*-methylpiperidine with ethyl 5-bromovalerate, followed by acid hydrolysis of ester function [31]. Piperidine (0.2 mol) was mixed on cooling with ethyl 5-bromovalerate (0.1 mol). The piperidine hydrobromide was filtered off, and the ethyl 5-piperidinevalerate was heated with 15% HCl or 24% HBr for 8 h. After evaporation of the acid and water under reduce pressure, the solid was recrystallized from acetonitrile-methanol solution (10 : 1). The *N*-(4-carboxybutyl)piperidinium, chloride (5-piperidinevaleric acid hydrogen chloride) (**4HCl**) m.p. 204°C–205°C. Analysis for $C_{10}H_{20}NClO_2$: calculated: C, 54.17%; H, 9.09%; N, 6.32%; found C, 54.13%; H, 9.06% N, 6.35%; **4HBr**, mp 202°C. Analysis for $C_{10}H_{20}NBrO_2$: calculated: C, 45.12%; H, 7.57%; N, 5.26%; found C, 45.10%; H, 7.62%; N, 5.19%. The 5-piperidinevaleric acid (**1**) was obtained from the reaction of **4HCl** with K_2CO_3 in small amount of water. After water evaporation, the acid was extracted with chloroform and the extract was dried over Na_2SO_4. The solvent was evaporated and the residue was stored over P_2O_5 and recrystallized from anhydrous acetonitrile, m.p. 79°C. 5-(*N*-Methylpiperidine)valerate (*N*-(4-carboxybutyl)-*N*-methylpiperidinium inert salt, betaine) (**2**) and its hydrobromides (**3HBr**) were prepared from *N*-methylpiperidine and ethyl 5-bromovalerate

Table 1
Crystal data and structure of refinement for *N*-(4-carboxybutyl)piperidinium bromide **(4)**

Empirical formula	$C_{10}H_{20}BrNO_2$
Formula weight	266.18
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	6.204(1)
b (Å)	32.775(7)
c (Å)	6.416(1)
β (deg)	106.21(3)
Volume(Å^3)	1252.7(4)
Z	4
Density (calculated) (Mg m^{-3})	1.411
Absorption coefficient (mm^{-1})	3.261
F(000)	552
Crystal size (mm)	0.10 × 0.22 × 0.45
θ range for data collection (deg)	1.24–27.06
Index ranges	$-7 \le h \le 7, 0 \le k \le 35, 0 \le 1 \le 8$
Reflections collected	2861
Independent reflections	2646 [R(int) = 0.1103]
Computer Programs	SHELXS-86[38] SHELXL-93[39]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2637/0/129
Goodness-of-fit on F^2	1.239
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0685, wR2 = 0.2094
Largest diff. peak and hole (e Å^{-3})	0.945 and−1.142

Table 2
Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for *N*-(4-carboxybutyl)piperidinium bromide **(4)**. $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	*y*	*z*	$U_{(eq)}$
Br	9068(2)	1502(1)	7864(2)	56(1)
N(1)	4902(15)	1396(3)	3517(14)	44(2)
C(2)	2954(20)	1549(4)	4210(22)	59(3)
C(3)	3143(23)	2008(4)	4614(24)	69(4)
C(4)	3388(28)	2235(5)	2724(31)	93(5)
C(5)	5377(26)	2078(4)	2048(24)	76(4)
C(6)	5149(22)	1622(4)	1573(19)	59(3)
C(7)	4700(20)	953(4)	3157(20)	57(3)
C(8)	6668(20)	748(4)	2595(19)	55(3)
C(9)	6564(22)	292(4)	2827(20)	57(3)
C(10)	8398(24)	68(4)	2125(21)	65(3)
C(11)	8401(23)	−378(4)	2321(19)	57(3)
O(1)	10118(18)	−536(3)	1836(18)	85(3)
O(2)	7016(22)	−559(3)	2809(22)	102(4)

Table 3
Anisotropic displacement parameters (Å^2 × 10^3) for *N*-(4-carboxybutyl)piperidinium bromide **(4)**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11} + \cdots + 2hka^*b^*U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br	50(1)	64(1)	49(1)	−8(1)	6(1)	6(1)
N(1)	40(4)	51(6)	40(4)	−9(4)	13(4)	−6(4)
C(2)	57(7)	57(8)	73(8)	−9(6)	33(6)	−11(6)
C(3)	63(8)	70(9)	78(9)	−26(7)	23(7)	3(7)
C(4)	82(10)	55(9)	122(14)	13(9)	−2(10)	15(7)
C(5)	92(11)	65(9)	67(8)	15(7)	16(8)	0(7)
C(6)	65(7)	70(9)	45(6)	9(6)	20(5)	−7(6)
C(7)	62(7)	60(8)	54(7)	3(6)	23(6)	6(6)
C(8)	51(6)	65(8)	46(6)	3(5)	12(5)	5(6)
C(9)	77(8)	46(7)	51(7)	5(5)	22(6)	9(6)
C(10)	83(9)	62(9)	60(8)	3(6)	34(7)	5(7)
C(11)	70(8)	56(8)	49(7)	4(5)	25(6)	8(6)
O(1)	102(7)	66(6)	102(8)	4(6)	55(6)	11(6)
O(2)	122(9)	56(7)	156(11)	8(7)	86(9)	−1(6)

according the procedure given in Ref. [31]. Compound **2**·H_2O was recrystallized from acetonitrile, m.p. 210°C–213°C dec. **3HBr**, m.p. 127–130°C from acetonitrile. Analysis for $C_{11}H_{24}NBrO_2$: calculated: C, 47.15%; H, 7.91%; N, 5.00%; found C, 47.14%; H, 7.92%; N, 4.92%.

Structures and energies were calculated by means of the PM3 semiempirical method [32], as implemented in the AMPAC 5.0 program package [33]. The ab initio calculations were performed with GAUSSIAN 94 program package [34]. The B3LYP exchange correlation functional [35,36] has been used throughout. This consists of the Lee–Yang–Parr [35] correlation functional in conjugation with a hybrid exchange functional first proposed be Becke [36]. The split-valence polarized 6-31G(d,p) basis set [37] was used. Relative energy (kcal/mol), E_{rel}, was taken as the difference in molecular energy E between that conformation and the minimum-energy conformation.

X-ray diffraction analysis was carried out using a KUMA-4 diffractometer equipped with graphite monochromator. The Br ion position was found from the Patterson map, the remaining non-hydrogen atoms from Fourier and difference Fourier syntheses. The positions of hydrogen atoms are derived from geometric conditions and refined as riding on the heavier atoms. The crystal data and details concerning data collection and structure refinement are given in

Table 4
Heats of formation (kcal/mol), dipole moments and selected geometrical parameters for the various conformations of 5-piperidinevaleric acid and its derivatives calculated by the PM3 method[a]

	ΔH	E_{rel}	μ	N···O_1	N···X	N···H	H···X	< NHX	O_1···X	O_1···H	H···X	< O_1HX
1ft	− 122.1	1.2	6.23	2.785	–	1.818	–	–	–	0.971	–	–
1ec	− 123.3	0	1.26	7.138	–	–	–	–	–	0.952	–	–
1et	− 121.3	2	4.05	6.891	–	–	–	–	–	0.949	–	–
2f1	− 68.98	5.1	15.39	3.477	–	–	–	–	–	–	–	–
2f2	− 74.11	0	14.24	3.067	–	–	–	–	–	–	–	–
2e	− 37.91	36.2	31.17	6.756	–	–	–	–	–	–	–	–
3ft1HF	− 136.6	7.2	14.81	5.313	3.422	–	–	–	2.623	0.977	1.659	168.1
3ft2HF	− 143.8	0	13.60	4.928	2.843	–	–	–	2.636	0.976	1.661	176.8
3ec1HF	− 131.1	12.7	8.38	7.075	2.794	–	–	–	6.727	0.952	7.413	–
3ec2HF	− 133.7	10.1	9.43	6.851	2.817	–	–	–	7.349	0.952	8.006	–
3et HF	− 131.1	12.7	11.08	6.906	2.815	–	–	–	7.217	0.949	6.968	–
3ft1HCl	− 128.8	4.6	15.09	5.435	3.561	–	–	–	2.782	0.983	1.811	168.5
3ft2HCl	− 133.4	0	14.92	5.237	3.156	–	–	–	2.783	0.983	1.803	174.0
3ec1HCl	− 122.6	10.8	9.55	7.082	2.991	–	–	–	6.758	0.952	7.429	–
3ec2HCl	− 126.6	6.8	10.31	6.830	2.976	–	–	–	7.401	0.952	8.052	–
3etHCl	− 124.0	9.4	11.89	6.901	2.997	–	–	–	7.264	0.949	7.016	–
3ft1HBr	− 119.0	4.2	13.67	5.578	3.621	–	–	–	3.529	0.955	2.612	161.0
3ft2HBr	− 123.2	0	14.19	5.701	3.187	–	–	–	3.544	0.983	2.612	165.4
3ec1HBr	− 114.9	8.3	9.86	7.082	2.980	–	–	–	6.794	0.952	7.465	–
3ec2HBr	− 117.0	6.2	11.04	6.830	2.976	–	–	–	7.401	0.952	8.052	–
3etHBr	− 114.3	8.9	12.56	6.899	2.974	–	–	–	7.255	0.949	6.985	–
3ft1HI	− 106.6	4.5	16.93	5.547	4.266	–	–	–	3.795	0.956	2.877	161.2
3ft2HI	− 111.1	0	18.38	6.044	3.987	–	–	–	3.939	0.956	3.008	176.8
3ec1HF	− 106.5	4.6	14.40	7.105	3.745	–	–	–	6.463	0.952	7.062	–
3ec2HI	− 109.6	1.5	17.63	6.773	3.949	–	–	–	7.784	0.952	8.378	–
3etHI	− 106.9	4.2	17.84	6.704	3.944	–	–	–	7.380	0.953	6.793	–
4ftHF	− 193.4	0	7.94	4.733	2.740	1.784	0.966	169.8	2.719	0.963	2.454	172.8
4fc1HF	− 188.6	4.8	1.93	3.844	2.760	1.803	0.958	178.7	8.093	0.953	7.108	–
4fc2HF	− 191.5	1.9	3.67	4.699	2.760	1.802	0.958	178.8	6.648	0.952	8.673	–
4ecHF	− 191.7	1.7	3.65	6.917	2.762	1.805	0.957	179.7	8.878	0.952	9.857	–
4etHF	− 189.4	4	4.31	6.945	2.763	1.806	0.957	179.8	8.863	0.949	8.403	–
4ftHCl	− 152.2	0	9.35	4.927	3.020	1.677	1.351	171.9	3.624	0.973	1.851	175.9
4fc1HCl	− 148.6	3.6	3.31	3.844	3.040	1.716	1.326	179.1	8.376	0.953	7.370	–
4fc2HCl	− 151.5	0.7	4.89	4.643	3.041	1.715	1.326	179.2	6.878	0.952	8.892	–
4ecHCl	− 151.6	0.6	4.77	6.916	3.044	1.721	1.324	177.3	9.140	0.952	10.110	–
4etHCl	− 149.2	3	4.83	6.949	3.046	1.723	1.323	177.8	9.110	0.949	8.647	–
4ftHBr	− 137.8	0	12.58	5.135	2.826	1.111	1.721	170.7	3.540	0.954	2.590	173.9
4fc1HBr	− 131.5	6.3	8.48	3.848	2.826	1.133	1.701	171.3	8.240	0.953	7.151	–
4fc2HBr	− 132.6	5.2	10.09	4.372	2.827	1.133	1.701	172.0	7.080	0.953	9.134	–
4ecHBr	− 133.7	4.1	9.44	6.911	2.825	1.139	1.697	169.8	9.114	0.952	10.110	–
4etHBr	− 130.9	6.9	8.37	6.981	2.826	1.141	1.695	170.1	9.130	0.949	8.690	–
4ftHI	− 116.6	2.5	13.98	5.332	3.003	1.074	1.941	169.0	3.896	0.955	2.943	175.5
4fc1HI	− 117.6	1.5	10.38	3.878	2.895	1.066	1.960	144.5	7.923	0.953	7.275	–
4fc2HI	− 119.1	0	11.98	3.855	2.898	1.063	1.971	143.9	6.420	0.953	8.428	–
4ecHI	− 118.7	0.4	11.62	7.036	2.979	1.083	1.909	168.8	8.996	0.952	9.004	–
4etHI	− 115.9	3.2	10.89	6.967	2.975	1.083	1.908	167.7	8.785	0.949	8.299	–

[a] Abbreviations. e: extended (*trans*-zig–zag) and f: folded (gauche) conformation on the $N(CH_2)_4COO$ moiety, respectively; c: *cis* and t: *trans* arrangement of the C=O/OH bonds, respectively.

Table 5
Selected dihedral angles for the various conformations of 5-piperidinevaleric acid and its derivatives calculated by the PM3 method[a]

	$O_2C_{11}O_1H$	$N_1C_7C_8C_9$	$C_7C_8C_9C_{10}$	$C_8C_9C_{10}C_{11}$	$C_9C_{10}C_{11}O_1$	$C_{10}C_{11}C_{12}O_2$	$MeN_1C_7C_8$
1ft	− 177.5	77.9	− 93.3	108.9	− 67.0	114.0	−
1ec	− 0.14	− 173.9	− 178.9	− 178.1	− 113.7	63.6	−
1et	− 178.9	− 174.4	− 179.4	− 179.9	− 71.5	109.0	−
2f1	−	119.9	− 75.2	− 56.2	89.1	− 89.5	160.9
2f2	−	130.8	− 74.8	84.8	− 66.2	113.9	− 172.9
3ft1HF	174.4	140.3	− 136.4	− 64.6	95.5	− 85.2	175.9
3ft2HF	− 179.1	143.5	− 79.2	134.7	− 92.6	87.4	− 173.4
3ec1HF	1.51	− 168.0	179.5	− 175.7	106.3	− 74.2	− 60.2
3ec2HF	− 1.33	179.9	179.5	178.6	− 78.3	102.3	− 179.8
3etHF	− 178.3	− 178.5	− 179.2	− 178.7	− 65.1	116.4	− 179.7
3ft1HCl	173.7	141.5	− 139.4	− 66.1	98.4	− 82.7	175.1
3ft2HCl	− 179.9	151.9	− 83.2	139.1	− 97.0	82.9	176.4
3ec1HCl	1.71	− 168.0	179.6	175.3	106.7	− 73.9	− 59.9
3ec2HCl	− 1.50	− 179.1	− 179.4	178.5	− 75.6	105.2	− 178.5
3etHCl	− 178.2	− 178.6	− 178.8	− 178.6	− 64.1	117.5	− 179.2
3ft1HBr	178.1	145.7	− 160.9	− 67.1	99.2	− 80.8	175.2
3ft2HBr	178.7	161.2	− 86.4	150.0	− 100.2	79.2	174.8
3ec1HBr	1.74	− 167.3	− 179.9	175.2	106.8	− 73.7	− 60.1
3ec2HBr	− 1.50	− 179.1	− 179.4	178.5	− 75.6	105.2	− 178.5
3etHBr	− 178.0	− 177.4	− 177.8	− 177.8	− 62.6	119.2	− 178.2
3ft1HI	176.4	− 179.8	169.9	− 78.7	100.6	− 79.0	178.7
3ft2HI	− 178.4	159.1	− 68.8	161.6	− 133.2	47.3	179.7
3ec1HI	2.84	− 173.0	179.2	173.5	105.7	− 75.2	− 57.4
3ec2HI	− 1.96	− 179.3	− 177.7	178.3	− 68.5	112.7	− 178.8
3etHI	− 176.1	− 177.0	− 177.6	171.2	− 30.8	151.9	− 178.9
4ftHF	176.1	73.1	64.0	− 165.2	44.7	− 137.2	−
4ftHCl	177.8	73.5	56.0	− 172.5	70.3	− 110.7	−
4ftHBr	177.6	76.4	56.3	− 177.8	67.9	− 113.2	− 61.9[b]
4ftHI	177.3	84.8	60.6	− 177.5	64.8	− 116.4	− 64.8[b]
4fc1HF	− 0.47	126.3	− 71.9	− 67.3	102.4	− 77.8	−
4fc2HF	− 0.22	163.6	− 64.7	− 76.8	− 92.2	87.9	−
4ecHF	− 0.35	− 166.1	− 178.2	− 178.2	− 102.4	77.8	−
4etHF	− 178.9	− 165.9	− 178.2	− 178.7	− 71.1	109.5	−
4fc1HCl	− 0.75	126.6	− 72.1	− 67.3	101.7	− 78.5	−
4fc2HCl	− 0.03	162.3	− 64.5	− 76.4	− 97.7	82.4	−
4ecHCl	− 0.32	− 165.9	− 178.0	− 178.0	− 102.3	77.8	−
4etHCl	− 178.8	− 165.6	− 177.9	− 178.6	− 71.5	109.1	−
4fc1HBr	− 1.89	127.7	− 73.2	− 67.6	97.4	− 82.5	166.4[b]
4fc2HBr	0.18	132.7	− 76.6	− 73.1	− 96.2	83.8	165.7[b]
4ecHBr	− 0.15	− 165.6	− 177.3	− 177.3	− 102.9	77.2	177.3[b]
4etHBr	− 179.2	− 164.7	− 176.9	− 176.4	− 73.1	107.3	177.6[b]
4fc1HI	− 1.95	127.7	− 73.8	− 68.8	94.8	− 85.1	170.7[b]
4fc2HI	0.34	127.3	− 70.5	− 64.0	− 98.9	81.2	170.9[b]
4ecHI	− 0.50	− 179.6	− 178.9	− 177.7	− 94.7	85.4	− 179.7[b]
4etHI	− 178.9	− 178.7	− 177.2	− 175.2	− 71.9	108.7	− 179.2[b]

[a] Abbreviations. e: extended (*trans*-zig–zag) and f: folded (gauche) conformation on the $N(CH_2)_4COO$ moiety, respectively; c: *cis* and t: *trans* arrangement of the C=O/OH bonds, respectively.

[b] $HN_1C_7C_8$

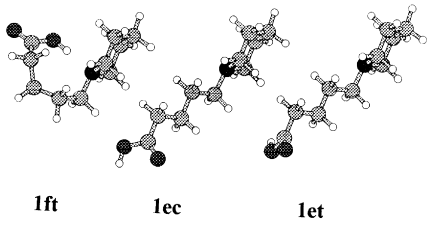

Fig. 1. Optimized PM3 structures for three most stable conformers of 5-piperidinevaleric acid (**1**).

Table 1. The atomic coordinates, equivalent anisotropic displacement parameters are presented in Tables 2 and 3, respectively.

The FTIR spectra were measured at 2 cm^{-1} resolution using a Bruker IFS 113v instrument, which was evacuated to avoid water and CO_2 absorptions. Each spectrum consists of 250 scans at ca. 30°C. The solid spectra were measured in Nujol and Fluorolube. The solution spectra (0.3 mol dm^{-3} in $CHCl_3$ and saturated solution (ca. 0.2 mol dm^{-3}) in CH_3CN) were measured in cell with KBr windows, 0.22 mm thick. Samples were prepared in a dry box.

3. Results and discussion

Table 4 shows heats of formation, relative energies, dipole moments and selected hydrogen bond distances calculated by the semiempirical PM3 method, for the most stable conformations of 5-piperidinevaleric acid (**1**), and 5-(*N*-methylpiperidine)valerate (**2**) and their hydrogen halides (**3** and **4**). Dihedral angles for the flexible N-$CH_2CH_2CH_2CH_2COO$ moiety are collected in Table 5. In folded conformers dihedral angles are in range between gauche and eclipsed. Figs. 1–4 show

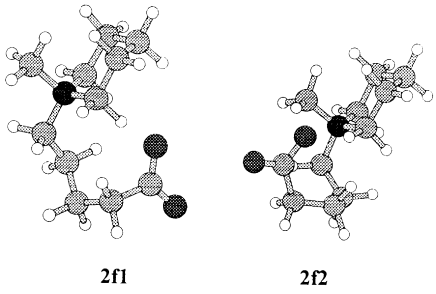

Fig. 2. Optimized PM3 structures for two most stable conformers of 5-(*N*-methylpiperidine)valerate (**2**).

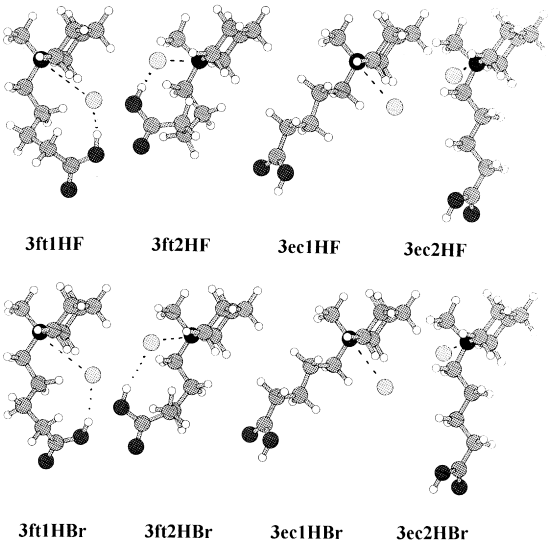

Fig. 3. Optimized PM3 structures for the most stable conformers of *N*(4-carboxybutyl)-*N*-methyl-piperidinium fluoride and bromide (**3**).

the PM3 optimized conformers. Selected data obtained from the B3LYP/6-31G(d,p) calculations are given in Table 6.

3.1. Conformers of 5-piperidinevaleric acid (*1*)

From Table 4 it is apparent that according to the

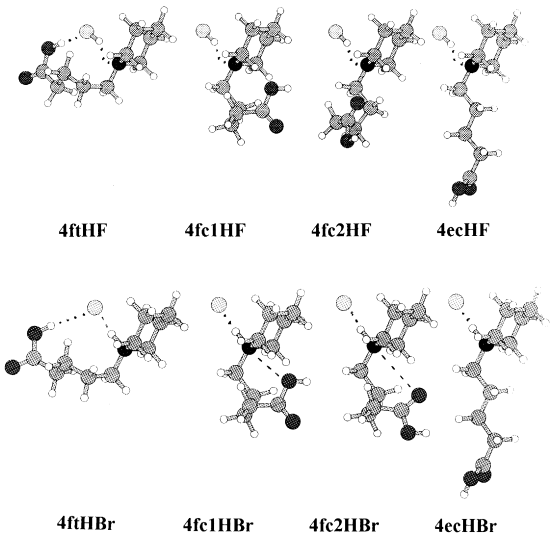

Fig. 4. Optimized PM3 conformers of *N*-(4-carboxybutyl)piperidine hydrogen fluoride and bromide (**4**).

Table 6
Dipole moments, relative energies (kcal mol^{-1}) and selected geometrical parameters for various conformers of 5-piperidinevaleric acid and its hydrogen bromide and hydrogen chloride[a]

Parameters	B3LYP/6-31/G(d,p)						HF/6-31G(d,p)
	1ft	**1ec**	**1et**	**3ftHF**	**4ftHF**	**4ftHCl**	**4ftHBr**
μ	6.45	1.23	3.52	14.20	9.15	13.02	14.28
E(eV)	− 597.753918	− 597.753427	− 597.744179	− 733.4787608	− 698.217140	− 1058.584506	− 3164.479532
E_{rel} (kcal mol^{-1})	0	0.3	6.1	–	–	–	–
< O=C − O − H	− 182.7	− 0.08	− 179.9	174.7	− 178.1	− 178.0	182.7
N···O	2.706	7.425	7.488	5.026	4.631	5.066	5.253
N − H	1.706	–	–	–	1.440	1.092	1.038
O − H	1.008	0.972	0.968	1.044	0.984	0.988	0.955
< OHN	171.4	–	–	–	–	–	–
X···H(O)	–	–	–	1.401	1.697	2.166	2.466
X − H(N)	–	–	–		1.041	1.881	2.153
N···X	–	–	–	3.265	2.476	2.965	3.183
< NHX	–	–	–	–	172.3	171.9	171.2
O···X	–	–	–	2.437	2.681	3.153	3.418
< OHX	–	–	–	171.1	178.9	179.4	159.6
$N_1C_7C_8C_9$	65.9	− 186.0	174.3	94.8	52.8	60.9	61.4
$C_7C_8C_9C_{10}$	− 80.5	− 180.2	− 179.8	− 133.4	58.2	63.6	62.4
$C_8C_9C_{10}C_{11}$	− 108.3	− 180.8	179.5	− 54.7	183.1	177.1	− 190.3
$C_9C_{10}C_{11}O_1$	− 3.425	− 180.2	− 179.0	95.8	71.2	76.7	77.7
$C_9C_{10}C_{11}C_2$	115.4	− 1.1	0.1	− 82.2	− 107.2	− 100.9	− 100.0

[a] Abreviations. e: extended (*trans*-zig–zag) and f: folded (gauche) conformation of the $N(CH_2)_4COO$ moiety, respectively; c: *cis* and t: *trans* arrangement of the C=O/OH bonds, respectively.l a.u. = 627.51 kcal mol^{-1}.

semiempirical PM3 data, conformer **1ec** (extended without hydrogen bond, with the *trans*-zig–zag conformation of N–$CH_2CH_2CH_2CH_2COOH$ moiety, and the *cis* arrangement of the C=O/OH bonds) is ca. 1.2 kcal mol^{-1} more stable than conformer **1ft** (folded with intramolecular hydrogen bond and *trans* C=O/OH bonds). However, conformer **1et** (with *trans* arrangement of the C=O/OH bonds) is less stable than **1ft** by ca. 0.8 kcal mol^{-1}. The B3LYP method predicts opposite stability trend; **1ft** has the lowest energy (Table 6). The *trans* arrangement of the C=O/OH bonds in **1ft** and **1et** contributes to the magnitude of the dipole moment and lowering stability. Similar observation were made for different orientations of the C=O/OH bonds in *N*, *N*-dimethylglycine [1] and formic acid [40].

The small energy difference between **1ft** and **1ec** suggests that the energy of the intramolecular hydrogen bond in **1ft** is comparable with the energy difference between *trans* and gauche of the N–$CH_2CH_2CH_2CH_2COOH$ moiety and between *cis*–*trans* of the C=O/OH bonds in **1ec**.

3.2. Conformers of 5-(N-methylpiperidine) valerate(**2**)

According to the results listed in Tables 4 and 5 two folded conformers are formed, **2f1** and **2f2** (Fig. 2). Both conformers are stabilized by the intramolecular Coulombic attraction between the positively charged nitrogen atom and the negatively charged oxygen atoms of the COO^- group. Similar folding of the carboxybutyl unit was observed in the pyridine betaine [7]. Conformer **2f2** is more stable than **2f1** by 5 kcal mol^{-1} and has lower dipole moment and similar molar volume (Table 4). Extended conformer (**2e**) is less stable by 36 kcal mol^{-1} than **2f2**. This suggests that the attractive coulombic energy is much larger than the energy difference between *trans* and gauche conformations of methylene groups in the $N^+–CH_2CH_2CH_2CH_2COO^-$ moiety. In general, molecules with smaller dipole moments are favored in the gas phase [41–43]. Conformation of the investigated compound in a crystal would be significantly different from these in the gas phase. Methylene units in the tether would have *trans*-zig–zag conformation and would be arranged antiparallel as in pyridine betaines [7]; the intramolecular charge compensation would be replaced by intermolecular one.

3.3. Conformers of N-(4-carboxybutyl)-N-methylpiperidinium halides (**3**)

Five conformers, **3ft1HX**, **3ft2HX**, **3ec1HX** **3ec2HX,** and **3etHX** could be located at the PM3 calculations. Conformers **3ft1HX** and **3ft2HX** can be derived by addition of HX to **2f1** and **2f2**, respectively. Analogous to **2**, conformers **3ft2HX** are more stable than **3ft1HX**. These conformers are stabilized by the Coulombic attraction between the N^+ atom and X^- ion, and additionally by the hydrogen bonds between the X^- ion and HOOC group. Extended conformers without hydrogen bonds, **3ec1HX**, **3ec2HX**, and **3etHX**, are less stable than the folded. The N···X distances in **3ft2HX** are slightly longer than these in **3etHX.** These differences indicate that hydrogen bonding between OH and X^- decreases electrostatic interaction of the X^- anion with the positive charged nitrogen atom. However, the electrostatic interaction decreases proton acceptor property of X^- anions and in consequence the proton is closer the oxygen atom.

3.4. Conformers of N-(4-carboxybutyl)piperidinium halides (**4**)

So, far 5-piperidinevaleric acid (**1**) was treated as alkylated amino acid. However, (**1**) can also be considered as tertiary amine with COOH as a substituent.

IR spectra of strongly hydrogen-bonded complexes between ammonia and amines (methylamine, dimethylamine and trimethylamine) and hydrogen halides were measured in the gas phase, argon and nitrogen matrices [44]. In those complexes the extent of the proton transfer increases from HF through to HI, with increasing base strength and with increasing polarity of the matrix. The N···H···X stretching mode which passes through a minimum at methylamine-

Table 7
Cis–trans energy difference for COOH group (kcal mol^{-1})

Method	**1**	**4HF**	**4HCl**	**4HBr**	**4HI**
B3LYP	5.8				
PM3	2.0	2.3	2.4	2.8	2.8

Table 8
Bond lengths (Å), bond angles and dehedral angles (deg) for 5-piperidinevaleric acid and its hydrogen halides.

Method Compound	X-ray **4ecHBr**	HF **4ftHBr**	B3LYP **4ftHF**	B3LYP **4ftHCl**	B3LYP **3ftHF**	B3LYP **1ft**	B3LYP **1ec**
Bond lengths							
N(1)– C(7)	1.470(14)	1.4957	1.4753	1.5075	1.5402	1.4753	1.4632
N(1)– C(2)	1.487(14)	1.4921	1.4892	1.5021	1.5297	1.4814	1.4661
N(1)– C(6)	1.495(14)	1.4977	1.4870	1.5087	1.5291	1.4778	1.4663
C(2)– C(3)	1.53(2)	1.5251	1.5307	1.5293	1.5293	1.5310	1.5315
C(3)– C(4)	1.47(2)	1.5273	1.5343	1.5333	1.5358	1.5337	1.5336
C(4)– C(5)	1.51(2)	1.5276	1.5340	1.5333	1.5354	1.5334	1.5331
C(5)– C(6)	1.53(2)	1.5241	1.4863	1.5278	1.5291	1.5311	1.5318
C(7)– C(8)	1.52(2)	1.5286	1.5356	1.5313	1.5316	1.5345	1.5333
C(8)– C(9)	1.50(2)	1.5335	1.5371	1.5375	2.5540	1.5415	1.5330
C(9)– C(10)	1.52(2)	1.5370	1.5414	1.5409	1.5453	1.5566	1.5289
C(10)– C(11)	1.47(2)	1.5185	1.5281	1.5290	1.5363	1.5296	1.5125
C(11)– O(2)	1.16(2)	1.1878	1.2102	1.2115	1.2191	1.2117	1.2173
C(11)– O(1)	1.30(2)	1.3189	1.3449	1.3410	1.3255	1.3416	1.3558
O(1)– H	1.10(3)	0.9545	0.9845	0.9876	1.0436	1.0076	0.9722
N(1)– H	0.91(3)	1.0379	1.4405	1.0918	–	1.7058	–
N(1)···O(1)	–	5.2532	4.6309	5.0666	–	2.706	5.067
N(1) ···X	3.247(11)	3.1831	2.4759	2.2945	3.2655	–	–
O(1) ···X	3.188(11)	3.4175	2.6809	3.1547	2.4371	–	–
Me···N(1)	–	–	–	–	1.4982	–	–
Bond angles							
C(7)– N(1)– C(2)	109.9(8)	114.12	110.22	114.11	109.93	110.46	111.70
C(7)– N(1)– C(6)	112.5(9)	109.62	112.68	109.86	110.62	112.54	112.71
C(2)– N(1)– C(6)	111.3(9)	111.65	110.24	111.29	108.51	110.23	110.79
N(1)– C(2)– C(3)	110.7(9)	111.11	111.30	111.13	112.41	111.60	111.25
C(4)– C(3)– C(2)	112.3(12)	111.51	111.04	111.60	110.46	111.21	110.92
C(3)– C(4)– C(5)	110.4(12)	109.74	109.96	109.79	110.32	110.03	110.01
C(4)– C(5)– C(6)	110.7(13)	111.46	111.21	111.48	110.31	111.04	110.00
N(1)– C(6)– C(5)	110.2(10)	112.13	110.90	111.85	112.47	111.24	111.29
N(1)– C(7)– C(8)	115.7(10)	116.54	115.53	116.24	116.99	115.91	113.63
C(9)– C(8)– C(7)	110.8(10)	117.48	115.89	117.01	116.22	117.32	112.18
C(10)– C(9)– C(8)	113.2(11)	113.79	114.33	114.12	114.14	117.30	112.56
C(11)– C(10)– C(9)	116.0(11)	110.47	111.52	110.78	111.66	114.87	113.22
O(2)– C(11)– O(1)	125.5(13)	121.30	121.47	121.38	123.00	122.38	122.35
O(2)– C(11)– C(10)	123.4(13)	122.01	123.19	122.40	120.93	121.48	126.17
O(1)– C(11)– C(10)	111.1(12)	116.65	115.32	116.18	116.04	116.14	111.48
C(11)– O(1)–H	109.5	114.03	111.31	112.54	112.41	112.40	105.94
C(7)– N(1)– H	107.6	108.12	111.31	108.07	–	107.50	–
C(2)– N(1)– H	107.6	107.42	103.56	108.15	–	107.50	–
C(6)– N(1)– H	107.6	105.39	106.19	104.89	–	113.73	–
N(1)– H–X	170.6(3)	171.23	–	171.84	–	–	–
O(1)– H–X	164.1(3)	174.73	–	177.96	–	–	–
O(1)H–Br–H(N1)	–	104.17	109.77	–	–	–	–
C(2)– N(1)– Me	–	–	–	–	110.51	–	–
C(6)– N(1)– Me	–	–	–	–	110.92	–	–
C(7)– N(1)– Me	–	–	–	–	106.34	–	–
Torsial angles							
C(4)– C(5)– C(6)– N(1)	− 57.26(15)	54.53	− 57.22	55.17	− 57.75	− 57.32	− 56.40
C(4)– C(3)– C(2)– N(1)	− 55.44(15)	− 56.72	56.69	− 56.60	57.28	56.04	56.66
C(5)– C(6)– N(1)– C(7)	179.38(10)	177.4	− 177.03	177.01	177.21	− 176.60	− 174.31
C(6)– N(1)– C(7)– C(8)	59.62(13)	179.04	62.94	176.53	− 54.88	69.24	73.38

Table 8 (*continued*)

Method Compound	X-ray **4ecHBr**	HF **4ftHBr**	B3LYP **4ftHF**	B3LYP **4ftHCl**	B3LYP **3ftHF**	B3LYP **1ft**	B3LYP **1ec**
N(1)– C(7)– C(8)– C(9)	165.47(10)	61.45	52.77	60.91	94.79	69.95	173.99
C(7)– C(8)– C(9)– C(10)	175.78(10)	62.39	58.20	63.62	− 133.37	− 80.54	179.77
C(8)– C(9)– C(10)– C(11)	179.68(11)	169.66	183.12	177.07	− 54.68	108.28	179.20
C(9)– C10)– C(11)– O(1)	− 175.33(11)	77.71	71.23	76.49	95.85	115.39	179.00
C(9)– C(10)– C(11)– O(2)	5.95(20)	− 100.03	− 107.18	− 101.13	− 82.24	− 63.89	− 1.09
C(10)– C(11)– O(1)– H	179.97(14)	4.97	3.41	4.53	− 3.31	− 3.43	179.83
O(2)– C(11)– O(1)– H	− 1.35(2.2)	− 177.28	− 178.14	− 177.83	174.74	− 182.72	− 0.08
C(6)– N(1)– H–X	− 171.7	− 18.76	63.33	4.85	–	–	–
C(2)– N(1)– H–X	51.6	100.41	− 57.81	123.69	–	–	–
C(5)– C(6)– N(1)– H	61.03(14)	–	− 52.16	61.09	–	–	–
C(3)– C(2)– N(1)– Me	–	–	–	–	65.56	–	–
C(5)– C(6)– N(1)– Me	–	–	–	–	− 65.04	–	–

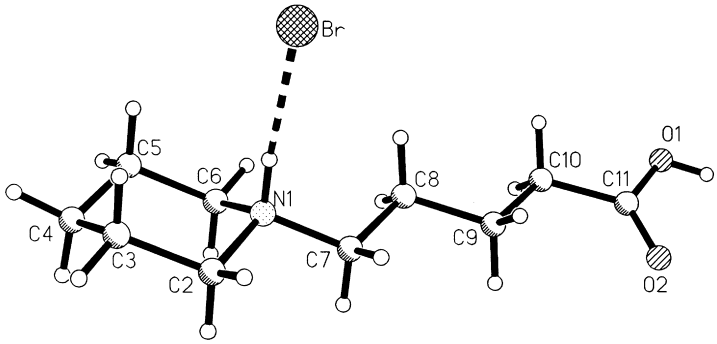

Fig. 5. X-ray molecular structure and atomic numbering of *N*-(4-carboxybutyl)piperidinium bromide (**4HBr**). The thermal ellipoids were drawn at the 50% probability level.

hydrogen chloride or ammonia-hydrogen bromide in argon matrix (but at ammonia-hydrogen chloride in nitrogen matrix), then increases as to extent of the proton transfer to the nitrogen increases [45]. Barnes and Legon [44] from the nitrogen nuclear quadrupole coupling constants, χ(N)/MHz, estimated in the gas phase the following percentage of ionic character of Me_3N–HX complexes: 12% (HF), 60% (HCl), 83% (HBr), and 100% (HI). Golubev and Denisov [46] studied the complexes of trimethylamine with hydrogen chloride and hydrogen bromide in the gas phase by NMR specrtroscopy and reported that a strongly hydrogen bonds complex was formed with hydrogen chloride whereas the complex with hydrogen bromide was close to an ion pair.

The most stable conformers of complexes of 5-piperidinevaleric acid with hydrogen fluoride and hydrogen bromide are shown in Fig. 4. According to the PM3 data in complexes with HF and HCl proton is closer to halide atom (a molecular complex), whereas in the case of HBr and HI proton is transferred to the nitrogen atom (an ion pair) (Table 4). The B3LYP calculations gave slightly different results, which are in excellent agreement to the experimental results of complexes of Me_3N with HX in the gas phase [44]. Thus no proton transfer take place in **4ftHF** while in **4ftHCl**, **4ftHBr** and **4ftHI** complexes proton is transferred from these hydrogen halides to the 5-piperidinevaleric acid (Table 8).

In **4ftHX** conformers two hydrogen bonds, NHX and OHX, are present. Generally formation of the second hydrogen bonds elongate the first one. This trend was observed in the 1 : 1 and 2 : 1 complexes of pentachlorophenol with pyridine N-oxides [47]. In

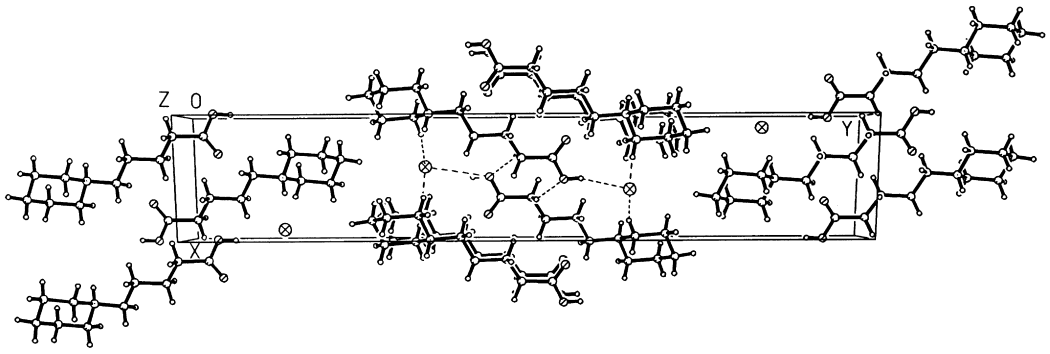

Fig. 6. Molecular packing in the unit cell at *N*-(4-carboxybutyl)piperidinium bromide (**4HBr**).

4ftHI the N···X distance is ca. 0.1 Å longer than these with one hydrogen bond. However, this rule is broken in complexes with HF, HCl and HBr. Formation of OHX hydrogen bonds shortening the NHX one by ca. 0.02 Å.

Considering hydrogen iodides the most stable is conformer **4fc2HI** and the less stable is conformer **4etHI**. Conformer **4fc2HI** is stabilized by the $I^-\cdots HN^+$ hydrogen bond and the electrostatic interaction between the N^+ atom and the oxygen atom of COO^- group. Conformer **4fc2HI** is very similar to conformer **2f1**. The longer O···N distance in conformer **4fc2HI** (ca. 0.4 Å) than in conformer **2f1**, suggests that the positively charged nitrogen atom in the former compound is mainly neutralized by I^- ion via hydrogen bond. In complexes with HF, HCl and HBr the electrostatic interaction between the N^+ atom and the oxygen atom (**4fc1HX** and **4fc2HX**) are weaker as the most stable conformers are **4ftHX**.

3.5. Conformation of COOH group

Carboxylic acids may have their hydroxyl proton either *cis* (*syn*) or *trans* (*anti*) to the C=O bond for which we use the description c or t, respectively. Ab initio calculation with 4-31G(d) basis set predicted that c rotamer of formic acid is 6.2 kcal mol $-$ 1 more stable than t [48]. The experimental values are in the range of 2–4 kcal mol^{-1} [48]. Table 7 lists calculated *cis–trans* energy difference for **1** and **4**. Value obtained by the B3LYP method is in good agreement with datum for formic acid. The semiempirical data are ca. three time lower but are close to the experimental data for formic acid [49].

*3.6. X-ray structure of N-(4-carboxybutyl)piperidinium bromide (**4HBr**)*

Perspective drawing of the complex of 5-(piperidine)valeric acid with hydrogen bromide (**4HBr**) and numbering scheme of its atoms are shown in Fig. 5. The piperidine ring adopts the usual chair conformation with the $(CH_2)_4$–COOH chain at the equatorial position and the proton at the axial position as it is seen from Fig. 5. Geometrical parameters are collected in Table 8. The asymmetry parameters of the chair conformation are equal 0.4 [50]. The angle between the best plane of hydrocarbon chain and C(2)C(3)C(5)C(6) ring atoms is 26.5(6)°. The carboxyl group is twisted relative to the carbon chain by 6.6(2)°. The carboxyl group has a cis arrangement and forms H-bond with the bromide ion; O···Br is 3.188(20) Å and ∠O–H···Br is 164°. The Br^- ion forms also H-bond with the N–H proton; Br···N is 3.247(14) Å and ∠ Br···H–N is 170° (Fig. 6). The Δ*HA* parameters are 22 and 19, respectively for NHBr and OHBr hydrogen bonds [51]. This indicates that NHBr bond is stronger than OHBr. The intermolecular N···Br distance is 4.364 Å (sym. code: 1 + *x*, *y*, 1 + *z*) and O···Br distance is 3.201 Å (sym. code: 2.5 + *x*, 0.5 + *y*, 1 + *z*). As Fig. 6 shows that contribution of the bromide ion to stabilization the crystal structure is significant.

3.7. FTIR spectra

The FTIR spectra of powdered and solution

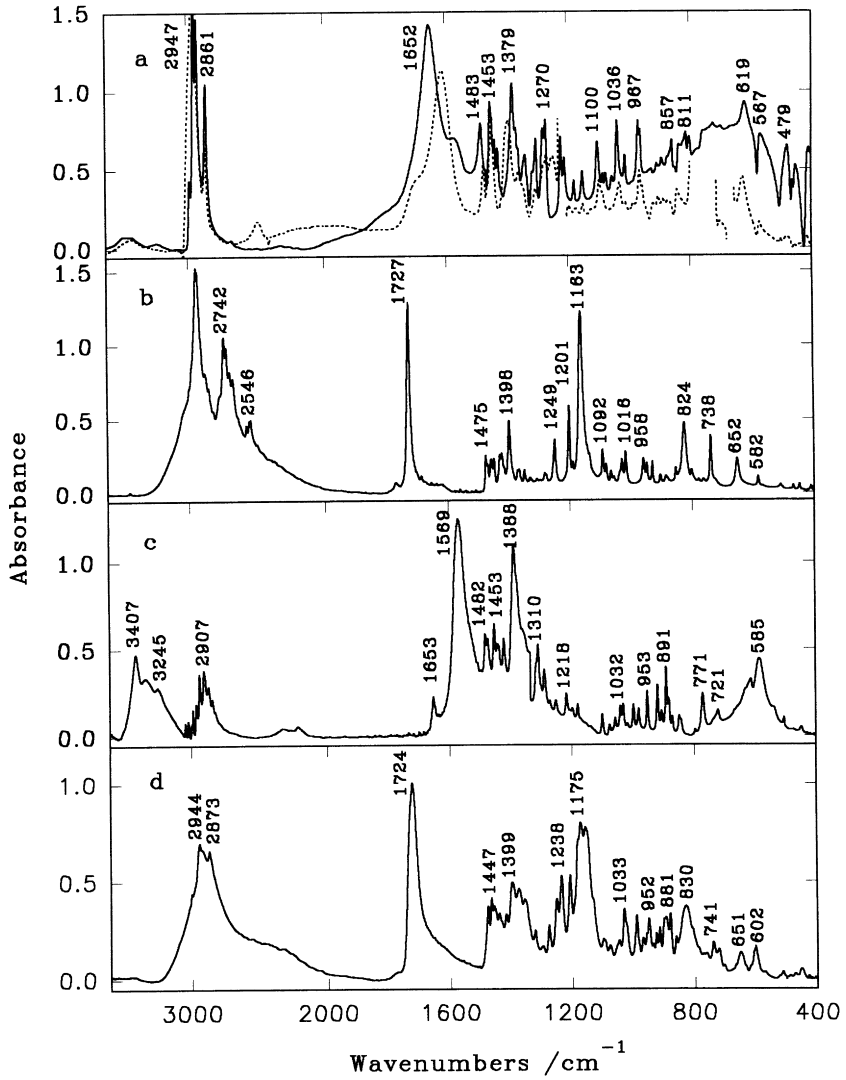

Fig. 7. FTIR spectra in Nujol and Fluorolube mulls (—) and $CHCl_3$ solution (…) of (a) 5-(piperidine)valeric acid **(1)**, (b) *N*-(4-carboxybutyl)piperidinium bromide (**4HBr**), (c) 5-(*N*-methylpiperidine)valerate **(2)**, (d) *N*-(4-carboxybutyl)-*N*-methyl-piperidinium bromide (**3HBr**).

samples of the investigated compounds at room temperature are shown in Fig. 7. The most striking feature of the solid state spectrum of **1** is presence of a very broad and intense absorption below 1600 cm^{-1} (Fig. 7a). Another interesting feature is intense band at 1650 cm^{-1}. This band is in the middle between the νC=O band at 1727 cm^{-1} in the complex of 5-piperidinevaleric acid with hydrogen bromide (**4HBr**) (Fig. 7b) and the $\nu_{as}COO^-$ at 1569 cm^{-1} in 5-(*N*-methylpiperidine)valerate (**2**) (Fig. 7c). These spectroscopic data are typical for short hydrogen bonds, O···N distance close to 2.5 Å with nearly symmetric location of the H-atom [52,53]. In solution the broad absorption is shifted slightly toward higher wavenumber. The spectrum of **1** in $CHCl_3$ in general is very similar to that in Ref. [28] and suggests that hydrogen bond in solution is slightly longer than that in the solid state. In CD_3CN solution two bands due to the νC=O and $\nu_{as}COO^-$ vibrations at 1709 cm^{-1} and 1615 cm^{-1}, respectively,

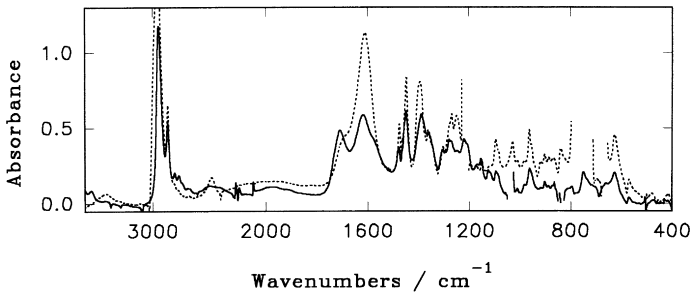

Fig. 8. FTIR spectra of 5-piperidinevaleric acid in CD_3CN (—) and $CHCl_3$ (…).

proving $OH\cdots N \leftrightharpoons O^-\cdots HN^+$ prototropic equilibrium. In $CHCl_3$ solution the $\nu C{=}O$ vibration appears as a shoulder at ca. 1710 cm^{-1}, but the $\nu_{as}COO$ band at 1613 cm^{-1} is very strong. This suggests that an ionic pair is the dominant species in $CHCl_3$ solution (Fig. 8). The spectra of hydrogen bromides **4** and **3** show a broad absorption in the 3200–2200 cm^{-1} region (Fig. 7b and d), typical for hydrogen bond longer then 3 Å [54]. This absorption in Fig. 7b is because of νNH and νOH vibration, while in Fig. 7c to the νOH.

4. Conclusions

The PM3 semiempirical calculations were carried out on the most stable conformers of **1**, **2** and their hydrogen halides **3** and **4**. Selected compounds were analyzed by the B3LYP/6-31G(d,p) method.

The relative stabilities of three conformers of **1** vary with the calculation methods. According to the B3LYP data **1ft** form with intramolecular N···HO hydrogen bond has the lowest energy. The most stable conformers of dimethylglycine is also stabilized by similar intramolecular N···HO bond.

Owing to the Coulombic interaction between the positively charged nitrogen atom and the negatively charged COO group of **2**, from two folded conformers **2f2** has lower dipole moment and shorter N···O distance, and is the most stable.

From five conformers of **3HX**, the most stable are conformers derived from **2f2** by addition of HX. The most stable conformers have **3ft2HX** form and are stabilized by the Coulombic attraction between the N^+ atom and X^- ions, and by the $COOH\cdots X^-$ hydrogen bond. The electrostatic interaction decreases proton acceptor properties of the X^- ions and in consequence the proton is closer to the oxygen atom.

Complexes of **4HX** are the most complicated system, owing to protonation problem. The extent of proton transfer in all **4HX**, predicted by the B3LYP calculations, is quite similar to that found in the gas phase in $Me_3N{\cdot}HX$ [44]. Thus no proton transfer take place in **4HF**, while in **4HCl**, **4HBr** and **4HI** the proton from XH is transferred to the nitrogen atom. According to the PM3 data **4HCl** exists as a molecular complex. In the case of complex with HF, HCl and HBr the most stable is **4ftHX** conformer, stabilized by two hydrogen bonds, NHX and the OHX. Considering complex with HI, the most stable is conformer **4fc2HI**, stabilized by the $I^-\cdots HN$ hydrogen bond and the electrostatic interactions between the N^+ atom and O=C bond.

The **4HBr** complex in the crystal has an extended structure. The Br^- ion forms $Br^-\cdots HN$ and $Br^-\cdots HOOC$ hydrogen bonds with two molecules of protonated 5-(piperidine)valeric acid.

The FTIR spectrum of **1** in the solid state shows an intense broad absorption in the 1600–400 cm^{-1} region typical for a very short NHO hydrogen bond. In solution the hydrogen bond seems to be longer. The $OH\cdots N \rightleftharpoons O^-\cdots HN^+$ prototropic equilibrium is present in CD_3CN solution.

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