

SPECTRAL ANALYSIS OF ACETYLCHOLINE HALIDES BY DENSITY FUNCTIONAL THEORY CALCULATIONS

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The optimized molecular structures, vibrational frequencies and ^1H and ^{13}C NMR chemical shifts of acetylcholine halides (F, Cl, and Br) have been investigated using density functional theory (B3LYP) method with 6-311G(d) basis set. The comparison of their experimental and calculated IR, R and NMR spectra of the compounds has indicated that the spectra of three optimized minimum energy conformers can simultaneously exist in one experimental spectrum. Thus, it was concluded that the compounds simultaneously exist in three conformations in the ground state. The calculated optimized geometric parameters (bond lengths and bond angles), vibrational frequencies and NMR chemical shifts for the minimum energy conformers were seen to be in a good agreement with the corresponding experimental data. All the assignments of the theoretical frequencies were performed by potential energy distributions using VEDA 4 program.

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INTRODUCTION

Acetylcholine [$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$] plays a central role in neurotransmission. Within the last decades, choline and acetylcholine derivatives attract many research teams to analyze their vibrational frequencies using various computational levels, including medium and/or large basis sets because of the molecular complexity, the computational costs or hardware performance [1-3]. The determination of the minimum energy conformers on the potential energy hypersurface of acetylcholine has been subject by many theoretical works.

These studies have showed that low energy conformations appear corresponding to the orientation of the acetoxy group with respect to the rest of the molecule. The different minima on the hypersurface have been related to the muscarinic and nicotinic activity of acetylcholine [4]. Marino and et al. have investigated the conformational behavior and molecular motion of acetylcholine in vacuo and aqueous solution [5]. They have calculated five low lying conformations by molecular mechanics computing. The *ab initio* data of acetylcholine have indicated that the most stable conformation is the *trans-gauche* arrangement of the two essential torsion angles (τ_1 ; C–C–O–C and τ_2 ; N–C–C–O) [6, 7]. The observed conformation of acetylcholine is *trans-gauche* ($\tau_1 = -166.9^\circ$ and $\tau_2 = 84.7^\circ$) in the crystal of its chloride, [8, 9] *gauche-gauche* ($\tau_1 = 78.9^\circ$ and $\tau_2 = 78.4^\circ$) in the crystal of its bromide [10] and *gauche-gauche* ($\tau_1 = \pm 83^\circ$ and $\tau_2 = \pm 89^\circ$) in the crystal of its iodide [11]. Theoretical study of acetylcholine bromide has denoted that the experimental *gauche-gauche* conformation corresponds only to a local energy

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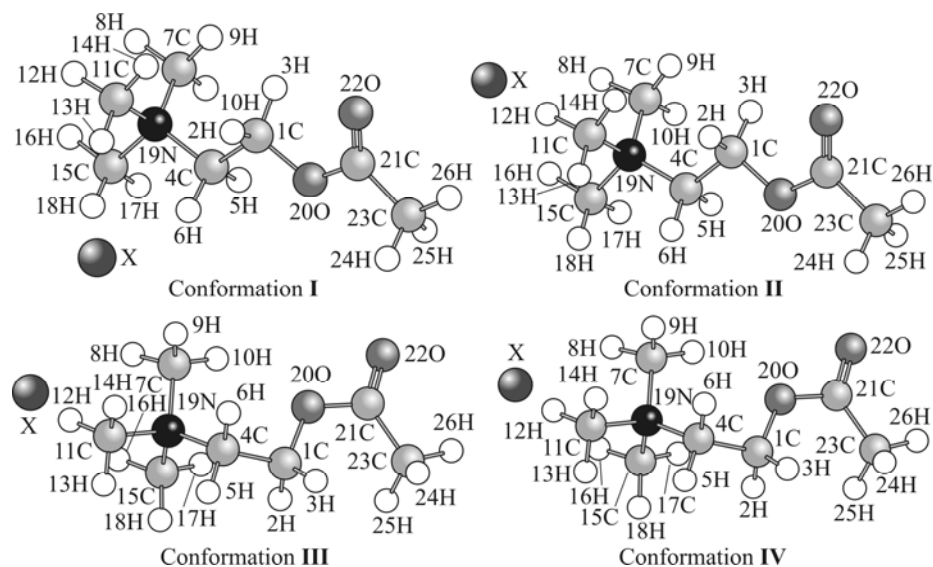


Fig. 1. Molecular structures of all optimized conformers of acetylcholine halides (X = F, Cl or Br).

minimum about $2 \text{ kcal}\cdot\text{mol}^{-1}$ above the global one associated with a different *gauche-gauche* conformation [12].

As seen from the above discussion the ground state conformation of acetylcholine is labile and influenced by its environment. In this study we wish to report the vibrational and NMR analysis of acetylcholine halides to obtain the minimum energy conformations in the ground state by means of density functional theory (B3LYP) method.

COMPUTATIONAL DETAILS

The optimized structure parameters and vibrational frequencies for acetylcholine halides (AChF, AChCl and AChBr) were calculated by density functional theory (B3LYP) method at 6-311G(*d*) basis set level. All the computations were performed by using Gaussian 03 package [13] and Gauss-View molecular visualization programs [14] on the personal computer. In the calculation the position of halide anion (X) was taken with an torsion angle X(27)–C(11)–N(19)–C(4) and an X...N distance of $3.62 \text{ \AA}$, in which the angle C(4)–N(19)–C(11) was frozen, and scanned around this torsion angle from 180° to -180° at increments of 20° . Potential Energy Surface (PES) Scan of the compounds showed four minimum-energy structures. These structures were chosen to obtain the further optimized ones which have no imaginary frequencies. The calculated vibration frequencies were scaled with a scale factor of 0.9614 [15] and clarified by means of the potential energy distribution (PED) analysis and assignments of all the fundamental vibrational modes using VEDA 4 program [16]. For the ^1H and ^{13}C NMR chemical shift calculations both in vacuum and in solvent media of the title compounds the GIAO approach was used. The molecular geometries together with that of tetramethylsilane (TMS) in vacuum or in solvent media is fully optimized. The theoretical chemical shift ^1H and ^{13}C values were obtained by subtracting the GIAO isotropic magnetic shielding (IMS) values [17, 18]. For instance, the average ^{13}C IMS value of TMS was taken into account for the calculation of ^{13}C chemical shift of any X carbon atom by considering the following equation $\text{CS}_x = \text{IMS}_{\text{TMS}} - \text{IMS}_x$.

RESULTS AND DISCUSSION

Ground state conformations. The molecular structures of all the calculated optimized conformers for the acetylcholine halides can be seen in Fig. 1. The conformations are defined the two essential torsion angles τ_1 [C(21)–O(20)–C(1)–C(4)] and τ_2 [O(20)–C(1)–C(4)–N(19)]. The angles τ_1 and τ_2 for all the conformations of the compounds are listed in Table 1.

TABLE 1. Two Essential Torsion Angles τ_1 [C(21)–O(20)–C(1)–C(4)] and τ_2 [O(20)–C(1)–C(4)–N(19)] for All the Conformers of Acetylcholine Halides

Molecule	Conformer							
	I		II		III		IV	
	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2
AChF	–179.0	–171.4	85.2	172.8	–180.0	–180.0	173.8	79.3
AChCl	–178.6	–170.2	84.7	174.5	–180.0	–180.0	171.9	66.0
AChBr	–178.8	–169.2	84.6	174.8	–180.0	–180.0	171.9	65.6

TABLE 2. Sum of Electronic and Zero Point Energies, Relative Energies and Mean Calculated Vibrational Deviations Between the Conformers of Acetylcholine Halides

Molecule	Conformer	Energy, Hartree/part.	Relative energy, kcal/mol	Vib. deviation $ \Delta v _{ave}$
AChF	I	–581.283035	0.00	0.00
	II	–581.282394	0.40	12.57
	III	–581.282491	0.34	10.30
	IV	–581.269489	8.49	14.77
AChCl	I	–941.673284	0.00	0.00
	II	–941.673161	0.08	9.04
	III	–941.672759	0.33	7.05
	IV	–941.660100	8.27	13.33
AChBr	I	–3055.598607	0.00	0.00
	II	–3055.598489	0.07	9.47
	III	–3055.598064	0.34	6.49
	IV	–3055.585442	8.26	12.42

In Table 2 are given the electronic energies, relative energies and mean vibrational deviations. The relative energy values and calculated vibrational deviations in the table are respect to the lowest energy conformer **I**. As seen the mean vibrational deviation increases while the relative energy increases. Therefore, we state that the more different the molecular structures of two conformers is the higher the relative energy is between them, and so, the bigger mean vibrational deviation occurs. This comment has also been given for pyridine carboxaldehyde and difluorobenzaldehyde molecules in our previous studies [19, 20]. From Table 2 we also see that the relative energy and mean calculated vibrational deviation between the conformers **I** and **II** or **I** and **III** are very low while those between the conformers **I** and **IV** are fairly high.

Vibrational frequencies. The resulting vibrational frequencies for the lowest energy conformer **I** of all the title compounds are given in Table 3. For comparison the table also show the experimental vibrational frequencies (IR and R) of powder AChCl and AChBr [21], but, those of AChF have not been found in the literature. In the table are also given the assignments of all the fundamental vibrational modes of AChCl obtained by using VEDA 4 program and they correspond well to the ones given in the literature [2]. The correlation values between the experimental and calculated frequencies in the last line of the table show a good agreement with each other.

The frequency of the X–H stretching vibration (X = F, Cl, and Br) remarkably depends upon the molecular conformation and the weight of halide anion. This frequency for the conformer **I** was calculated at 199 cm^{–1}, 167 cm^{–1}, and 125 cm^{–1} as coupled with some vibrations for AChF, AChCl and AChBr, respectively, but for the conformer **III** at 168 cm^{–1}, 147 cm^{–1}, and 110 cm^{–1}, respectively. As seen the frequency of the X–H stretching vibration decreases while the weight of anion increases. In addition it decreases while the conformation changes. Similar result was found by normal coordinate analyses of *n*-propane derivatives, which suggests that the C–X (X = Cl and S) stretching vibration couples with the O–C–C

TABLE 3. Experimental and Calculated Vibrational Frequencies of Lowest Energy Conformer **I** of Acetylcholine Halides. ν Shows Stretching, δ Bending, γ out of Plane Bending, τ Torsion modes; Sym, Symmetric; Asym, Antisymmetric

Assignments (%PED ^a)	Experimental Frequencies, cm ⁻¹ AChCl [21]		Experimental Frequencies, cm ⁻¹ AChBr [21]		Calculated Frequencies, (cm ⁻¹) B3LYP 6-311G(d)		
	IR	R	IR	R	AChF	AChCl	AChBr
1	2	3	4	5	6	7	8
CH ₃ [ν_{CH} (83)asym]	—	—	—	—	3043	3052	3053
CH ₃ [ν_{CH} (72)asym]	—	—	—	3043	3040	3042	3042
CH ₃ [ν_{CH} (85)asym]	—	—	—	—	3033	3041	3041
CH ₃ [ν_{CH} (58)asym]+CH ₂ [ν_{CH} (12)asym]	—	3037	—	—	3028	3039	3039
CH ₃ [ν_{CH} (74)asym]	—	3025	—	3020, 3014	3022	3034	3034
CH ₃ [ν_{CH} (82)asym]	3021, 3010	3016, 3006	3017, 3013	3005	2997	3010	3007
CH ₂ [ν_{CH} (56)asym]+CH ₃ [ν_{CH} (21)asym]	—	—	—	—	2996	3004	3003
CH ₃ [ν_{CH} (60)asym]+CH ₂ [ν_{CH} (13)asym]	—	—	—	—	2987	3001	2999
CH ₃ [ν_{CH} (89)asym]	—	—	—	—	2977	2998	2997
CH ₂ [ν_{CH} (80)asym]	—	2980	2981	2984	2973	2987	2986
CH ₃ [ν_{CH} (75)sym]+CH ₂ [ν_{CH} (13)sym]	2962, 2932	2960	2954, 2924	2976, 2959	2954	2959	2960
CH ₃ [ν_{CH} (92)sym]	—	—	—	—	2939	2940	2940
CH ₂ [ν_{CH} (82)sym]	—	2936, 2928	—	2925	2936	2938	2939
CH ₃ [ν_{CH} (36)sym]+CH ₂ [ν_{CH} (16)]	—	—	—	2905	2802	2906	2898
CH ₃ [ν_{CH} (24)sym]+CH ₂ [ν_{CH} (22)]	—	2887	2871	2879	2736	2885	2878
CH ₃ [ν_{CH} (56)sym]	2879, 2863	2866, 2852	2855	2854	2728	2881	2875
$\nu_{O=C}$ (88)	1756, 1745	1735	1748	1746	1748	1753	1753
CH ₃ [δ_{HCH} (23)]	1506, 1496	1491	1496	1499, 1492	1521	1488	1488
CH ₂ [δ_{HCH} (70)]+CH ₃ [δ_{HCH} (27)]	—	—	1484, 1478	—	1508	1477	1478
CH ₂ [δ_{HCH} (24)]+CH ₃ [δ_{HCH} (27)]	—	1476	—	1473	1502	1476	1476
CH ₃ [δ_{HCH} (33)]+CH ₂ [δ_{HCH} (15)]+ τ_{HCNC} (10)	1467, 1449	—	1465, 1453	—	1480	1470	1469
δ_{HCH} (43)+ τ_{HCHX} (11)	—	1462, 1449	—	1459, 1451	1472	1457	1459
γ_{HCH} (49)	—	—	—	—	1463	1454	1454
CH ₃ [γ_{HCH} (56)]	—	—	—	—	1457	1447	1449
δ_{HCH} (16)+ δ_{CCH} (11)	—	1441	1442	—	1450	1441	1441
δ_{HCH} (69)+ δ_{CCH} (11)+ τ_{HCNC} (13)	1437	—	—	—	1434	1434	1434
CH ₃ [δ_{HCH} (67)]+ τ_{HCNC} (24)	—	—	—	—	1432	1432	1432
δ_{HCH} (50)	1422	—	1427	—	1427	1431	1431
δ_{HCH} (56)	1416	1423, 1414	1408	1416	1408	1408	1409
τ_{HCHX} (27)+ δ_{HCH} (22)+ δ_{CCH} (10)	—	1393	—	1405	1386	1399	1401
CH ₃ [δ_{HCH} (45)]+ τ_{HCHX} (11)	1388, 1374	—	1380, 1369	1387	1366	1388	1392
CH ₃ [δ_{HCH} (54)]	—	1368	—	1371	1359	1362	1362

TABLE 3. (Continued)

1	2	3	4	5	6	7	8
$\tau_{\text{HCOC}}(21)+\text{CH}_3[\delta_{\text{HCH}}(12)]+\delta_{\text{CCH}}(10)$	1353	1356	1349	1346	1353	1351	1351
$\tau_{\text{HCNX}}(35)+\tau_{\text{HCNC}}(18)$	1320	—	1311	1309	1313	1314	1312
$\delta_{\text{HCO}}(49)$	1299	1296	1289	1283	1265	1263	1260
$\tau_{\text{HCNC}}(26)$	1282, 1243	1245	—	1248	1259	1259	1258
$\delta_{\text{HCN}}(19)+\tau_{\text{HCNC}}(12)+\nu_{\text{NC}}(10)$	—	1228	1234	1225	1225	1222	1223
$\delta_{\text{HCO}}(14)+\tau_{\text{HCNC}}(11)$	—	—	—	—	1210	1205	1203
$\nu_{\text{O-C}}(30)+\nu_{\text{CC}}(14)+\delta_{\text{OCC}}(14)$	1163	—	—	1162	1207	1202	1201
$\tau_{\text{HCNC}}(16)$	1147	1159	1153	1143	1147	1140	1140
$\tau_{\text{HCNC}}(10)$	1112	1148	1137	—	1127	1121	1121
$\tau_{\text{HCNC}}(10)+\nu_{\text{CC}}(10)$	1091	1107	1081	1089	1065	1060	1059
$\nu_{\text{CC}}(33)$	1066, 1047	1079	1056, 1037	1055	1061	1053	1053
$\tau_{\text{HCNC}}(33)+\delta_{\text{HCN}}(16)$	—	1061, 1052	—	—	1056	1050	1049
$\nu_{\text{OC}}(54)$	1035	1029	—	1038	1033	1035	1035
$\tau_{\text{HCCO}}(41)+\gamma_{\text{OCCO}}(19)+\delta_{\text{HCN}}(13)$	1021	1015	1016	1015	1031	1033	1033
$\tau_{\text{HCCO}}(34)+\nu_{\text{CC}}(19)+\nu_{\text{OC}}(17)$	—	956	960, 955	958, 951	967	961	960
$\nu_{\text{NC}}(39)$	944	940	—	—	956	943	944
$\nu_{\text{NC}}(39)$	927	—	917	920	924	924	924
$\nu_{\text{NC}}(35)+\nu_{\text{OC}}(17)$	884	878	873	872	889	894	894
$\nu_{\text{NC}}(29)+\nu_{\text{OC}}(20)$	856	848	825	826	848	851	850
$\delta_{\text{CCH}}(20)+\tau_{\text{HCOC}}(15)$	835	—	—	—	809	792	794
$\text{N-CH}_3[\nu_{\text{NC}}(76)]$	731	721	723	724	730	725	725
$\nu_{\text{CC}}(36)+\delta_{\text{O-CC}}(29)+\delta_{\text{COC}}(10)+\delta_{\text{CCO}}(10)$	617	647	651	654	631	631	631
$\gamma_{\text{OCOC}}(71)$	549	604	609	610	582	580	580
$\delta_{\text{CNC}}(16)+\delta_{\text{O-CC}}(10)$	488	541	545	545	514	511	510
$\gamma_{\text{OCOC}}(16)+\delta_{\text{CNC}}(14)$	473, 463	464, 454	481	479	508	458	457
$\delta_{\text{CNC}}(36)+\gamma_{\text{NCCC}}(15)$	—	—	455	453	452	442	442
$\delta_{\text{O-CC}}(21)+\delta_{\text{CCO}}(20)+\delta_{\text{CNC}}(12)$	—	420	—	426	419	421	420
$\delta_{\text{CNC}}(32)+\delta_{\text{CCO}}(18)$	—	369	—	385	386	367	370
$\delta_{\text{CNC}}(57)$	—	—	—	351	372	351	350
$\tau_{\text{HCHX}}(37)+\tau_{\text{HCNC}}(15)$	—	—	—	—	369	325	333
$\tau_{\text{HCNC}}(34)+\tau_{\text{HCHX}}(13)$	—	292	—	301	334	299	302
$\delta_{\text{COC}}(24)+\nu_{\text{CC}}(11)+\delta_{\text{OCC}}(11)$	—	264	—	—	290	251	252
$\delta_{\text{CCO}}(12)$	—	—	—	—	265	238	240
$\tau_{\text{HCNC}}(61)+\tau_{\text{HCHX}}(11)$	—	213	—	234	255	235	237
$\tau_{\text{CCOC}}(33)+\tau_{\text{NCHX}}(16)$	—	—	—	173	242	177	173
$\tau_{\text{CCOC}}(23)+\tau_{\text{XHCN}}(17)+\tau_{\text{CNCH}}(11)+\nu_{\text{XH}}(11)$	—	—	—	—	199	167	152
$\delta_{\text{XHC}}(24)+\tau_{\text{NCHX}}(16)+\tau_{\text{CNCH}}(12)$	—	130	—	—	174	141	125
$\tau_{\text{CNCH}}(20)+\delta_{\text{COC}}(15)+\delta_{\text{OCC}}(10)+\tau_{\text{CCHX}}(10)$	—	—	—	114	166	115	112
$\delta_{\text{OCC}}(22)+\delta_{\text{COC}}(17)+\tau_{\text{CCHX}}(13)+\tau_{\text{HCNC}}(12)$	—	—	—	—	100	92	91
$\tau_{\text{HCCO}}(69)$	—	—	—	—	94	84	80
$\tau_{\text{XHCN}}(20)+\tau_{\text{COCC}}(20)+\tau_{\text{CNCH}}(11)$	—	—	—	—	64	64	59
$\tau_{\text{OCCN}}(63)+\tau_{\text{CCOC}}(16)$	—	—	—	—	35	37	36
$\tau_{\text{COCC}}(60)$	—	—	—	—	29	26	21
						$R^2=0.9997$	$R^2=0.9998$

^aPotential energy distribution (PED), less than 10% are not shown.

TABLE 4. Experimental and Calculated Chemical Shift Values for Minimum Energy Conformers of Acetylcholine Halides

Atom	Experimental, ppm [23]		Calculated TMS B3LYP/6-311G(<i>d</i>) GIAO											
	AChCl (in CDCl ₃)	AChBr (in D ₂ O)	AChF (in vacuum)				AChCl (in CDCl ₃)				AChBr (in water)			
			I	II	III	Average	I	II	III	Average	I	II	III	Average
C1	58.07	59.15	61.05	59.89	60.92	60.62	60.23	59.38	60.29	59.97	60.50	59.69	60.52	60.24
C4	64.58	65.50	63.77	64.84	67.19	65.27	64.15	65.27	67.54	65.65	64.34	64.90	67.07	65.44
C7	54.05	54.71	51.74	51.55	51.64	51.64	53.16	51.66	51.69	52.17	53.05	51.95	52.04	52.35
C11	54.05	54.56	51.92	51.14	51.64	51.57	51.46	51.28	51.69	51.48	51.69	51.60	52.03	51.77
C15	54.05	54.87	58.32	58.22	58.46	58.33	56.99	56.92	57.05	56.99	57.05	56.95	57.12	57.04
C21	170.04	173.94	175.06	176.09	174.38	175.18	177.62	178.79	177.15	177.85	178.54	179.77	178.31	178.87
C23	21.03	21.19	21.42	21.48	21.28	21.39	21.94	21.87	21.74	21.85	22.04	22.03	21.96	22.01
R²							0.9982	0.9979	0.9979	0.9981	0.9984	0.9982	0.9983	0.9984
RMSE							3.7870	3.8000	3.4823	3.4888	2.4604	2.8297	2.4676	2.5137
H(2)			4.05	3.70	4.02	3.92	4.14	3.90	4.13	4.06	4.16	4.02	4.18	4.12
H(3)			3.80	4.69	4.02	4.17	4.07	4.71	4.13	4.30	4.23	4.74	4.17	4.38
H(CH₂)	4.600		3.93	4.20	4.02	4.05	4.11	4.31	4.13	4.18	4.20	4.38	4.18	4.25
H(5)			2.08	3.00	2.87	2.65	2.78	3.17	3.21	3.05	3.02	3.28	3.37	3.22
H(6)			8.65	2.40	2.87	4.64	6.20	2.80	3.21	4.07	5.92	3.01	3.37	4.10
H(CH₂)	4.170		5.37	2.70	2.87	3.65	4.49	2.99	3.21	3.56	4.47	3.15	3.37	3.66
H(8)			2.32	8.01	8.16	6.16	2.67	5.45	5.55	4.56	2.79	5.14	5.23	4.39
H(9)			2.70	1.75	1.85	2.10	2.97	2.38	2.43	2.59	3.05	2.55	2.57	2.72
H(10)			2.27	1.78	1.59	1.88	2.59	2.38	2.26	2.41	2.71	2.53	2.46	2.57
H(N-CH₃)	3.562		2.43	3.85	3.87	3.38	2.74	3.40	3.41	3.18	2.85	3.41	3.42	3.23
H(12)			1.70	8.25	8.16	6.04	2.30	5.62	5.55	4.49	2.48	5.26	5.23	4.32
H(13)			8.18	1.55	1.59	3.77	5.60	2.23	2.26	3.36	5.27	2.45	2.46	3.39
H(14)			1.81	1.85	1.85	1.84	2.30	2.44	2.43	2.39	2.44	2.61	2.58	2.54
H(N-CH₃)	3.562		3.90	3.88	3.87	3.88	3.40	3.43	3.41	3.41	3.40	3.44	3.42	3.42
H(16)			1.79	8.23	8.30	6.11	2.42	5.62	5.71	4.58	2.62	5.29	5.38	4.43
H(17)			1.92	1.82	1.85	1.87	2.55	2.41	2.46	2.47	2.71	2.58	2.64	2.64
H(18)			8.05	1.78	1.85	3.89	5.48	2.40	2.46	3.45	5.19	2.59	2.64	3.47
H(N-CH₃)	3.562		3.92	3.94	4.00	3.95	3.48	3.48	3.54	3.50	3.51	3.49	3.55	3.52
H(24)			2.23	2.11	2.08	2.14	2.35	2.27	2.24	2.29	2.32	2.31	2.30	2.31
H(25)			2.00	1.98	2.08	2.02	2.17	2.13	2.24	2.18	2.26	2.19	2.30	2.25
H(26)			1.63	1.70	1.72	1.68	1.72	1.75	1.76	1.74	1.72	1.73	1.71	1.72
H(CH₃)	2.128		1.95	1.93	1.96	1.95	2.08	2.05	2.08	2.07	2.10	2.08	2.10	2.09
R²			0.5456	0.4487	0.4582	0.7741	0.8020	0.7386	0.8249	0.9480	0.8430	0.8029	0.8851	0.9644
RMSE			0.7577	0.6692	0.6372	0.3850	0.4190	0.5055	0.4456	0.3475	0.3621	0.4348	0.3781	0.2933

bending vibration in the *trans* conformation but not in the *gauche* conformation. The coupling gives rise to the high frequency shift of the C–X stretching vibration [22].

Chemical shifts. The calculated ¹H and ¹³C NMR chemical shifts (with respect to TMS) for the minimum energy conformers of the title compounds are tabulated in Table 4. The experimental chemical shifts in the table have been obtained from Spectral Database for Organic Compounds Web Page [23]. Since the experimental ¹H chemical shift values of individual hydrogen nucleus are not available the average values of ¹H chemical shifts for the CH₂ and CH₃ hydrogen atoms have been found and given as bold. Because the experimental NMR spectra are taken in liquid phase we think they show an average state of all these conformers having very close energies. So, we have also found the average ¹H and ¹³C NMR

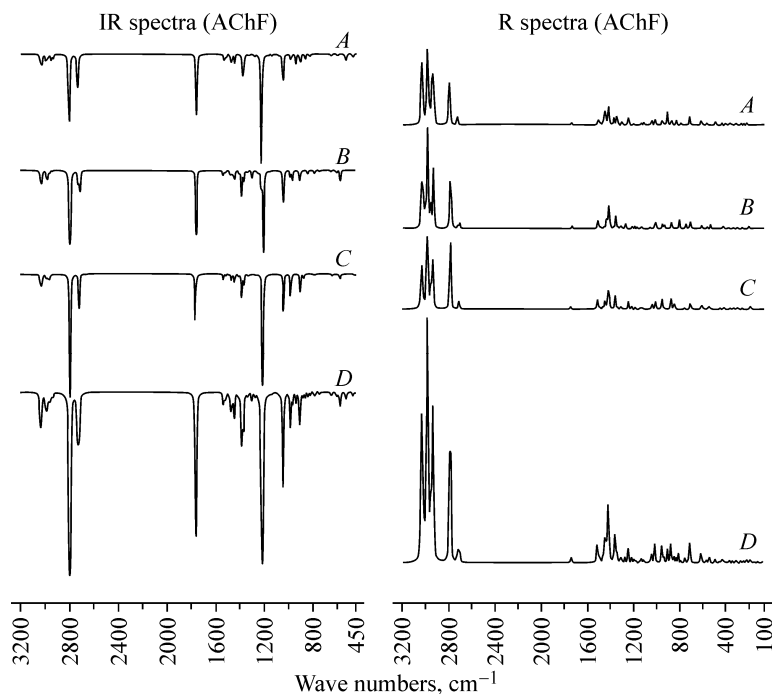


Fig. 2. Calculated IR and R spectra of conformers **I**, **II**, and **III** of AChF as labeled *A*, *B*, and *C*, respectively. *D* shows the sum of *A*, *B*, and *C*.

chemical shift values of the conformers **I**, **II**, and **III**, and listed them in Table 4. The correlation values between the experimental and theoretical chemical shifts can be seen in the last line of the table. All the calculated ^1H NMR chemical shift values were compared with the experimental available data for AChCl. Additionally, the root mean square errors (RMSE) were also given in the table. The RMSE is defined by

$$RMSE(w_i) = \sqrt{\sum \frac{(\delta_i^{\text{calc}} - \delta_i^{\text{exp}})^2}{n}},$$

where δ_i^{calc} and δ_i^{exp} are the calculated and experimental chemical shifts of atom *i*., respectively, and *n* denotes the number of atoms. According to these values it can be stated the agreement between the experimental and calculated chemical shifts are good.

From Table 4 we also see the ^1H chemical shifts [as example H(6), H(13) and H(18) for the conformer **I**] close to the electronegative halogen atom at the X position are highest. This indicates that the local electron density is affected due to the halogen atom deshielding for H nucleus. The highly electronegative fluoride halogen leads to a strong electron-density-withdrawing effect on the resonance of H. Therefore, the ordering of the halogen effect for H nucleus is $\delta(\text{F}) > \delta(\text{Cl}) > \delta(\text{Br})$.

Molecular geometries. The calculated optimized structure parameters of the lowest energy conformer **I** of the compounds are summarized in Table 5, in accordance with the atom numberings in Fig. 1. The table compares the calculated bond lengths and angles with those obtained experimentally from the X-ray data of AChCl [8] and AChBr [10]. Taking into account that the molecular geometry in the vapour phase may be different from the one in the solid phase, owing to extended hydrogen bonding and stacking interactions, there is reasonable agreement between the calculated and experimental geometric parameters. The correlation values in the table also show their agreement.

Spectral analysis. The calculated IR and R spectra of the minimum energy conformers **I**, **II**, and **III** of all the compounds are given in Fig. 2-4*A*, *B* and *C*'s, respectively. For comparison the experimental spectra of the powder compounds are also given in the figures, as labeled *E*'s. As seen the experimental spectra do not fit well to the calculated spectra of the conformers, individually. The experimental spectra show the peaks splinted two near doublings, and thus, have

TABLE 5. Calculated Optimized Geometric Parameters for the Conformers I of Acetylcholine Halides

Parameters	Experimental		Calculated B3LYP [6-311G(<i>d</i>)]		
	AChCl [8]	AChBr [10]	AChF	AChCl	AChBr
1	2	3	4	5	6
Bond lengths, Å					
N(19)–C(7)	1.50	1.496	1.490	1.496	1.496
N(19)–C(11)	1.49	1.498	1.514	1.512	1.511
N(19)–C(15)	1.52	1.502	1.514	1.512	1.511
N(19)–C(4)	1.49	1.513	1.526	1.525	1.525
C(1)–C(4)	1.47	1.500	1.521	1.522	1.522
C(1)–O(20)	1.45	1.452	1.439	1.434	1.434
O(20)...N(19)	3.26	3.201	3.738	3.731	3.730
O(20)...C(7)	3.17	2.985	4.289	4.276	4.268
C(11)–H(12)	—	0.97	1.090	1.089	1.089
C(11)–H(13)	—	1.00	1.106	1.095	1.096
C(11)–H(14)	—	0.92	1.089	1.088	1.088
C(7)–H(8)	—	0.98	1.089	1.089	1.089
C(7)–H(9)	—	0.90	1.088	1.087	1.087
C(7)–H(10)	—	0.93	1.090	1.089	1.089
C(15)–H(16)	—	1.01	1.090	1.089	1.089
C(15)–H(17)	—	0.91	1.090	1.089	1.089
C(15)–H(18)	—	0.94	1.105	1.094	1.095
C(1)–H(2)	—	0.96	1.091	1.091	1.091
C(1)–H(3)	—	1.03	1.094	1.093	1.093
C(4)–H(5)	—	0.93	1.092	1.091	1.091
C(4)–H(6)	—	0.94	1.107	1.095	1.096
C(21)–C(23)	1.49	1.487	1.506	1.505	1.505
C(21)–O(20)	1.38	1.358	1.357	1.362	1.362
C(21)–O(22)	1.18	1.192	1.203	1.202	1.202
C(23)–H(24)	—	1.00	1.093	1.093	1.093
C(23)–H(25)	—	1.00	1.092	1.091	1.092
C(23)–H(26)	—	0.95	1.088	1.088	1.088
X(27)–H(6)	—	—	1.770	2.391	2.529
X(27)–H(13)	—	—	1.777	2.403	2.544
X(27)–H(18)	—	—	1.793	2.456	2.593
X(27)–C(4)	—	—	2.736	3.369	3.518
X(27)–H(8)	—	—	—	—	—
X(27)–H(12)	—	—	—	—	—
X(27)–H(16)	—	—	—	—	—
X(27)–C(15)	—	—	—	—	—
R^2			0.9401	0.9771	0.9415
Bond angles, deg					
C(7)–N(19)–C(11)	109	109.8	111.2	109.9	109.9
C(7)–N(19)–C(15)	111	108.6	110.4	109.4	109.3
C(4)–N(19)–C(7)	111	112.2	112.4	111.2	111.2
C(4)–N(19)–C(11)	111	110.7	109.7	111.0	111.0
C(4)–N(19)–C(15)	107	107.1	106.0	107.0	107.0

TABLE 5. (Continued)

1	2	3	4	5	6
N(19)–C(4)–C(1)	119	116.4	114.4	114.7	114.7
N(19)–C(7)–H(9)	—	110	110.2	110.0	110.0
C(1)–O(20)–C(21)	115	115.7	115.6	115.3	115.3
C(11)–N(19)–C(15)	108	108.3	107.0	108.3	108.3
H(2)–C(1)–H(3)	—	109	108.2	108.4	108.5
H(6)–C(4)–H(5)	—	109	112.0	110.3	110.2
H(6)–C(4)–N(19)	—	104	102.6	105.7	105.8
H(14)–C(11)–N(19)	—	109	109.1	109.1	109.1
H(13)–C(11)–N(19)	—	108	103.8	107.5	107.6
H(12)–C(11)–N(19)	—	107	107.9	108.0	108.0
H(12)–C(11)–H(13)	—	110	112.3	110.8	110.7
H(12)–C(11)–H(14)	—	112	109.6	109.6	109.7
H(16)–C(15)–H(17)	—	114	110.1	110.1	110.1
H(8)–C(7)–H(9)	—	107	109.1	109.3	109.3
H(8)–C(7)–N(19)	—	109	108.9	108.9	108.9
X(27)–C(15)–N(19)	—	—	80.1	84.3	85.4
O(20)–C(21)–O(22)	123	122.8	123.1	122.7	122.7
O(22)–C(21)–C(23)	129	125.9	126.2	126.6	126.6
O(20)–C(1)–C(4)	111	111.6	104.1	103.8	103.9
O(20)–C(21)–C(23)	108	111.3	110.7	110.7	110.7
H(24)–C(23)–H(25)	—	106	107.2	107.3	107.3
H(24)–C(23)–H(26)	—	106	109.5	109.4	109.5
H(25)–C(23)–H(26)	—	108	110.2	110.3	110.3
N(19)–C(7)–H(10)	—	107	109.3	109.2	109.2
N(19)–C(15)–H(16)	—	104	108.3	108.4	108.4
H(17)–C(15)–H(18)	—	111	112.9	111.0	110.9
C(4)–C(1)–H(3)	—	115	114.7	114.4	114.4
O(20)–C(1)–H(2)	—	109	108.9	109.2	109.2
C(21)–C(23)–H(24)	—	115	109.6	109.3	109.4
R^2			0.8366	0.8516	0.7612
Dihedral angles, deg					
C(15)–N(19)–C(4)–C(1)	171.4/170.8 ^a	175.49	–171.5	–171.4	–171.0
N(19)–C(4)–C(1)–O(20)	84.7	78.44	–171.4	–170.2	–169.2
C(4)–C(1)–O(20)–C(21)	–166.9	78.90	–179.0	–178.6	–178.8
C(1)–O(20)–C(21)–O(22)	5.2	4.10	–2.8	–4.2	–4.2
X(27)–C(21)–O(20)–C(1)	–173.6 ^a	—	66.6	71.8	72.4
C(1)–C(4)–N(19)–C(7)	53.0 ^a	—	64.9	69.2	69.6
C(1)–C(4)–N(19)–C(11)	–70.02 ^a	—	–59.3	–53.5	–53.1
X(27)–N(19)–C(4)–C(1)	—	—	–115.4	–110.2	–109.9

^aRef. [9].

more spectral lines than the calculated ones. Since the relative energy values between these conformers of the compounds are very low (see Table 2) we think that the spectra of these three conformers can simultaneously exist in one experimental spectrum. So, we have drawn the sum of the calculated spectra (IR or R) of these conformers, and obtained the spectra in Figs. 2–4D's. By confronting them to the experimental ones (Fig. 3 and 4E's) it can easily be seen that they fit well to each other.

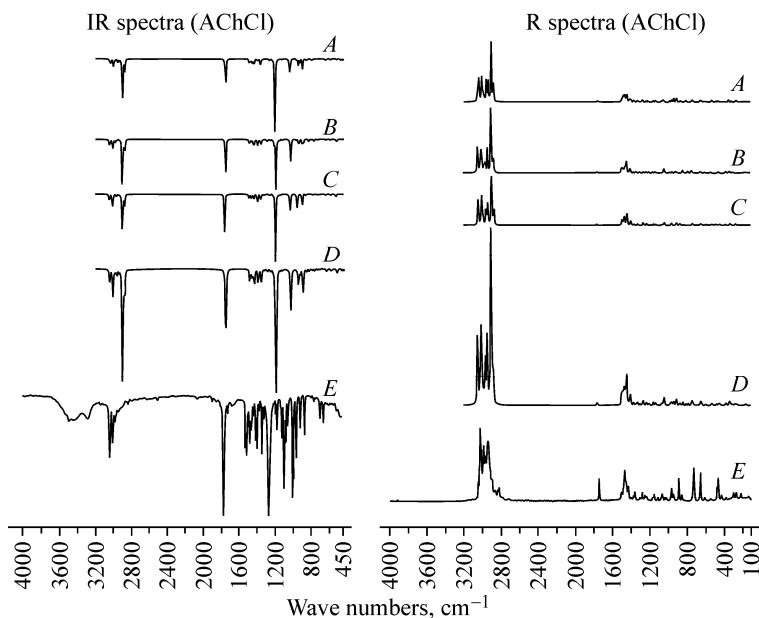


Fig. 3. Calculated IR and R spectra of conformers **I**, **II**, and **III** of AChCl as labeled *A*, *B*, and *C*, respectively. *D* shows the sum of *A*, *B*, and *C*, and *E* the experimental spectrum.

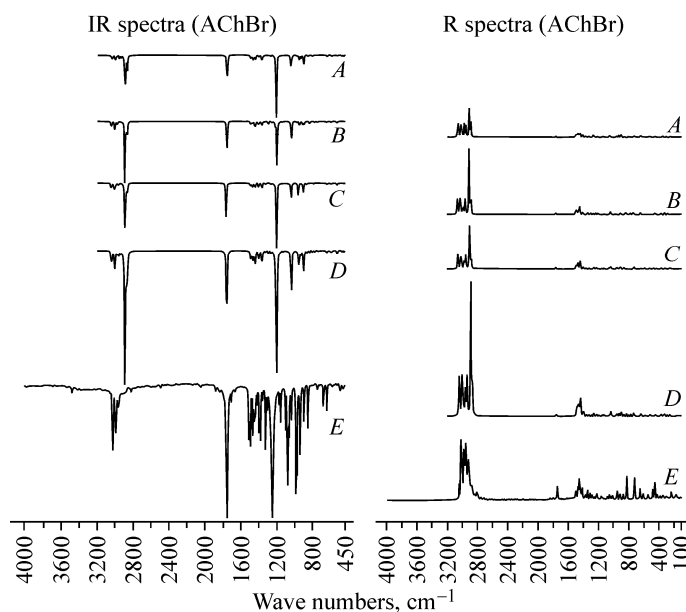


Fig. 4. Calculated IR and R spectra of conformers **I**, **II**, and **III** of AChBr as labeled *A*, *B*, and *C*, respectively. *D* shows the sum of *A*, *B*, and *C*, and *E* the experimental spectrum.

If we comment the relationship between the calculation and experiment chemical shifts taking into account the linear correlation values (R^2) and RMSE. We see from Table 4 the agreement between the experimental and calculated chemical shifts are much good for the average values of the minimum energy conformers **I**, **II**, and **III**. This also confirms the simultaneous presence of the three conformers regarding one experimental NMR spectrum for all the conformers since of their fast motions in the liquid phase. The observing of only one conformer from the experimental X-ray data can also be attributed to that choline compounds are highly deliquescent.

CONCLUSIONS

The optimized molecular structures, vibrational frequencies and ^1H and ^{13}C NMR chemical shifts of acetylcholine halides (fluoride, chloride and bromide) have been calculated using density functional theory (B3LYP) method at 6-311G(d) basis set level. The detailed assignments with PED% analysis for the vibrational frequencies have been presented. The comparison of the experimental and calculated IR, R and NMR spectra has showed that the title compounds simultaneously exist in the three minimum energy conformations in the ground state.

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