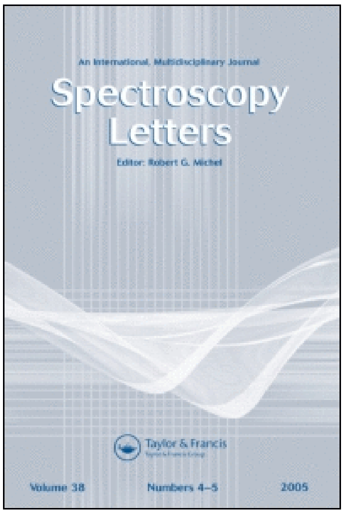

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Vibrational Analysis and Geometry Optimization of a Local Anesthetic by Means of the Am1 Semiempirical Method

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VIBRATIONAL ANALYSIS AND GEOMETRY OPTIMIZATION OF A LOCAL ANESTHETIC BY MEANS OF THE AM1 SEMIEMPIRICAL METHOD

Key words: Vibrational frequencies, geometry optimization, AM1, local anesthetics

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ABSTRACT

The semiempirical method AM1 was used to optimize the geometric parameters: bond lengths, bond angles and torsional angles in the local anesthetic benzocaine hydrochloride. The frequencies and intensities of the normal modes were computed. These results were compared with the infrared and Raman spectroscopic data. A theoretical spectrum using several scale coefficients was plotted. Electron density maps in two and three dimensions were drawn. Several calculated thermodynamic parameters are discussed.

INTRODUCTION

The study of the mechanism of local anesthesia has been a subject of considerable interest. One approach is to study the interaction between an anesthetic and various biomolecules. Another is to calculate the molecular physical constants and the charges on the atoms which may be related to the anesthetic potency. However, the interpretation of results from these types of studies will depend on the knowledge of the conformation and structure of the anesthetic compounds.

Among the many synthetic molecules in the therapeutic group of local anesthetics, two well known local anesthetics extensively used clinically[1,2], benzocaine (BEN), and procaine (PRC) with free basis, were studied using semi-empirical molecular orbital calculations and Infrared and Raman spectroscopy[3-6]. The data obtained in the present study refer to benzocaine hydrochloride (BEN-HCL). The differences produced in the structure of the *p*-aminobenzoate group result from the protonation of the amino substituent in the benzocaine molecule.

EXPERIMENTAL

The BEN-HCL was synthesized in our laboratory from benzocaine with free basis, by three procedures: 1) A flux of CL_2 is passed during 30 minutes on the sample of benzocaine finely pulverized and placed on a porous dish. The benzocaine not converted into chlorhydrate is removed by solution of the sample in $CHCL_3$. The solid is dried in a vacuum stove at moderate temperature (≃40°C). 2) In this procedure, the sample is a solution of BEN in $CHCL_3$ or ethanol. The CL_2 is bubbled through the solution, precipitating the chlorhydrate formed. The solid is washed several times with $CHCL_3$ and also dried in the vacuum stove. 3) The BEN is solved in concentrated CLH. The solution is softly warmed until the total dryness of the sample. Thus CL_2 is formed inside the solution reacting with the BEN and precipitating its chlorhydrate. A similar process can be carried out by the addition of CLH to an ethanolic solution of BEN. The solid is also washed several times with $CHCL_3$ and dried in a vacuum stove.

In all the cases three recrystallizations were carried out until a high purity was reached, recognized by constancy in the form and position in the bands of the spectra. The crystals were of monoclinic structure.

Infrared absorption spectra of samples in KBr pellets were recorded using a Perkin-Elmer 599B spectrotrophotometer.

Raman spectra were recorded on samples in special glass U-cells using a Jobin-Yvon laser-Raman spectrophotometer, model Ramanor U-1000 with double monochromator and holographic gratings. Detection was realized with a photon counting detector and the source was a 2 ω Spectra- Physics, model 165 Argon ion laser. The used laser power was in the range 100-400 mω.

COMPUTATIONAL METHODS

The calculations were carried out by using the standard AM1 procedure, as implemented in the AMPAC package of computer programs[7,8], indicated for analyzing problems of molecular structure and reaction mechanism.

The AMPAC package[9] was used in its VAX/IV2 version with standard parameters. Only the AM1 method was utilized. All the geometry was optimized by minimizing the energy with respect to all the geometrical variables without imposing molecular symmetry constraints. The BEN-HCL was theoretically considered and analyzed as a molecule of benzocaine with a proton on the nitrogen of the amino group. Thus it was studied as a cation, the charge on the system being +1. All the calculations were performed accordingly. In the geometry optimization, the GAUSSIAN 92 package was also used[10].

The DRAW program[11] was applied to evaluate graphically the correctness of geometries and plot the motions in each vibration, in our case 66 for the BEN-HCL. Thus the identification and assignation of all the vibrations theoretically calculated were facilitated. The graphic representations were observed in high-resolution computer terminals, Tektronic 4105 model.

The GAUSSIAN 90 and 92 with the keyword CUBEDENSITY were used[10] to get the electron density values by AM1. These data were introduced in the FCI DENSIT program[12] for plot maps in two and three dimensions.

The Figures obtained were prepared with a Macintosh microcomputer, using the BALL and STICK program[13].

RESULTS AND DISCUSSION

GEOMETRY OPTIMIZATION

The optimized bond lengths and angles using AM1 are given in the second column of Table 1, while the torsional angles appear in Table 2. The labelling of the atoms is plotted in Fig. 1. In the third column are collected the geometric parameters obtained with AM1 for a second stable conformation of the molecule, in which C7-O8-C9-C10 is 80.45°, instead of -179.81° (conformation 1). This conf. 1 is ca. 0.11 kcal/mol more stable than conformation 2. However a crystal structure corresponds to a free energy minimum that can usually be identified with a potential energy minimum, which is not necessarily the global minimum[16]. Because of this energy compatibility, the torsional angles will be the geometric parameters most affected by the crystal forces, stabilizing in general planar conformations instead of out-of-plane structures. Thus the conf. 1 could be tentatively established as the predominante conformation in the crystal, while in solution the conf. 2, or both, could be present[16]. According to this feature, all the discussion of this section and the next one, frequency calculation, refers to this conf. 1, with the experimental spectra in the solid state.

In the fourth column of these Tables are shown the experimental results obtained[14] on p-aminobenzoic acid hydrochloride (ABZ-HCL), a molecule closer to BEN-HCL in which crystallographic data have been reported. The fifth column lists the data on the complex of BEN with bis-*p*-nitrophenylphosphoric acid[15]. Curiously, the BEN crystallizes in this complex in the ionized form, because it is normally regarded as a neutral, non-ionizable drug. This event is explained by the fact that the amino group of BEN is protonated by the bis-p-nitrophenylphosphoric acid, all three amino hydrogen atoms participating in hydrogen bonds with the phosphate group. The BEN has also been crystallized as the guest molecule with cyclomaltoheptaose[17], but their geometric parameters differ remarkably from those listed in Table 1.

Comparing the geometric parameters of the two conformations determined by AM1, slight differences are observed, except in several torsional angles especially C7-O8-C9-C10. Unfortunately no crystal data have been reported on this torsional angle in order to know the established conformation in the crystal.

Table 1[a]. Values of the bond lengths in Å, and bond angles in degrees calculated in BEN-HCL by the AM1 method.

Bond lengths and angles	AM1		x-ray[b]	x-ray[c]	Angles (°)	AM1		x-ray[b]	x-ray[c]
	conf. 1	conf. 2				conf. 1	conf. 2		
r C(1)-C(2)	1.3990	1.3989	1.392	1.364	C(1)-C(6)-C(5)	120.21	120.23	119.9	120.0
r C(2)-C(3)	1.3939	1.3940	1.387	1.367	C(2)-C(1)-C(7)	121.33	121.34	121.7	123.6
r C(3)-C(4)	1.4054	1.4051	1.382	1.374	C(6)-C(1)-C(7)	118.26	118.27	117.9	117.3
r C(1)-C(6)	1.4012	1.4013	1.393	1.400	C(1)-C(7)-O(8)	113.93	113.68	114.0	112.1
r C(5)-C(6)	1.3929	1.3928	1.385	1.370	C(7)-O(8)-C(9)	116.16	117.51	-	115.7
r C(1)-C(7)	1.4811	1.4821	1.493	1.495	O(8)-C(9)-C(10)	105.86	110.88	-	107.3
r C(7)-O(8)	1.3593	1.3598	1.321	1.322	C(1)-C(7)=O(11)	126.14	125.93	122.4	124.2
r O(8)-C(9)	1.4493	1.4444	-	1.447	O(8)-C(7)=O(11)	119.93	120.39	123.5	123.7
r C(9)-C(10)	1.5075	1.5066	-	1.471	C(3)-C(4)-N(12)	119.40	119.45	118.7	119.3
r C(7)=O(11)	1.2320	1.2316	1.211	1.201	C(5)-C(4)-N(12)	119.34	119.31	119.5	119.8
r C(4)-N(12)	1.4648	1.4648	1.463	1.464	C(4)-N(12)-H(13)	109.97	110.00	112.	
r N(12)-H(13)	1.0264	1.0263	.90	.92	C(4)-N(12)-H(14)	109.95	109.89	111.	
r N(12)-H(14)	1.0265	1.0265	.89	.98	H(13)-N(12)-H(14)	109.25	109.24	111.	
r N(12)-H(24)	1.0274	1.0273	.85	1.15	C(4)-N(12)-H(24)	109.44	109.45	106.	
r C(3)-H(15)	1.1024	1.1026	.89	.91	H(13)-N(12)-H(24)	109.12	109.13	104.	
r C(2)-H(16)	1.1062	1.1062	.96	.94	C(2)-C(3)-H(15)	119.27	119.23	117.	
r C(6)-H(18)	1.1070	1.1070	1.01	1.02	C(4)-C(3)-H(15)	121.75	121.76	124.	
r C(9)-H(19)	1.1210	1.1211	-	1.16	C(1)-C(2)-H(16)	119.74	119.75	121.	
r C(10)-H(21)	1.1161	1.1172	-	.86	C(3)-C(2)-H(16)	120.08	120.07	119.	
r C(10)-H(23)	1.1172	1.1170	-	1.02	C(1)-C(6)-H(18)	119.44	119.43	118.	
					C(5)-C(6)-H(18)	120.35	120.33	122.	
C(1)-C(2)-C(3)	120.19	120.18	119.9	121.3	O(8)-C(9)-H(19)	108.28	109.45	-	
C(2)-C(3)-C(4)	118.98	119.01	119.0	119.3	C(9)-C(10)-H(21)	110.80	110.37	-	
C(3)-C(4)-C(5)	121.26	121.24	121.8	120.8	H(21)-C(10)-H(22)	108.51	108.74	-	
C(2)-C(1)-C(6)	120.40	120.39	120.4	119.1	H(21)-C(10)-H(23)	109.03	108.78	-	

[a] In Tables 1-4 the last digit shown in the calculated values is to aid in reproduction of the results and is not thought to be physically meaningful. [b] On *p*-aminobenzoic acid hydrochloride[14]. [c] On the complex of BEN with *bis*-*p*-nitrophenylphosphoric acid[15].

Table 2. Values of the torsional angles in degrees calculated by AM1 in BEN-HCL.

Torsional angles	conf. 1		conf. 2		x-ray[a]	
C(3)-C(2)-C(1)-[C(6), C(7)]	-0.05	-179.98	0.03	-179.94		
H(16)-C(2)-C(1)-[C(7), C(6)]	-0.03	179.90	-0.02	179.95		
C(1)-C(2)-C(3)-[C(4), H(15)]	-0.08	179.89	-0.10	179.84		
H(16)-C(2)-C(3)-[H(15), C(4)]	-0.06	179.96	-0.08	179.98		
C(2)-C(3)-C(4)-[C(5), N(12)]	0.20	-179.48	0.12	-179.53		
H(15)-C(3)-C(4)-[N(12), C(5)]	0.54	-179.77	0.53	-179.82		
C(6)-C(5)-C(4)-[C(3), N(12)]	-0.19	179.50	-0.07	179.58		
H(17)-C(5)-C(4)-[N(12), C(3)]	-0.53	179.78	-0.49	179.86		
C(5)-C(6)-C(1)-[C(2), C(7)]	0.06	180.00	0.02	179.99		
H(18)-C(6)-C(1)-[C(7), C(2)]	0.04	-179.90	0.06	-179.92		
C(1)-C(6)-C(5)-[C(4), H(17)]	0.06	-179.92	0	-179.94		
H(18)-C(6)-C(5)-[H(17), C(4)]	0.04	-179.99	0	179.94		
O(8)-C(7)-C(1)-[C(2), C(6)]	-0.07	180.00	0.89	-179.09	-11.0	170.7
O(11)=C(7)-C(1)-[C(6), C(2)]	0	179.94	0.37	-179.66	-11.4	166.9
C(9)-O(8)-C(7)-[O(11), C(1)]	0	180.00	0.83	-179.68		
H(13)-N(12)-C(4)-[C(3), C(5)]	-30.02	150.29	-26.71	153.63	-53	126
H(14)-N(12)-C(4)-[C(3), C(5)]	-150.35	29.96	-147.02	33.32	-177	2
H(24)-N(12)-C(4)-[C(3), C(5)]	89.83	-89.87	93.18	-86.48	60	-121
C(7)-O(8)-C(9)-C(10)	179.81		80.45			
C(7)-O(8)-C(9)-[H(19), H(20)]	59.11	-59.49	-42.99	-160.14		
H(21)-C(10)-C(9)-[H(19), H(20)]	57.69	-178.28	56.23	-179.25		
H(22)-C(10)-C(9)-[H(19), H(20)]	178.20	-57.78	176.77	-58.70		
O(8)-C(9)-C(10)-[H(21), H(22)]	-60.31	60.19	-66.02	54.53		
O(8)-C(9)-C(10)-H(23)	179.94		174.43			
H(23)-C(10)-C(9)-[H(19), H(20)]	-62.06	61.97	-63.33	61.20		

[a]On *p*-aminobenzoic acid hydrochloride[14].

The bond lengths and angles of the ring calculated by AM1 in BEN-HCL generally conform to the axial symmetry observed in the majority of the *para*-substituted benzene derivatives, showing no special quinonoid character. It is also noted that AM1 computes a value for the **r** N(12)-H(24) bond length higher than those with the hydrogens H(13) and H(14).

Concerning the differences detected between the second and fourth columns in Table 1, by AM1 were obtained higher values ca. 0.04 Å, 0.02 Å and 0.15 Å in **r** C(7)-O(8), **r** C(7)=O(11) and **r** N(12)-H(13,14) respectively. A remarkable increase in the **r** C-H(aromatic), especially on C-H(15), was also computed by AM1. In the angles, only small differences, ca. 4°, involving the bond angles on O(11) and H(24) are observed.

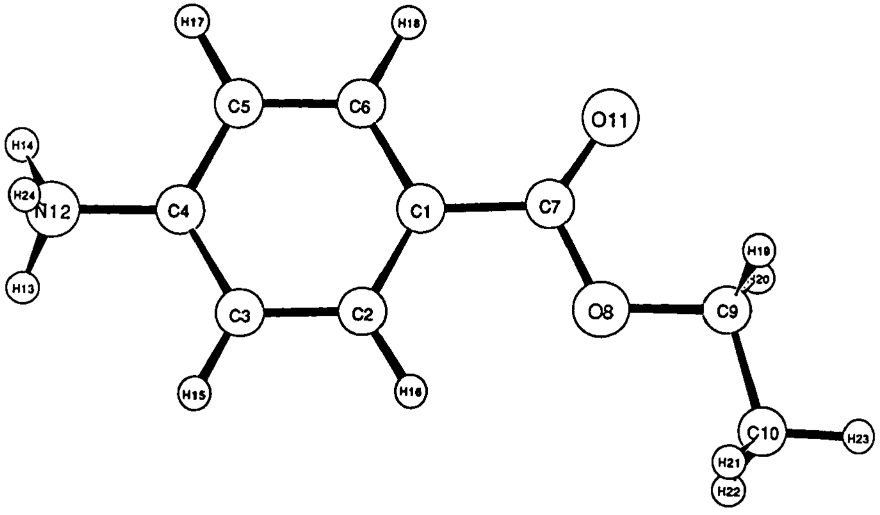


Fig. 1. Labelling of the atoms in Benzocaine hydrochloride. The geometry of the molecule corresponds to the equilibrium in the conformation 1.

The NH_3^+ cannot be conjugated with the aromatic ring as found in the amino group of BEN structure. Thus the experimental C(4)-N bond lengths of 1.463, 1.464 Å (the fourth and fifth columns), the C(1)-C(7) of 1.493, 1.495 Å, and the nearly equal lengths within the benzene ring are consistent with the predicted values from AM1 in BEN-HCL and larger than those computed in BEN[6], C(4)-N: 1.388 Å and C(1)-C(7): 1.464 Å. In the structure of *o*-aminophenol hydrochloride[18], the C-NH_3^+ bond is 1.474 Å and in *p*-phenylenediamine dihydrochloride[19], 1.490 Å.

The remaining bond lengths and angles (fourth and fifth columns) are all in agreement with the crystal, except in C-H(chain) and N-H(13,14) which are greater by AM1. The average differences established between the computed values and the experimental results in many molecules[7] are in accordance with our data.

Concerning planarity, the benzene ring shown by AM1 very slight deviations as in ABZ-HCL. The internal angles in the *ipso* positions $\alpha(NH_3^+)=121.3°$ and $\alpha(COO)=120.4°$, are close to those reported[14] in ABZ-HCL: $\alpha(NH_3^+)=121.8°$ and $\alpha(COOH)=120.4°$. Due to the similar geometric parameters with ABZ-HCL, the cations as BEN-HCL, are possibly linked in endless chains by direct hydrogen bonds, O···H-N, and bridging CL^- ions, O-

H···CL⁻···H-N. Other CL⁻···H-N hydrogen bonds connect adjacent chains, forming a three-dimensional network.

In the complex of BEN with *bis-p*-nitrophenylphosphoric acid[15], the atoms of the ethyl carboxylate group exhibit remarkable deviations from the plane of the benzene ring, which is the result of small conformational variations in the side chain. Thus e.g., the carboxyl group is rotated about the C(1)-C(7) bond by 9.4° while another conformational variation involves the torsion angle about the carboxylate ester bond ∠C(7)-O(8)-C(9)-C(10), -168.6°. In ABZ-HCL also the oxygens O(8) and O(11) have torsional angles ca. 11°, outside the planarity with the aromatic ring[14], in disagreement with the planar structure computed by AM1. A saturated chain totally planar is also predicted by AM1.

The hydrogens on the amine group show in the crystal[14] greater torsional angles than those calculated by AM1, Table 2. AM1 computes a *tilt* angle on N(12) of 0.27°, and inversion angles on H(13) and H(14) of 53.88°, while in H(24) the inversion angle has the very low value of 1.68°.

Interatomic distances are also computed by AM1. Therefore the possibilities of intramolecular hydrogen bonds formation are evaluated. Thus the **r** O(11)···H(18) is 2.5646 Å while **r** O(8)···H(16) is 2.4079 Å in good agreement with those distances reported on BEN[6].

VIBRATIONAL FREQUENCIES

The theoretical frequencies computed by AM1 for the normal modes in BEN-HCL are shown in Table 3. In the second column appear the values of these vibrations while the theoretical intensities, calculated dividing each computed value by the intensity of the strongest line (in the present study, line no. 54), are shown in the third column. The seventh and eighth columns collect the frequencies and intensities computed by AM1 in the conf. 2 of the molecule. Few differences are found between both conformations. In the fourth column appear the scale factors available[6,20] used to correct the deficiency of the AM1 method. The scaling frequencies resulted with conf. 1 are listed in the fifth column. The theoretical spectrum computed with these new frequencies is shown in Fig. 2, together with the infrared spectrum recorded in the solid state[5]. The % errors determined in this way regarding the infrared data are collected in the sixth column. Very low values are obtained, in the majority of the cases being less than 4 %.

The infrared bands and Raman lines of BEN-HCL in the solid state with their relative intensities, are shown in the ninth and tenth columns. Computed frequencies are systematically higher than experimental ones. Such an over-estimation by quantum-mechanical calculations is a general finding in the bibliography[6,21], especially for high frequencies. In the eleventh column the

Table 3. Harmonic vibrational frequencies (cm^{-1}) in benzocaine hydrochloride[a].

No	Conformation 1					Conformation 2		Experimental		Characterization
	Frequency (cm^{-1})	relative intensity[b] (%)	scale factors used[c]	scaled frequency (cm^{-1})	% error[d]	Frequency (cm^{-1})	relative intensity[b] (%)	Infrared	Raman	
1	24	15.1				10	8.3			τ(NH$_3^+$-ring-C=O) + τ(CH$_3$)*
2	27	15.0				28	21.7			τ(NH$_3^+$) + τ(ring-C=O)* + τ(CH$_3$)*
3	54	17.9				50	32.0			τ'(COO-CH$_2$-CH(21)H(22))
4	77	30.9				83	24.0			τ(chain) + τ''(NH$_3$-ring-C=O)*
5	98	29.1				113	21.6			Γ(CH$_3$) + Γ(NH$_3$-ring-COO)* + Γ(-CH$_2$-)*
6	115	11.2				126	21.4		116 s	τ(CH$_3$) + γ'(ring-COO)*
7	154	9.5				157	14.2		150 vs	τ''(-CH$_2$-CH$_3$) + γ(C-O) in O(8)C(9) + γ'(ring-COO)*
8	253	28.2				276	37.8		234.5 vw	Γ(NH$_3$-ring) + Γ(COO) + Γ(-CH$_2$-CH$_3$)
9	284	40.6				315	38.6	-	247.5 m	γ(NH$_3$) + γ(COO) + 10b, γ(C-H)
10	351	30.2				340	31.2	300 w	313 w	Γ''(NH$_3$-ring) + Γ''(COO-CH$_2$-CH(23))
11	367	3.2	0.9322	394		367	2.9	366 w?	369.5 m	16a [γ(C=C) + γ(C-H)]
12	394	43.3				402	40.0	390 m	-	τ(NH$_3^+$)? + Γ(ring) + Γ(COO) + Γ''(-CH$_2$-CH$_3$)
13	420	23.0				463	35.9	-	424 vw	τ(NH$_3^+$)? + Γ(ring-COO) + Γ(-CH$_2$-CH$_3$)
14	489	37.5	0.9322	525	0	493	35.4	478 s 525 m	471 w 529 m	16b, [γ(C=C)+γ(C-H)]+γ(COO)+γ(NH$_3$)mainly in H(24)
15	525	29.0				524	31.7	602 w	585.5 vw 599 vw	Γ(ring) + Γ(NH$_3^+$) or γ + Γ(chain)
16	616	42.8	0.9754[e]	632	2.8	616	44.0	650 sh	619 vw 666.5 s	γ(COO) + 4, [γ(C=C)+γ(C-H)]
17	662	20.5	0.8068[e]	820	1.2	656	21.6	810 m	772 vw	γ(NH$_3^+$) + 6a, δ(C=C) + Γ''[CH$_2$-CH(21)H(22)]
18	672	10.6	1.0693 0.9754[e]	628 689	0.6 1.3	670	8.6	632 m 680 w	632 s 682.5 w	6b, δ(C=C) coupled with C-R vibration + δ(C-C) + γ(COO)
19	747	44.6				747	45.8	- 740 m 753 w	722.5 w 742 w 755.5 w	γ(CCOO) + γ(C-H) ring

20	845	6.9				823	30.9	-	824 s	γ(C-H) in CH_2 and CH(21)H(22)
21	868	47.5	1.0473^c	829	2.7	877	31.2	852 w	837 s	δ(COO) + 12, δ(C=C) + γ(C-H) in CH_3 + $\delta(NH_3^+)$
22	884	6.2	1.0532	839		883	7.2	-	-	10a, γ(C-H)
23	895	35.9	1.0227	875	1.7	894	36.8	860 w	-	17b, γ(C-H)
24	976	15.7	1.0080^c	968	0.4	990	23.6	964 vw	970 m	δ(C-H) in CH_3 mainly in H(23) + Δ_s(COO) + δ(C=C)
25	999	6.7	1.0227	977	0.9^h	999	7.3	990 vw	986 w	17a, γ(C-H)
26	1002	16.3	1.0222	980	4.4	1002	17.1	-	927 w 939 w	5, γ(C-H)
	-	-	-	-	-	-	-	-	1001 m	γ(C-H)
27	1023	24.3				1012	19.2	1020 m	1035 w	δ(C-H) in C(10)H(23) + 7a, ν(C-H) + Δ_s(COO)
28	1114	15.8				1110	18.8	-	1050 w	18a, δ(C-H) coupled with 19a
29	1123	10.2				1122	10.1	1080 vw	1092 vw	$\Gamma(NH_3^+)$ in H(13)H(14) + 18b, δ(C-H) coupled with 19b
30	1151	22.8				1159	26.2	-	1076 w	Γ(C-H) in CH_2 and CH(21)H(22)
31	1159	25.7				1167	15.3	1209 vw	1213 m	$\Gamma(NH_3^+)$ mainly in H(24)
32	1201	29.1	1.1051	1087	2.1	1195	31.8	1110 s	-	18b, δ(C-H) + $\Gamma(NH_3^+)^*$
33	1221	19.8				1201	30.6	1120 s?	1117 s?	$\Gamma(CH_2)$
34	1232	31.8				1226	25.1	1180 m	1175 s	ν(C-C) + δ(C-H) in CH_2 and CH(21)H(22)
35	1242	31.0				1245	22.2	-	1194 m	δ(C-H)ring + $\nu_s(CCO)^*$ in CC(9)O(8)
36	1254	49.0	1.0039^c	1249	0.3	1280	47.1	1245 vs	1240 s	ν_s(CCO) in CC(9)O +9a, δ(C-H)+δ(C-H) in CH_2+ $\delta_{as}(COO)^*$
37	1292	40.6				1301	29.3	-	1274 w	18a, δ(C-H) coupled strongly with 19a
38	1320	21.9	0.9844	1341		1321	20.4	-	-	3, δ(C-H)
39	1377	20.8	1.0080^c	1366	4.8	1375	31.9	1303 w?	1298 w?	δ_s(C-H) in CH_3, mainly in H(23)
40	1389	17.6	1.0080^c	1378		1380	22.3	-	-	δ_s(C-H) in CH_3, mainly in H(21)H(22)
41	1394	22.0	1.0447^c	1334		1386	49.4	-	-	$\Delta_s(CH_2)$ + 14, $\nu(C=C)^*$
42	1398	45.5	1.0451	1338	1.4^h	1387	25.5	1318 m	1319 w	14, ν(C=C)+$\Delta_s(CH_2)$+$\nu(C\text{-}O)^*$+$\delta(NH_2)^*$in H(13)H(14)
43	1404	47.0	1.0447^c	1344	3.5	1400	60.0	1393 vs	1397 m	$\Delta_s(CH_2)$ + 14, $\nu(C=C)^*$ + $\nu_{as}(COO)^*$
44	1426	35.8	0.9910^c	1439	3.3	1427	28.4	1393 vs	1397 m	δ_{as}(C-H) in CH_3 + $\nu(C=C)^*$ + $\nu_{as}(COC)^*$
45	1451	47.9	1.0136^c	1431	2.7	1456	42.4	1393 vs	1397 m	δ_{as}(C-H) in CH_2+ 13,ν(C-R) in CN+ν_{as}(COO)+ν(C-C)

(continued)

Table 3. (continued)

46	1547	78.9	1.0207^g	1516	0.2	1545	75.9	1505 m	1519 w	ν(C-O) in C(7)O(8)+19a, ν(C=C)+β(NH$_3^+$)*+ν(C-C)*
47	1577	56.4	1.0654	1480	3.7^h	1577	56.2	1423 s	1427 w	19b, ν(C=C)coupled stongly with 18b+ν_{as}(COO)*+δ(NH$_3^+$)*
48	1625	36.5	1.0312^h	1576	1.7	1625	37.7	1550 m	-	β(NH$_3^+$)
49	1630	54.5	1.0114^e	1612	0.1?	1629	51.4	1610 vs?	-	ν_{as}(COC) mainly in C(7)O(8) + 19a, ν(C=C)
50	1638	28.6				1638	29.4	-	-	δ(NH$_3^+$)
51	1652	36.6				1652	37.5	-	1654 vw	β(NH$_3^+$) in H(13)H(14)
52	1761	29.4	1.1051	1594	1.0	1761	28.8	-	-	8a, ν(C=C)
53	1765	17.8	1.1051	1597	1.1^h	1765	19.5	1572 w	1580 vs	8b, [ν(C=C) + δ(C-R)]
54	2066	100.0	1.2214^e	1691	0.5	2068	100.0	1700 vs	1697 s	ν(C=O)
								1947 w		β(NH$_3^+$)+ δ(C-H)?
								2350 vw		ν(C-N) + Γ(NH$_3^+$)?
								2460 w		Combination band
								2480 w		Combination band
								2600 s		Combination band or ν(N-H···)$_{inter.}$
55	3040	16.7	1.0585^f	2872		3042	20.8	Very broad and strong band centered at 2910 and 3000 cm^{-1}	2955 vw	ν_s(C-H) in CH$_2$
56	3066	24.5	1.0593^e	2894		3065	24.4			ν(C-H) in C-H(23)
57	3074	23.2	1.0593^e	2902		3072	25.3			ν_s(C-H) in CH(21)H(22)
58	3103	22.3	1.0486^e	2959		3098	27.7			ν_{as}(C-H) in CH$_2$
59	3133	45.2	1.0429	3004		3133	46.2			7b, ν(C-H)
60	3140	42.2	1.0427	3011		3140	43.0			20a, ν(C-H)
61	3161	20.1	1.0593^g	2984	<.05	3158	19.6		2984.5 vw	ν_{as}(C-H) in CH$_3$
62	3167	46.4	1.0427	3037		3167	47.6			20b, ν(C-H)
63	3171	29.0	1.0427	3041		3171	29.1			2, ν(C-H)
									3014.5 w	ν(N-H···)$_{inter.}$
64	3199	52.0	1.0428^e	3068	0.6	3200	53.2		3049 m	ν_s(N-H) mainly in N-H(24)
65	3210	50.7	1.0428^e	3078	0.6	3210	51.8		3060 vw	ν_s(N-H) in NH(13)H(14)
66	3335	51.4	1.0221^e	3263	6.0	3335	52.6		3077.5 m	ν_{as}(N-H) mainly in NH(13)H(14)

[a]vs: very strong, s: strong, m: medium, w: weak, vw: very weak, inter.: intermolecular, R: substituent, (τ', τ'', γ' and Γ') are according to ref. 6. [*]Very weak contribution of this mode. [b]Related to line 54. [c]Calculated $\nu_{AM1}/\nu_{exp.}$ from benzene molecule[20]. [d] 100 $|\nu_{exp}-\nu_{AM1\ scaled}|$ / $\nu_{exp.}$, ν_{exp} is from infrared. [e,f]From infrared data in the solid state and solution phase respectively, of BEN[6]. [g]From Raman data in the solid state of BEN. [h]$\nu_{exp.}$ is from the Raman spectra.

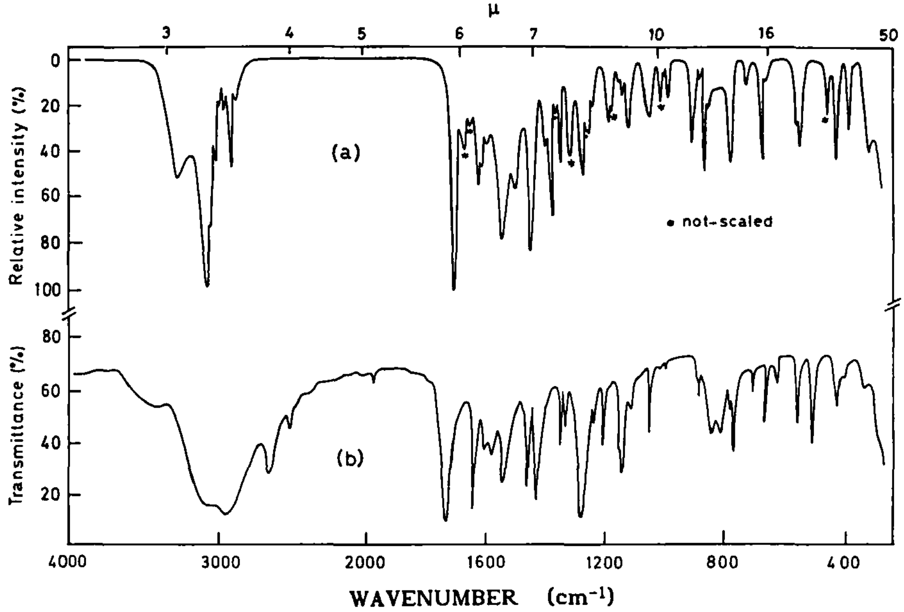


Fig. 2. Spectra of benzocaine hydrochloride, a) calculated by AM1 with the scaled frequencies, (*) vibrational frequencies without counterpart in the infrared spectrum, b) infrared spectrum obtained in the solid state.

assigments for each theoretical frequency are indicated. The normal modes of the ring are identified by numbers according to Wilson's notation[22].

The theoretical error of the semiempirical methods, AM1 in our case, in which the antisymmetric vibration appears in general at lower frequencies than the symmetric mode, mainly when both frequencies are very close, was corrected in Table 3, when it was observed.

It is possible in general to relate each calculated frequency to a specific observed band, except in the low frequency range, in which many experimental bands are registered. AM1 can only calculate normal modes; therefore, the experimental bands corresponding to $\nu(\text{N-H}\cdots)_{\text{inter.}}$, overtones and combinations bands are not related to theoretical frequencies. The study of the vibrational modes in the spectra was carried out as follows:

Amino group vibrations: Due to a very broad infrared absorption between 2800 and 3100 cm^{-1}, the N-H stretchings were not observed. In Raman spectroscopy the antisymmetric and symmetric N-H stretchings were detected at 3077.5 cm^{-1} and 3060, 3049 cm^{-1} respectively. Using the scale factors reported in BEN for the NH_2 group[6], a closer agreement with the Raman data was obtained.

In-plane bendings of the NH_3^+ group were determined by AM1 at 1652, 1638 and 1625 cm^{-1}, while the bands at 1654 cm^{-1} in Raman and 1550 cm^{-1} in infrared were assigned to the scissors mode.

The frequencies computed at 1159 and 1123 cm^{-1} as rocking mode in the amino group corresponded to the experimental bands at 1209, 1213 cm^{-1}, and at 1080, 1092 cm^{-1}, infrared and Raman respectively. In these last bands, a significant contribution of the ring mode 18b was also estimated.

The frequencies computed at 662 and 525 cm^{-1} had a slight contribution due to the amino group, and they were related to the bands observed at 810, 772 cm^{-1} and at 602, 585.5 cm^{-1}, infrared and Raman respectively, which were assigned as wagging mode in NH_3^+ group. The frequency calculated at 489 cm^{-1} also received a significant contribution from the wagging mode, but it corresponded mainly to ring mode 16b. The vibrations determined at 394 and 420 cm^{-1}, with a significant contribution from the amino group, were related respectively to the infrared band at 390 cm^{-1} and to the Raman line at 424 cm^{-1}. Both vibrations were tentatively ascribed to a torsional mode, and they were very close to those observed at 366 and 369.5 cm^{-1}, infrared and Raman respectively, and assigned as $\Gamma''(NH_3\text{-ring})$ mode. The Raman line at 247.5 cm^{-1} was related to the band computed at 284 cm^{-1} as wagging mode in NH_3 group.

Another band with remarkable contribution from the amino group and estimated at 253 cm^{-1} was associated with the line at 234.5 cm^{-1}, designated as rocking mode. The very low frequencies calculated at 24 and 27 cm^{-1} were mainly $\tau(NH_3^+)$ torsion.

Ester group vibrations: AM1 computes, as reported[6] in BEN, a $\nu(C{=}O)$ frequency far from the experimental value, probably because, as in other semiempirical methods, such as CNDO/2, they fail when open electronic deslocalization exists in the moiety. Calculations by MINDO on CH_2O molecule[23] give for the $\nu(C{=}O)$ a value of 2006 cm^{-1} in contrast with the experimental data of 1746 cm^{-1}. In HCOOH the values were 1941 cm^{-1} by MINDO and 1770 cm^{-1} experimentally. Concerning the intensity predicted for the $\nu(C{=}O)$ mode in BEN-HCL, it was the strongest computed in the spectra, in good agreement with that observed at 1700 cm^{-1} by infrared and 1697 cm^{-1} in Raman.

The C-O-C stretchings were good calculated by AM1, with scale factors close to the unity. The frequencies computed at 1630 and 1547 cm^{-1} received a strong contribution from the antisymmetric mode, mainly on the C(7)-O(8) bond, while at 1451 cm^{-1} it was on the O(8)-C(9) bond. The strong intensity vibration determined at 1254 cm^{-1}, corresponded to the symmetric mode, was related to the very strong infrared absorption at 1245 cm^{-1} and the Raman line at 1240 cm^{-1}.

A slight contribution of the COO in-plane bending mode was computed at 1023, 976 and mainly at 868 cm^{-1}, while the out-of-plane vibration was calculated at 747, 616 cm^{-1} and with an important contribution at 672, 489, 284 and 154 cm^{-1}. The weak infrared and Raman bands at 753, 755.5 cm^{-1} and 680, 682.5 cm^{-1} were assigned to the γ(COO) mode.

Ethyl group vibrations: The stretchings in $-CH_3$ and $-CH_2-$ groups were not detected by infrared because they were hidden by the very strong and broad absorption at 3000-3400 cm^{-1}. However, in Raman two very weak bands at 2984.5 and 2955 cm^{-1}, were observed. AM1 computed the antisymmetric mode at 3161 and 3103 cm^{-1}, in $-CH_3$ and $-CH_2-$ groups respectively, while the symmetric vibration was predicted at 3074, 3066 cm^{-1} in $-CH_3$ and at 3040 cm^{-1} in the $-CH_2-$ group.

The bending modes were characterized in the frequency range 800-1450 cm^{-1}, generally close to the experimental results. At very low frequencies, less than 150 cm^{-1} were identified the torsional modes in $-CH_3$ and $-CH_2-$ groups.

Normal vibrations of the ring: The assignments for the observed infrared bands and Raman lines are listed in Table 3. The ring normal modes were divided into tangential, radial and out-of-plane vibrations.

In the tangential vibrations, the 8b and 19b C-C stretchings appear at frequencies higher than those corresponding to 8a and 19a modes. Thus the frequencies at 1765 and 1761 cm^{-1} by AM1 were assigned to the 8b and 8a vibrations respectively, while those computed at 1577 and 1547 cm^{-1} were characterized as 19b and 19a modes. An important contribution of the 19a mode was also calculated at 1630 cm^{-1}. In the *b* modes, a coupling with δ(C-R) vibration was observed, in accordance with that reported in benzene derivatives[18].

Mode 14 was identified in infrared as a band of medium intensity at 1318 cm^{-1}, and in the Raman spectra as a weak band at 1319 cm^{-1}, being computed by AM1 at 1398 cm^{-1} with medium intensity.

Concerning the δ(C-H) bending vibrations, 18a was determined at 1292 and 1114 cm^{-1} coupled with the 19a mode, while 18b was calculated at 1201 cm^{-1}. A slight contribution of the 9a mode was computed at 1254 cm^{-1}, in accordance with the same frequency obtained in BEN[6]. The 9b mode and the 15 mode were not characterized by AM1. The very weak intensity predicted for the 3 mode at 1320 cm^{-1} was in agreement with its not being detected in the infrared and Raman spectra.

In the C-H and C-R radial vibrations, a slight contribution of the 7a stretching mode was calculated at 1023 cm^{-1}, while the pair 20b and 20a was computed at 3167 cm^{-1} and 3140 cm^{-1}. Mode 2 was characterized at 3171 cm^{-1}.

Table 4. Several thermodynamic parameters calculated in BEN-HCL by AM1.

Parameters		Conf. 1	Conf. 2	BEN[a]
Heat of formation (Kcal/mol)		92.13485	92.02931	-69.90100
Electronic energy (eV)		-10823.24614	-10880.07433	-10594.01460
Ionization potential (eV)		13.74856	13.95495	8.83539
Principal moments of inertia:	A:	0.08496	0.09503	0.08662
(cm^{-1})	B:	0.01435	0.01426	0.01464
	C:	0.01236	0.01288	0.01259

[a] Values calculated on BEN by AM1[6]

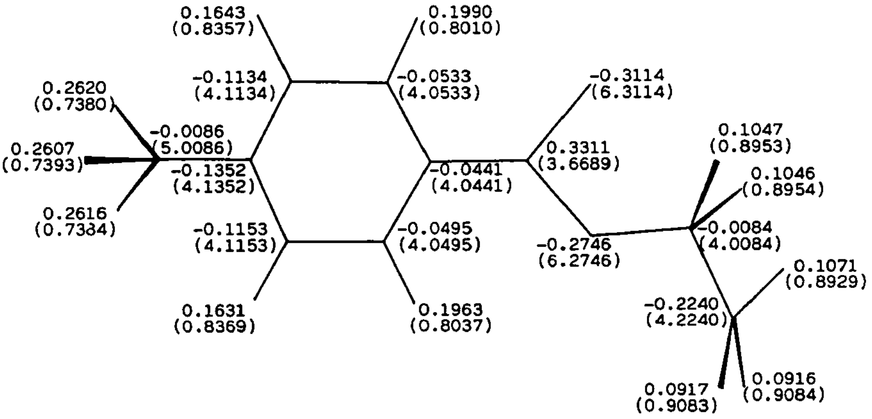


Fig. 3. Net atomic charges and atomic electron density (values in parentheses) of Benzocaine hydrochloride, computed by the AM1 method with the AMPAC package.

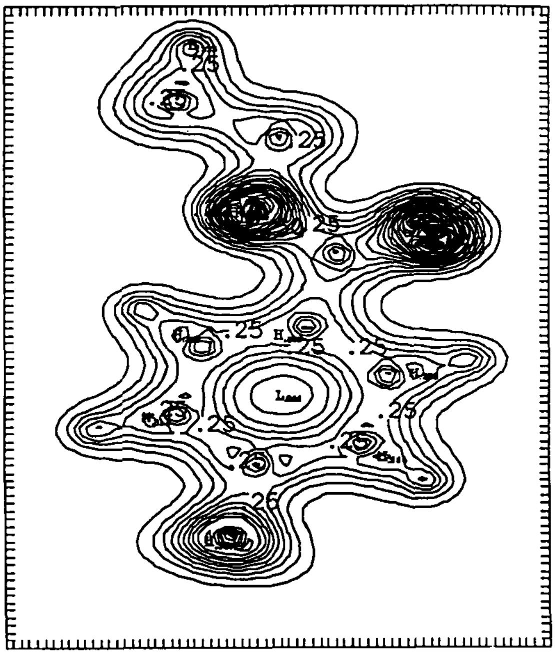
Table 5. Values of the charge and atomic eletron density calculated by AM1 with AMPAC and GAUSSIAN 90 program packages.

Atom No.	Charge					Atomic electron density		
	BEN-HCL				BEN[a]	BEN-HCL		BEN
	AMPAC		GAUSSIAN		AMPAC	AMPAC		AMPAC
	Conf. 1	Conf. 2	Conf. 1	Conf. 2		Conf. 1	Conf. 2	
C 1	-0.0441	-0.0449	-0.0685	-0.0694	-0.1694	4.0441	4.0449	4.1694
C 2	-0.0495		-0.1090		-0.0260	4.0495		4.0260
C 3	-0.1153	-0.1150	-0.1718	-0.1714	-0.2219	4.1153	4.1150	4.2219
C 4	-0.1352		-0.1517		0.1104	4.1352		3.8896
C 5	-0.1134	-0.1139	-0.1699	-0.1703	-0.2198	4.1134	4.1139	4.2198
C 6	-0.0533	-0.0535	-0.1134	-0.1136	-0.0289	4.0533	4.0535	4.0289
C 7	0.3311	0.3328	0.3922	0.3939	0.3554	3.6689	3.6672	3.6446
O 8	-0.2746	-0.2744	-0.3198		-0.2836	6.2746	6.2744	6.2836
C 9	-0.0084	-0.0088	-0.1100	-0.1106	-0.0097	4.0084	4.0088	4.0097
C 10	-0.2240	-0.2494	-0.3651	-0.3929	-0.2183	4.2240	4.2494	4.2183
O 11	-0.3114	-0.3109	-0.3401	-0.3397	-0.3678	6.3114	6.3109	6.3678
N 12	-0.0086		-0.2327		-0.3448	5.0086		5.3448
H 13	0.2616		0.3256		0.2011	0.7384		0.7989
H 14	0.2620		0.3260		0.2014	0.7380		0.7986
H 15	0.1631		0.2325		0.1368	0.8369		0.8632
H 16	0.1963		0.2748		0.1526	0.8037		0.8474
H 17	0.1643		0.2340		0.1378	0.8357		0.8622
H 18	0.1990	0.1988	0.2783	0.2780	0.1554	0.8010	0.8012	0.8446
H 19-	0.1047	0.1117 0.1199	0.1615	0.1698 0.1777	0.0911 0.0904	0.8953	0.8883 0.8801	0.9089 0.9096
H 21-	0.0916	0.0891 0.0979	0.1411	0.1379 0.1488	0.0864 0.0859	0.9084	0.9109 0.9021	0.9136 0.9141
H 23	0.1071	0.1061	0.1582	0.1571	0.0853	0.8929	0.8939	0.9147
H 24	0.2607		0.3253		-	0.7393		-

[a] Values reported on BEN[6].

The radial skeletal mode 1 was not determined while a slight contribution of the mode 12 was computed at 868 cm^{-1}. The strong intensity calculated for this frequency was in agreement with the great intensity of the Raman band at 837 cm^{-1}. The pair 6a and 6b was identified as an important contribution in the frequencies at 662 and 672 cm^{-1}, but mode 6b, as in heavy substituents[24], was coupled strongly to a C-R stretching vibration.

In the out-of-plane vibrations, a remarkable contribution from skeletal mode 4 was calculated at 616 cm^{-1}, which is strongly coupled to a C-H out-of-



CONTOUR FROM .05 TO 1.2 BY .05

Fig. 4. Electron density map on two dimensions calculated in the ring plane of benzocaine hydrochloride with AM1 in the conformation 1. The scale is 85 points with 0.15 step on axis X and 70 points with 0.1 step on axis Y.

plane vibration. The frequency of the vibrational components 16 rises also, on substitution on benzene, as a result of coupling to out-of-plane C-R vibrations of lower frequencies[24]. Thus mode 16b at 489 cm^{-1}, computed at higher frequency than 16a (367 cm^{-1}), were both coupled tentatively to the strong C-H out-of-plane 10b mode.

The C-H out-of-plane vibrations, represented by normal modes 5, 10a, 17a and 17b, were characterized at the frequencies 1002, 884, 999 and 895 cm^{-1} respectively. The very low intensity calculated for 10a mode was in agreement with its not being detected in the spectra, as in BEN. Also the weak or very weak intensity, determined by AM1 in the other modes, were in good accordance with those experimentally observed, with scale factors very close to the unity.

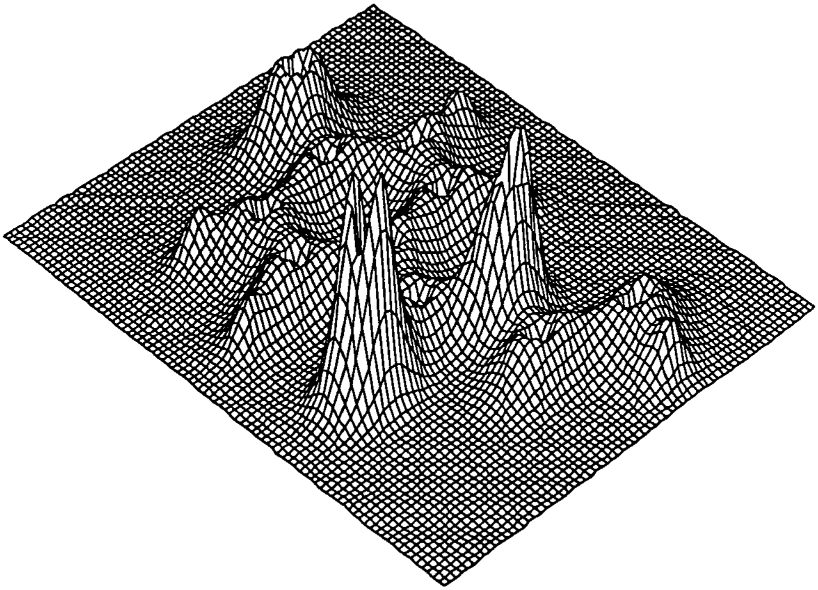


Fig. 5. Electron density maps in three dimensions. The out-of-plane axis represents the number of electrons per unit volume.

OTHER PROPERTIES

Table 4 summarizes for the two conformations, several thermodynamics properties calculated by AM1, such as heat of formation, electronic and ionization energies and main moments of inertia. Similar values were found for both conformations, conformation 1 being slightly more stable than conf. 2. An increase concerning BEN (fourth column) was noted, especially on the heat of formation (positive), and ionization potential, which is due to the formation of the chlorhydrate with the presence of a positive charge on the molecule. The enthalpies of formation of compounds containing carbon, hydrogen , oxygen and nitrogen by AM1 have been reported[7,25] to be in agreement with MNDO and the experimental data, the mean absolute errors being 6.64 (MNDO) and 5.88 kcal mol^{-1} (AM1).

The values of the net atomic charge using AM1 for the conformation 1 are shown in Fig. 3, and in parentheses, the atomic electron density. These values are in agreement with those reported[26] in other molecules.

Table 5 collects the data of net atomic charges obtained with AM1 on AMPAC, the total atomic charges with AM1 on GAUSSIAN 90, and the atomic electron density with AMPAC. Values of the charge and electron density calculated on benzocaine with free basis are also listed.

Figs. 4 and 5 draw, in the aromatic ring plane, the electron density maps in two and three dimensions respectively, obtained with AM1. The axes represent the distance in Å with a scale of 85 points (0.15 step) on axis X and 70 points (0.1 step) on axis Y. The topology of the maps represents the electron density of the valence shell of an atom, the core of the atoms not being represented. Therefore by AM1 in the positions of the atoms appear holes (Fig. 5), at difference of ab initio methods, which characterize the core of the atoms. In these figures, the two highest peaks correspond to oxygen atoms, and the other peaks indicated the positions of all the carbon and hydrogen atoms in the ring plane and in the ethyl chain.

SUMMARY AND CONCLUSIONS

The equilibrium geometry computed for benzocaine hydrochloride was in agreement with the available experimental structural parameters on ABZ-HCL. The ring aromaticity was kept. Two stable conformations, differing in the C10-C9-O8-C7 torsional angle, were computed by AM1.

The calculated frequencies and, in many cases, the intensities described qualitatively well those observed from the infrared and Raman spectra. The modes not detected experimentally were in general those with the lowest calculated intensities. The ring vibrations were rather stable in frequency with regard to benzene, therefore the scale factors used, characterize a theoretical spectrum very close to the experimental one. The % error obtained was very small, less than 4.0% in the majority of the cases.

The interaction between ring and substituent vibrations was generally weak, because ring and substituent internal vibration frequencies lie within very limited intervals, and frequency variations of ring radial skeletal vibrations were due to coupling to C-R stretching normal modes.

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