

Study of the torsion, inversion and *tilt* angle variation of the amino group in some local anesthetics

M ALCOLEA PALAFOX

*Departamento de Química-Física I (Espectroscopia) Facultad de Ciencias Químicas.
Universidad Complutense, Madrid-28040, SPAIN*

In the *p*-amino group of the local anesthetics Benzocaine and Procaine of free basis, the pathway of minimum energy was obtained, corresponding to the torsion and inversion motions with a simultaneous change of the *tilt* angle, using the AM1 and CNDO/2 semiempirical methods. The optimum geometric parameters and related potential functions were determined. The Raman bands in the 100-600 cm^{-1} range were recorded and identified.

1 Introduction

The mechanism of action of the local anesthetics remains today unknown^{1,2}. This problem has been extensively studied, and the important role of the amino group in the anesthetic action has been noted^{3,4}. In the present work were studied the local anesthetics benzocaine and procaine of free basis (Fig 1), commonly used in pharmaceutical applications.

The $-\text{NH}_2$ (or $-\text{ND}_2$) group of the compounds under study has four characteristic modes of vibration: stretching, bending, torsion and inversion. The torsion and inversion modes are perhaps the less studied in aniline derivatives or in *p*-amino benzoic acid derivatives. Thus in a previous work the torsion and inversion motions were studied⁵ separately. Due to the close connection between both modes, in a second research the jointly torsion-inversion motion⁶ was studied. Owing to the geometric characteristics of this amino group, a *tilt* angle ϵ appears between the C-N bond and the ring plane, Fig 2. This *tilt* angle affects the torsion and inversion modes. Thus the present paper studies this influence on the torsion motion, on the inversion motion, and on the jointly torsion-inversion function.

2 Experimental

The samples of procaine and benzocaine of free basis were of MERCK and were used without further purification. D_2O was obtained from Junta de Energia Nuclear (Spain) with a purity of 99.7 %. The deuterated samples were prepared by several standard methods⁷⁻⁹.

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. Photon counting detector and the source was a 2 ω Spectra- Physics, model 165 Argon ion laser. All the Raman spectra were obtained with the 514.5 nm line at a laser power in the range 100-400 mw. The slit widths were at 100-400 μm . The observation direction was perpendicular to the incident beam direction.

3 Computational Methods

The calculations were carried out by using the standard AM1 procedure, as implemented in the AMPAC package of computer programs^{10,11}. The geometry was previously optimized¹². The CNDO/2 semiempirical method was used with standard parametrization. The initial geometry was from the crystal data¹³⁻¹⁵ and from the values previously⁵ optimized with this method.

The Figures of the molecules were prepared with a Macintosh microcomputer, using the BALL and STICK program¹⁶.

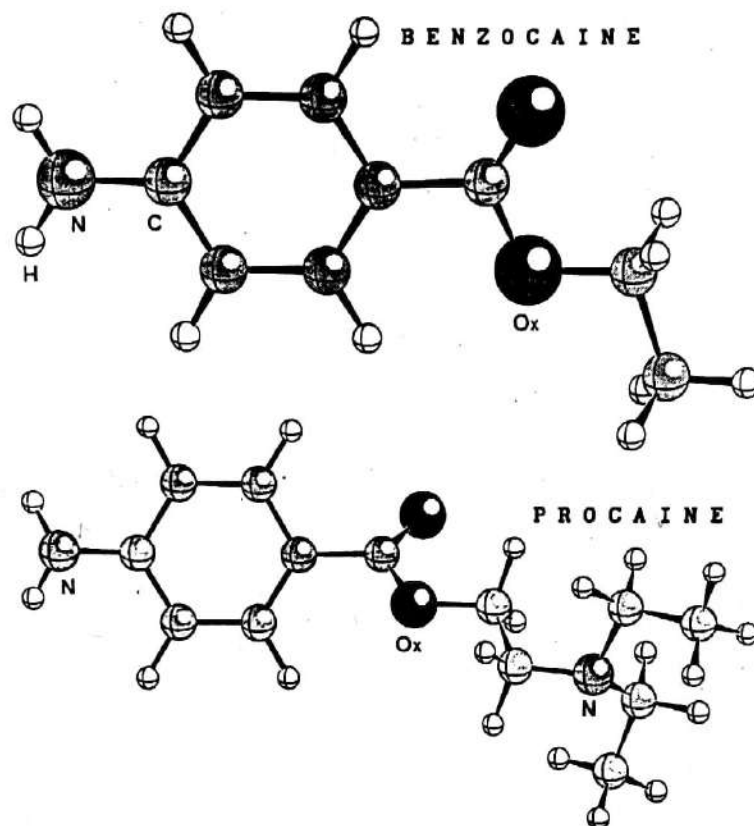


Fig 1 Optimum geometry calculated in the molecules of benzocaine and procaine.

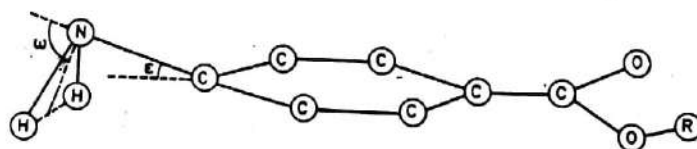


Fig 2 Description of the inversion and *tilt* angles.

4 Results and Discussion

Influence of the *tilt* angle on the torsion potential function: The *tilt* angle is identified as the result of two combined effects: the *inertial*⁵, characteristic of the NH₂ group, and the *electronic*, estimated by the data calculated by both semiempirical methods. This *tilt* angle is coherent with the spectroscopic results obtained⁷, and with those reported in aniline or their halogenated derivatives¹⁷.

The optimized values of this *tilt* ϵ for different torsional angles, is listed in Table 1 and plotted in Figs 3 and 4. Due to the close results calculated between Benzocaine and Procaine, the values shown in all the Tables and Figures can be considered for both molecules.

Table 1 Optimum values of the *tilt* angle ϵ for different torsional angles.

Parameter	Torsional angle α ($^\circ$)			
	0	30	60	90
Tilt angle ϵ ($^\circ$)	3.60	3.16	3.07	3.24

The minimum energy of the molecule corresponds to $\alpha=0$ and $\epsilon=3.6^\circ$, Fig 3. When the torsional angle α increases, the energy is incremented and the *tilt* angle is reduced. The minimum value of ϵ is obtained with $\alpha=45^\circ$. In the barrier height $\alpha=90^\circ$, the value of the *tilt* is $\epsilon=3.24^\circ$. This small change in the geometry with the torsional angle, causes a slight variation in the torsional constant B_0 . The results obtained with different *p*-amino groups, non-deuterated ($-\text{NH}_2$), partially deuterated (NHD) and deuterated ($-\text{ND}_2$), are listed in Table 2 and plotted in Fig 5.

In Fig 6 is shown the influence of the *tilt* angle in the barrier height ($\alpha=90^\circ$). The minimum, $V_2=1792.9 \text{ cm}^{-1}$, corresponds to $\epsilon=3.6^\circ$. This value of the barrier height is slightly lower than that calculated in a simple torsion⁵, 1795 cm^{-1} .

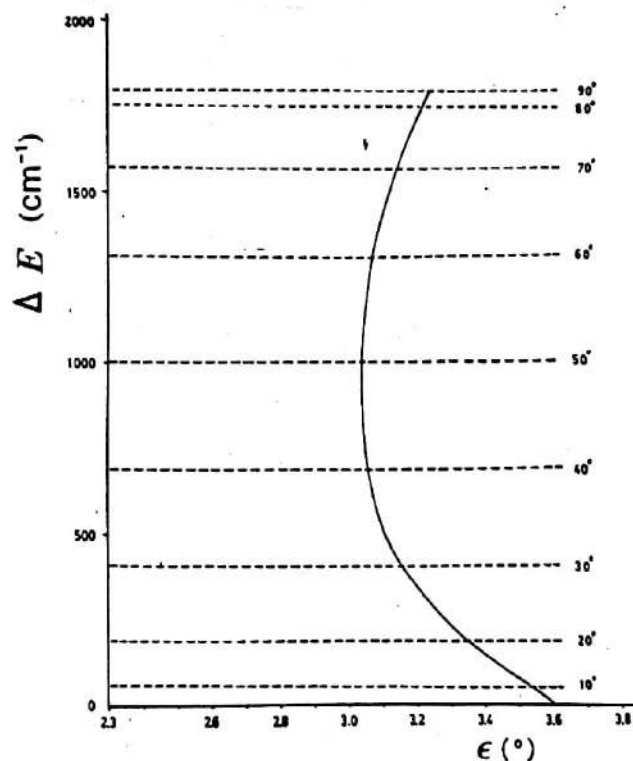
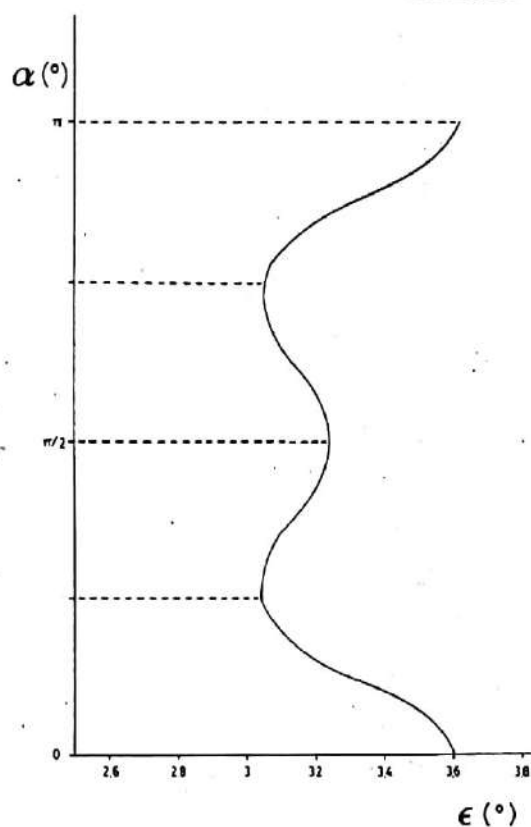


Fig 3 (....) Energy curves for different torsional angles α and distinct *tilt* angles ϵ .
(—) Geometric place of the minimum of the curves.

The potential function obtained can not be exactly adjusted to an analytical function¹⁸ of the form $V(\alpha) = V_2 (1 - \cos 2\alpha)/2$. Thus a Fourier expansion is carried out for the first four even terms ($n=1-4$). The coefficients calculated are listed in Table 3.

Fig 4 Optimum *tilt* angles ϵ , obtained in a rotation of 180° .Table 2 Values of the torsional constant B_0 with the optimum geometry calculated for different torsional angles in the torsion-*tilt* angle variation.

<i>p</i> -amino group	B_0 (cm^{-1})			
	$\alpha = 0^\circ$	$\alpha = 30^\circ$	$\alpha = 60^\circ$	$\alpha = 90^\circ$
-NH ₂	8.8435	8.8443	8.8445	8.8436
-NHD	6.0089	5.9831	5.9783	5.9871
-ND ₂	4.5504	4.5206	4.5151	4.5254

Table 3 Coefficients in a Fourier expansion of the torsion potential function (in cm^{-1}), for the torsion-*tilt* angle variation.

Coefficients	n			
	2	4	6	8
	1795.59	-55.70	-2.67	0.96

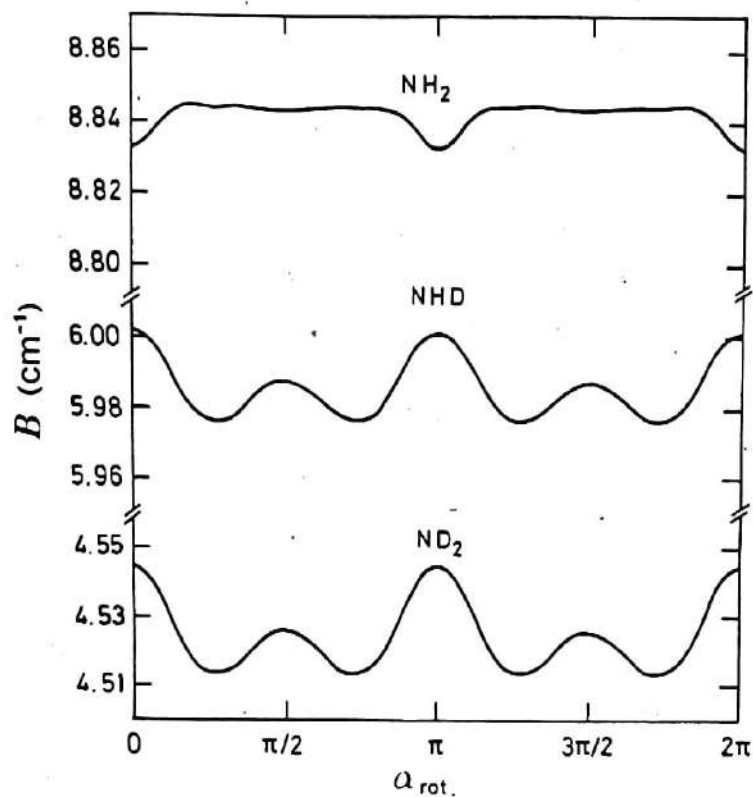


Fig 5 Variation of the constant B_0 in the torsion-tilt motion with respect to the torsional angle α , for different amino groups.

If it is considered that, apart from the electronic influence, the values of ϵ depend mainly on the inertial properties of the rotating NH_2 group, the H-D exchange should give rise to an increase in ϵ . It should be noted that the HNH plane intersects the rotation axis on a point very close to the gravity center of the NH_2 group⁵. The values obtained for several selected torsional angles are listed in Table 4. The parameters ϵ_x and ϵ_y refer to the x and y axis, on which can be traced the *tilt* angle. Geometrical considerations indicate that $\epsilon(\text{ND}_2) \approx 2\epsilon(\text{NH}_2)$.

Table 4 Optimum values of the inertial contribution in the *tilt* angle, in a torsional motion.

<i>p</i> -amino group	Torsional angle α (°)							
	0		30		60		90	
	ϵ_x	ϵ_y	ϵ_x	ϵ_y	ϵ_x	ϵ_y	ϵ_x	ϵ_y
- NH_2	2.49	0	2.58	0	2.70	0	2.73	0
-NHD	3.46	1.98	3.59	1.99	3.76	1.99	3.81	2.00
- ND_2	4.30	0	4.47	0	4.68	0	4.75	0

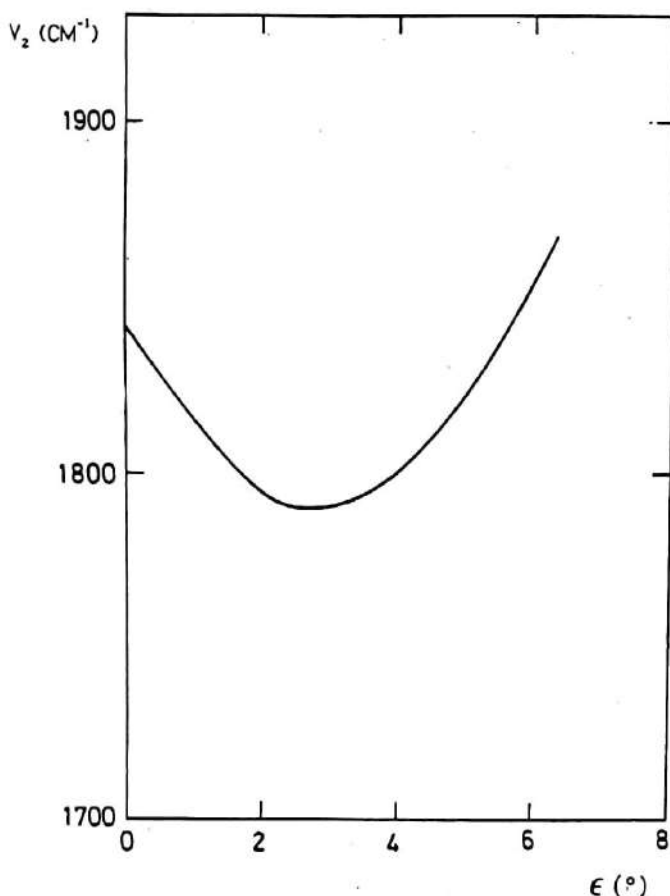


Fig 6 Variation of the barrier height V_2 of the torsion potential function, with the *tilt* angle ϵ .

For the calculation of the torsional frequencies, two procedures are used: In the harmonic approximation (AA), the frequencies of the $-\text{NH}_2$, NHD and ND_2 groups are determined by the eqn. $\nu_\tau = 2\sqrt{B_0 V_2}$, the second column of Table 5. The calculations were with $V_2 = 1792.9 \text{ cm}^{-1}$, and $B_0 = 8.8435 \text{ cm}^{-1}$ (for NH_2), 6.0089 cm^{-1} (for NHD) and 4.5504 cm^{-1} (for ND_2), Table 2. If the potential function is expanded, the results of the third column of Table 5 are obtained.

The second procedure for the frequencies uses a torsional Hamiltonian^{19,20} (RH). The torsional constant B_0 is expanded in Fourier series, cutting off the four term ($n = 0, 2, 4, 6$), Table 6. The frequencies calculated are shown in the fourth column of Table 5. With an expansion of the potential function ($\sum V_n$), the values of the fifth column are obtained. These frequencies are

Table 5 Torsional frequencies (cm^{-1}) calculated through the torsion potential function in the NH_2 , NHD and ND_2 groups, for the torsion-*tilt* angle variation.

<i>p</i> -amino group	$\nu_\tau^{\text{AA}}(V_2)$	$\nu_\tau^{\text{AA}}(\sum V_n)$	$\nu_\tau^{\text{RH}}(V_2)$	$\nu_\tau^{\text{RH}}(\sum V_n)$
$-\text{NH}_2$	252	235	242	229
$-\text{NHD}$	208	194	201	190
$-\text{ND}_2$	181	169	175	-

Table 6 Coefficients in a Fourier expansion of the torsional constant (in cm^{-1}), for the torsion-tilt motion.

p-amino group	n			
	0	2	4	6
-NH ₂	8.8435	0.0073	0.0083	0.0035
-NHD	6.0089	-0.0128	-0.0181	-0.0015
-ND ₂	4.5504	-0.0166	-0.0229	-0.0027

lower than with the other procedures. Comparing the results of Table 5, it is noted that by an harmonic approximation or by using a more sophisticated procedure as the torsional Hamiltonian, close values are obtained.

In Figs 7 and 8 are shown the Raman spectra of benzocaine and procaine respectively in the 100-600 cm^{-1} range, in their non-deuterated and deuterated forms. The frequencies of their lines and their characterization by AM1 are listed in Table 7. The values of the $\tau(\text{NH}_2)/\tau(\text{ND}_2)$ relationship between the frequencies calculated for the non-deuterated and deuterated amino group, 1.39 (by AA) and 1.38 (by RH), are very close to those obtained in the spectra. This fact confirms our assignation. Moreover, infrared and Raman studies^{8,22} with these molecules, in other phases and conditions, give similar values.

Table 7 Raman frequencies of benzocaine and procaine, in the 100-600 cm^{-1} range.

Benzocaine		Procaine		Characterization ^a
non-deuterated	deuterated	non-deuterated	deuterated	
-	-	-	591 br	
590 sh	-	-	-	$\gamma(\text{NH}_2)$ wagging
-	-	-	564.5 vw	$\gamma(\text{NHD})$ wagging
-	-	536 vw	539.5 vw	$\Gamma(\text{CCOO}) + \delta(\text{CCN})$ in amine 3 rd
513 m	-	496.5 w	495.5 vw	$\gamma(\text{NH}_2) + \Gamma[\text{CH}_2\text{-N-(CH}_2\text{-CH}_2\text{)}_2]$
507 m	507 m	519 vw	518.5 vw	16b, $\gamma(\text{CCC})$
-	467 w	-	453 vw	$\gamma(\text{ND}_2)$ wagging
-	-	414 vw	419 vw	$\Gamma(\text{NH}_2) + \Gamma(\text{ring})^b + \Gamma(\text{COO-CH}_2\text{-CH}_2)^b$
406 w	-	401 w	-	$\tau(\text{NH}_2)$ torsion
390vw	390 vw	-	-	16a, $\gamma(\text{CCC})$
-	-	-	383 vw	$\gamma(\text{NHD})$ wagging
-	375 w	-	367.5 vw	$\gamma(\text{ND}_2)$ wagging
322 m	322 m	338.5 vw	338.5 vw	$\Gamma'(-\text{CH}_2\text{-CH}_2)^b + \gamma(-\text{CH}_2\text{-CH}_2)^*$
-	-	-	328 vw	$\tau(\text{NHD})$ torsion
306 m	306 w	-	-	$\tau(\text{CH}_3)$
-	-	300.5 m	299.5 m	$\Gamma(\text{COO-CH}_2\text{-CH}_2)^b + \Gamma'(\text{NH}_2\text{-ring})^b$
-	266 vw	-	-	$\tau(\text{ND}_2)$ torsion
261 vw	258 vw	273.5 vw	270.5 vw	$\gamma(\text{NH}_2) + \gamma(\text{COO}) + 10b, \gamma(\text{C-H})$
-	-	-	259 vw	$\tau(\text{ND}_2)$ torsion
240 vw	-	225 vw	221.5 vw	
-	-	182 w	182 vw	$\gamma(\text{NH}_2) + \gamma'(\text{ring-COO-CH}_2)^b$
-	174 vw	-	-	$\gamma(\text{ND}_2)$ wagging

Abbreviations: m, medium; w, weak; vw, very weak; br, broad; sh, shoulder. ^aNumbers are of the benzene ring, according to Wilson notation²¹. ^bAccording to ref. 12. ^{*}Weak contribution.

Influence of the *tilt* angle on the inversion potential function: Figs 9-10 and Table 8 show the variation of the optimized *tilt* angles for different inversion angles ω . The minimum energy corresponds to $\omega=51.8^\circ$ and $\epsilon=3.6^\circ$. With values of $\omega>100^\circ$, a huge increase of the energy is observed. The highest value of ϵ is for $\omega=43^\circ$.

The close relation is noted between the angles ω and ϵ , thus for $\omega=0^\circ$, the optimum value of ϵ is 0° , corresponding to a totally planar conformation with sp^2 hybridization, because in this case the deslocalization of the electrons of the amino group inside the ring π system is favored²³.

As in the torsion-*tilt* motion, the inversion potential function is traced with the energy calculated through a process in which the *tilt* angle is optimized for each inversion angle. The results obtained are plotted in Fig 11. The barrier height, $V_i=2957.31\text{ cm}^{-1}$, is slightly lower than that for a simple inversion⁵, $V_i=3051\text{ cm}^{-1}$ and $\epsilon=3.6^\circ$. The minimum value of V_i , 2861 cm^{-1} , corresponds to $\epsilon=0^\circ$. The frequencies computed by different procedures are shown in Table 9.

The contribution of the inertial effect in the inversion-*tilt* angle variation, is also calculated. The results with the $-\text{NH}_2$, NHD and ND_2 groups are plotted in Fig 12. A clearer representation in the $52\text{--}59^\circ$ interval is shown in Fig 13. With angles lower than $\omega < 60^\circ$, the values are very close to those with the CNDO/2 method.

Influence of the *tilt* angle on the torsion-inversion potential function: With the description in the two preceding sections of the $\alpha\text{--}\epsilon$ and $\omega\text{--}\epsilon$ motions, and the $\alpha\text{--}\omega$ reported previously⁶, are traced the curves corresponding to the jointly $\alpha\text{--}\omega\text{--}\epsilon$ motion, Fig 14. In shaded line the values of minimum energy are illustrated. The rotation is represented only in the $0\text{--}180^\circ$ interval. The global minimum of energy corresponds to $\alpha=0^\circ$, $\omega=51.8^\circ$ and $\epsilon=3.6^\circ$. The 3D diagram with the optimum geometric parameters for the $0\text{--}360^\circ$ torsion is plotted in Fig. 15. A short range of values is obtained for these parameters.

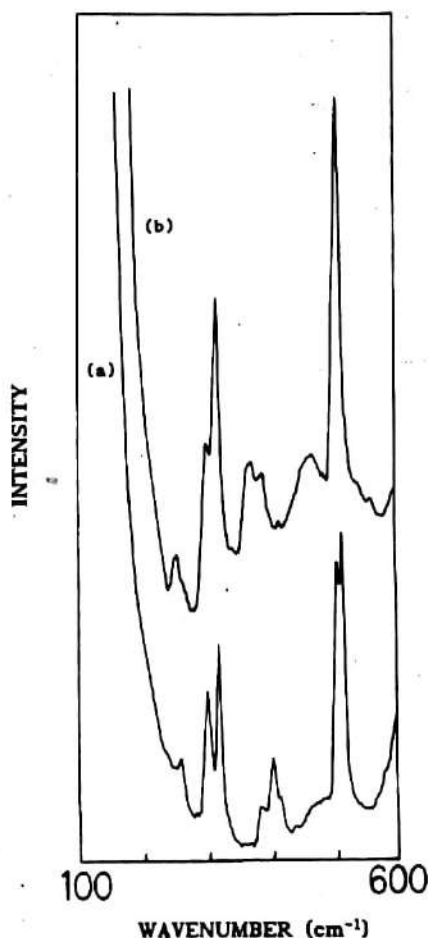


Fig 7 Raman spectra of Benzocaine, Laser = 100 mw, slits = 300 mic. a) non-deuterated, b) deuterated.

Table 8. Optimized values of the *tilt* ϵ calculated in several inversion angles.

Parameters	Inversion angles ω ($^\circ$)				
	0	20	40	60	80
<i>Tilt</i> angle ϵ	0	2.7	3.73	3.35	2.55

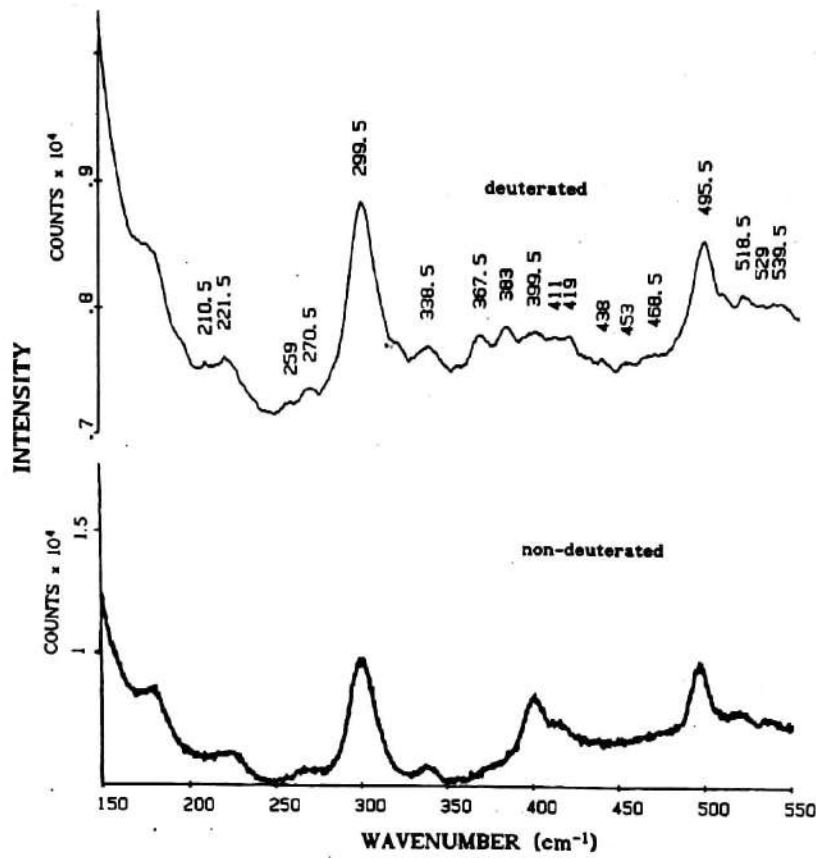


Fig 8 Raman spectra of Procaine, deuterated and non-deuterated, Laser = 300 mw, slits = 400 mic., time: 0.5 sec./pt., points spaced by 0.5 wavenumber.

Table 9. Wagging frequencies in cm^{-1} computed theoretically and obtained experimentally in the infrared and

Raman spectra of Benzocaine and Procaine.

	Molecules	Infrared	Raman	AMI
non-deuterated	Benzocaine	590, 518	590, 513	476
	Procaine	575, 470	622, 496.5	473, 458
deuterated	Benzocaine	440, 365	467, 375	
	Procaine	400, 367	453, 367.5	

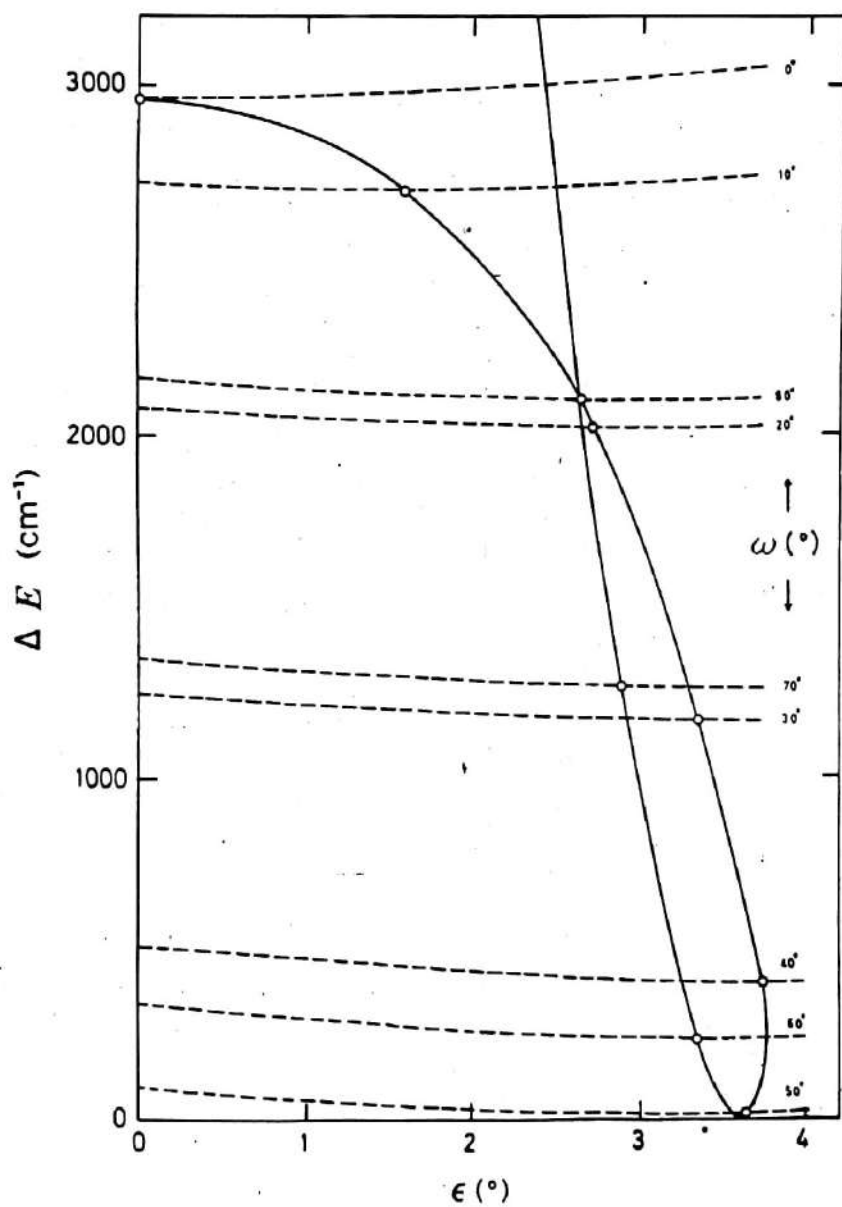


Fig 9 (....) Energy curves for different inversion angles and distinct *tilt* angles ϵ .
 (—) Geometric place of the minimum of the curves.

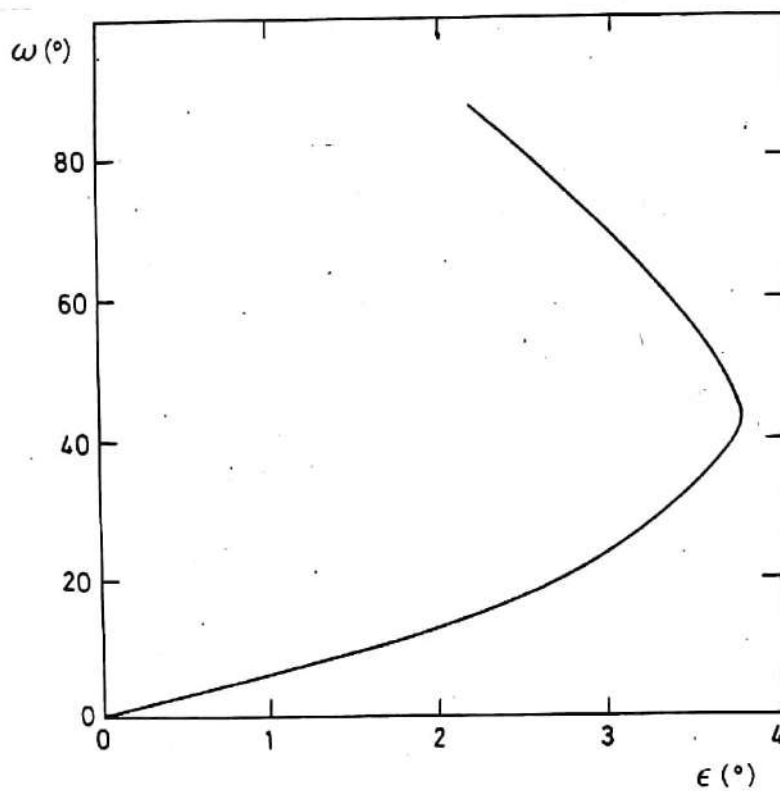


Fig 10 Optimum *tilt* angles calculated in the inversion motion to 90°.

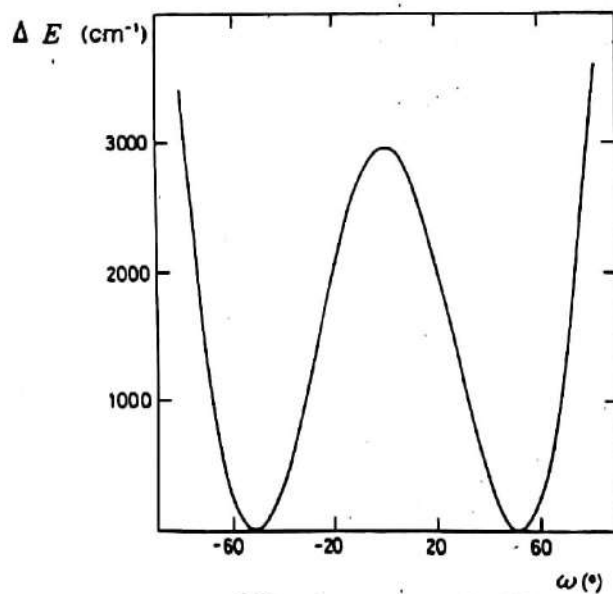


Fig 11 Inversion potential function obtained optimizing in each point the energy, with respect to the *tilt* angle ϵ .

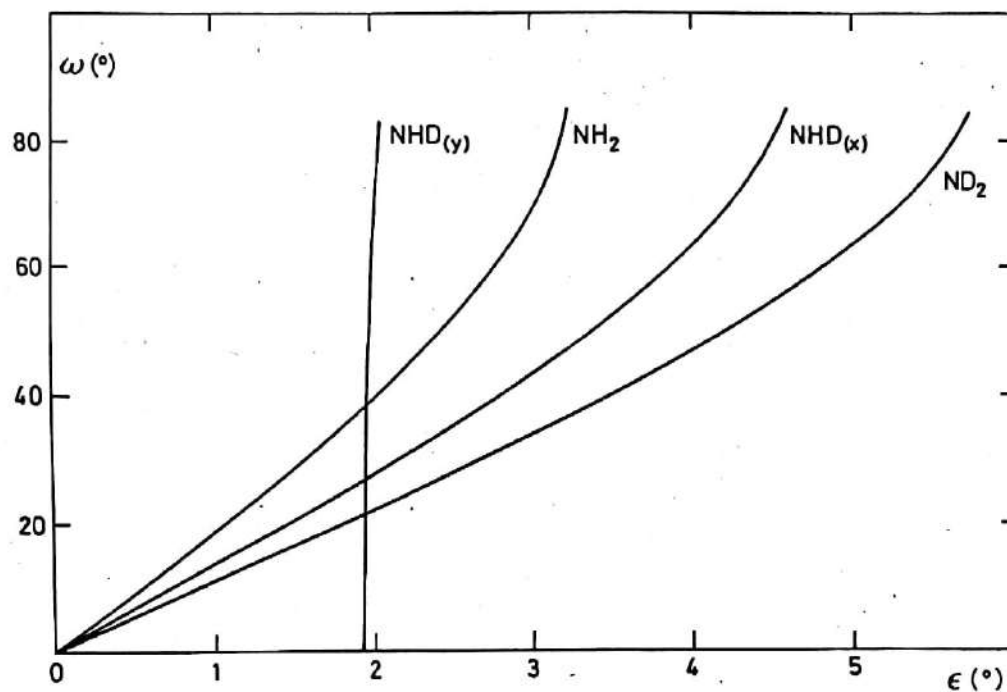


Fig 12 Variation of the inertial contribution of the *tilt* angle, as function of the inversion angle ω , for the different forms of the *p*-amino group.

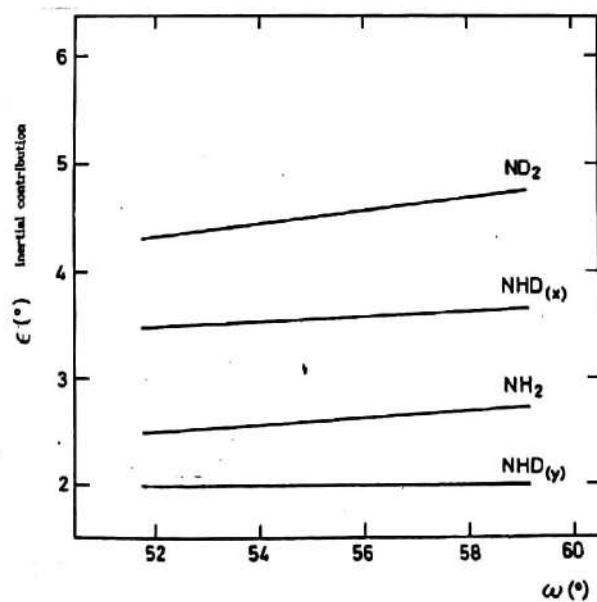


Fig 13 Values of the inertial contribution in the *tilt* angle ϵ calculated in the 52-59° interval of the inversion potential function, and for different forms of the *p*-amino group.

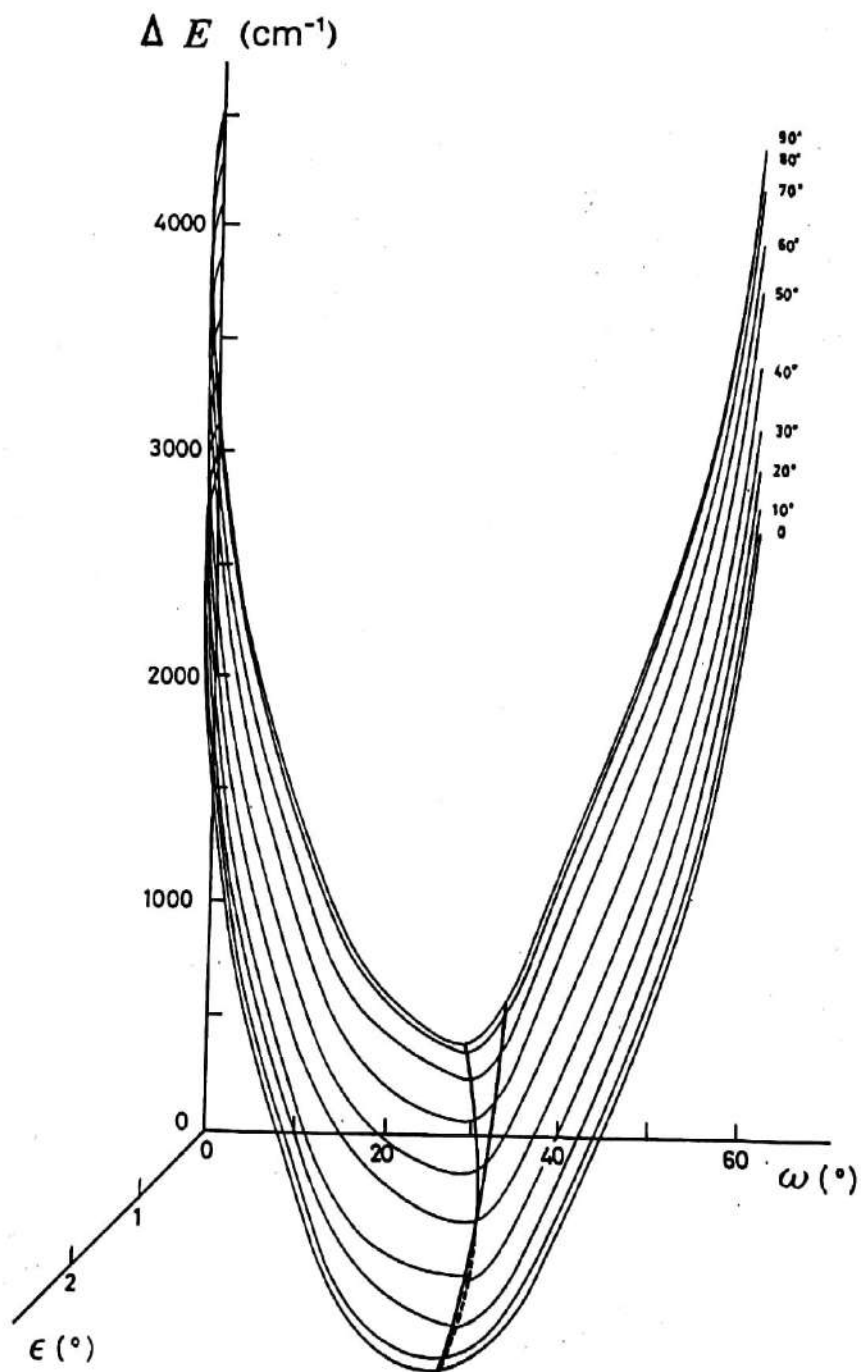


Fig 14 3D representation of the values of the minimum energy in a torsion of 360° of the *p*-amino group, with the optimization in each case of both, the inversion ω and *tilt* angle ϵ .

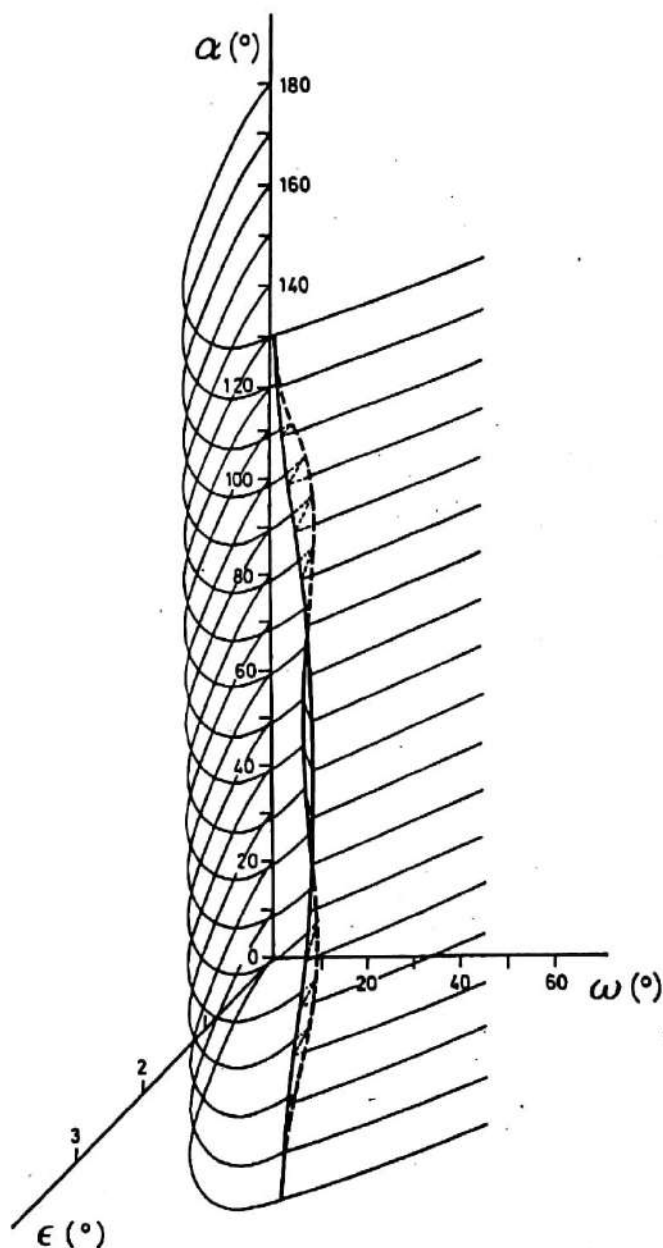


Fig 15 3D representation of the optimum values of the inversion ω and tilt angle ϵ obtained both jointly in a rotation of the *p*-amino group of 360° .

In the global minimum, the results by AM1 for benzocaine are $\epsilon=2.86^\circ$ and $\omega=34.50^\circ$, close to those of procaine, $\epsilon=2.83^\circ$ and $\omega=34.17^\circ$. The value of ϵ determined by AM1 is similar to that computed by CNDO/2, and also close to that calculated considering the inertial effect, 2.49° for NH_2 . However, in the values of ω , both methods differ significantly, although by AM1 the angle is very close to that reported by microwave in the aniline molecule²³, $37.5 \pm 2^\circ$. This fact has already been explained^{17,24}.

4 Conclusions

In the *p*-amino group of the local anesthetics Benzocaine and Procaine of free basis a *tilt* angle was identified between the C–N bond and the aromatic ring plane, which is due to electronic and inertial effects. Both contributions were calculated, and their influence on the torsion and inversion motions analyzed.

A better description of the torsion and inversion potential functions was obtained with the study of the α - ω - ε motion. The corresponding geometric changes were determined and analyzed.

The values calculated for the $\nu_r(\text{NH}_2)/\nu_r(\text{ND}_2)$ relationship with the α - ω - ε motion were in agreement with those recorded experimentally in the spectra.

Close values were obtained between the electronic (calculated by CNDO/2 and AM1) and the inertial contribution in the angle ε . However in the values computed by AM1 and CNDO/2 for the inversion angle ω , the differences were remarkable.

References

- 1 Remko M & Van Duijnen P T, *J Mol Struct*, 104 (1983) 451; 105 (1983) 1.
- 2 Kamaya U I, *Anesth Analg (N Y)*, 63 (1984) 929.
- 3 Sax M, Pletcher J & Gustaffson R, *Acta Crystallog*, B26 (1970) 114; Pletcher J, Sax M & Yoo C S, *Acta Crystallog*, B28 (1972) 378.
- 4 Dideberg P O, Lamotte J & Dupont L, *Acta Crystallog*, B36 (1980) 1500.
- 5 Alcolea Palafox M, *Rev Roum Chim*, 34 (1989) 1667; *Asian J Phys*, 2 (1993) 72.
- 6 Alcolea Palafox M, *Spectrosc Letters*, in press.
- 7 Alcolea Palafox M, *Spectrochim Acta*, 44A (1988) 1465.
- 8 Alcolea Palafox M, *Spectrosc Letters*, 27 (1994) 613; *Rev Roum Chim*, 38 (1993) 573.
- 9 Kydd R A & Krueger P J, *Chem Phys Lett*, 49 (1977) 539.
- 10 Dewar M J S, Zoebisch E G, Healy E F & Stewart J J P, *J Am Chem Soc*, 107 (1985) 3902.
- 11 (a) Liotard D A, Healy E F, Ruiz J M & Dewar M J S, in Dennington R D, II & Healy E F (Eds), *AMPAC MANUAL. Version 2.1. A General Molecular Orbital Package*, Univ. of Texas at Austin, USA (1989). (b) Dewar M J S & Stewart J J P, *QCPE Bull*, 6 (1986) 506.
- 12 Alcolea Palafox M, *J Mol Struct (Theochem)*, 236 (1991) 161; *Vibrational Spectrosc*, 6 (1994) 149.
- 13 Sinha B K & Pattabhi V, *Proc Indian Acad Sci (Chem Sci)*, 98 (1987) 229.
- 14 Lai T F & Marsh R E, *Acta Crystallog*, 22 (1967) 885.
- 15 Kashino S, Ikeda M & Haisa M, *Acta Crystallog*, B38 (1982) 1868.
- 16 Müller N & Falk A, *BALL AND STICK Program*, Version 2.2r4, Austria, 1981-89.
- 17 Niu Z, Dunn K M & Boggs J E, *Mol Phys*, 55 (1985) 421.
- 18 Lewis J D, Malloy T D, Tainer J R, Chao T H & Laane J, *J Mol Struct*, 12 (1972) 427.
- 19 Brauler A, Mathier E, Meyr R, Ribeaud M & Gunthard H H, *Mol Phys*, 15 (1968) 597.
- 20 Onda M, Motoda T & Yamaguchi I, *Bull Chem Soc Jpn*, 58 (1985) 242.
- 21 Varsanyi G, *Assignments for Vibrational Spectra of Seven Hundred Benzene Derivatives*, vol. 1, Adam Hilger, London 1974.
- 22 Alcolea Palafox M, *J Raman Spectrosc*, 20 (1989) 765.
- 23 Lister D G, Tyler J K, Hog J H & Larsen N W, *J Mol Struct*, 23 (1974) 253.
- 24 Niu Z & Boggs J E, *J Mol Struct (Theochem)*, 109 (1984) 381.

[Received 14.08.1997; accepted 09.12.1997]