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Ab initio molecular orbital and infrared spectroscopic study of the conformation of secondary amides: derivatives of formanilide, acetanilide and benzylamides

S. Ilieva, B. Hadjieva, B. Galabov*

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria

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Abstract

Ab initio molecular orbital calculations at HF/4-31G level and infrared spectroscopic data for the frequencies are applied to analyse the grouping in a series model aromatic secondary amides: formanilide; acetanilide; *o*-methylacetanilide; 2,6-dimethylformanilide, 2,6-dimethylacetanilide; *N*-benzylacetamide and *N*-benzylformamide. The theoretical and experimental data obtained show that the conformational state of the molecules studied is determined by the fine balance of several intramolecular factors: resonance effect between the amide group and the aromatic ring, steric interaction between various substituents around the –NH–CO– grouping in the aromatic ring, conjugation between the carbonyl bond and the nitrogen lone pair as well as direct field influences inside the amide group. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Molecular orbital calculations; Secondary amides; Conformational isomerism

1. Introduction

Secondary amides are the preferred models for in-depth studies of the conformational isomerism of the –CO–NH– grouping, the basic structural element in peptides and proteins. The flexibility of the –CO–NH– group and the stabilisation of different conformational forms depending on molecular environment has long inspired a considerable interest [1–6]. For the first time pure *cis* and *trans* isomers of secondary amides have been experimentally isolated by Siddal et al. [7] in the case of *o*-methylformanilide. In a previous study we have applied ab initio quantum mechanical calculations to study the intramolecular

factors determining the relative stability of the two conformers of *o*-methylformanilide [8]. In this article we present results from ab initio molecular orbital studies of the conformational isomerism in several aryl-substituted secondary amides: formanilides, acetanilides and benzylamides. The theoretical results are substantiated by infrared spectroscopic data for the compounds.

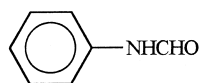
2. Calculations and experiments

Saito et al. [9] have established that HF/4-31G split-valence basis set ab initio calculations satisfactorily describe the conformational state of *N*-methylamides. The authors have found that the HF/4-31G basis set results are in agreement with higher basis set calculations. We therefore, apply the 4-31G basis set

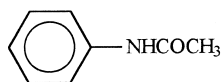
* Corresponding author. Tel.: +359-2-6256-421; fax: +359-2-9625-438.

E-mail address: galabov@chem.uni-sofia.bg (B. Galabov)

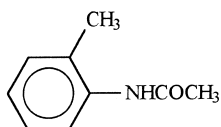
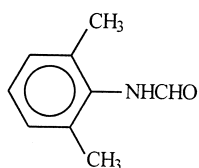
to study the conformational isomerism of the following relatively large secondary amides:



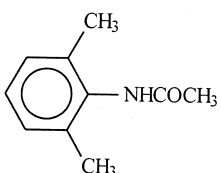
formanilide



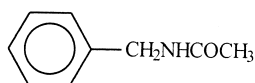
acetanilide

*o*-methylacetanilide

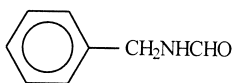
2,6-dimethylformanilide



2,6-dimethylacetanilide



N-benzylacetamide



N-benzylformamide

The GAUSSIAN 94W program package [10] was used. Full geometry optimisation was carried out at the Hartree–Fock level. The optimised geometry parameters for different stable rotameric forms of the studied anilides and benzylamides were obtained. The vibrational frequencies for the fully optimised structures were also calculated. The absence of imaginary frequency shows that the geometry's obtained corresponds to an energy minimum in all cases.

Five of the compounds studied were synthesised by known procedures [11]. Their structure was proved by comparison with literature data for the melting temperatures and also by their infrared spectra. The

infrared spectra were obtained on a Perkin–Elmer 983G spectrometer in dilute solution of CCl₄. The characteristic –CO–NH– stretching frequencies recorded are given in Table 1.

3. Results and discussion

The relative stabilisation of *cis*, *trans* or intermediary rotameric forms of the amide –NH–CO– grouping is determined by the hindered rotation around the central C–N bond. Various factors can influence the conformational stability of differently substituted secondary amides: the degree of conjugation between the C=O group and the lone-pair of electrons at the nitrogen atom, further resonance effects with adjacent aromatic rings, steric effects of bulky aliphatic or aromatic substituents, intramolecular hydrogen bonding, and others.


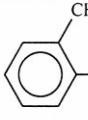



The molecules studied were selected to reflect the influence of resonance and steric effects on the conformational stability of secondary amides containing an aromatic ring.

In Table 2 the *ab initio* results for the total energy and the N–H stretching mode frequencies for the *cis* and *trans* forms of the compounds studied are presented. Considering the total energies it is seen that for most of the compounds studied, the favoured forms are the *trans* structures. The exception is 2,6-dimethylformanilide. In general, the results obtained are in accord with the experimental infrared spectroscopic data as presented in the last column in Table 2. The higher frequency N–H band in the interval 3429–3453 cm^{–1} corresponding to a *trans* conformer is either the only band present or possesses much higher intensity than the lower frequency *cis* N–H band (3393–3402 cm^{–1}). The infrared spectra of acetanilide, formanilide and *o*-methylacetanilide in the N–H stretching frequency region are shown in Fig. 1.

The *ab initio* calculated N–H stretching mode frequencies for the different conformers of the compounds are compared with the experimental frequencies as given in the last column of Table 2. The theoretically estimated characteristic N–H frequencies for the *trans* conformers are higher (with 29–71 cm^{–1}) than the respective frequencies of the *cis* forms. The decrease in N–H stretching

Table 1

Characteristic C=O and N – H stretching frequencies

No	Molecular formula	$\nu_{\text{NH}} [\text{cm}^{-1}]$	$\nu_{\text{C=O}} [\text{cm}^{-1}]$
1	 <chem>NC(=O)Cc1ccccc1</chem>	3441	1702
2	 <chem>NC(=O)Cc1ccccc1C</chem>	3453 3434 3393	1702
3	 <chem>NC(=O)CNc1ccccc1</chem>	3452	1685
4	 <chem>N=O)c1ccccc1</chem>	3429 3402	1691
5	 <chem>N=O)CNc1ccccc1</chem>	3443	1698

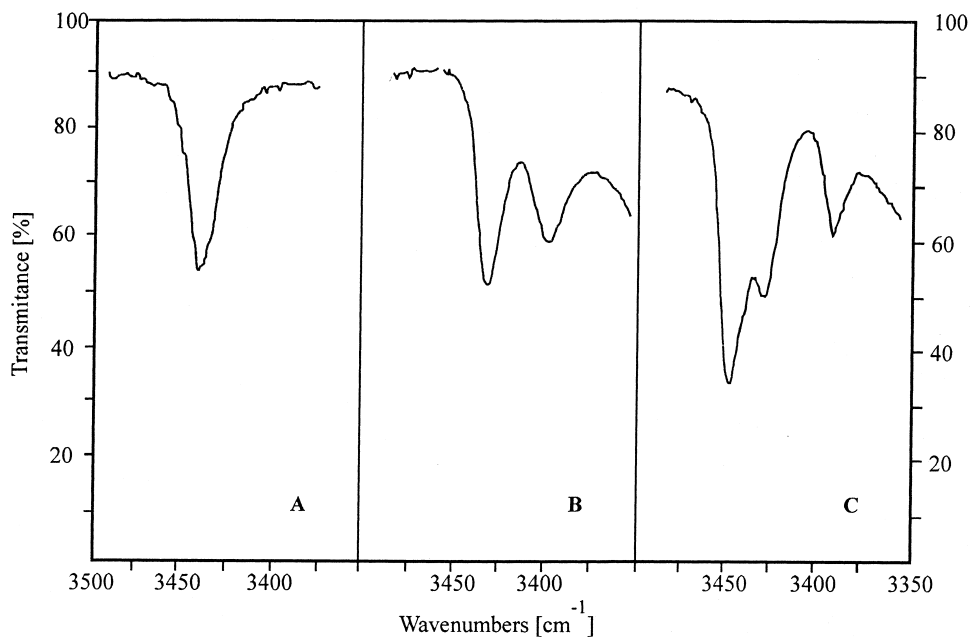
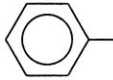
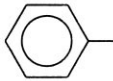
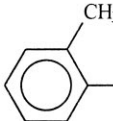
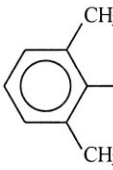
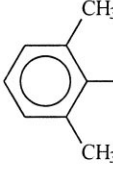
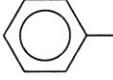
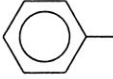
Fig. 1. Infrared spectra in dilute solution of CCl_4 in the N–H stretching region of: A – acetanilide; B – formanilide; C – *o*-methylanilide.

Table 2

Ab initio 4-31G calculated total energies and N–H stretching frequencies (calculated and experimental) for substituted anilides and benzyl-amides

Molecular formula	Name	Isomer	E_{total} [Hartree]	$\nu_{\text{N-H}}^{\text{calc.}}$ [cm ⁻¹]	$\nu_{\text{N-H}}^{\text{calc.*}}$ [cm ⁻¹]	$\nu_{\text{N-H}}^{\text{exp.}}$ [cm ⁻¹]
	formanilide	cis trans	-397.8957 -397.8977	3826 3852	3418 3441	3402 3429
	acetanilide	cis trans	-436.8837 -436.8875	3820 3855	3412 3444	3441
	o-methylacetanilide	cis trans A trans B	-475.8641 -475.8660 -475.8645	3814 3893 3852	3407 3478 3441	3393 3453 3434
	2,6-dimethylformanilide	cis trans	-475.8856 -475.8546	3812 3844	3405 3434	-
	2,6-dimethylacetanilide	cis trans	-514.8439 -514.8445	3808 3846	3402 3435	-
	N-benzylacetamide	cis trans	-475.8588 -475.8648	3837 3873	3428 3460	3452
	N-benzylformamide	cis trans	-436.8718 -436.8747	3833 3872	3424 3459	3443

* Calculated frequencies are scaled by a factor of 0.8933 [10].

mode frequencies in the *cis* structures is attributed to the direct field effect of the carbonyl group in the specific mutual orientation of the C=O and N–H bonds [12]. The ab initio calculations predict almost identical absolute intensities for the absorption bands associated with the N–H stretching vibrations for *cis* and *trans* structures. It can, therefore, be assumed that the integrated intensities in the infrared spectra reflect quantitatively the concentrations of the *cis* and *trans* conformational forms.

From the experimental spectra, as shown in Fig. 1, it is clearly seen that the higher frequency band, 3429 cm^{-1} in the case of formanilide and 3453 cm^{-1} in the case of *o*-methylacetanilide, is more intense. The concentration of the *trans* isomer is, therefore, also higher. The result is in full accord with the ab initio estimated total energies showing higher stability for the *trans* conformers of formanilide and *o*-methylacetanilide.

There is a single N–H stretching band at 3441 cm^{-1} in the infrared spectrum of acetanilide (Fig. 1A). The band position shows that the compound is in *trans* conformation. The calculated energy difference between the *cis* and *trans* form of acetanilide (2.38 kcal/mol) is higher than the respective energy difference in formanilide (1.22 kcal/mol) and *o*-methylacetanilide (1.19 kcal/mol) (Fig. 1B and C). The *cis* conformer of acetanilide is unstable at room temperature, most probably because of steric hindrance between the methyl group and the *o*-hydrogen atom. The benzene ring takes a perpendicular orientation with respect to the plane of the amide group as can be seen from the structural data presented in Table 3. Such mutual orientation of the aromatic ring and the –CO–NH– group results in loss of resonance energy, respectively in higher energy for the *cis* conformer.

According to literature data, three different conformational forms of the amide group are possible: *trans*, *cis* and non-planar ('out'). The 'out' form is discussed in interpreting the N–H stretching mode frequencies in amide containing bulky substituents [13]. The existence of an 'out' form has not been, however, decisively proven. It can be accepted that small deviations of up to 5° in D , the dihedral angle between CO and NH, do not correspond to 'out' conformations. The data for the dihedral angle D presented in Table 3 show that for all compounds studied the ab initio

results predict that either *cis* or *trans* planar structures are stable.

In the case of formanilide, for both *cis* and *trans* conformers the aromatic ring is coplanar with the amide grouping. For acetanilide, as discussed earlier, a steric hindrance in the case of the *cis* conformer is causing a turn of the aromatic ring to an angle of 90° (angle dh in Table 3) with respect to the –CO–NH– plane. In the case of the *trans* conformer the dihedral angle (dh) is 180° corresponding to a planar molecule with considerable stabilisation. The introduction of *o*-methyl substituent in the aromatic ring in *o*-methylacetanilide results in further steric interactions. In the *cis* conformer the dh angle is equal to 79.8° (Table 3). Two *trans* structures are possible for the *trans* conformer depending on the position of the *o*-methyl substituent (Fig. 2). In the case of the *trans*-A structure the molecule is planar ($\text{dh} = 180^\circ$). Because of resonance stabilisation the total energy of this conformer is lower. In the *trans*-B form the steric interaction leads to an angle between the aromatic ring and the –CO–NH– group of 64.6° (Table 3).

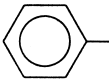
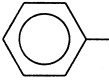
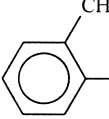
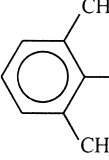
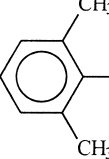
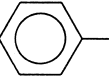
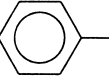
In accord with these structural findings the theoretically estimated N–H stretching frequency is highest in the planar *trans*-A *o*-methylacetanilide (Fig. 1C). The band has also highest intensity. The differences in total energy between the three possible conformers are small ($\Delta E = 1.26\text{ kcal/mol}$). As result the three forms coexist at ambient temperature.

The introduction of a second *o*-methyl substituent in the aromatic ring may result in sterically hindered structure. Both the *cis* and *trans* rotational isomers of *o,o'*-dimethylformanilide and *o,o'*-dimethylacetanilide are non-planar. The angle between the aromatic ring and the plane of the amide group varies in the $66\text{--}110^\circ$ range. In the case of 2,6-dimethylacetanilide the presence of methyl group in the acyl grouping leads to greater steric hindrance in the *cis* isomer. As a result the *trans* conformer is more stable. In contrast, in the case of 2,6-dimethylformanilide the *cis* form is preferred. An earlier ab initio molecular orbital and infrared spectroscopic study [8] of *o*-methylformanilide has shown that the *cis* form of the compound is more stable. The present results for *o*-methylacetanilide show that for this compound the *trans* form is energetically favoured (Table 3).

The introduction of a methylene bridge between the aromatic ring and the amide grouping eliminates the

Table 3

Ab initio HF/4-31G calculated structural parameters for aromatic amides. dh: angle between the aromatic ring and the amide group; D: dihedral angle between N–H and C=O bonds

Molecular formula	Name	Isomer	dh [°]	D[°]
	formanilide	cis trans	180 180	0 180
	acetanilide	cis trans	90 180	0 180
	o-methylacetanilide	cis trans A trans B	79.8 180 64.6	0.7 180 182
	2,6-dimethylformanilide	cis trans	89.775 66.282	0 181
	2,6-dimethylacetanilide	cis trans	89.1 110.4	0 182
	N-benzylacetamide	cis trans	55.5 113.1	2 176
	N-benzylformamide	cis trans	115.4 113.1	0 176

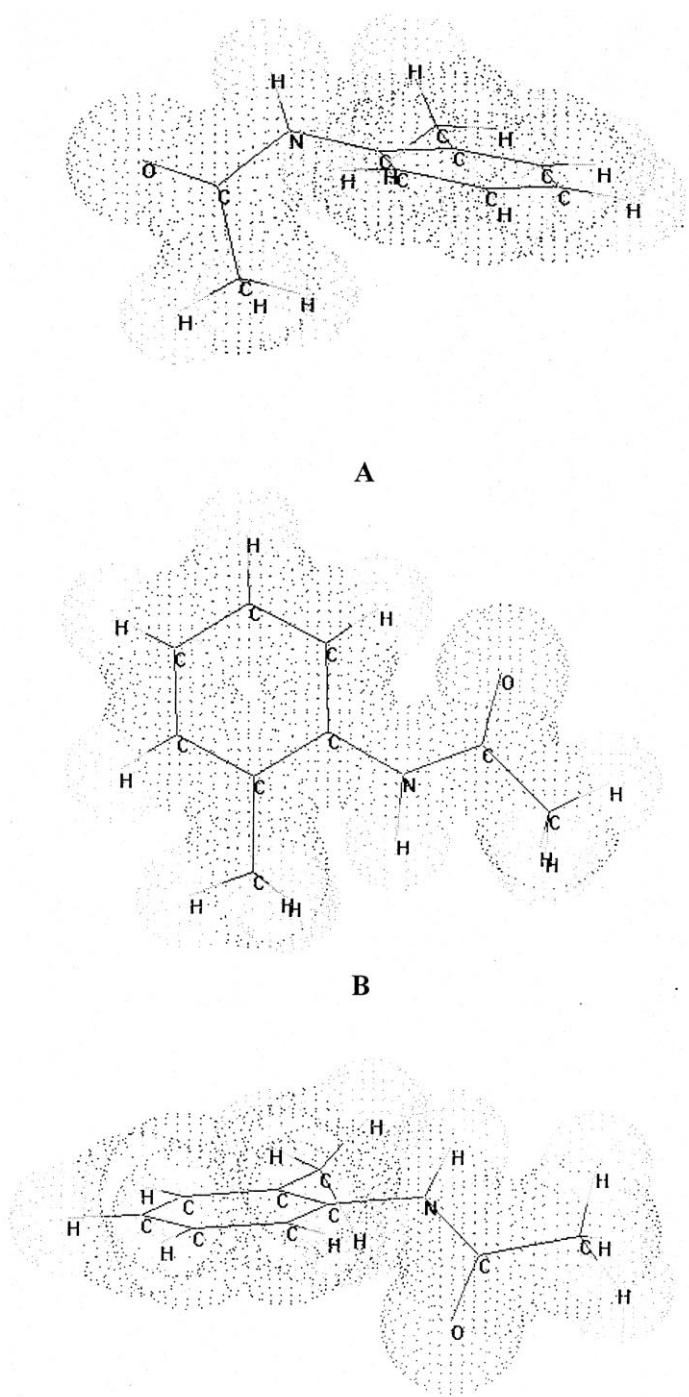


Fig. 2. Spatial structure of the conformers of *o*-methylacetanilide: A – *cis*; B – *trans* A; C – *trans* B.

resonance between the unsaturated moieties. For the benzylamides studied, the spatial orientation of the benzene ring is, therefore, not influenced by conjugation effects. The structural parameters of the benzyl amides are shown in Table 3. The energy difference between the respective *cis* and *trans* isomers of the two molecules is in the 1.88–3.76 kcal/mol range. The *trans* isomers in both cases predominate (Table 2). In the experimental infrared spectra of *N*-benzylformamide and *N*-benzylacetamide a single N–H stretching band is observed with position typical for *trans* –CO–NH– conformation (Table 2).

4. Conclusions

The ab initio HF/4-31G basis set molecular orbital calculations and experimental infrared spectra can successfully be used to characterise the conformational isomerism of secondary amides containing aromatic substituents. A good correlation between theoretical and experimental results has been found. The conformational state of the compounds is determined by the fine balance of several intramolecular effects, most importantly resonance interactions and steric hindrance.

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