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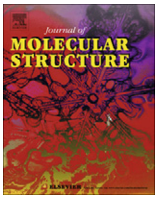

Conformational preferences for some 3-(4′-substituted phenylsulfonyl)-1-methyl-2-piperidones through spectroscopic and theoretical studies

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HIGHLIGHTS

- ▶ Conformational analysis study of alpha-phenylsulfonyl-delta-valerolactams.
- ▶ Solvent effect on the conformational equilibrium through IR.
- ▶ Theoretical calculation in the gas-phase and with solvent effect (PCM).
- ▶ Single crystal X-ray diffraction analysis.

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Dedicated to Prof. Blanka Wladislaw (in memoriam) for her outstanding contribution to the Organic Chemistry of Sulfur compounds

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ABSTRACT

The analysis of the infrared (IR) carbonyl band of some 3-(4′-substituted phenylsulfonyl)-1-methyl-2-piperidones **1–5** bearing as substituents: OMe **1**, Me **2**, H **3**, Cl **4** and NO_2 **5**, supported by B3LYP/6-31G(d,p) calculations along with NBO analysis (for **1**, **3** and **5**) and X-ray diffraction (for **5**), indicated the existence of three stable conformations i.e. *quasi-axial* (*q-ax*), *syn-clinal* (*s-cl*) and *quasi-equatorial* (*q-eq*). In the gas phase, the *q-ax* conformer is calculated as the most stable (*ca.* 88%) and the least polar, the *s-cl* conformer is less stable (*ca.* 12%) but more polar, and the *q-eq* conformer is the least stable (*ca.* 1%) and the most polar of the three conformers evaluated. The sum of the most important orbital interactions from NBO analysis and the trend of the electrostatic interactions accounts for the relative populations as well as for the ν_{CO} frequencies of the *q-ax*, *s-cl* and *q-eq* conformers calculated in the gas phase. The unique IR ν_{CO} band in CCl_4 may be ascribed to the most stable *q-ax* conformer. The more intense (60%) high frequency doublet component in $CHCl_3$ may be assigned to the summing up of the least stable *q-eq* and the less stable *s-cl* conformers, as their frequencies are almost coincident. The occurrence of only a single ν_{CO} band in both CH_2Cl_2 and CH_3CN supports the fact that the ν_{CO} band of the two more polar conformers appear as a single band. Additional support to this rationalization is given by the single point PCM method, which showed a progressive increase of the *q-eq* + *s-cl*/*q-ax* population ratio going from the gas phase to CCl_4, to $CHCl_3$, to CH_2Cl_2 and to CH_3CN. X-ray single crystal analysis of **5** indicates that this compound displays a *quasi-axial* geometry with respect to the [O=C—CH—S] moiety, and that the 2-piperidone ring assumes a slightly distorted half-chair conformation. In the crystal packing, molecules of **5** are arranged into supramolecular layers linked through C—H···O interactions along with $\pi\cdots\pi$ interactions between adjacent benzene rings.

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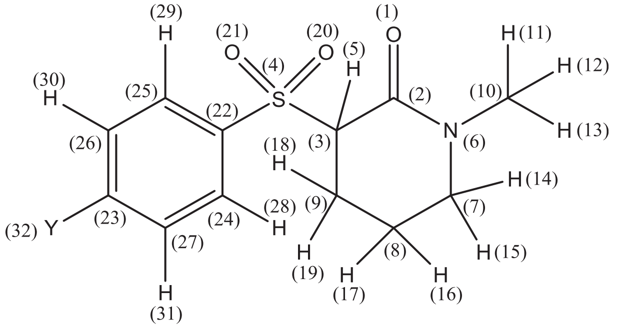
1. Introduction

Recent work from this laboratory on the infrared (ν_{CO}) band and theoretical [B3LYP/6-31G(d,p)] calculations of some *N*,*N*-diethyl-2-[(4′-substituted) phenylsulfonyl] acetamides $Et_2NC(O)CH_2SO_2C_6H_4$—Y (Y = OMe, Me, H, Cl, Br, NO_2) [1] has shown the occurrence of three pairs (*anti* and *syn*) of *cis* (*c*) and *gauche* (g_1 and g_2) conformers in the gas phase, with the *gauche* conformers being more stable than the *cis* ones. The summing up of the orbital (NBO) and electrostatic interactions justifies the populations and ν_{CO} frequencies of the referred conformers. In the apolar solvent, CCl_4, there is a predominance of the least polar *gauche* conformers (90%) with respect to the most polar *cis* conformers (10%). In the polar solvent, $CHCl_3$, a reversal of the *cis* (*c*)/*gauche* (g_1 and g_2) population ratio is observed i.e. 60% (*c*)/40% (g_1 and g_2) and in the highly polar solvent, CH_3CN, the most polar *cis* conformer is the only one present. This trend was only partially supported by PCM [HF/6-31G(d,p)] computations.

Theoretical and spectroscopic (IR, NMR and microwave) studies [2–5] of 2-piperidones showed that the piperidone ring exists, both in the gas phase and in solution, almost exclusively in the half-chair or slightly twisted half-chair conformations. X-ray crystal analysis of 3-chloro-2-piperidone [6] and 3-(phenylsulfonyl)-1-methyl-2-piperidone [7] has shown that, in both compounds, the piperidone ring has a slightly distorted half-chair conformation with the 3-substituent having *quasi-equatorial* [Cl—C—C=O (dihedral angle) = −30.3°] and the *axial* [S—C—C=O (dihedral angle) = 73.2°] geometries, respectively.



Y = OMe **1**, Me **2**, H **3**, Cl **4** and NO_2 **5**.

α = O(1)-C(2)-C(3)-S(4)

β = C(2)-C(3)-S(4)-C(22)

γ = C(2)-C(3)-S(4)-O(20)

γ’ = C(2)-C(3)-S(4)-O(21)

δ = C(3)-S(4)-C(22)-C(24)

θ = O(1)-C(2)-N(6)-C(10)

ω = O(1)-C(2)-N(6)-C(7)

ω’ = O(1)-C(2)-C(3)-C(9)

φ = C(2)-N(6)-C(7)-C(8)

φ’ = C(2)-C(3)-C(9)-C(8)

ψ = O(21)-S(4)-C(22)-C(25)

ψ’ = O(20)-S(4) -C(22)-C(24)

Scheme 1. Atom labelling of 3-(4′-substituted phenylsulfonyl)-1-methyl-2-piperidones and definition of relevant torsion angles.

With the view of understanding the nature of the electronic and electrostatic interactions which influence the stability of the *cis–gauche* conformers along with the abnormal solvent effect noticed in the *cis*/*gauche* conformational equilibrium of the *N*,*N*-diethyl-2-[(4′-substituted) phenylsulfonyl] acetamides [1], this paper reports the IR study of some 3-(4′-substituted phenylsulfonyl)-1-methyl-2-piperidones bearing in the 4′ position electron-donating and electron-attracting substituents i.e. Y = OMe **1**, Me **2**, H **3**, Cl **4**, NO_2 **5** (Scheme 1) along with density functional theory (DFT), polarisable continuum model (PCM) and Natural Bond Orbital (NBO) calculations for **1**, **3** and **5**, and X-ray diffraction analysis of **5**. These compounds were chosen taking into account some conformational rigidity of the piperidone ring which allows the 3-substituent to occupy the *quasi-equatorial* and *axial* conformations almost exclusively.

2. Experimental

2.1. Materials

All solvents for IR measurements were spectrograde and were used without further purification. The 3-(4′-substituted phenylsulfonyl)-1-methyl-2-piperidones **1**, **2**, **4** and **5** are new compounds and were prepared as described for **3** [7] i.e. through the oxidation of 3-(4′-substituted phenylsulfanyl)-1-methyl-2-piperidones with H_2O_2 and SeO_2 in methanol to give the appropriate lactam-sulfone. After extraction with chloroform and rotoevaporation a crude solid was obtained in 66–98% yield. The product was submitted to flash chromatography with a solution of ethyl acetate and hexane in a 7:3 ratio. Suitable crystals for X-ray analysis for **5** were obtained by vapor diffusion from chloroform/*n*-hexane at 283 K. The physical, ^{1}H and ^{13}C NMR, and elemental analysis of the lactam-sulfones **1–5** are presented in Table 1. The starting 3-(4′-substituted phenylsulfanyl)-1-methyl-2-piperidones of **1**, **2**, **4** and **5** were prepared as described for the precursor of **3** [7].

2.2. IR measurements

The IR spectra were obtained on a FTIR Michelson-Bomem-MB100 spectrophotometer, with 1.0 cm^{-1} resolution. The carbonyl region (1800–1600 cm^{-1}) was recorded for carbon tetrachloride, chloroform, dichloromethane and acetonitrile solutions, at a concentration of 2.0×10^{-2} mol dm^{-3}, using a 0.519 mm sodium chloride cell. The carbonyl first overtone region (3500–3100 cm^{-1}) was recorded for carbon tetrachloride and chloroform solutions (2.0×10^{-2} mol dm^{-3}) using a 1.00 cm quartz cell. The overlapped carbonyl bands (fundamental and first overtone) were deconvoluted by means of the Grams/32 curve fitting program, version 4.04 Level II [8]. The populations of the different conformers were estimated from the maximum of each component of the resolved carbonyl doublet expressed in percentage of absorbance, assuming equal molar absorptivity coefficients for the studied compounds **1**–**5**.

2.3. X-ray measurements

Crystal data; $C_{12}H_{14}N_2O_5S$, M = 298.31, triclinic, $P\bar{1}$, a = 7.0639(3), b = 9.7598(3), c = 10.2140(5) Å, α = 71.311(4)°, β = 80.077(4)°, γ = 87.607(3)°; V = 657.00(5) Å^3, Z = 2, D_x = 1.508 Mg/m^3, λ (Cu Kα) = 1.54184 Å, R (all data) = 0.043.

2.3.1. Data collection and processing

X-ray diffraction data were collected on an Agilent SuperNova Dual diffractometer with Atlas detector and the ω scan technique, using a mirror monochromator. The structure was solved by direct