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Low inversion energy barrier of cytisine NH group—an explanation for the FT-IR bands splitting

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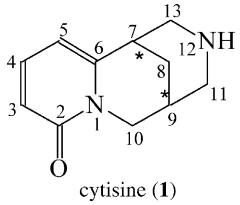
Abstract

The DFT calculations using B3PW91 hybrid functional and 6-311++G** basis set were performed for the two most stable isomers of cytisine (**1a** and **1b**). The conformation **1a** differs from **1b** by the orientation (*equatorial* and *axial*, respectively) of the hydrogen atom at the piperidine nitrogen atom. In terms of the Gibbs free energy, the conformation **1a** is less stable than **1b** by 0.25 kcal mol^{-1}, only. The isomers are separated by 3.6 kcal mol^{-1}—an activation energy barrier, which is higher in energy than the vibrational modes inverting one isomer into another. Presence of such a barrier explains the existence of the two isomers (*equatorial* and *axial*) observed previously in apolar solvents.

Keywords: Cytisine; DFT; IR; Isomerism; Inversion energy barrier

1. Introduction

Many attention has recently been devoted to cytisine (**1**)—a toxic quinolizidine alkaloid, present in various plants, e.g. *Cytisus*, *Baptisia*, *Laburnum vulgare* [1–11]. Although in large doses, it can kill by respiratory failure, in small doses it may be useful in treating of various diseases such as some forms of epilepsy, schizophrenia, Parkinson or Alzheimer. It may also be helpful in quitting smoking. To understand the pharmacological activity of compounds of potential therapeutic interest, it is very important to know its structure and physicochemical properties.



cytisine (**1**)

Recently, we used FT-IR and Raman techniques [12,13] and semiempirical (AM1 and PM3) and ab initio (HF/6-31G* and MP2/6-31G*) calculations [14] to study the structure of cytisine in different environments. In this paper, the B3PW91 hybrid DFT functional [15–18] and the 6-311++G** basis set [19] were selected to study the most stable isomers of cytisine in the gas phase and to estimate the inversion energy barrier for the NH group in the piperidine ring. The energy barrier higher than the appropriate NH vibrations converting one cytisine isomer into another means that splitting of the FT-IR bands can originate from these very isomers. Geometrical parameters calculated at the DFT(B3PW91)/6-311++G** level were compared with those obtained on the basis of X-ray measurements [20–22]. Aromatic character of the pyridone moiety in cytisine was quantitatively measured by the HOMA index (harmonic oscillator model of aromaticity, [23,24]). Difference between the HOMA values based on the computed and experimental geometries, respectively, is also a measure of accuracy the DFT values taken for vacuum can reproduce the experimental values taken for the solid phase.

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2. Experimental and computational details

2.1. Materials

Polycrystalline cytisine (**1**) was commercial compound of Aldrich. Solvents (CCl_4, $CDCl_3$ and Et_2O) were analytical, HPLC or spectroscopic grade compounds of Aldrich or Fluka dried over molecular sieves (3 Å).

2.2. Infrared measurements

FT-IR spectra were recorded at the room temperature using Perkin–Elmer 2000 spectrometer with resolution of 4 cm^{-1}. The ν(NH), ν(CH) and ν(C=O) spectral regions were selected for thorough analysis. Depending on concentration, solvent type and infrared region, the FT-IR spectra were measured for cytisine solutions in quartz cell of 50 mm or in KBr cells of 10, 0.625 and 0.064 mm. The ν(C=O) band was decomposed by band fitting routine as implemented in the PEGRAMS program using a sum of Gaussian and Lorentzian functions.

2.3. Computational details

Geometries of the two stable cytisine isomers (**1a** and **1b**, Fig. 1) found at the semiempirical level [14] were reoptimised without symmetry constraint at the B3PW91/6-311++G** level [15–19]. The harmonic IR spectra, calculated numerically at the same level of theory, exhibited no imaginary frequency thus the isomers found have corresponded to true energy minima. The level of theory used here is frequently applied in the literature to study the most stable structure(s) as well as for analyses of the experimental FT-IR spectra of biomolecules, because of its high predictive value [25–30]. To interpret the experimental IR spectra in terms of the calculated harmonic frequencies the frequency scaling routine, developed by Alcolea Palafox [31], has been applied and the following scaling equation ($\nu_{scal} = 0.955\nu_{calc} + 25.7$) was used. The inversion barrier energy for the NH group in the piperidine cycle was estimated for the isolated molecule by changing the CCNH dihedral angle by 15° steps. For all calculations, GAUSSIAN 98 program [32] running on Cray SV1ex-1-32 computer at the Interdisciplinary Center for Mathematical and Computer Modelling (ICM, Warsaw) was applied.

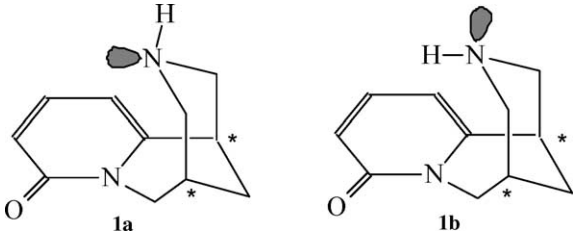

Fig. 1. The most stable conformations for cytisine.

3. Results and discussion

3.1. The most stable structures

Semiempirical calculations performed for different isomers of cytisine indicated that structures **1a** and **1b** are the most stable [14]. Isomers **1a** and **1b** possess the same configuration on the asymmetric carbons (C^7R and C^9S) and different orientation (*axial* and *equatorial*) of the lone pair of electrons (or the hydrogen atom) at the piperidine nitrogen (Fig. 1). This orientation may be important for *N*-substituted derivatives, whose activity depend more on substituent than on basicity [2].

The B3PW91/6-311++G** total electronic energy (*E*) of **1a** is almost the same as that for **1b** (Table 1). Zero point vibrational energies (ZPVE) and thermal corrections to the Gibbs free energy (G_c) are also similar for both isomers and the Gibbs free energies (*G*) differ only by 0.25 kcal mol^{-1}. This indicates that cytisine exists as a mixture of two conformers in the gas phase, among which **1b** seems to be slightly more stable than **1a** {their abundances are ca. 60 and 40%, respectively, at the DFT(B3PW91)/6-311++G** level}.

Dipole moment of **1a** (5.660 D) is larger than that for **1b** (4.302 D) indicating that **1a** can be more stabilized in stronger polar environment (where intermolecular hydrogen bonds may take place). Indeed, structure **1a** has been found as the most stable in the solid state by X-ray measurements [20–22], where two independent molecules of identical conformation (linked together by the intermolecular hydrogen bond between the NH and C=O groups) have been identified in the unit cell. On the other hand, FT-IR and NMR measurements indicate that both isomers (**1a** and **1b**) are present in apolar solvents [12,20].

3.2. Geometries

The geometrical parameters for both isomers of cytisine (**1a** and **1b**) obtained at the B3PW91/6-311++G** level are collected in Table 2. The literature X-ray data are available for the two non-equivalent cytisine molecules in the crystal elementary cells [20–22]. In the computed

Table 1
Relative energy parameters (Δ) between the most stable cytisine isomers (**1a** and **1b**) calculated at the DFT(B3PW91)/6-311++G** level

Thermodynamic parameter	Isomer[a]		Δ(**a**−**b**)[b]
	1a	**1b**	
E	−612.267975	−612.268514	0.34
ZPVE	0.240594	0.240733	−0.09
E+ZPVE	−612.027381	−612.027781	0.25
G_c	0.204638	0.204786	−0.15
G	−612.063337	−612.063728	0.25

[a] In Hartree, 1 Hartree = 627.5095 kcal mol^{-1}.
[b] In kcal mol^{-1}, 1 cal = 4.184 J.