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The tautomerism of fluorinated indazolinones in the solid state

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HIGHLIGHTS

- The tautomerism of fluorinated indazolinones in the solid state has been established.
- Substituents at positions 4,5,6 and 7 determine the tautomerism.
- DFT calculations adequately reproduce the experimental CPMAS chemical shifts.
- The crystal structures of two fluorinated indazolinones are described.

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Dedicated to our friend Professor Elena Pinilla of the Universidad Complutense de Madrid on the occasion of her retirement

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ABSTRACT

The structure of three fluorinated N*H*-indazolinones, two oxo derivatives and one 3-hydroxyindazole, has been determined by ^{13}C and ^{15}N solid state NMR. For two of them, X-ray crystallography confirmed the results on the tautomeric forms, 4,5,6,7-tetrafluoroindazolin-3-one crystallizing in $P2_1/c$ monoclinic space group and 6,7-difluoroindazolin-3-one in $P2_1/n$ monoclinic space group, proving once more the efficiency of the combined use of both techniques in structural determination. DFT theoretical calculations, gas phase, water-PCM and one explicit water molecule, support the results.

1. Introduction

There are many ways to classify all classes of tautomeric compounds. One of them, seldom used but interesting, considers the difference in energy between tautomers (for a particular family of tautomers, this is an usual practice [1]). If the difference in energy is small, say a few kJ mol^{-1}, the tautomers will be present in comparable amounts. This is the case, for instance, of the keto/enol tautomerism of acetylacetone [2,3] and of the annular tautomerism of most pyrazoles [4]. In heterocyclic chemistry, with the exception of annular tautomerism, functional tautomers show, in general, large differences in energy, to the point that is possible to say that amino heterocycles exist in the amino tautomer (and not in the imino one) and oxo heterocycles exist in the oxo tautomer (and not in the hydroxy one) [5–7]. Indazolin-3-ones/3-hydroxy-indazoles tautomerism is one of the rare cases where there are, at least, two functional tautomers of similar energy (Scheme 1).

We have been interested in the structure of indazolin-3-ones for more than 25 years when we described the crystal structure of indazolin-3-one itself **1** [8]. This was followed by a description of the ^{13}C NMR spectra of this class of compounds within indazoles [9], the structures of indazolin-3-one **1** and 7-nitroindazolin-3-one [10], the discovery of an extraordinary fast proton transfer in the solid state between two indazolinone tautomers [11] and the tautomerism of trifluoroindazolinones [12]. In the first paper [8], only a polymorph of **1c** was characterized, but in a subsequent paper, another polymorph was identified [10].

Here we present the experimental studies (crystallography and CPMAS NMR) on 4,5,6,7-tetrafluoroindazolin-3-one (**2**), 6,7-difluoroindazolin-3-one (**3**) and 4,6-difluoro-7-nitro indazolin-3-one

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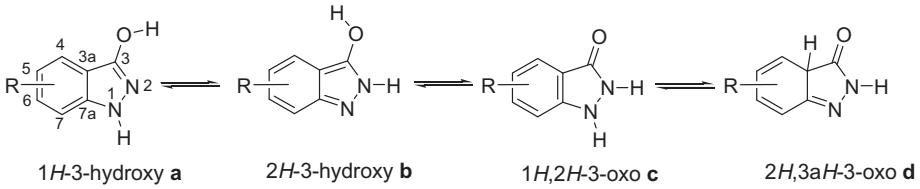
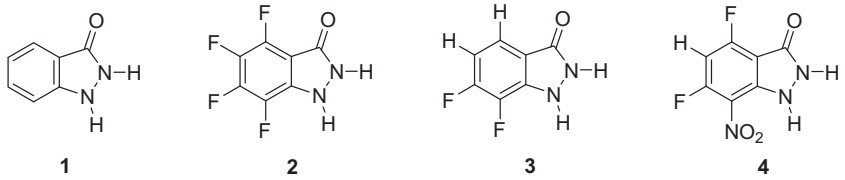


Scheme 1. Tautomerism of indazolinones.



Scheme 2. The four studied indazolinones (**1**–**4**).

(**4**) comparatively to indazolin-3-one (**1**) itself, as well as theoretical calculations on the tautomerism of compounds **1**–**4** (Scheme 2).

Literature results concerning the tautomerism of indazolinones can be summarized in a chronological order. It must be noted that all these publications deal exclusively with indazolinone **1**. The first results from IR (KCl) and UV (EtOH), concluded erroneously that, both in the solid state and in solution, the hydroxy tautomer **a** predominates [13]. The situation till 1976–1978 was summarized in a book [1] and a review [14] indicating that probably in ethanol the major tautomer should be **1a** while in the solid state it should be **1c** (tautomers **1b** and **1d** were eliminated). Then appears in 1985 a paper in which ^{15}N NMR was used to determine the **a**/**c** ratio of **1** in different solvents and solvent mixtures [15]: 75/25 in dimethylsulfoxide, 24/76 in methanol, and 3/97 in trifluoroethanol with an error estimated of 3%; the authors conclude that the more acidic the solvent the more stable the oxo tautomer **c**, due to hydrogen bonding through its carbonyl group. In 1986 we reached the conclusion that in the solid state (X-ray and ^{13}C CPMAS NMR) the tautomer was **1c** and in dimethylsulfoxide there was an 85/15 mixture of **1a** and **1c** [8]. Basicity measurements were used twice to determine the tautomerism of **1**. In the first paper [16] measurements of the pK_as in the ground and the excited states led the authors to conclude that in non-polar solvents, cyclohexane, the major tautomer is **1a** while in polar, hydrogen bonding solvents, e.g. methanol and water, the major tautomer is **1c**. A second and much elaborate paper reports that in water there are 95% of **1c**, 5% of **1a** and $10^{-4.7}$ of **1b** [17]. When indazolinone is included in a cyclodextrin and the circular dichroism is measured in dimethylsulfoxide, the major tautomer resulted to be **1a** [18]. Finally, DFT and MP2 calculations have been reported for **1** in the gas phase to explain its thermochemistry data; the authors conclude that B3LYP calculations give the best result and that tautomers **1a** and **1c** have comparable stabilities in the gas-phase [19]. They note that **1c** is calculated to be non-planar, a fact we have also encountered in our calculations. Assuming some simplifications, we have summarized the previous results for indazolinone **1** in Table 1.

Table 1
The functional tautomerism of indazolinone **1**.

Phase	**1a** (1*H*-3-hydroxy)	**1c** (1*H*,2*H*-3-oxo)	Refs.
Gas phase (DFT calculations)	45%	55%	[19]
Solution, non-polar solvent	>90%	<10%	[16]
Solution, cyclodextrin (DMSO)	>95%	<5%	[18]
Solution, polar solvent (DMSO)	80%	20%	[8,15]
Solution, HB solvent, ROH	25%	75%	[15,16]
Solution, HB solvent, H_2O	5%	95%	[17]
Solid phase	–	100%	[8,10]

The solid state, due to the presence of multiple hydrogen bonds, resembles a highly hydrogen bonding solvent like water. Although **1d** was never observed, very small amounts of **1b** were detected in water [17].

2. Experimental

2.1. Origin of the compounds

Compound **1** is commercially available while we prepared compounds **2**–**4**; the experimental procedure for 4,5,6,7-tetrafluoroindazolin-3-one (**2**) is described in [20], whereas those of 6,7-difluoroindazolin-3-one (**3**) and 4,6-difluoro-7-nitroindazolin-3-one (**4**) are reported in [21].

2.2. Solid state NMR experiments

^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra have been obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead and a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. The non-quaternary suppression (NQS) technique to observe only the quaternary carbon atoms was employed [22]. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si [for the carbonyl atom δ (glycine) = 176.1 ppm] and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N(nitromethane) = δ ^{15}N(ammonium chloride) – 338.1 ppm.

2.3. X-ray crystallographic data

Suitable crystals for X-ray diffraction experiments were obtained by crystallization from dichloromethane for **2** and from ethyl acetate for **3**. In the case of **4** all attempts to get crystals of good quality to be analyzed, from dichloromethane, chloroform, ethanol and dimethylsulfoxide, failed.

Data collection for both compounds was carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) operating at 40 mA for **2** and 50 kV and 30 mA for **3**. In both cases, the data were collected over a hemisphere of the reciprocal space by combination