Fast degenerate double proton transfer in the solid state between two indazolinone tautomers†‡

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The neutral dimer formed by 4,6-difluoro-1*H*,2*H*-indazolin-3-one and 3-hydroxy-4,6-difluoro-1*H*-indazole linked by two hydrogen bonds presents a very fast intermolecular double proton transfer in the solid state (ISSPT). The combined use of crystallography, solid state NMR and DFT [B3LYP/6-311++G(d,p)] calculations supports this interesting observation and allows us to estimate a barrier of about 20 kJ mol^{-1}.

There has been a continuous research interest focused on intermolecular solid state proton transfer (ISSPT), one of the simplest chemical reactions where covalent bonds are broken and created. One of the limitations of these reactions, where multiple protons are transferred, besides being cyclical is that the initial and final states should be identical or, at least, very similar. This has limited the examples to pyrazole cyclamers, for instance, trimers $\mathbf{1}_3$,[1] and to benzoic acid dimers $\mathbf{2}_2$ (Scheme 1).[2]

The case of pyrazoles corresponds to what is known as "annular tautomerism", and for 3,5-dimethyl-1*H*-pyrazole (**1**) and benzoic acid (**2**) they are examples of "degenerate tautomerism" because both tautomers are identical. *N*-Unsubstituted pyrazoles with different substituents at positions 3 and 5 also show ISSPT if the substituents are slightly different and the number of types of tautomers remains unchanged after proton transfer in an even cyclic structure (dimers, tetramers, and hexamers).[3] This is about the only molecules that present ISSPT, other less common examples are amidine, triazene and guanidine dimers, aza analogues of $\mathbf{2}_2$.[4] The proton transfer rate constants in dimers of carboxylic acids and amidines are in the nanosecond time scale and in pyrazole cyclamers in the millisecond to second time scale.

With functional tautomerism (oxo/hydroxy or imino/amino) no examples were known because in general both tautomers differ considerably in stability. Besides, both tautomers must co-crystallize and this is an even rarer phenomenon, to the point that, to the best of our knowledge only one example has been reported, 1-phenyl-3-methylpyrazolin-5-one (**3**).[5] But this compound, a catemer $\mathbf{3}_n$, lacks the *sine qua non* condition of being a cyclamer (Scheme 2).

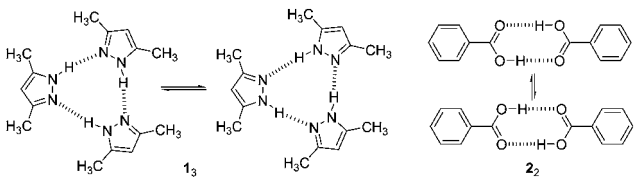
Some time ago we started a program aimed at obtaining cyclamers formed by two different functional tautomers. We selected indazolinones because the two most stable tautomers, **4a** (3-oxo-1*H*,2*H*-indazole or 1*H*,2*H*-indazolin-3-one) and **4b** (3-hydroxy-1*H*-indazole), have similar energies (Scheme 3)[6] and because 1*H*-indazoles often crystallize forming cyclic dimers.[7]

Several indazolinones bearing different substituents on the benzene ring were studied by us and in two cases their X-ray structures determined, indazolin-3-one itself (**4**)[8] and 7-nitroindazolin-3-one (**5**).[9] A search in the CSD did not show other examples (Table 1).[7]

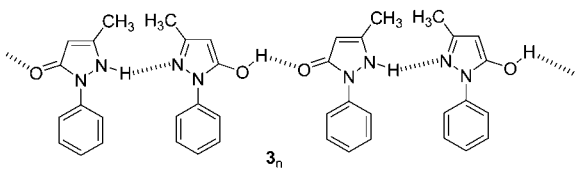
Here we present our results on a new compound, the 4,6-difluoroindazolinone (**6**) whose X-ray structure is shown in Fig. 1. This molecule forms cyclic dimers containing both tautomers **6a** (3-one) and **6b** (3-hydroxy) held together by hydrogen bonds.

In the dimeric structure of **6**, each molecule is almost planar but they are situated in different planes. The dimer has a symmetry binary axis going through the tautomeric OHO bond, with the H2B in special position at the middle of both N2 atoms and the main geometrical characteristics are summarized in Scheme 4. The most obvious explanation for the structure is a mixture of two identical situations: **6a/6b** and **6b/6a**, but the X-ray analysis does not allow us to determine if the disorder is static or dynamic.§

When the ^{15}N CPMAS NMR spectrum of the crystals of the **6a/6b** dimer obtained from methanol was recorded at 300 K and 40.60 MHz, two signals were obtained at −169.0 and −240.9 ppm. When these chemical shift values were compared with the NMR data of two similar derivatives (Scheme 5),[10] 4,6-difluoro-7-nitroindazolinone (**7**)



Scheme 1 Two classical examples of ISSPT showing the cyclamers held by hydrogen bonds (HBs).



Scheme 2 The 1-phenyl-3-methylpyrazolin-5-one (**3**) catemer.

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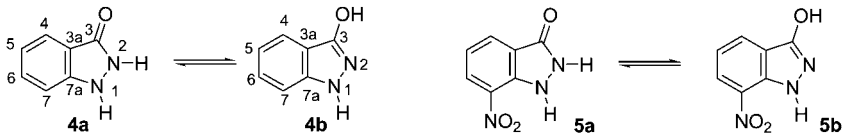
‡ Dedicated to Professor Carmen Nájera on her 60th anniversary.



Scheme 3 The functional tautomerism of indazolinones.

Table 1 Crystal structure of indazolinones

Compd.	Tautomer	Secondary structure (*via* HBs)	Ref code[7]
4	**4a**	Cyclic dimer (two N2–H···O = C3)	FADMIG
5	**5b**	Cyclic dimer (two N1–H···N2)	—

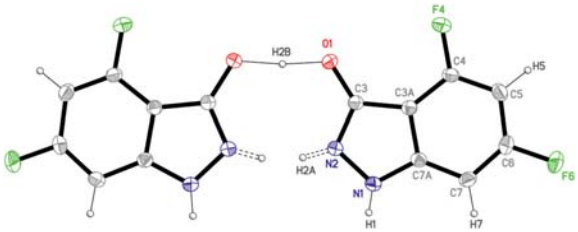


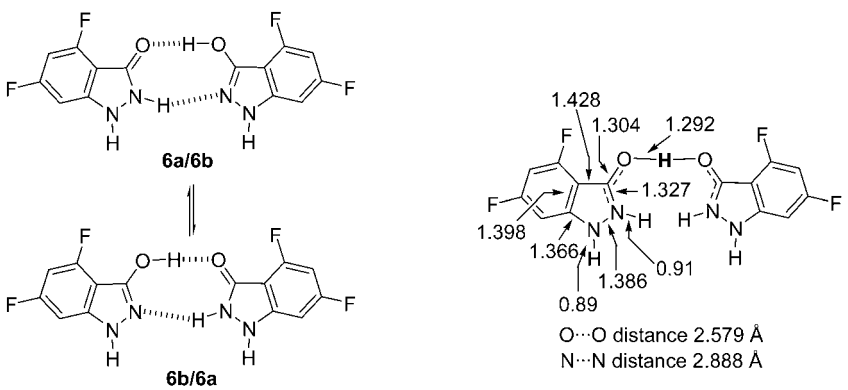
Fig. 1 ORTEP plot (30% probability for the ellipsoids) of the **6a/6b** dimer at 296(2) K showing the labelling of the asymmetric unit. Dotted lines are used to express the alternate situation for the hydrogen on the N2 atoms.

a 3-hydroxy tautomer **7b** and 6,7-difluoroindazolinone (**8**) a 3-oxo tautomer **8a**, it appears that the signals of 4,6-difluoroindazolinone (**6**) are near the middle of those model compounds (average of **7b** and **8a**, −172.2 and −241.1 ppm) (Fig. 2). The NMR data support the dynamic situation in **6** with a rapid double proton transfer between **6a/6b** and the complementary situation **6b/6a**.

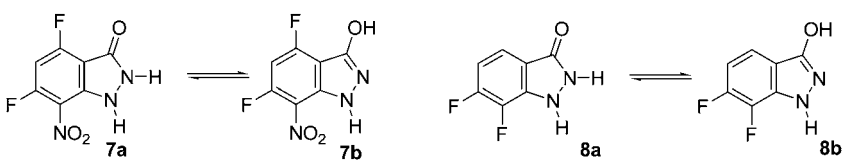
In order to perform ^{15}N NMR low temperature studies we prepared the 89% double labeled derivative **6-$^{15}N_2$**.¶ In solution, this compound shows two ^{15}N signals at −224.1/−121.8 (DMSO-d_6, 300 K), −229.5/−118.3 (THF-d_6, 300 K) and −227.6/−119.3 (THF-d_6, 193 K), which clearly correspond to the 3-hydroxy tautomer **6b**. In solid state, at 173 K (40.60 and 60.81 MHz) we were not able to slow down the ISSPT, the chemical shifts resulted in −169.4 and −241.8 ppm, proving that the double proton transfer is very fast since not even line broadening was observed at such temperature. Similar conclusions concerning the solution and the solid state are reached using ^{1}H NMR and ^{13}C NMR (see ESI†).

To estimate the double tautomerization barrier, $\Delta G^{\ddagger}$, we need to know the chemical shifts in the absence of prototropy. For such purpose we carried out theoretical calculations at the B3LYP/6-311++G(d,p) level. Concerning tautomer stabilities, **6a** (indazolin-3-one) isolated in the gas phase is only 1.6 kJ mol^{-1} less stable than **6b** (3-hydroxyindazole) which corresponds to 66% of **6b** at 300 K. The formation of the **6a/6b** dimer supposes a stabilization of 59.6 kJ mol^{-1} with regard to both monomers. To the double transfer process (both tautomeric protons on the middle, Fig. 3, a transition state TS with only one imaginary frequency) corresponds a barrier of 40.4 kJ mol^{-1}, that after ZPE correction at the same level lowers to 19.6 kJ mol^{-1}.

Moreover, we calculated the absolute shieldings σ of monomers **6a** and **6b** as well as the **6a/6b** dimer (fully optimized, 0 imaginary frequencies) at the GIAO/B3LYP/6-311++G(d,p) level, and



Scheme 4 ISSPT in 4,6-difluoroindazolinone (**6**) at 296(2) K.



Scheme 5 The structure of model compounds **7** and **8**.

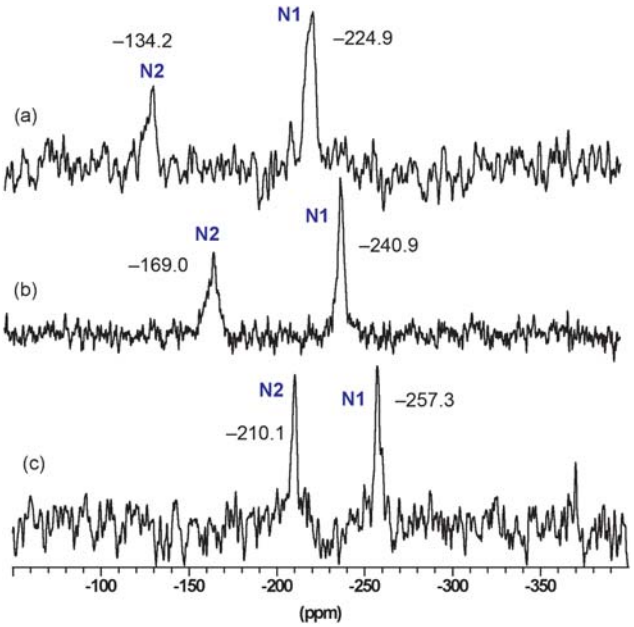


Fig. 2 ^{15}N CPMAS NMR spectra of: (a) **7b**, (b) 4,6-difluoro-indazolinone (**6**), and (c) **8a** at 40.60 MHz and 300 K.

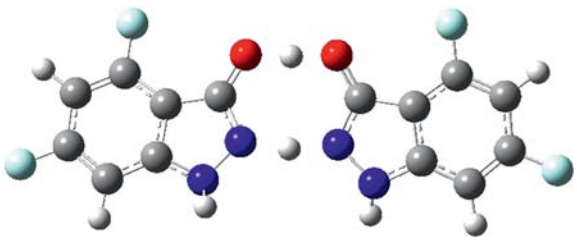


Fig. 3 The calculated structure of the TS.

transformed the σ^{15}N into chemical shifts by means of the equation $\delta^{15}\mathrm{N} = -152.0 - 0.946\sigma^{15}\mathrm{N}$.[11] It results in the following values:

	δN1/ppm	δN2/ppm
6a monomer	−276.6	−239.0
6b monomer	−235.0	−120.9
	$\Delta\delta$N1 = 41.6	$\Delta\delta$N2 = 118.1
6a in the dimer	−273.3	−227.1
6b in the dimer	−242.2	−139.1
	$\Delta\delta$N1 = 31.1	$\Delta\delta$N2 = 88

The formation of the HBs modifies some chemical shifts, mainly those of N2 involved in the HB. The averaged values of the dimer are −257.8 for N1 and −183.1 ppm for N2 to be compared with the experimental values of Fig. 2b (−240.9 and −169.0 ppm) showing a shift of about 15 ppm due to crystal field effects.[12] By applying the equation $\delta^{15}\mathrm{N} = -152.0 - 0.84\sigma^{15}\mathrm{N}$ we had proposed in ref. 12*a* for solid state CPMAS measurements, we obtained values closer to the experimental ones: averaged values of the **6a/6b** dimer −245.9 for N1 and −179.6 ppm for N2.

These data will serve to estimate the double tautomerization barrier. For this, we have used the ^{15}N CPMAS NMR spectrum at 60.81 MHz and 173 K (Fig. 4). We have estimated the w_e (line width) to be 4 ppm (245 Hz) for N1 and 8 ppm (485 Hz) for N2. The

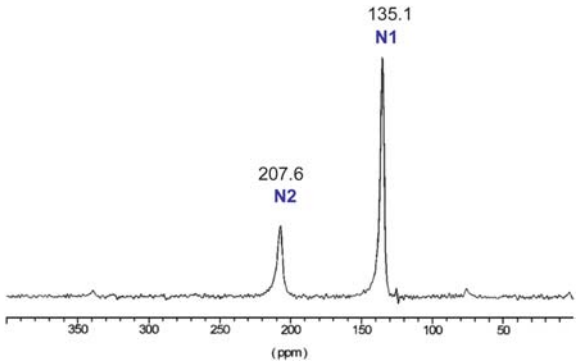


Fig. 4 ^{15}N CPMAS NMR spectrum of **6-^{15}N$_2$** dimer at 60.81 MHz and 173 K (reference NH_3).

calculated differences of tautomeric signals between **6a** and **6b** in the dimer are 31.1 ppm (1890 Hz) for N1 and 88.0 ppm (5350 Hz) for N2. Applying the equation for fast processes $k = (\pi/2)(\nu_A - \nu_B)^2/w_e$,[13] we obtain the rates: $k = 22\,900\ \mathrm{s}^{-1}$ and $k = 93\,000\ \mathrm{s}^{-1}$ for N1 and N2 respectively.

Using the $\Delta G^{\ddagger} = 19.12T(10.32 + \log T/k)$ equation for $T = 173$ K, to these rates correspond barriers of 27.1 for N1 and 25.0 kJ mol^{-1} for N2. So the energy barrier for the double tautomerization process should be 25 ± 5 kJ mol^{-1}.

In conclusion, we have prepared a new indazolinone that constitutes a rare example of cocrystallization between two distinct functional tautomers (oxo **6a** and hydroxy **6b**) through intermolecular hydrogen bonding. The existence of a very fast double proton transfer in the solid state has been proved by combination of several techniques: X-ray crystallography, solid state NMR (both unlabeled and ^{15}N-labeled samples) and DFT calculations.

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Notes and references

§ Crystal data for the **6a/6b** dimer: monoclinic, space group $C2/c$, $M_r = 170.12$, $a = 9.0766(7)$ Å, $b = 11.6167(9)$ Å, $c = 12.4603(10)$ Å, $\beta = 103.471(2)°$, $V = 1277.67(17)$ Å^3, $Z = 8$, $\rho_c = 1.769$ g cm^{-3}, $F(000) = 688$, $T = 296(2)$ K, 4493 reflections collected, 1083 unique with [$R_{int} = 0.0380$], R_1 [$I > 2\sigma(I)$] = 0.0363, wR_2 = 0.940, final (for all data) R_1 = 0.0481, wR_2 = 0.1008, GOF = 1.049.

¶ Synthesis of **6** and **6-^{15}N$_2$**: 0.51 g (3.9 mmol) of hydrazine sulfate (normal or double ^{15}N labeled) in 3 mL of water was slowly added to a solution of sodium bicarbonate (0.77 g, 7.7 mmol) in 3 mL water. The mixture was stirred 1 h at room temperature. The solution was filtered off to remove the sodium sulfate and added to a solution of 2,4,6-trifluorobenzoic acid methyl ester[10] (0.34 g, 1.8 mmol) in tetrahydrofurane (THF). The mixture was heated 48 h at 70 °C and then filtered. The solid was washed with THF. The solution was evaporated under vacuum and the residue washed with water: yield 260–275 mg of pure compound (85–90% yield). **6**, mp 293.5 °C, and **6-^{15}N$_2$**, mp 290.2 °C. Anal. Found: C 49.44, H 2.49, N 16.27. Calcd for $C_7H_4F_2N_2O$: C 49.42, H 2.37, N 16.47%.

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