A computational approach to intermolecular proton transfer in the solid state: assistance by proton acceptor molecules

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Ab initio (B3LYP/6-311++G**) calculations have been carried out on the proton transfer of 2*H*-tetrazole and 5-phenyl-2*H*-tetrazole with and without the assistance of different nitrogen bases (hydrogen cyanide, ammonia and imidazole). In the absence of base, the proton transfer barrier amounts to 210 kJ mol^{-1} while in the presence of ammonia it is lowered to 119 kJ mol^{-1}. Moreover, the inclusion of a solvent cavity of the Onsager type, which increases the first barrier, decreases the second one to 67 kJ mol^{-1} (for $\varepsilon = 5$) which is consistent with experimental data for *irbesartan* (a 5-aryl-2*H*-tetrazole derivative).

Introduction

A rather limited number of molecules present intermolecular solid state proton transfer (SSPT), *N*-unsubstituted pyrazoles being one class of them.[1–3] The phenomenon generally involves concerted or stepwise multiproton transfer between a set of identical[2] or nearly identical[3] tautomers. An example of the most studied case, that of 3,5-dimethylpyrazole (DMP),[4] is depicted in Scheme 1.
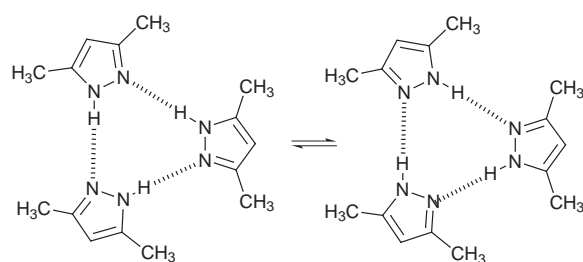
Scheme 1

Recently, Harris *et al.*[5] described an interesting case of proton transfer present in the crystals of *irbesartan* **1**, a powerful angiotensin II antagonist used for the treatment of hypertension.[6] Using the combined approach of solid state NMR and X-ray crystallography[7] they were able to interpret their surprising findings. The results of the Harris *et al.* discovery which are relevant for our study will be summarized below.
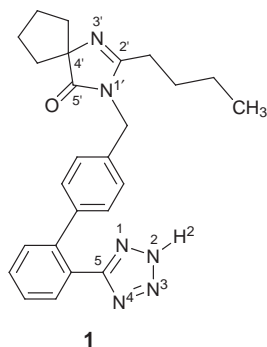
1

The *irbesartan* structure can be represented as a 5-aryltetrazole plus an imidazolinone ring linked to it (see Fig. 1). The 2*H*-tetrazole (polymorph B) presents an intermolecular hydrogen-bond (HB) with the N(3') atom of the imidazolinone moiety of another molecule in the unit cell. The distance
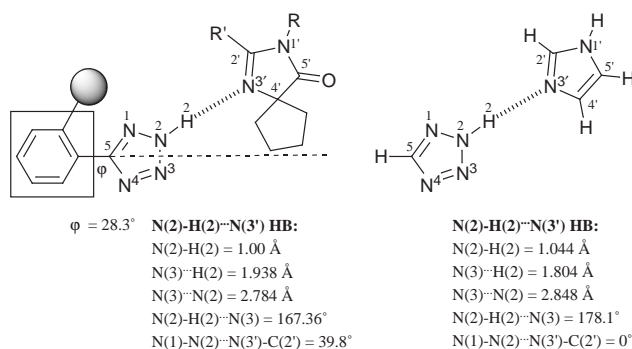
φ = 28.3° | **N(2)-H(2)···N(3') HB:** | **N(2)-H(2)···N(3') HB:**
N(2)-H(2) = 1.00 Å | N(2)-H(2) = 1.044 Å
N(3)···H(2) = 1.938 Å | N(3)···H(2) = 1.804 Å
N(3)···N(2) = 2.784 Å | N(3)···N(2) = 2.848 Å
N(2)-H(2)···N(3) = 167.36° | N(2)-H(2)···N(3) = 178.1°
N(1)-N(2)···N(3')-C(2') = 39.8° | N(1)-N(2)···N(3')-C(2') = 0°

Fig. 1 N–H··· N hydrogen bonds present in polymorph B of irbesartan **1** and in the model system 2*H*-tetrazole···imidazole.

N(2)–H(2) = 1.00 Å is from a difference Fourier map.[7b] The torsion $\varphi = 28.3°$ results from the presence of a bulky substituent at the *ortho* position of the phenyl ring.

Apparently the X-ray structure neither shows any indication of a dynamic phenomenon taking place in *irbesartan* polymorph B, nor proton disorder because the internal angles of the tetrazole ring have normal values [in particular, the angle on N(2) is 114.2°, consistent with an NH nitrogen atom].[7] [15]N CPMAS experiments, however, show that at room temperature (295 K), the four tetrazole nitrogen atoms appear as a very broad signal; on the other hand, the signals belonging to the imidazole nitrogens N(1') and N(3') appear as narrow signals. Lowering the temperature to 253 K blocks the prototropic exchange and the four tetrazole signals (plus the two imidazole ones) appear as narrow signals. The proposed explanation for the combined X-ray and CPMAS results is that the process taking place in the *irbesartan* crystal involves simultaneous proton-hopping between N(2) and N(3) and a 180° internal rotation of the tetrazole ring about the C(5)–C(ar) bond as defined by the φ angle.

Intramolecular proton transfer between two adjacent nitrogen atoms in NH-azoles is a very high energy demanding process. In the case of pyrazole **2** (Scheme 2), B3LYP/6-31G* calculations yield a barrier of 198 kJ mol^{-1} for the transition
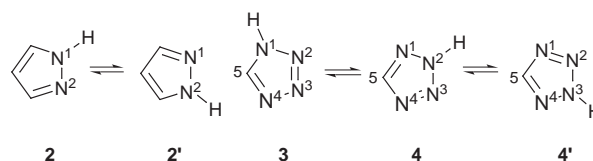
Scheme 2

state [TS(**2**)] between **2** and **2′** (identical tautomers) with the proton equidistant from both N atoms and outside the plane of the ring.[8] In the case of tetrazole, Wentrup *et al.*[9] have calculated the barrier for the intramolecular proton transfer between tautomers 1*H* **3** and 2*H* **4** (the tautomerism present in *irbesartan* **1** is of the type **4**/**4′**, being degenerate as in pyrazole). The obtained value of 211.5 kJ mol^{-1}, at the QCISD(T)/6-311+G(2d,2p) + ZPE level, is similar to that of pyrazole (207 kJ mol^{-1} for **3**→**4** and 216 kJ mol^{-1} for **4**→**3**).[8] It is interesting to report that when Wentrup *et al.* calculated the effect of a polar solvent of $\varepsilon = 40$ on the barrier, they found an increase of 12 kJ mol^{-1}, which they attribute to the fact that the TS (geometry similar to that of pyrazole) is less polar than 1*H*-tetrazole (by 2.3 D).

If intramolecular H migrations in azoles are 'forbidden', HB solvents like water make the transfer very easy (water-assisted proton transfer).[10] Scheme 3 represents the case of pyrazole
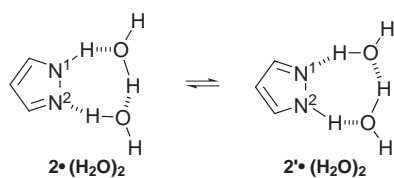
Scheme 3

with two water molecules; the INDO calculated barrier[11] for the triple proton jump is 2 kJ mol^{-1}; other authors have described similar results.[12,13] Wentrup suggests a similar occurrence would take place in complexes of tetrazole with water, contrary to general solvent effects which increase the barrier when the dielectric constant is increased.[9]

Methods

The geometry of all the systems has been optimized with the program GAUSSIAN94[14] using the 6-31G* and the large 6-311++G** basis sets[15] as required to study hydrogen bonding interactions. The B3LYP function was used, which combines Becke's three parameter exchange function[16] with the correlation function of Lee, Yang and Parr.[17] Symmetry conditions have been used whenever possible, especially for the calculation of the transition states. The nature of the stationary points, at the B3LYP/6-31G* level, of all the calculated systems has been established by verifying the number of imaginary frequencies. In the case of minimum structures all the frequencies should be real and in the transition states only one should be imaginary.

Results and discussion

Although Harris *et al.*[5] do not estimate the barrier corresponding to the process they observed for *irbesartan*, a barrier of 56 ± 3 kJ mol^{-1} can be calculated {$\Delta G^{\ddagger}_{T_c} = 19.12\ T_c\ [10.32 + \log (T_c/k_c)]$, $k_c = (\pi/\sqrt{2})\Delta\nu$} from the coalescence temperatures [N(2)/N(3), $\Delta\nu = 2599$ Hz, $T_c = 310$ K; N(1)/N(4), $\Delta\nu = 869$ Hz, $T_c = 295$ K]. This barrier cannot correspond to a [1,2]-intramolecular motion for which a barrier around 200 kJ mol^{-1} would be expected. Moreover, it cannot be a water-assisted proton transfer as in solution. Therefore, it must be of a new type we have called either SSPT intramolecularly zwitterion-assisted (if the donor **A** and acceptor **B** belong to the same molecule) or, more generally, base-promoted SSPT. Using the classical notation[18] for describing two tautomers H–**A** and **A**–H (either identical such as **2** and **2′** or different such as **3** and **4**), Scheme 4 represents the new mechanism.

In the case of *irbesartan* this mechanism supposes that the proton is transferred from N(2) to N(3′) with concomitant formation of a tetrazolide anion and an imidazolium cation,
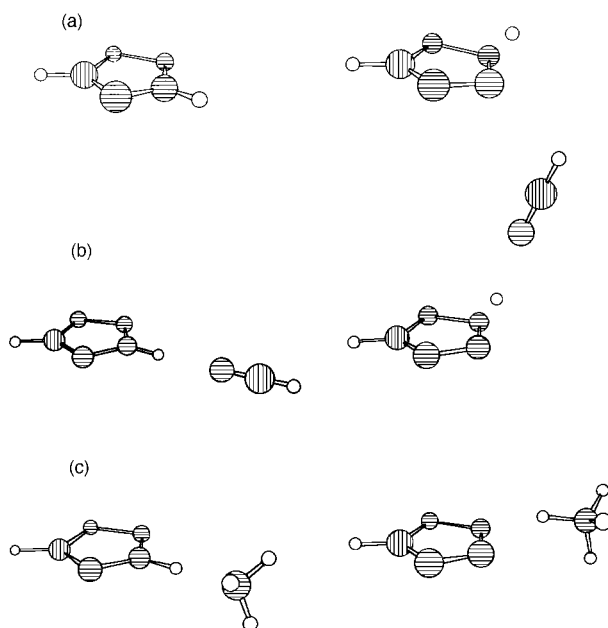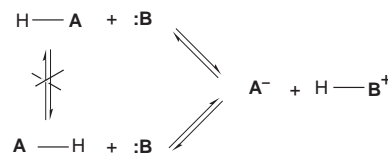
Fig. 2 Ground and transition state geometries in the case of 2*H*-tetrazole: (a) isolated molecule, (b) HCN complex, (c) NH$_3$ complex.

Scheme 4

then the tetrazolide anion would rotate 180° about the C(5)–C(ar) bond and, finally, the proton would come back from N(3′) to N(3) (see Fig. 1). To examine this possible mechanism we have carried out a series of calculations at the B3LYP/6-311++G** level including a Zero Point Energy correction (calculated at the B3LYP/6-31G* level).

Proton transfer in isolated 2*H*-tetrazole tautomers

The **4**/**4′** proton transfer (Scheme 2) has a calculated barrier of 209.2 kJ mol^{-1} (Table 1), in perfect agreement with the **1**/**2** and **3**/**4** processes (198 and 211.5 kJ mol^{-1}).[8,9] The TS(**4**) represented in Fig. 2 is of C_s symmetry. Compared with the TS(**3**) reported for the **3**/**4** intramolecular proton transfer ($d_{N\cdots H} = 1.262$ Å, out-of-plane angle 59°, NHN angle 71°),[9] TS(**4**) has a $d_{N\cdots H} = 1.263$ Å, out-of-plane angle 65.5°, and an NHN angle of 70.4°. Therefore, both transition states are very similar in geometry and energy, verifying that B3LYP/6-311++G** calculations of TS's yield similar results to MP2/6-31G* calculations.[9] In Table 1 the dipole moments of 2*H*-tetrazole (2.32 D) and the corresponding transition state (1.47 D) are reported. Although the decrease in dipole moment (0.85 D) is less marked than in the case of 1*H*-tetrazole (2.3 D),[9] the effect of a polar solvent (for instance, $\varepsilon = 5$) similarly resulted in a 1.8 kJ mol^{-1} increase of the barrier (see Table 1). In summary, the intramolecular proton transfer is too high in energy in the gas phase and even higher in the solid state (assimilating the crystal to a solvent with a given ε value) to be responsible for the behaviour of *irbesartan* polymorph B. To situate the relative permittivities ε (previously called dielectric constants) used in this work, liquids such as pyridine and 4-methylpyridine have relative permittivities of 12.3 and 9.8,[19] while solid camphor has a relative permittivity of 11.4.[20]

Effect of the presence of a base on the barrier height

It is known that barriers to proton transfer are very sensitive to

Table 1 Proton transfers in 2*H*-tetrazole. Absolute energies in hartrees and relative energies in kJ mol⁻¹ (1 E_h = 2626 kJ mol⁻¹). Relative permittivity used in the calculations (ε = 1, vacuum). Dipole moments (μ) in D. Calculated at the B3LYP/6-311++G** level (ZPE calculated at the B3LYP/6-31G* level)

| Compound (or complex) | ε | Total energies | | Barrier $E_{TS} - E_{Min}$ | Barrier + ZPE | μ | |
		Minimum	TS			Minimum	TS
Isolated							
2*H*-Tetrazole	1	−258.32890	−258.24253	226.8	209.2	2.32	1.47
2*H*-Tetrazole	5	−258.33016	−258.24303	228.8	211.0	2.63	1.64
Complex with hydrogen cyanide							
2*H*-Tetrazole · · · NCH	1	−351.79361	−351.70652	228.6	210.3	6.27	5.54
Complexes with ammonia							
2*H*-Tetrazole · · · NH₃	1	−314.92940	−314.88336[a]	120.9	119.0	5.28	10.35[a]
2*H*-Tetrazole · · · NH₃	5	−314.93532	−314.90939[a]	68.1	66.7	6.54	14.87[a]
2*H*-Tetrazole · · · NH₃	10	−314.93669[b]				6.85	
Tetrazolide · · · NH₄⁺	10	−314.93000[b]					
Complexes with imidazole							
2*H*-Tetrazole · · · imidazole	1	−484.63101	−484.59026[a]	107.0	104.3	8.27	13.99[a]
2*H*-Tetrazole · · · imidazole	5	−484.63909[c]	−484.61825[a]	54.7	52.2	10.05	17.72[a]
Tetrazolide · · · imidazolium	5	−484.63215[c]				20.33	

[a] This value corresponds to a TS where the proton has been transferred to ammonia (or to imidazole). [b] The difference in energy between these two minima is 17.6 kJ mol⁻¹ and, with the ZPE correction, 14.6 kJ mol⁻¹. [c] The difference in energy between these two minima is 18.2 kJ mol⁻¹ and, with the ZPE correction, 16.4 kJ mol⁻¹.
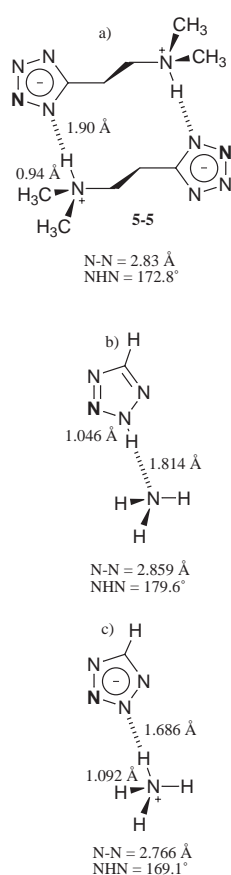
Fig. 3 Geometries of the hydrogen bonds in a) dimer **5**–**5** (experimental);[21] b) 2*H*-tetrazole · · · ammonia dimer (calculated), and c) tetrazolide · · · ammonium dimer (calculated) for ε = 10.

environmental factors, such as cations.[21] We have calculated the transition state **4/4′** in the presence of two bases, N≡C–H and NH₃. In the case of hydrogen cyanide nothing spectacular occurs. Although in both the ground and the transition states there is a N–H · · · NCH HB, the barrier remains unchanged

(Table 1). In the presence of ammonia, however, something different takes place: the N–H · · · NH₃ hydrogen bond (HB) structure of the ground state becomes an ion pair in the transition state (N⁻ · · · H–NH₃⁺) with a concomitant decrease of 106 kJ mol⁻¹ of the barrier (Table 1). The geometries represented in Fig. 2 for the proton transfer in the absence of any base ($d_{N \cdots H}$ = 1.263 Å, out-of-plane angle 65.5°, NHN angle 70.4°) and in the presence of ammonia are considerably different ($d_{N \cdots H}$ = 1.780 Å, out-of-plane angle 23.5°, NHN angle 44.3°). The fact that the proton has been transferred to ammonia considerably decreases the out-of-plane angle, the motion of the proton now occurring close to the plane of the tetrazole ring.

Considering that in complexes of the type X–H · · · NH₃ zwitterionic structures are never found in the gas phase, but appear when field effects such as those found in the crystal are applied,[22] this result constitutes a first indication in favour of the base-promoted SSPT mechanism. A similar situation to the TS is found in the crystal structure of 5-(dimethylaminoethyl)-tetrazole **5** (Fig. 3), where the compound exists as a zwitterion forming dimers **5**–**5**.[23] Note that dimer **5**–**5** corresponds to a 1*H*-tetrazole and not to the 2*H*-tetrazole we have calculated.

When a relative permittivity of ε = 10 is used, two minimum states result, one with the proton on the tetrazole (tetrazole–ammonia complex) and the other with the proton transferred (tetrazolide–ammonium complex), 14.6 kJ mol⁻¹ less stable. The geometry of the zwitterion, although obviously slightly dependent on ε, can be compared with that of **5**–**5**, with surprisingly good agreement (taking into account, moreover, that the experimental N–H distance of 0.94 Å is probably underestimated by X-ray crystallography).

In order to have a situation more similar to that present in crystals of *irbesartan*, we replaced ammonia with imidazole. The geometry (Fig. 1) shows great similarity, highlighting that imidazole, and even ammonia, can simulate the *irbesartan* structure.
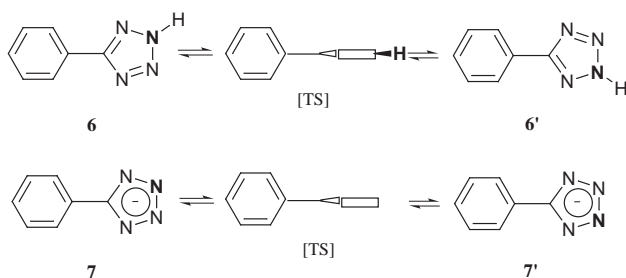
Barrier to the rotation about the C(aryl)–C(tetrazolyl) single bond

We have calculated the barriers to rotation of 5-phenyl-2*H*-tetrazole **6** and 5-phenyltetrazolide anion **7** (Scheme 5 and

Table 2 Barriers to rotation in 5-phenyl-2H-tetrazole **6** and in 5-phenyltetrazolate anion **7**. Absolute energies in hartrees, relative energies in kJ mol^{-1} (1 E_h = 2626 kJ mol^{-1}) and dipole moments (μ) in D. Calculated at the B3LYP/6-311++G** level (ZPE calculated at the B3LYP/6-31G* level)

Compound	Planar	90°	Barrier[a]	Barrier + ZPE	μ_{planar}	$\mu_{90°}$
6	−484.44729	−489.43936	20.8	19.5	2.10	2.18
7	−488.91361	−488.90322	27.3	25.9	—	—

[a] Barrier = $E_{90°}$ − E_{planar}.

Scheme 5

Fig. 4 Profile of the proton transfer and tetrazolide rotation for the 5-phenyltetrazole–imidazole complex.

Table 2). Both molecules are planar in their equilibrium geometries (inter-ring distances of 1.466 and 1.462 Å, respectively). In the solid state, the tautomer of compound **6** (5-phenyl-1H-tetrazole) is planar with a C(aryl)–C(tetrazolyl) bond length of 1.459 Å (CSD: TOSJOA).[24,25] As expected, even though the barrier is higher in the anion (25.9 instead of 19.5 kJ mol^{-1}) due to the conjugation between the electron-donating (π-excedent) tetrazole and the phenyl ring, it is still low compared to experimental data concerning **1** (about 56 kJ mol^{-1}). Since the tetrazole anion is more electron-donating than the neutral tetrazole, the double bond character of the central C–C bond should increase. This fact is reflected in the modification of the inter-ring distances between the minimum ($\varphi = 0°$) and the TS ($\varphi = 90°$), which increase 0.016 Å for **6** and 0.021 Å for **7**.
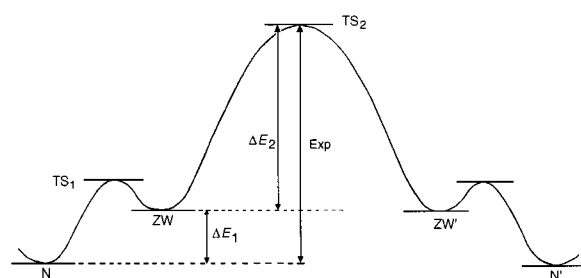
Proton transfer and rotation

The calculations of proton transfer **4/4′** in the presence of a base correspond to situations where the base (HCN, NH$_3$, imidazole) 'follows' the proton transfer (Fig. 1). This does not seem possible in the crystal, where the base is fixed, although it can take place in solution. A closer examination of the possible transition state in *irbesartan* and in the models so far studied (**5** or **6** plus ammonia or imidazole) shows that if the phenyl ring and the base remain fixed and the tetrazole ring rotates, then the geometry of the TS is exactly that represented in Fig. 2 for ammonia as well as for imidazole.

Conclusions

Fig. 4 is intended to represent both the case of *irbesartan* and that of the 5-phenyltetrazole–ammonia complex. Starting from the neutral molecule (N), a transfer of proton along the HB, without or with little displacement of the heavy atoms, yields the zwitterionic complex (ZW) through a transition state TS$_1$. From ZW, the rotation of the tetrazolide ring with concomitant weakening of the N$^-\cdots$H–N$^+$ HB leads to TS$_2$ in which the phenyl and tetrazole rings are perpendicular and which is devoid of HBs. From TS$_2$, compound N′ is formed which differs from N only in that the nitrogen atoms of the tetrazole have been exchanged.

The actual shape of the profile depends on three factors: i) the nature of the HB acceptor (ammonia, imidazole, imidazolinone); ii) the geometry of the N–H$\cdots$N HB (distances and angle); and iii) the 'solvent-like' effect of the crystal field. In the case of *irbesartan*, we have estimated from Harris experiments[5] that TS$_2$ is approximately 56 ± 3 kJ mol^{-1} above N; in our model complex with imidazole, the difference in energy between N and ZW amounts to 16.5 kJ mol^{-1} (Table 1) and the

rotation for the phenyltetrazolide anion amounts to 25.9 kJ mol^{-1} (Table 2). Thus, the sum, 42.4 kJ mol^{-1}, is in reasonably good agreement with the experimental value. Another way to estimate the difference in energy between N and TS$_2$ in *irbesartan* uses the calculated barrier for the 2H-tetrazole–imidazole system (Table 1) which amounts (for $\varepsilon = 5$) to 52.2 kJ mol^{-1}, which is still similar to the experimental value. The consistency of values demonstrates that the HB present in the ground state is not broken, only weakened in the TS (an Atoms in Molecules, AIM,[26] analysis of these structures shows three-centered HBs in the TS). The conclusion of this study is that the SSPT mechanism can explain the crystal behaviour of *irbesartan* and probably of similar situations in other compounds in the solid state.

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