The annular tautomerism of 4(5)-phenylimidazole

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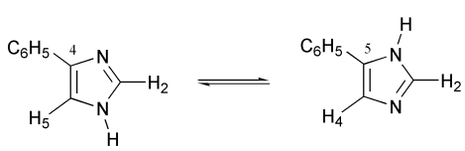
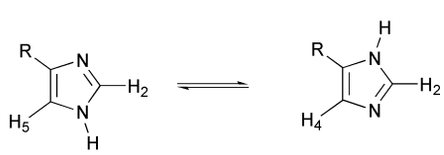
A new polymorph of 4-phenylimidazole **1a** has been characterised by X-ray crystallography. Both polymorphs present a secondary structure of chains, and the observed differences in the topology of their crystal packing are related to the conformational differences in the primary and secondary structural levels. NMR experiments (^{13}C and ^{15}N) reveal that tautomer **1a** is the only one observed in the solid state, being also the most abundant in solution (80%) in agreement with high-level theoretical calculations which favour this tautomer over the 5-phenyl one. The results obtained for this compound are relevant for the structure of the related 4(5)-porphyrinylimidazole.

Introduction

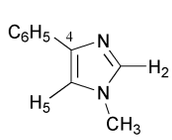
Although most problems related to tautomerism are well understood,[1–3] there remain some cases that still deserve attention either due to their difficulty or to their relevance. An example of the latter is the annular tautomerism of 4(5)-phenylimidazole **1**, *i.e.* the equilibrium between 4-phenyl **1a** and 5-phenyl **1b** tautomers. For instance, the steric effect of **1** on the axial substitution in an iron(II) phthalocyanine depends on its tautomeric form.[4] When **1** yields reversible silver(I) complexes, it has been established that they are constituted by tautomer **1a**.[5] Finally, the biological properties of 2-substituted derivatives of **1** have been assigned to 4-phenyl tautomers.[6]





Recently, Kobuke *et al.* have discussed the related case of 4(5)-porphyrinylimidazole **2** [5,15-bis(imidazol-4-yl)-10,20-bis-(4-dodecyloxyphenyl)porphyrin].[7] According to these authors, the supramolecular assembly formed by **2** is due to tautomer **2b**. Moreover, they assigned the ^{13}C NMR signals that appear at 135 and 120 ppm to C-4 and C-2, respectively, which seems to be in contradiction with our results on imidazole itself.[8] For all these reasons, we decided to reconsider the tautomerism of 4(5)-phenylimidazole.

Let us summarise the information presently available on compound **1**. In water (basicity measurements) the tautomeric equilibrium constant, as defined by K_T = [**1a**]/[**1b**], has been calculated to be between 10 and 37,[1] which corresponds to ΔG_{298} between 5.7 and 8.9 kJ mol^{-1}. This result came from an old publication of Ridd and Smith based on the pK_a of **1** and that of 1-methyl-4-phenylimidazole **3**.[9] The absence of data for 1-methyl-5-phenylimidazole **4** made the determination of K_T at best only an estimation. From the comparison of the electronic spectrum of **1** in ethanol with those calculated by using the π-electron PPP method for **1a** and **1b**, it follows that calculations for **1a** tautomer match slightly better the experimentally observed spectra.[3,10]



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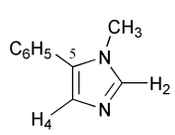

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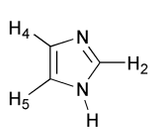

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The X-ray molecular structure of **1** has been determined by Sridhar, Prasad *et al.* and corresponds to tautomer **1a**.[11] However, this paper deserves some comments: i) it is not reported in the Cambridge Structural Database (October 2000 release);[12] ii) the title of the paper "Crystal Structures of Two Triazoles" is misleading since only one of them is a triazole; iii) even the triazole was named 3,5-diphenyltriazole (a 1,2,4-triazole with both substituents on the carbon atoms?) when the structure corresponds to 1,5-diphenyl-1,2,3-triazole.

Theoretical studies, which can be assimilated to the gas phase, have been carried out on this compound. Ögretir *et al.* reported AM1 and PM3 calculations on a series of imidazoles; for compound **1** they found that **1a** is more stable than **1b** by about 3 kJ mol^{-1}.[13] Tomás *et al.* have calculated by mixed *ab initio*–semiempirical methods (3-21G*/AM1) that tautomer **1a** is the most stable (6.4 kJ mol^{-1}).[14] Maye and Venanzi have calculated (*ab initio* 3-21G) the energies and rotational barriers of both **1a** and **1b**.[15,16] The difference in energy is 7.5 kJ mol^{-1} in favour of **1a** (planar, rotational barrier 23.4 kJ mol^{-1}) compared to **1b** (twisted 35.3°, rotational barriers 3.9 and 7.9 kJ mol^{-1}).

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Table 1 Selected geometrical parameters (distances, Å and angles, °)

N1–C2	1.343(6)	C4–C5	1.370(8)	C6–C7	1.383(8)	C9–C10	1.378(9)
C2–N3	1.305(7)	N1–C5	1.368(6)	C7–C8	1.381(8)	C10–C11	1.386(8)
N3–C4	1.384(5)	C4–C6	1.472(7)	C8–C9	1.392(9)	C6–C11	1.394(7)
C2–N1–C5	105.8(3)	N3–C4–C6	123.0(5)	C6–C7–C8	121.3(4)		
N1–C2–N3	113.6(3)	C5–C4–C6	128.0(4)	C7–C8–C9	119.8(6)		
C2–N3–C4	104.9(4)	C4–C6–C11	119.8(5)	C8–C9–C10	119.2(5)		
N3–C4–C5	108.9(4)	C4–C6–C7	121.3(4)	C9–C10–C11	121.0(5)		
N1–C5–C4	106.9(4)	C7–C6–C11	118.8(5)	C6–C11–C10	119.9(6)		
C2–N3–C4–C6	−176.8(5)	N3–C4–C6–C7	38.7(8)	C4–C6–C7–C8	176.5(5)		

Results and discussion

Ab initio calculations

At the HF/6-311G** level we found −1193212.57 kJ mol^{-1} for **1a** (dipole moment 3.91 D) and −1193204.77 kJ mol^{-1} for **1b** (dipole moment 3.62 D), thus, the difference in stability is 7.80 kJ mol^{-1}. Therefore, at this high level, the result is very similar to that obtained by Venanzi using the now abandoned 3-21G* basis set,[16] allowing us to conclude that in the gas phase the 4-phenyl tautomer should be greatly predominant (about 96% at 25 °C). Since the dipole moments are similar, no important effects of the condensed phases (solid state and solution) are expected.

Crystal and molecular structure determination

We obtained suitable crystals of compound **1** by slow evaporation of a saturated chloroform solution. The structure is different from that reported previously by Prasad *et al.* (solvent of crystallisation not reported),[11] thus constituting a new polymorph. The main molecular characteristics of our trigonal polymorph of 4-phenylimidazole **1a** are reported in Table 1 according to the numbering scheme depicted in Fig. 1. The other polymorphic form of **1a**, solved by Prasad *et al.*, shows monoclinic symmetry [*Pa*, lattice parameters: a = 7.0291(13), b = 12.5142(8), c = 9.4476(12) Å, β = 100.639(12)°],[11] but no metric reduction of one form to another is possible.[17] The bond distances and angles of both polymorphs are not significantly different, and the main difference between them lies in the conformation around the bond joining the phenyl and the imidazole ring [τ = 38.7(8)° for the trigonal polymorph, and 21.1(6)° and 21.2(7)° for the two independent molecules in the monoclinic polymorph]. The geometry of these imidazole rings follows a pattern of bond distances and angles similar to the mean values retrieved from the Cambridge Structural Database, CSD,[12] for imidazole itself. Comparisons with the optimised geometry of **1a** and with the reported geometry of 1-methyl-4-phenylimidazole **3** [τ = 7.3(3)°][18] show that the ring distances and angles are in all cases very similar. Therefore **3** is a good fixed model for tautomer **1a**, while 1-methyl-5-phenylimidazole **4**, whose X-ray crystal structure has not been determined, is probably not such a good model because both rings should present an important torsion angle.

Both polymorphs (trigonal and monoclinic) exhibit a secondary structure of chains through N–H ··· N intermolecular hydrogen bonds (HBs), Fig. 1, but the angles between consecutive imidazole rings in the chains change, and so the conformation of these chains is different (··· NH, N, NH, N ···) (Table 2).

The chains in the title compound are interacting through several C–H ··· π contacts, giving the 3D structure represented in Fig. 2 (Table 3). There are no voids in the structure and the total packing coefficient is 0.64.[19]

NMR spectroscopy in solution and in the solid state

Several authors[20–24] have reported the ^{13}C NMR spectra of imidazoles, amongst them, ourselves.[8,25] For instance, Koskinen has described the spectrum of **1** in DMSO-d$_6$ but only a list of chemical shifts without assignment is provided,[22] Begtrup[20] has published the ^{13}C NMR spectrum of compound **3**, but his assignment was wrong, and Kashima[23] those of **3** and **4** without assignment and moreover that of **4** incomplete. In Table 4 we have summarised the different results assigned through standard, HMQC and HMBC experiments (we have assigned those of Koskinen and Kashima by analogy and corrected that of Begtrup).

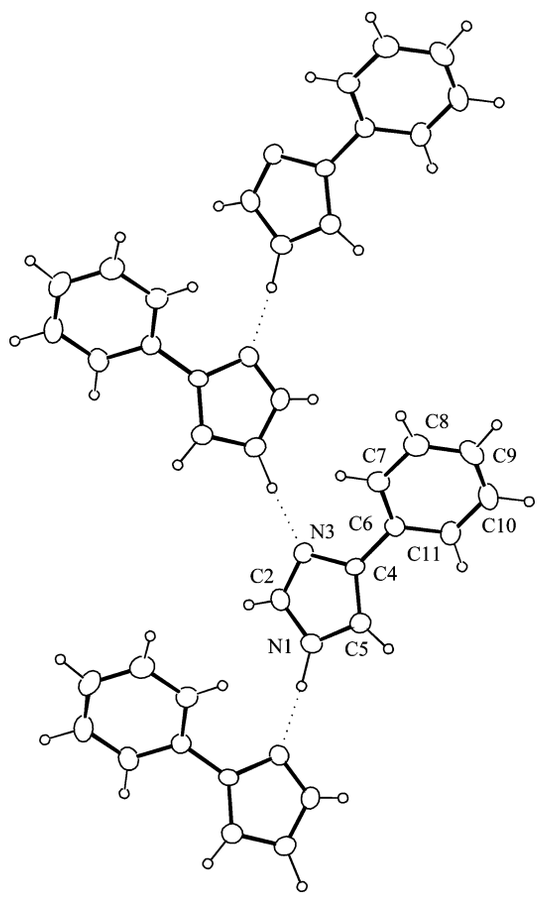
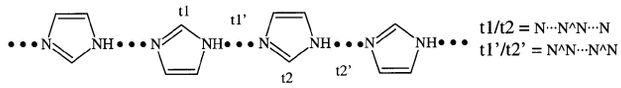


Fig. 1 View of a chain, through N–H ··· N interactions, showing the atomic numbering scheme. Ellipsoids are drawn at the 30% probability level for non-H atoms.

We will discuss first the ^{13}C NMR spectrum of a solid sample of **1** where we know, from crystallography, that it is pure **1a**. Considering the deshielding effect of the *N*-methyl group on C-2 and C-5,[8,25,27] data of **3** allow the assignment of all the signals of **1a** in the solid state. Then, we recorded the spectrum of **1** at 280 K in HMPA-d$_{18}$, [(CD$_3$)$_2$N]$_3$PO, a solvent known to slow down the annular prototropic equilibria.[1] The spectrum corresponds to a mixture of 80% of **1a** and 20% of **1b**, the most abundant tautomer being identified without ambiguity by comparison with the CPMAS spectrum. Thus, for the first time, all the signals of two tautomeric imidazoles were identified and assigned. In DMSO-d$_6$, only the ^{1}H NH signals were split (but

Table 2 Torsion angles (°) in the secondary structure to the polymorphs of 4-phenylimidazole



	*t*1	*t*1′	*t*2	*t*2′
Monoclinic polymorph [10]	−65.8(7)	−119.5(6)	−36.2(10)	−128.2(6)
Trigonal polymorph (this work)	−34.1(11)	178.8(6)	34.1(11)	−178.8(6)

Table 3 Geometry of hydrogen bonds (distances, Å and angles, °). C0105 and C0611 represent the centroids of the imidazole and phenyl rings respectively

	D–H	H ··· A	D ··· A	D–H ··· A
N1–H1 ··· N3 (1 − *y*,1 − *x*,1/2 + *z*)	1.01(−)	1.88(−)	2.856(−)	165(−)
C10–H10 ··· C0105 (*x* − 1/3,*x* − *y* −2/3,*z* − 1/6)	1.08(−)	2.63(−)	3.581(−)	149(−)
C2–H2 ··· C0105 (1 − *y*,*x* − *y*,*z*)	1.08(−)	2.58(−)	3.463(−)	135(−)
C8–H8 ··· C0611 (4/3 − *x* + *y*,2/3 − *x*,*z* − 1/3)	1.08(−)	2.86(−)	3.805(−)	154(−)
C5–H5 ··· C0611 (1 − *x* + *y*,*y*,1/2 + *z*)	1.08(−)	3.15(−)	4.028(−)	141(−)

Table 4 ^{1}H, ^{13}C and ^{15}N chemical shifts of 4(5)-phenylimidazoles **1**–**3** and imidazole **5** (unless specified, all spectra at 300 K)

Compd.	Solv.	H-1	H-2	H-4	H-5	C-2	C-4	C-5	C_{ipso}	C_{ortho}	C_{meta}	C_{para}	N-1	N-3
1	$CDCl_3$	N.o.[a]	7.70	CPh	7.35	135.5	138.7	115.2	133.0	124.9	128.7	127.0	N.o.	N.o.
1	DMSO-d_6	12.16 12.54	7.70	CPh	7.59	135.8	140.1	112.5	135.1	124.4	128.4	125.9	−211.4	−123.0
1	DMSO-d_6 [21]	——	——	——	——	135.6	138.6	111.5	132.8	124.9	128.7	126.9	——	——
1a	HMPA-d_{18} [b]	13.31	7.56	CPh	7.75	135.6	140.9	113.0	136.4	124.8	128.3	125.6	−211.4	−123.9
1b	HMPA-d_{18} [b]	13.62	7.56	7.39	CPh	136.3	125.8	131.1	131.6	124.3	129.0	126.4	−217.0	−117.3
1a	CPMAS	——	——	CPh	——	136.6	142.0	113.1	134.9	127.9	127.9	127.9	−199.8	−130.2
3	$CDCl_3$ [20]	NMe	——	CPh	——	137.4	141.7	115.5	133.6	124.3	128.1	126.2	——	——
3	$CDCl_3$ [23]	NMe	——	CPh	——	137.9	142.2	115.9	134.3	124.7	128.5	126.6	——	——
4	$CDCl_3$ [23,c]	NMe	——	——	CPh	138.1	128.0	133.0	130.3	128.2	128.8	128.7	——	——
5	CD_3OD [27,d]	——	——	——	——	136.8	127.7	118.5	——	——	——	——	−216.3	−143.4
5	HMPA-d_{18} [b]	13.19	7.52	6.85	7.05	135.2	128.0	115.7	——	——	——	——	−213.6	−119.9
5	CPMAS [8,26]	——	——	——	——	136.3	126.8	115.3	——	——	——	——	−210	−138

[a] Not observed. [b] 280 K. [c] The chemical shifts are those of the 1-butyl derivative. [d] 178 K.

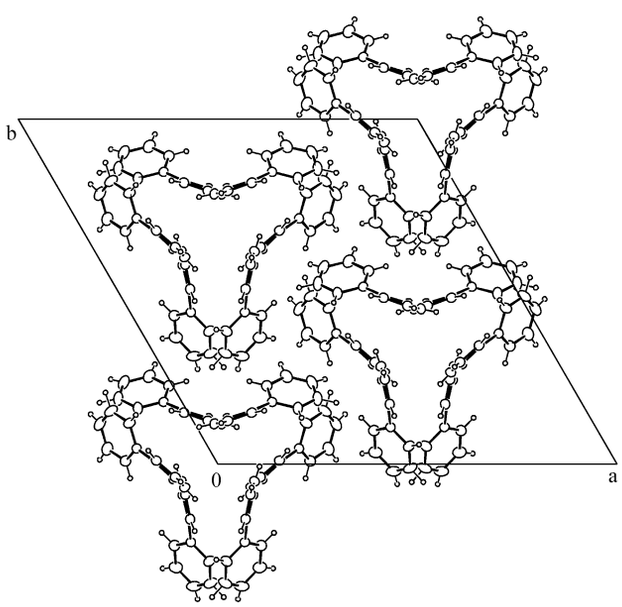


Fig. 2 Crystal packing diagram as projected along the *c* axis.

note that imidazole protons at 7.59 and 7.70 ppm were broad), the most abundant (12.16 ppm, 85%) belongs to **1a**. The remaining signals correspond to an average mixture very rich in **1a**; the same happens in $CDCl_3$ where the compound is rather insoluble and a saturated solution was employed.

A first consequence of the ^{13}C data reported in Table 4 is that the assignment of Kobuke (135 and 120 ppm to C-2 and C-4)[7] should be reversed: the signal at 135 ppm should be C-2 and that at 120 ppm C-4. Therefore, his assignment of protons H-2 and H-4 (by means of a ^{1}H ^{13}C COSY spectrum) is also wrong and this has important consequences for Kobuke's interpretation of the supramolecular assemblies through intermolecular N–H ··· N hydrogen bonds.

Another consequence of the ^{13}C chemical shifts of **1a** and **1b** in HMPA-d_{18} is related to the dihedral angle between the phenyl and imidazolyl rings.[20] The difference, $\Delta\delta$, between *ortho* and *meta* carbons is 3.5 ppm for **1a** and 4.7 ppm for **1b** and should correspond, according to Venanzi's calculations,[15,16] to $\tau = 0°$ for **1a** and to $\tau = 35.3°$ for **1b**. Our calculations yield 0° for both tautomers which is more consistent with such small differences in $\Delta\delta$. Note that in the 1-methyl derivatives $\Delta\delta$ values are 3.8 ppm for **3**,[20,23] and 0.6 ppm for **4** (both *N*-methyl and *N*-butyl derivatives).[23] This is related to our comment that **4** is not a good model for **1b**.

Concerning ^{15}N NMR, compound **1a** presents in the solid state two signals at −199.8 and −130.2 ppm, respectively, attributable to N_1 and N_3.[26,27] Tautomer **1a** in HMPA-d_{18} shows the same signals at −211.4 (−11.6 ppm) and −123.9 (+6.3 ppm). The differences are related to intermolecular HBs, chains of N–H ··· N in the solid state and N–H ··· OP-$[(CD_3)_2N]_3$ in solution. Recently we have reported that the annular tautomerism of imidazole itself, **5**, is blocked in CD_3OD at 178 K (Table 4).[26] The ^{13}C NMR signals are close to those reported for other compounds of Table 4 but the ^{15}N NMR signals in methanol, particularly those of N-3, are considerably shifted by the solvent O–H ··· N HBs in methanol.[27] To check this result we have recorded the ^{15}N NMR spectrum of **5** in HMPA-d_{18} at 280 K and observed two signals at −213.6

Table 5 Percentages, equilibrium constants and energy differences of 4(5)-phenylimidazole **1** annular tautomerism

Solvent	% **1a**	% **1b**	K_T	ΔG_{298}/kJ mol^{-1}	E_T^N
Gas phase	96	4	23	7.8	——
Water (lower limit)	91	9	10	5.7	1.000
Water (upper limit)	97	3	37	8.9	1.000
Water (average)	——	——	——	7.3	1.000
DMSO	85	15	5.7	4.3	0.444
HMPA	81	19	4.3	3.6	0.315

Table 6 Crystal data and structure determination details at room temperature

Chemical formula	$C_9H_8N_2$	Crystal system	Trigonal
Formula weight	144.2	Space group	*R*3*c*
Crystal habit	Colourless needles	θ range for lattice parameters/°	2–35
Crystal size/mm	0.57 × 0.07 × 0.03	No. of reflections for lattice parameters	48
Z	18		
Wavelength/Å	1.5418	*a*/Å	20.627(2)
Absorption coefficient/cm^{-1}	5.80	*b*/Å	20.627(2)
No. reflect. independent	705	*c*/Å	9.766(1)
No. reflect. observed [2(*I*) criterion]	663	*V*/Å^3	3598.6(6)
R(%)	5.3	*wR*(%)	6.1

(N-1) and −119.9 ppm (N-3), thus verifying our assumption. Note also that the signal of N-3 in the solid state (−138 ppm) is also considerably affected by the HBs and that it cannot be used as a reference for tautomeric studies.

Conclusions

We have collected in Table 5 all the present information about the tautomerism of **1**. If one uses, for the tautomeric equilibrium in water, an average value of ΔG_{298} = 7.3 kJ mol^{-1}, the results in water, in DMSO and in HMPT are linearly correlated with Reichardt's E_T^N solvent parameter:[28] ΔG_{298} = (1.901 ± 0.003) + (5.400 ± 0.005) E_T^N, n = 3, r^2 = 1.000. This provided conclusive evidence of the consistency of our results.

Experimental

Calculations

The *ab initio* molecular orbital calculations were carried out using the GAUSSIAN 98 program[29] within the Spartan (release 5.0.2).[30] Geometries for all structures were fully optimised. The restricted Hartree–Fock calculations with the split-valence 6-311G** basis set were used in these calculations.[31,32]

X-Ray analysis †

A summary of the data collection and refinement process is given in Table 6. All non-hydrogen atoms were found by direct methods, SIR92,[33] and the structure was refined with a full matrix least squares procedure on F_{obs} using anisotropic displacement parameters. The alternative space group $R\bar{3}c$ was disregarded as the molecule after refinement presented no doubts about the lack of a possible internal symmetry. All hydrogen atoms were located on a difference Fourier map but they have been introduced in idealized positions.[37] The atomic scattering factors were taken from the International Tables for X-Ray Crystallography[34] and most of the calculations were carried out with the XTAL,[35] PESOS[36] and PARST[37] programs running on an AXP 600 computer.

NMR spectroscopy

^{1}H (400.13 MHz), ^{13}C (100.62 MHz) and ^{15}N NMR (40.56 MHz) spectra were obtained using a Bruker DRX 400 instrument. All the chemical shifts are expressed in ppm, ^{1}H and ^{13}C chemical shifts are reported with respect to external TMS and ^{15}N chemical shifts to an external sample of pure nitromethane. The NMR experiments (^{1}H–^{13}C) HMQC and (^{1}H–^{13}C) HMBC with pulse field gradients[38] were performed in order to assign the signals obtained in the one-dimensional spectra. ^{15}N chemical shifts were obtained using (^{1}H–^{15}N) HMBC experiments with pulse field gradients. Cross polarisation magic angle spinning (CPMAS) NMR spectra have been obtained on a Bruker AC-200 spectrometer at 298 K using a 7-mm BRUKER DAB 7 probehead that achieves rotational frequencies of about 3.5–4.5 kHz. Samples (approximately 200 mg of material) were carefully packed in ZrO_2 rotors and the standard CPMAS pulse sequence was applied.[39] Recording of the ^{15}N CPMAS spectrum (natural abundance) required 25 h.

† CCDC reference number 171752. See http://www.rsc.org/suppdata/p2/b1/b109079h/ for crystallographic files in .cif or other electronic format.

Note added in proof

Recently, the crystal structure of 4-phenylimidazole has been published,[40] and it corresponds to the structure described in ref. 11, which is not quoted, probably because it is not reported in the CSD.

Acknowledgements

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