Structure and spectroscopy of imidazo [1,2-*a*]imidazoles and imidazo[1,2-*a*]benzimidazoles

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Dedicated to Professor Marcial Moreno Mañas on his 60th anniversary
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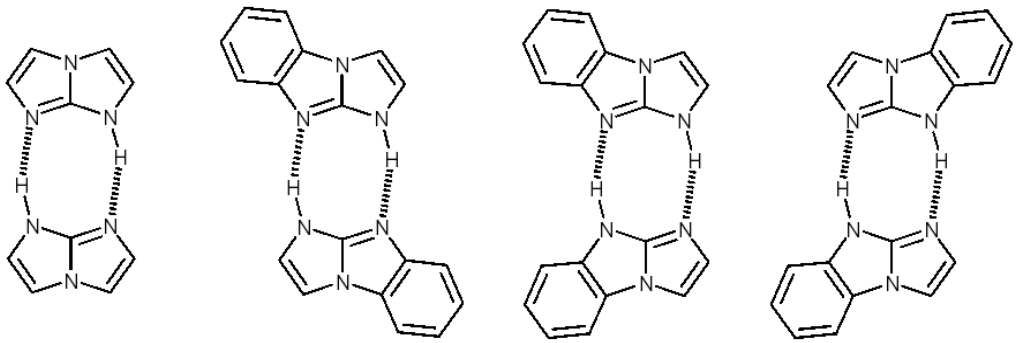
Abstract
Two azapentalenes containing fused imidazoles have been synthesized and their NMR (solution and solid state) and UV properties recorded. Tautomerism in the case of imidazo[1,2-*a*]benzimidazole (9*H* tautomer) and the structure of the cations resulting from protonation in both cases have been determined. *Ab initio* calculations (HF/6-311G**) confirm the greater stability of 9*H* over 1*H*- imidazo[1,2-*a*]benzimidazole tautomer.

Keywords: Imidazo[1,2-*a*]imidazoles, imidazo[1,2-*a*]benzimidazoles, spectroscopy, structure

Introduction

In search of systems that form cyclic motifs linked by intermolecular hydrogen bonds, we focused our attention on imidazo[1,2-*a*]imidazole **1** and its monobenzo derivative **2**. These compounds, formally derived from pentalene,[1] can form dimers both in the solid state and in solution (Scheme 1). Parent imidazo[1,2-*a*]imidazole **1** has only one annular tautomer but imidazo[1,2-*a*]benzimidazole **2** can exist in two tautomeric forms depending if the proton is on the imidazole **2a** or on the benzimidazole ring **2b**.



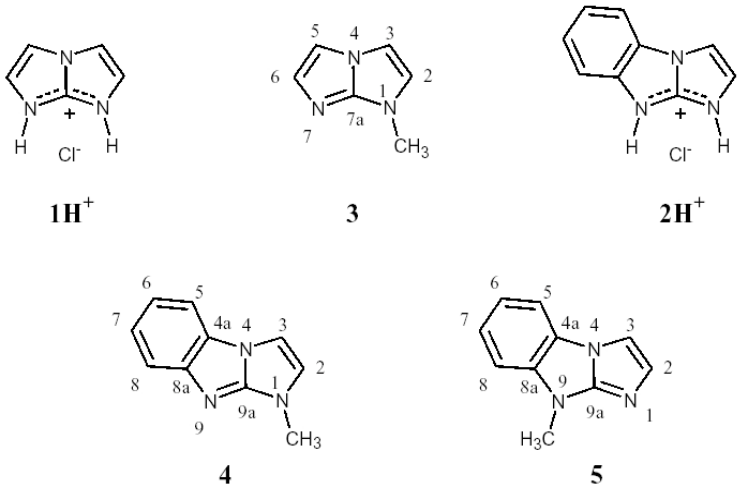
Scheme 1

This family of azapentalenes has been known from a long time [1] but their structural properties have not been explored until recently.[2,3] Compernolle and Toppet prepared for the first time the parent compound, 1*H*-imidazo[1,2-*a*]imidazole **1**, its hydrochloride and its 1-benzyl derivative and reported their ^{1}H, ^{13}C and ^{15}N NMR data.[2] McNab *et al*. prepared by a new method compound **2** and determined its X-ray structure and its ^{1}H and ^{13}C NMR data.[3] The compound crystallizes in dimers of the **2b**-**2b** type and, according to these authors, the same tautomer **2b** (9*H*-imidazo[1,2-*a*]benzimidazole) probably predominates in solution.

Results and Discussion

Chemistry

Compound **1** and its salt $\mathbf{1H^{+}\ Cl^{-}}$ have been prepared according to Compernolle and Toppet.[2] Starting from **1H**+ we have obtained 1-methyl-imidazo[1,2-*a*]imidazole **3**. Although the free base **1** is described in the original publication as "a viscous oil" without analytical supporting data,[2] our compound melted at 180 °C. Compound **2** and its hydrochloride $\mathbf{2H^{+}}$ have been synthesized according to the procedure described by Ogura *et al*.[4] The two possible *N*-methyl derivatives were prepared from **2**: 1-methyl **4** and 9- methyl **5** (Scheme 2). Compounds **3**-**5** have not been described previously.



Scheme 2

NMR spectroscopy

We have gathered in Tables 1-3 all the information available on the compounds under study. A series of COSY, NOESY, HMQC and HMBC experiments were carried out to assign the ^{1}H, ^{13}C and ^{15}N signals. 1-Substituted imidazoles **6** were used as model compounds to assign C-2 and C-3 in **2** (Scheme 3).[5] The only case that deserves discussion in detail is the ^{1}H NMR spectrum of compound **2**. McNab *et al.* assigned proton H-3 through a NOE experiment with H-5: in acetone they appear at 7.10 and 7.72 ppm, respectively.[3] Therefore, their signal corresponding to H-2 is at 7.58 ppm. Although we agree that H-5 is at 7.71 ppm (Table 1), we have assigned H-2 at 7.13 ppm and H-3 at 7.65 ppm in DMSO-d_6. Since these two solvents are rather similar, it is not probable that both assignments are correct. Ours is based on a ^{1}H-^{13}C 2D experiment since the ^{13}C signals can be assigned without ambiguity.

Table 1. ^{1}H NMR data (δ_H ppm and coupling constants in Hz)

Comp	Solvent	H-2	H-3	H-5	H-6	NR
1	DMSO-d_6	6.91	7.10	7.10	6.91	10.8
		^{3}J=1.5	^{3}J=1.5	^{3}J=1.5	^{3}J=1.5	
1H$^+$	CF_3CO_2D	7.13	7.23	7.23	7.13	10.5 (2*NH*)
		^{3}J=2.2	^{3}J=2.2	^{3}J=2.2	^{3}J=2.2	
1H$^+$	DMSO-d_6	7.47	7.61	7.61	7.47	13.6 (2*NH*)
		^{3}J=2.0	^{3}J=2.0	^{3}J=2.0	^{3}J=2.0	
3	$CDCl_3$	6.66	6.91	7.01	7.09	3.66
		^{3}J=2.3	^{3}J=2.3	^{3}J=1.4	^{3}J=1.4	
		^{6}J=1.0			^{6}J=1.0	
3	DMSO-d_6	7.06	7.19	7.14	6.90	3.54
3H$^+$	CF_3CO_2D	7.01	7.24	7.23	7.15	3.78
		^{3}J=2.4	^{3}J=2.4	^{3}J=2.4	^{3}J=2.4	
		^{6}J=0.7			^{6}J=0.7	

Table 1. Continued

Comp	Solvent	H-2	H-3	H-5	H-6	H-7	H-8	NR
2	DMSO-d_6	7.13 ^3J=1.8	7.65 ^3J=1.8	7.71 ^3J=7.9	7.08 ^3J=7.9 ^3J=7.5 ^4J=1.1	7.20 ^3J=8.0 ^3J=7.5 ^4J=1.2	7.42 ^3J=8.0	10.5
2	Acetone-d_6[a]	7.58 ^3J=1.8	7.10 ^3J=1.8	7.72 ^3J=6.7	7.14 ^3J=7.7 ^4J=1.3	7.26 ^3J=7.7 ^4J=1.4	7.48 ^3J=6.0	n.r.
2H$^+$	CF_3CO_2D	7.21 ^3J=2.5	7.54 ^3J=2.5	7.70 ^3J=7.9	7.40 ^3J=^3J=7.9 ^4J=0.9	7.47 ^3J=^3J=7.8 ^4J=0.9	7.543 ^3J=7.8	10.5 10.7
2H$^+$	DMSO +HCl	7.53 ^3J=2.3	8.17 ^3J=2.3	8.02 ^3J=8.0	7.31 ^3J=8.0 ^3J=7.5	7.40 ^3J=8.1 ^3J=7.5	7.58 ^3J=8.1	14.2 (*2NH*)
4	$CDCl_3$	6.42 ^3J=2.5	6.94 ^3J=2.5	7.38 ^3J=8.0	7.02 ^3J=8.0 ^3J=7.4	7.23 ^3J=8.2 ^3J=7.4	7.68 ^3J=8.2	3.46
4H$^+$	CF_3CO_2D	6.96 ^3J=2.4	7.43 ^3J=2.4	7.55 ^3J=8.2	7.26 ^3J=8.2 ^3J=7.4	7.33 ^3J=8.3 ^3J=7.4	7.39 ^3J=8.3	3.71
5	$CDCl_3$	7.15 ^3J=1.6	7.31 ^3J=1.6	7.46 ^3J=7.9 ^4J=1.1 ^5J=0.6	7.14 ^3J=8.6 ^3J=7.9 ^4J=1.1	7.27 ^3J=8.6 ^3J=8.0 ^4J=1.1	7.21 ^3J=8.0 ^4J=1.1 ^5J=0.6	3.73
5H$^+$	CF_3CO_2D	7.10 ^3J=2.5	7.44 ^3J=2.5	7.61 ^3J=8.2	7.31 ^3J=8.2 ^3J=8.2	7.40 ^3J=7.2 ^3J=8.2	7.37 ^3J=7.2	3.76

[a] From reference 3; n.r. = not reported.

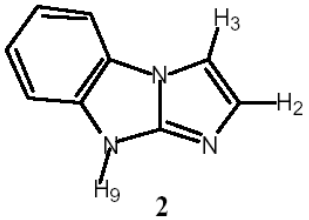
Table 2. ^{13}C NMR data (δ_C ppm and coupling constants in Hz)

Comp	Solvent	C-2	C-3	C-5	C-6	C-7a	NR
1	DMSO-d_6	124.0	105.1	105.1	124.0	147.9	
1	DMSO-d_6[a]	123.9 ^1J=189 ^2J=11.8	105.0 ^1J=196.5 ^2J=14.5	105.0	123.9	147.6	
1	CPMAS	117.9	106.1	106.1	128.6	147.9	
1H$^+$	CF_3CO_2D	118.8 ^1J=202.1 ^2J=12.1	108.1 ^1J=206.7 ^2J=11.4	108.1	118.8	138.0	
1H$^+$	DMSO-d_6[a]	120.3 ^1J=199 ^2J=12.4	108.7 ^1J=205.5 ^2J=12.2	108.7	120.3	138.9	
3	DMSO-d_6	121.1 ^1J=193.3 ^2J=12.3 ^3J=2.9	104.4 ^1J=199.6 ^2J=11.3	106.0 ^1J=194.1 ^2J=16.4	130.8 ^1J=185.4 ^2J=10.8	148.0	31.7 ^1J=139.9
3	$CDCl_3$	120.0	104.3	105.9	131.3	148.2	31.8
3H$^+$	CF_3CO_2D	123.1 ^1J=199.7	107.9 ^1J=207.3 ^2J=10.9	108.7 ^1J=207.0 ^2J=11.7	119.2 ^1J=201.9 ^2J=11.7	138.4	31.7 ^1J=143.6

Table 2. Continued

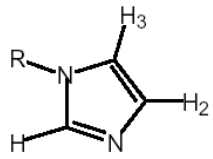
Comp	Solvent	C-2	C-3	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9a
2	DMSO-d_6	129.8 ^1J=189.2 ^2J=11.0	106.1 ^1J=197.4 ^2J=14.8	125.2	110.9 ^1J=163.5 ^3J=8.6	118.9 ^1J=161.5 ^3J=7.6	122.8 ^1J=159.3 ^3J=7.7	113.4 ^1J=160.4 ^3J=9.1	139.2	150.3
2	$CDCl_3$[b]	126.9 ^1J=189.7 ^2J=10.3	105.7 ^1J=196.1 ^2J=14.8	124.7	110.9 ^1J=161.4 ^3J=8.8	119.6 ^1J=161.1 ^3J=7.7	123.4 ^1J=157.3 ^3J=5.7	113.6 ^1J=163.9 ^3J=8.8	137.9	149.6
2	CPMAS	127.7	104.6	123.9	110.3	119.2	121.8	113.5	135.2	149.7
2H$^+$	CF_3CO_2D	118.1 ^1J=203.3 ^2J=11.6	107.7 ^1J=206.4 ^2J=11.4	123.1 ^3J=10.2 ^3J=7.8	110.9 ^1J=167.0 ^3J=8.5	123.4 ^1J=164.7 ^3J=7.5	126.2 ^1J=164.9 ^3J=7.7	112.7 ^1J=168.2 ^3J=8.6	132.6 ^3J=10.0 ^3J=7.6	140.6 ^3J=7.0 ^3J=7.0
2H$^+$	DMSO + HCl	119.9 ^1J=201.2 ^2J=12.3	109.3 ^1J=206.5 ^2J=12.2	123.9 ^3J=8.9	112.9 ^1J=167.8 ^3J=8.1	122.4 ^1J=163.8 ^3J=7.5	125.6 ^1J=164.8 ^3J=7.4	113.6 ^1J=168.2 ^3J=8.4	134.5 ^3J=8.0	142.1 ^3J=7.5
2H$^+$	CPMAS	120.3	111.5	123.0	113.6	121.8	123.5	113.6	134.8	141.0
4[c]	$CDCl_3$	119.2 ^1J=193.3 ^2J=10.9 ^3J=2.7	103.7 ^1J=199.4 ^2J=10.8	126.8	109.1 ^1J=160.8 ^3J=8.6	117.0 ^1J=159.8 ^3J=9.0	121.8 ^1J=158.4 ^3J=8.2	117.1 ^1J=159.6 ^3J=10.6	146.9	150.9
4[d]	CPMAS	117.5	108.4	127.6	112.7	114.9	122.9	117.5	148.1	151.5
4H$^+$[e]	CF_3CO_2D	122.3 ^1J=202.4 ^2J=12.0	107.7 ^1J=206.9 ^2J=11.8	123.5	110.9 ^1J=168.7 ^3J=8.3	123.5 ^1J=165.0 ^3J=7.4	126.1 ^1J=165.1 ^3J=7.7	112.6 ^1J=168.9 ^3J=8.3	132.7	140.9
5[f]	$CDCl_3$	129.8 ^1J=187.8 ^2J=10.1	104.9 ^1J=194.8 ^2J=15.5	122.8	109.2 ^1J=160.1 ^3J=11.0	118.2 ^1J=160.8 ^3J=7.3	121.5 ^1J=162.2 ^3J=7.6	107.6 ^1J=163.4 ^3J=8.5	134.7	148.8
5[g]	CPMAS	127.8	107.1	123.9	111.1	117.2	120.7	107.1	134.9	148.7
5H$^+$[h]	CF_3CO_2D	118.2	108.2	122.9	111.3	123.5	126.0	110.3	134.4	141.4

[a] From reference 2. [b] From reference 3 (unassigned save C-2 and C-3). [c] N-CH_3 31.1 (^1J=140.3).[d] N-CH_3 ,30.5. [e] N-CH_3 31.7 (^1J=143.9). [f] N-CH_3 27.5 (^1J=140.0). [g] N-CH_3 28.9. [h] N-CH_3 28.4.



2

^2J(C2/H3) = 11.8 Hz
^2J(C3/H2) = 14.8 Hz



6

^2J(C2/H3) = 10 Hz
^2J(C3/H2) = 16 Hz

Scheme 3

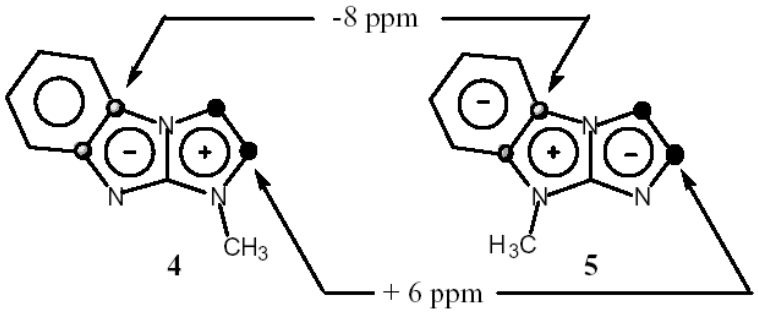
Table 3. ^{15}N NMR data (δ_N ppm)

Comp	Solvent	N-1	N-4	N-7	N-9
1	DMSO-d_6	-229.3	-197.6	-229.3	----
1	CPMAS	-258.5	-193.7	-193.7	----
1H$^+$	CF_3CO_2D	-267.2	-199.8	-267.2	----
1H^{+a}	DMSO-d_6	-259.1	-201.4	-259.1	----
1H$^+$	DMSO-d_6	-255.2	-197.3	-255.2	----
3	$CDCl_3$	-277.3	-199.9	-194.9	----
3	DMSO-d_6	-276.5	-198.7	-188.0	----
3H$^+$	CF_3CO_2D	-266.1	-200.4	-266.1	----
2	DMSO-d_6	-210.8	-209.7	----	-257.0
2	CPMAS	-191.3	-206.1	----	-273.2
2H$^+$	DMSO+HCl	-251.6	-209.8	----	-268.0
2H$^+$	CF_3CO_2D	-264.4	-211.8	----	-279.6
2H$^+$	CPMAS	-245.6	-206.9	----	-259.8
4	$CDCl_3$	-277.4	-213.5	----	-210.4
4	CPMAS	-275.1	-208.8	----	-206.0
4H$^+$	CF_3CO_2D	-263.9	-212.8	----	-282.0
5	$CDCl_3$	-191.9	-212.9	----	-289.4
5	CPMAS	-192.3	-209.5	----	-284.5
5H$^+$	CF_3CO_2D	-267.2	-213.9	----	-280.3

[a] From reference 2; the liquid ammonia scale was transformed into internal nitromethane scale by the relationship 381.9 – ammonia.[6]

In the imidazol[1,2-*a*]imidazole series, the most significant results are the $^6J_{26}$ coupling, useful for assignment purposes and the increase of the ^3J coupling constant on protonation. Notice also that in compound **3**, the moiety bearing the N-methyl group has a $^3J_{23}$ coupling constant of 2.3 Hz while the other moiety has a $^3J_{56}$ = 1.4 Hz, this being related to the dipolar structure of azapentalenes. Similar comments hold for the imidazo[1,2-*a*]benzimidazole series concerning now the $^3J_{23}$ coupling with values of 1.8 Hz (compound **2**, tautomer 9H, see later on tautomerism), 1.6 Hz (compound **5**) and 2.4- 2.5 Hz (compound **4** and cations **2H$^+$**, **4H$^+$** and **5H$^+$**).

Azapentalenes can be represented in a dipolar form with the positive charge (imidazolium) on the *N*-substituted ring and the negative charge (imidazolate) on the other ring.[1] The ^{13}C data summarized in Scheme 4 (average values for two carbon atoms) agree with those reported by Pugmire and Grant for imidazolium cations (C4 and C5 at 122.1 ppm) and imidazolate anions (C4 and C5 at 126.8 ppm).[7]



Scheme 4

The CPMAS chemical shifts are remarkably alike those found in solution. The main differences found for **2** are that the nitrogen signals are shifted 17 ppm in opposite directions. We assign this behaviour to the **2b-2b** dimeric structure of the crystal.

Compound **1** does not present SSPT: carbons C-3 and C-5 coincide (they appear at 104.4 and 106.0 ppm in **3**) but carbons C-2 and C-6 (see Figure 1) are well separated and resolved. The broadening of C-2 and C-7a is not related to tautomerism but most probably to dipolar couplings with N-1.

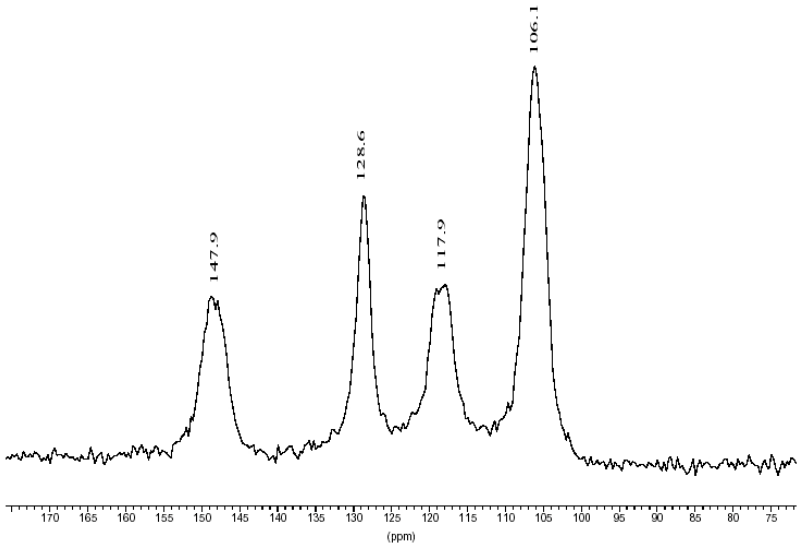


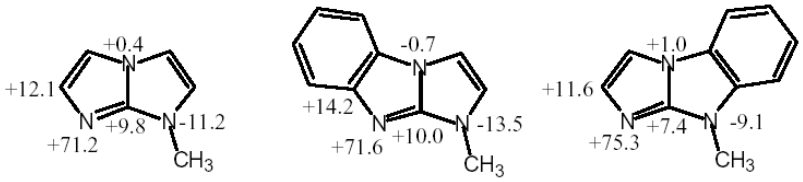
Figure 1. ^{13}C CPMAS spectrum of imidazo[1,2-*a*]imidazole **1**.

Tautomerism

In the case of compound **2** the comparison with model compounds **4** and **5** leaves no doubt that the tautomeric proton is on N-9. In ^{1}H NMR, the ^{3}J coupling constant between H-2 and H-3 has values of 1.8 Hz for **2**, 2.5 Hz for **4** and 1.6 Hz for **5**. In ^{13}C NMR, the ^{2}J coupling constants of C-2 and C-3 of **2** and **5** are very similar and rather different from those of **4**. ^{15}N NMR is less useful because large effects due to *N*-methylation and to the solvent blurred the tautomeric effects.

Protonation

The spectra of the cations reported in Tables 1-3, with the notation **nH**$^+$, have been obtained in three ways: dissolving the cation in DMSO, adding 37% HCl (50 μL) to a DMSO solution (0.5 mL) of the base ($5.10^{-2}M$ for ^{1}H NMR and $5.10^{-1}M$ for ^{13}C NMR) or recording the spectrum of the base in trifluoroacetic acid. Protonation results in large effects on all the signals. Particularly noteworthy are the effects on $^3J(^1H\text{-}^1H)$ (Table 1) and on $^1J(^1H\text{-}^{13}C)$ coupling constants (Table 2). We have summarized in Scheme 5 the ^{13}C chemical shifts effects on α-carbons (Table 2) to the protonated nitrogen, and on the ^{15}N chemical shifts (Table 3), defined as $\Delta\delta = \delta\ (CDCl_3) - \delta\ (CF_3CO_2H)$. They are very consistent and constitute the best method to determine the protonation site.



3 **4** **5**

Scheme 5

Solid state proton transfer (SSPT)

The necessary condition for SSPT is that the initial and final states should be degenerate or near degenerate.[8,9] This is not the case for compound **2** where both tautomers are very different in energy. At the HF/6-311G** level,[10,11] tautomer **2b** is 9.98 kJ mol^{-1} more stable than tautomer **2a**.

Note that a transformation **2a-2b** into **2b-2a** will satisfy the requirements of degeneracy, but the heterodimer must be also much less stable than the **2b-2b** homodimer. Only in dimer **1-1** SSPT would be possible, provided it crystallizes as a dimer, but we have been unable to obtain good single crystals suitable for X-ray crystallography.

Electronic spectra

We have recorded the electronic spectra of compounds **2**, **4** and **5** in three solvents of different polarity (Table 4).

Table 4. Electronic absorption spectra of imidazo[1,2-*a*]benzimidazoles, λ_{max} in nm (log ε between parentheses)

Comp	Solvent	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6
2	EtOH	223				291	300*sh*
		(4.47)				(3.71)	(3.44)
2	CH_3CN	225	236*sh*			293	
		(4.45)	(4.24)			(3.72)	
2	CyH[a]	225	236*sh*	241*sh*		293	300*sh*
		(4.41)	(4.29)	(4.21)		(3.68)	(3.63)
4	EtOH	224	233	260		290	299
		(4.48)	(4.44)	(3.67)		(3.58)	(3.56)
4	CH_3CN	226	238	271		292*sh*	302*sh*
		(4.43)	(4.48)	(4.07)		(3.95)	(3.82)
4	CyH[a]	230	240*sh*	266	274*sh*	295	306
		(4.51)	(4.37)	(3.84)	(3.74)	(3.66)	(3.69)
5	EtOH	224				295	
		(4.38)				(3.63)	
5	CH_3CN	226	240*sh*			299	
		(4.42)	(4.21)			(3.71)	
5	CyH[a]	229	240	244*sh*	249	301	315*sh*
		(4.34)	(4.17)	(4.16)	(4.10)	(3.64)	(3.23)

[a] CyH: Cyclohexane, fine structure (vibrationally resolved).

The spectra (band 5) are sensitive to their polarity as defined by the Reichardt's solvent parameter $E_T(30)$:[12]

2: $\lambda_{max} = (313\pm2) - (0.44\pm0.04)\ E_T(30)$, n = 3, $r^2 = 0.993$ (1)

4: $\lambda_{max} = (302\pm1) - (0.23\pm0.03)\ E_T(30)$, n = 3, $r^2 = 0.988$ (2)

5: $\lambda_{max} = (330\pm0.5) - (0.67\pm0.01)\ E_T(30)$, n = 3, $r^2 = 1.000$ (3)

When adding HCl to the ethanol solution, the spectrum bands shifted to shorter wavelengths (formation of the $\mathbf{2H^+}$ cation: 274 nm, log ε = 3.83 and 280 nm, log ε =3.82).

Concerning tautomerism, the spectra of **2** are more similar to those of **5** than to those of **4**. This is not very apparent from Table 4 but visual examination is conclusive. We should note that, in the case of **2**, they depend on the concentration, on dilution in acetonitrile, the main band shift to shorter wavelengths (blue shift, hypsochromic effect). We assign this effect not to a modification of the tautomerism, **2b** being always predominant, but the formation of **2b**-**2b** homodimers.

It is safe to assume that the *N*-methylation does not modify the dipole moment and that the effect of the polarity of the solvent on the electronic spectra is related to the dipole moment of the solute. Those calculated for **2a** (4.43 D) and **2b** (2.98 D) explain why the slope of eq. (3) (isomer **5** corresponds to **2b**) is nearly three times greater than that of eq. (2) (isomer **4** corresponds to **2a**) (remember that when discussing dipole moments, the square of ⌈ is the additive property). In

the case of **2** the slope (-0.44) is intermediate between those of **4** and **5**, may be an indication of the presence of both tautomers.

Conclusions

The heterocyclic systems of imidazo[1,2-*a*]imidazole **1** and its monobenzo derivative **2** have interesting properties but none has shown SSPT. In the case of **2** this has been explained by a too great difference in energy between tautomers and only the possibility to observe the phenomenon in the excited state remain. For the parent system **1** two explanations are possible: either the system do not crystallize in cyclic dimers but forms catemers like imidazole or the crystals contain dimers but the activation barrier is too high. Some "symmetrical" pyrazoles that forms cyclic patterns do not present SSPT.[8,9]

Experimental Section

General Procedures. Melting points were determined with a hot-stage microscope and are uncorrected. Unless otherwise stated, column chromatography was performed on silica gel (Merck 60, 70-230 mesh). The R_f values were measured on aluminium backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. HF/6-311G** *ab initio* calculations[10,13] were carried out through the Spartan 5.1.3 package running on a Silicon Graphics O2 workstation. NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 40.56 MHz for ^{15}N) spectrometer. Chemical shifts (δ in ppm) are given from internal $CHCl_3$ (7.26) for ^{1}H NMR, $^{13}CDCl_3$ (77.0) for ^{13}C NMR and external nitromethane for ^{15}N NMR. Coupling constants (*J* in Hz) are accurate to ± 0.2 Hz for ^{1}H and ± 0.6 Hz for ^{13}C and ^{15}N. 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. Mass spectra (HRMS) at 70 eV using electron impact mode was performed on a VG AUTOSPEC spectrometer by "Laboratorio de Espectrometría de Masas-UAM, Madrid." Room-temperature absorption spectra were obtained with a Shimadzu UV-2501PC spectrometer in solvents of Merck Uvasol grades.

Syntheses

1*H*-Imidazo[1,2-*a*]imidazole (1). The procedure of Compernolle[2] has been modified to increase the yields.

2-Amino-1-(2,2-diethoxyethyl)imidazole. To a magnetically stirred solution of 2-aminoimidazole sulfate (20.0 g, 152 mmol) and 2-bromoacetaldehyde diethylacetal (25.5 ml, 170 mmol) in anhydrous DMF (250 ml), 17.5 g of sodium amide (purity 90%; 404 mmol) are slowly added. The reaction mixture is stirred during 24 h, then cold water (350 ml) and Na_2CO_3 (50 g) are added. The solution is extracted with $CHCl_3$ (6 x 250 ml), and the organic layers evaporated to dryness under reduce pressure. 19.4 g of a crude red oil that solidify on the cooler is obtained. Flash column chromatography on silica gel of this mixture (silica gel 500 g; solvent $CHCl_3$/MeOH (97:3) allows to obtain 11.5 g of 2- amino-1-(2,2-diethoxyethyl)imidazole. Yield: 38 %, mp 91-92 °C, R_f = 0.26 (CH_2Cl_2/MeOH 85:15). Two other products were isolated in the chromatography: 2-(3,3- diethoxyethylamino)imidazole (oil, 1 g) and 1-(2,2-diethoxyethyl)-2-(3,3- diethoxyethylamino)imidazole (oil, 2.2 g). NMR data: 2-amino-1-(2,2-diethoxyethyl)imidazole: δ_H ($CDCl_3$) 6.52 (H-4, ^3J = 1.5 Hz), 6.44 (H-5, ^3J = 1.5 Hz), 4.54 (CH, ^3J = 5.1 Hz), 4.3 (NH_2), 3.78 (N-CH_2, ^3J = 5.1 Hz), 3.66 and 3.44 (O-CH_2), 1.13 (CH_3, ^3J = 7.1 Hz). δ_C ($CDCl_3$) 149.1(C-2), 123.1 (C-4, ^1J = 188.2, ^2J = 9.0), 115.8 (C-5, ^1J = 190.3, ^2J = 14.5), 102.1 (CH, ^1J = 160.9), 63.8 (O-CH_2, ^1J = 146.5), 48.2 (NCH_2, ^1J = 139.6), 15.1 (CH_3, ^1J = 126.3). δ_N ($CDCl_3$) -172.4 (N-3), -242.7 (N-1), -335.3 (NH_2). 2-(3,3-Diethoxyethylamino) imidazole: ™$_H$ ($CDCl_3$) 6.56 (H-4 and H-5), 4.56 (CH, ^3J = 5.3), 3.68 and 3.51 (O-CH_2), 3.33 (N-CH_2, ^3J = 5.3), 1.15 (CH_3, ^3J = 7.1). δ_C ($CDCl_3$) 151.1 (C-2), 117.4 (C-4 and C-5), 102.2 (CH), 63.1 (O-CH_2), 46.9 (N-CH_2), 15.2 (CH_3). 1-(2,2-Diethoxyethyl)-2-(3,3-diethoxyethylamino) imidazole: ™$_H$ ($CDCl_3$) 6.68 (H-4, ^3J = 1.7), 6.53 (H-5, ^3J = 1.7), 4.56 and 4.70 (CH, ^3J = 5.2), 3.8-3.4 (CH_2), 1.27 and 1.21 (CH_3, ^3J = 7.0).

Imidazo[1,2-*a*]imidazolium chloride ($1H^+$ Cl^-). A magnetically stirred solution of 2- amino-1-(2,2-diethoxyethyl)imidazole (2.6 g, 13.1 mmol) in HCl (20 ml 2*N*) is refluxed for 1 h. The solvent is evaporated under reduce pressure, the oily residue dissolved in MeOH, and the solvent evaporated. The same operation is repeated with $CHCl_3$ affording the crude hydrochloride salt of imidazo[1,2-*a*]imidazole after evaporation to dryness under reduced pressure. This solid is then vigorously stirred overnight in diethyl ether and recovered by filtration: 1.80 g . Yield: 96 %, mp 145 °C (Lit. mp 145-148 °C).[2] Total yield calculated on 2-aminoimidazole 36%, Lit. yield 16%[2].

1*H*-Imidazo[1,2-*a*]imidazole (1). A magnetically stirred solution of 2-amino-1-(2,2-diethoxyethyl) imidazole (5.6 g, 28.1 mmol) in HCl (45 ml 2*N*) is refluxed for 1 h. The water and excess of hydrogen chloride are entirely eliminated by co-evaporation as previously described. The crude hydrochloride salt of imidazo[1,2-*a*]imidazole is then vigorously stirred overnight in diethyl ether and recovered by filtration. This filtrate is dissolved in water (20 ml) containing $NaHCO_3$ (3.0 g, 35.7 mmol), and extracted first with $CHCl_3$ (5 x 50 ml; 1.336 g of pure 1*H*-imidazo[1,2-*a*]imidazole are obtained after evaporation to dryness under reduce pressure. A second extraction with CH_2Cl_2 (5 x 50 ml) affords another 884 mg of pure **1**. Another crop of the product (170 mg) is recovered by continue extraction using CH_2Cl_2 in a Soxhlet apparatus. In all, 2.4 g of the free base **1** (yield 80 %) was obtained. Lit. yield not reported.[2] An analytical sample of **1** was prepared by crystallizing 353 mg from MeOH. The compound, a slightly yellow crystalline powder, melts at 179.5°C (dec., by differential scanning calorimetry), Lit. mp not

reported, described as a viscous oil.[2] Anal. Calcd. for $C_5H_5N_3$: C 56.07, H 4.71, N 39.23. Found: C 55.95, H 4.80, N 38.72.

Exact mass: Calculated 107.04835. Found 107.04816. R_f between 0.25 and 0.5 in CH_2Cl_2/MeOH (85:15). Note that the R_f of this compound is particularly dependent on its concentration.

1-Methylimidazo[1,2-*a*]imidazole (3). To a magnetically stirred solution of **1H$^+$ Cl$^-$** (806 mg, 5.6 mmol) and NaOH (496 mg, 12.4 mmol) in H_2O (6 ml) containing 1 ml of MeOH, 0.56 ml of dimethyl sulfate (5.9 mmol) is added. The reaction mixture is stirred about 2 days and the methanol is evaporated under reduce pressure. 20 ml of water are then added and this aqueous solution is extracted with CH_2Cl_2 (3 x 50 ml). The organic layers are washed with water, dried with Na_2SO_4 and evaporated to dryness to afford only a small quantity of the crude product (124 mg). Another part of the product (200 mg) is recovered by continue extraction with CH_2Cl_2 using a Soxhlet apparatus. Flash column chromatography on silica gel of these two extracts [silica gel: around 10 g; solvent: CH_2Cl_2/MeOH (95:5)] yielded only 47 mg of analytically pure **3** as a slightly yellow oil. R_f = 0.48 CH_2Cl_2/MeOH (9:1).

Exact mass: Calculated 121.14180. Found 121.14135.

9*H*-Imidazo[1,2-*a*]benzimidazole (2). Ogura's procedure[4] has been slightly modified.

2-Amino-1-(2,2-diethoxyethyl)benzimidazole. To a magnetically stirred solution of NaOMe in MeOH [obtained by reaction of Na (1.65 g 71.8 mmol) and MeOH (45 ml) at 0 °C], 9 g of 2-aminobenzimidazole (67.6 mmol) and 11.45 ml of 2-bromoacetaldehyde diethylacetal (76.1 mmol) are added. After heating under reflux for 96 h, the reaction mixture is filtered (elimination of NaBr) and the filtrate evaporated under reduced pressure. The oily residue thus obtained is then extracted, first with Et_2O and second with $CHCl_3$. After evaporation to dryness of these extracts (in the form of a red oil), the major part of the product is recovered by fractional crystallization: most of the principal impurity (2-aminobenzimidazole that did not react; 1.83 g) is first eliminated by precipitation from $CHCl_3$–petroleum ether, and most of the desired compound (6.08 g) is next obtained by crystallization from diethyl ether. Flash column chromatography on silica gel of the oil obtained from the collection of the residual filtrates [eluent: CH_2Cl_2/MeOH (97/3)] yields a supplementary part (860 mg) of the desired compound. In all, 6.94 g of 2-amino-1-(2,2-diethoxyethyl)benzimidazole were obtained, mp 140-141 °C (rose-orange powder). Lit. mp 137-139 °C. Yield 41 %. Rf = 0.42 CH_2Cl_2/MeOH (9:1). Two other compounds were isolated by column chromatography: 2-(3,3-diethoxyethylamino)benzimidazole (790 mg, oil) and 1-(2,2-diethoxyethyl)-2-(3,3-diethoxyethylamino)benzimidazole (880 mg, oil). Finally, 3.33 g of 2- aminobenzimidazole that did not react is recovered. NMR data: 2-amino-1-(2,2- diethoxyethyl)benzimidazole: δ_H (DMSO-d_6) 7.17 (H-7, ^3J = 7.5), 7.15 (H-4, ^3J = 7.5), 6.94 (H-5, ^3J = ^3J = 7.5, ^4J = 1.3), 6.88 (H-6, ^3J = ^3J = 7.5, ^4J = 1.3), 6.42 (NH_2), 4.74 (CH, ^3J = 5.3), 4.07 (N-CH_2, ^3J = 5.3), 3.62 and 3.40 (O-CH_2), 1.01 (CH_3, ^3J = 7.0). δ_C (DMSO-d_6) 155.3 (C-2), 142.6 (C-3a), 134.7 (C-7a), 120.3 (C-5, ^1J = 157.2, ^3J = 7.3), 118.0 (C-6, ^1J = 158.7, ^3J = 7.6), 114.7 (C-4, ^1J = 155.4, ^3J = 8.7), 108.1 (C-7, ^1J = 160.0, ^3J = 8.2), 100.4 (CH, ^1J = 160.9), 63.0 (O-CH_2, ^1J = 142.3), 45.2 (N-CH_2, ^1J = 139.4), 15.1 (CH_3, ^1J = 125.9). δ_N (DMSO-d_6) -185.4 (N-3), -257.9 (N-1), -324.5 (NH_2). 2-(3,3-

Diethoxyethylamino)benzimidazole: δ_H ($CDCl_3$) 7.25 (H-5 and H6), 7.01 (H-4 and H-7), 4.62 (CH, ^3J = 5.1), 3.68 and 3.48 (O-CH_2), 3.57 (N-CH_2, ^3J = 5.1), 1.13 (CH_3, ^3J = 7.0). ™$_C$ ($CDCl_3$) 156.9 (C-2), 137.8 (C-3a), 120.4 (C-4 and C-7), 112.1 (C-5 and C-6), 102.0 (O-CH), 63.3 (O-CH_2), 46.1 (N-CH_2), 15.1 (CH_3). 1-(2,2-Diethoxyethyl)-2-(3,3-diethoxyethylamino)benzimidazole: δ_H ($CDCl_3$) 7.46 (H-4, ^3J = 7.7), 7.09 (H-5), 7.03 (H-6 and H-7), 5.46 (NH, ^3J = 5.6), 4.71 and 4.64 (CH, ^3J = 5.3), 3.97 (N-CH_2, ^3J = 5.1), 3.75 and 3.57 (NH-CH_2 and O-CH_2), 1.22 and 1.20 (CH_3, ^3J = 7.1). δ_C ($CDCl_3$) 155.5 (C-2), 142.3 (C-3a), 134.9 (C-7a), 121.3 (C-5), 119.5 (C-6), 116.5 (C-4), 106.7 (C-7), 101.8 and 101.1 (CH), 64.1 and 62.7 (O-CH_2), 46.4 and 45.7 (N-CH_2), 15.3 and 15.2 (CH_3).

Imidazo[1,2-*a*]benzimidazole (**2**) **and imidazo[1,2-*a*]benzimidazolium chloride (2H$^+$).** A magnetically stirred solution of 2-amino-1-(2,2-diethoxyethyl) benzimidazole (2.5 g, 10 mmol) in HCl (12.5 ml 2 *N*) is refluxed for 30 min. The reaction mixture is then divided in two equal portions: one of these is evaporated under reduce pressure, the oily residue obtained is dissolved in MeOH, and next evaporated to dryness. Thus, salt **2H**+ was obtained as a slightly gray powder, 930 mg; yield 96 %. The free base **2** (slightly yellow powder; 680 mg; yield 86 %) is recovered from the other portion by filtration of the precipitate obtained after addition of 10% aqueous $NaHCO_3$ until the pH reaches 8.

1-Methylimidazo[1,2-*a*]benzimidazole (**4**) **and 9-methylimidazo[1,2-*a*] benzimidazole (5).** To a magnetically stirred solution of **2** (1.70g, 10.8 mmol) and NaOH (476 mg, 11.9 mmol) in H_2O (12 ml) containing 1 ml of MeOH, 1.18 ml of dimethyl sulfate (12.5 mmol) is added. The reaction mixture is stirred around 2 h and the methanol is evaporated under reduce pressure. A few ml of water (about 10 ml) is added and this aqueous solution is extracted with CH_2Cl_2 (2 x 15 ml). The organic layers are washed with water, dried with Na_2SO_4 and evaporated to dryness to afford the crude mixture (1.45 g) of the two *N*-methyl derivatives, that are in an about 1:2 (**4**/**5**) ratio, according to the ^{1}H NMR analysis (integration of the *N*-methyl signals). The two compounds are separated by flash column chromatography on silica gel (silica gel: 65 g; solvent: CH_2Cl_2/MeOH, 985:15). 463 mg of **4** (mp 143 °C, yield 25 %, R_f = 0.37, CH_2Cl_2/MeOH 94:6) and 944 mg of **5** (mp 49 °C, yield 51 %, R_f = 0.41, CH_2Cl_2/MeOH 94:6) are obtained. A small quantity of compounds **4** and **5** was prepared in a high purity level for analytical purposes. 114 mg of **4** (slightly yellow small crystals) are obtained by crystallization from isopropyl ether-MeOH; 47 mg of **5** (white powder) are obtained by crystallization from isopropyl ether. Isomer **4**, Anal. Calcd. for $C_{10}H_9N_3$: C 70.16, H 5.30, N 24.54. Found: C 70.31, H 5.18, N 24.51. Isomer **5**, Anal: Found: C 70.22, H 5.32, N 24.24.

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