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^{13}C and ^{15}N NMR spectra of aminobenzimidazoles in solution and in the solid state

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The ^{13}C [hexadeutero-dimethylsulfoxide (DMSO-d_6), hexamethyl-phosphoramide (HMPA)-$d_{18}$and solid-state] and ^{15}N (solid-state) NMR spectra of six *C*-aminobenzimidazoles have been recorded. The tautomerism of 4(7)-aminobenzimidazoles and 5(6)-aminobenzimidazoles has been determined and compared with B3LYP/6-311++G(d,p) calculations confirming the clear predominance of the 4-amino tautomer and the slight preference for the 6-amino tautomer. GIAO-calculated absolute shieldings compare well with experimental chemical shifts.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{13}C; ^{15}N; benzimidazoles; tautomerism; CPMAS; DFT; GIAO

Introduction

We have been interested in the prototropic tautomerism of heterocycles, particularly in that concerning azoles and benzazoles.[1] We have devoted several papers to the annular tautomerism of benzimidazoles[2–7] but none to the *C*-aminobenzimidazoles. Amongst these compounds, the most studied are 2-aminobenzimidazoles due to their wide range of biological applications.[8,9] 4(7)-Aminobenzimidazoles[10–15] and 5(6)-aminobenzimidazoles[16,17] are much less studied but also biologically relevant.

Synthesis, reactivity and spectral properties of benzimidazoles are well known.[18,19] The nitrobenzimidazoles, precursors of the aminobenzimidazoles, were described by Leandri *et al.*[20] In the present paper, we will describe the ^{13}C and ^{15}N NMR spectroscopic properties of 4(7)-amino-1*H*-benzimidazole (**1**) and 5(6)-amino-1*H*-benzimidazole (**2**), as well as those of their *N*-methylated derivatives **3**-**6**, depicted in Scheme 1. Notice that these compounds are readily oxidized under open atmosphere similarl to related compounds, making their study difficult.[21]

Results and Discussion

Chemistry

We prepared the set of both prototropic aminobenzimidazoles and all four methylated isomers of Scheme 1 by catalytic reduction of the corresponding nitro derivatives with hydrogen over palladium on charcoal (10%, **3**, **4**) or Raney nickel (**1**, **2**, **5**, **6**), respectively. Due to fast oxidation of ethanolic solutions, the catalyst was filtered off under argon, as soon as possible, and then the solutions were evaporated to dryness and recrystallized from toluene. After filtering off the solvent, the crystals were shortly dried under argon and stored in a refrigerator for short time.

4(7)-nitro-1*H*-benzimidazole was prepared from 3-nitro-1,2-phenylenediamine[22] with formic acid,[23] and analogously 5(6)-nitro-1*H*-benzimidazole from commercial 4-nitro-1,2-phenylenediamine according to Ref. 23 to avoid formation of traces of 4(7)-isomer.[23] 4-Nitro-1-methylbenzimidazole (**3**) was synthesized in two-steps from 3-nitro-1,2-phenylenediamine with ethanolic formaldehyde in hydrochloric acid[24] followed by reduction,[25] similarly the 6-nitro isomer was prepared from 4-nitro-1,2-phenylenediamine.[26] 2,4-Dinitrochlorobenzene is the starting material for a four-step synthesis of 5-amino-1-methylbenzimidazole (**5**).[20,26,27] 7-Nitro-1-methylbenzimidazole was prepared by cyclization of 1-methyl-6-nitro-1,2-phenylenediamine[28] with formic acid using a seven-step procedure starting from chlorobenzene.[29] In all cases, the nitrobenzimidazoles precursors were prepared by unambiguous cyclization of nitro-1,2-phenylenediamines and not by nitration of *N*-methylbenzimidazoles[30] or by methylation of nitrobenzimidazoles[20,31] to avoid formation of mixtures of isomers. Alkylation of aminobenzimidazoles also affords mixtures of regioisomers.[32,33]

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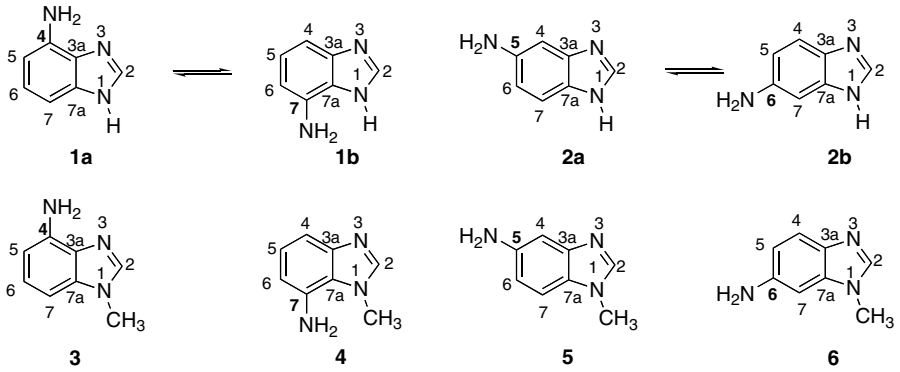
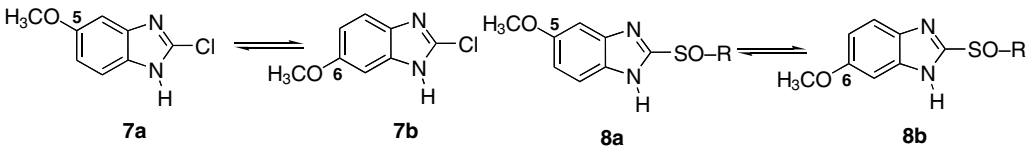


Scheme 1. The six aminobenzimidazoles and their numbering.



Scheme 2. Tautomerism of 5(6)-substituted benzimidazoles. **8**: omeprazole, 5(6)-methoxy -2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1*H*-benzimidazole.

NMR

The NMR data are reported in Table 1 [^{13}C NMR in hexadeutero-dimethylsulfoxide (DMSO-d_6) solution], Table 2 [^{13}C and ^{15}N NMR in hexamethyl-phosphoramide (HMPA)-d_{18} solution, only compounds **1** and **2**], Table 3 (^{13}C NMR in solid state) and Table 4 (^{15}N NMR in solid state). The assignments were carried out by standard 2D methodologies and also by comparison with other benzimidazoles.[34,35] The position of the *N*-methyl group in derivatives **3**-**6** being unambiguously established by the synthetic procedure used, we will note here only that the chemical shifts are consistent with the structure.

Tautomerism

Literature results on the annular tautomerism of NH-benzimidazoles are scarce. Using THF-d_8 at low temperature, the following proportions have been determined: 40% **7a**/60% **7b**[1a] and 37% **8a**/63% **8b** (Scheme 2).[36]

To slow down the prototropic rate in solution either the temperature must be lowered considerably (case of THF, −108°C) or the used solvent must break down the hydrogen bonds (solute/solute or solute/water) (case of DMSO, mp 18.5°C). HMPA is better than DMSO as hydrogen bond acceptor and its melting point is a little lower (7.2°C). In HMPA-d_{18}, the proportions of both tautomers have been determined by simple integration on different signals (Table 2): 60% **1a**/40% **1b** and 17% **2a**/83% **2b**.

In DMSO-d_6 at room temperature (Table 1), compound **2** behaves like in HMPA-d_{18} but the proportions are a little different: 24% **2a**/76% **2b**, that is a small increase in the proportion of **2a**.

The case of **1** in DMSO-d_6 at room temperature (Table 1) presents the typical problem of tautomerism that is difficult when only a series of signals are observed. Is this due to a rapid tautomerization or to the presence of only one tautomer? Assuming that the prototropic rates are the same for **1** than for **2**, we conclude that only one tautomer is present. However, the presence of small quantities of the minor isomer is difficult to determine, not only because they are of small intensity *but also because they could be very broad to the point of being lost in the baseline*. This often forgotten result is the simple consequence of the forward and backward rates of a process with very different barriers, barriers related to the tautomeric equilibrium constant.

The comparison of the chemical shifts of **1** with those of **3** and **4** shows that the 7-amino tautomer **1a** is the only present or, at least, very predominant tautomer in DMSO-d_6 solution. The

Table 1. ^{13}C NMR chemical shifts in DMSO-d_6 (δ in ppm) of aminobenzimidazoles **1**–**6**

Compound	C2	C3a	C4	C5	C6	C7	C7a	N-Me
1a	138.9	131.9	139.9	103.9	123.2	99.3	133.7	–
3	141.5	132.1	140.1	104.3	123.4	97.6	135.2	30.6
4	144.3	145.4	109.0	122.2	108.6	135.3	124.1	33.2
2a (24%)	140.8	~145[a]	102.5	~146[a]	111.2	111.2	~127(br)[a]	–
2b (76%)	138.9	134.5	118.9	111.2	144.7	94.7	135.3	
5	143.5	144.6	102.6	143.9	112.1	109.8	127.3	30.5
6	141.6	135.5	119.3	111.1	144.9	92.9	135.8	30.2

[a] These signals are under some signals of the most abundant tautomer.

Table 2. ^{13}C and ^{15}N NMR chemical shifts in HMPA-d_{18} (δ in ppm) of aminobenzimidazoles **1** and **2**

	Compound	C2	C3a	C4	C5	C6	C7	C7a	N_1	N_3	NH_2
(300 K)	**1a** (60%)	138.4[a]	133.2	141.2	103.8	122.9	99.0	134.6	−234.3[b]	−134.0	−328.5[c]
(300 K)	**1b** (40%)	139.4	144.8	106.8	121.7	105.2	136.0	123.6	−229.4[d]	−141.5	−328.5[e]
(283 K)	**2a** (17%)	140.2	143.1	103.1	143.1	110.2	112.7	126.2	−232.3	−136.4	−324.4
(283 K)	**2b** (83%)	138.1	136.0	118.7	111.2	146.5	94.8	135.1	−232.3	−136.4	−324.4[c]

Some coupling constants (Hz):
[a] $^1J_{CH} = 203.1$.
[b] $^1J_{NH} = 96.9$.
[c] $^1J_{NH} = 96.5$.
[d] $^1J_{NH} = 96.0$.
[e] $^1J_{NH} = 96.5$.

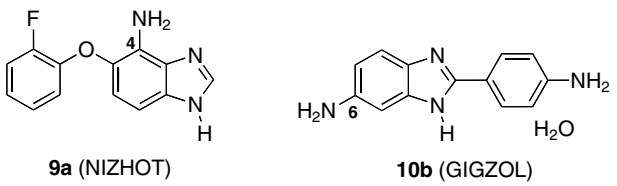
Table 3. ^{13}C CPMAS NMR chemical shifts (δ in ppm) of aminobenzimidazoles **1**–**6**

Compound	C2	C3a	C4	C5	C6	C7	C7a	N-Me
1a	139.6	131.2[a]	137.1[a]	103.1	121.6	103.1	133.3[a]	–
3	140.8	131.6[a]	140.1[a]	106.5	127.4	98.2	135.0[a]	29.8
				105.6	123.8	97.0		
				103.0	122.6	95.3		
4	145.5	145.4[a]	108.8	123.7	112.7	135.8[a]	126.7[a]	33.4
			110.5	121.1			124.6[a]	32.5
2a (50%)	142.0	142.5[a]	99.5	136.7[a]	111.2	119.5	134.0[a]	–
2b (50%)	140.8	133.0[a]	118.7	112.2	144.7[a]	94.6	136.7[a]	
5	146.1	144.7[a]	101.5	144.7[a]	111.8	111.8	128.0[a]	30.3
6	142.2	134.2[a]	118.9	109.7	146.9[a]	91.9	136.3[a]	29.7

[a] NQS signals.

Table 4. ^{15}N CPMAS NMR chemical shifts (δ in ppm) of aminobenzimidazoles **1**–**6**

Compound	N_1	N_3	NH_2
1a	−217.7	−149.9	−323.7
3	−229.8, −233.8	−143.7	−321.5
4	−232.3	−138.5, −141.4	−325.3
2a + 2b	−229.8, −225.7	−143.8, −149.4	−323.4
5	−232.0	−142.1	−320.5, −322.9
6	−234.9	−142.2	−319.2



9a (NIZHOT) **10b** (GIGZOL)

Scheme 3. Related structures found in the CSD.

best solution obtained by interpolation of the chemical shifts of **1** between those of **3** and **4** is 100% **1a** and 0% **1b**. The same result is obtained interpolating the data of **1** in DMSO-d_6 (Table 1) with those of **1a** and **1b** in HMPA-d_{18} (Table 2). Two kinds of $^1J_{NH}$ coupling constants were reported in Table 2: a −(96.5 ± 0.5) Hz value typical of azoles[35] and a −86.6 Hz value typical of anilines (*p*-nitroaniline, −86.4 Hz[37]).

The replacement of the methoxy group by the amino one shifts the difference in stability toward the 6-substituted tautomer **b** but in DMSO-d_6 or HMPA-d_{18} instead of THF-d_8.

The case of 4(7)-aminobenzimidazole **1** has been studied by a combination of theoretical (B3LYP/6-31++G**) and matrix-isolation Fourier Transform Infrared (FT-IR) methods.[38,39] In the Ar matrix only monomers exist. The main conclusions of this study are: (i) in the matrix there is a mixture of 78% of **1a**/22% of **1b** ($K_T = 0.28$, $\Delta G_{298} = 3.1$ kJ mol^{-1}; (ii) according to the calculations, $\Delta G_{340} = 15.5$ kJ mol^{-1} ($K_T = 0.004$, 0.4% **1a**/99.6 **1b**); (iii) the large difference between the experiment and calculation was attributed to the presence of water in the matrix that, according to the authors, should stabilize the minor isomer; (iv) the nonplanarity of the amino groups.

A priori, in the solid state (Tables 3 and 4) the tautomeric composition should be simpler. Only one tautomer or a 50/50 mixture of tautomers is expected, the first case being by large the most common. Very rare cases of 33/66 trimers or 25/75 tetramers are known.[40,41] A search in the CSD[42] shows that none of the X-ray structures of the compounds of Scheme 1 are known. However, we have found two structures, **9a** and **10b**, that shows that the tautomeric preferences in the solid state agree with the results in solutions: 4-aminobenzimidazoles and 6-amino benzimidazoles.

The results of Table 3 correspond to 4(7)-aminobenzimidazole existing in the solid state as the 4-amino tautomer **1a**, this being

Table 5. Regression equations between δ and σ values (ppm)

Eqn	Nucleus	Conditions	Number of points	R^2	Intercept	Slope
1	^{13}C	DMSO-d_6	53	0.993	(175.5 ± 0.7)	−(0.952 ± 0.011)
2	^{13}C	HMPA-d_{18}	28	0.966	(176.8 ± 2.0)	−(0.972 ± 0.036)
3	^{13}C	Both	81	0.990	(175.8 ± 0.7)	−(0.955 ± 0.011)

the expected result, and 5(6)-aminobenzimidazole existing in the solid state as a 50/50 mixture of 5-amino tautomer **2a** and 6-amino **2b** tautomers. Since, the difference in energy is small, this result is not in contradiction with the calculations (see below) nor with the results in solution, however is the first example of a benzimidazole crystallizing as a mixture of tautomers. A search in the CSD proves that there is no one example of the existence of pairs of benzimidazole tautomers in crystals.[42]

The solid-state ^{15}N NMR results of Table 4 are not very useful concerning tautomerism partly because most *N*-methyl derivatives present splitted signals due to crystal packing effects and partly because isomerism does not produce significant effects on none of the three N signals. Compound **1** shows only three signals and this is consistent with only one tautomer. The signals of N_1 and N_3 of compound **2** are splitted and probably the −229.8 ppm signal corresponds to **2b** and the −225.7 to **2a**.

Theoretical calculations

The minimum energy-calculated geometries of all compounds correspond to nonplanar amino groups, a point already found by other authors for **1a** and **1b**.[39] At the B3LYP/6-311++G(d,p) level, the differences in energy are **1a** (0.00)/**1b** (16.5 kJ mol^{-1}) and **2a** (2.3 kJ mol^{-1})/**2b** (0.00), the first one being similar to that calculated at the B3LYP/6-31++G(d,p) level.[39] The difference is smaller and in favor of the other tautomer in the case of **2**. The first difference corresponds at 298.15 K to 99.85% of **1a** and 0.15% of **1b**; the second one, to 28% of **2a** and 72% of **2b**: in both cases, the agreement with the experimental results in DMSO-d_6 is good (Table 1). In the case of HMPA-d_{18} (Table 2), there is an increase of tautomers **b** that reach 40% in the case of **1** and 83% in the case of **2**. This difference could be related to the higher hydrogen-bond basicity of HMPA compared to DMSO.[43] Important changes in the annular tautomeric equilibrium constant have been reported for other azoles when the solvent is changed (including HMPA).[1b]

We have calculated the absolute shieldings for all compounds of Scheme 1 within the GIAO approximation (Supporting Information) and compared them with the experimental data (Table 5).

For ^{13}C NMR data, the results are acceptable (Eqns (1–3)) and consistent with the assignments of Tables 1–4. In the case of ^{15}N NMR results, the calculations reproduce well the general trend of the three classes of nitrogen atoms but not within each class (note that the signals appear in a very narrow range (N1 4.9 ppm, N3 7.5 ppm and NH_2 4.1 ppm in HMPA).

Experimental

General procedures

Melting points determined on Kofler micro-hot stage, are uncorrected and in good agreement with previously described data for compounds **1**-**6** and all intermediates.[20,22–31] 4-Nitro-1,2-phenylenediamine, chlorobenzene and 2,4-dinitrochloro-benzene are commercial products (Sigma–Aldrich).

NMR spectroscopy

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil, at 300K. Chemical shifts (δ in ppm) for ^{1}H and for ^{13}C are given with respect to tetramethylsilane as external reference. Typical parameters for ^{1}H NMR spectra were spectral width 4800 Hz and pulse width 7.5 µs at an attenuation level of 0 dB. Typical parameters for ^{13}C NMR spectra were spectral width 21 kHz, pulse width 10.6 µs at an attenuation level of −6 dB and relaxation delay 2 s, WALTZ-16 was used for broadband proton decoupling; the free induction decays (FIDs) were multiplied by an exponential weighting (lb = 1 Hz) before Fourier transformation.

Inverse proton-detected heteronuclear shift correlation spectra, (^{1}H–^{13}C) gs-HMQC and (^{1}H–^{13}C) gs-HMBC, were acquired and processed using standard Bruker NMR software and in nonphase-sensitive mode. Gradient selection was achieved through a 5% sine truncated-shaped pulse gradient of 1 ms. Selected parameters for (^{1}H–^{13}C) gs-HMQC and (^{1}H–^{13}C) gs-HMBC spectra were: spectral width 4800 Hz for ^{1}H and 20.5 kHz for ^{13}C, 1024 × 256 data set, number of scans 2 (gs-HMQC) or 4 (gs-HMBC) and relaxation delay 1 s. The FIDs were processed using zero filling in the F_1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs-HMQC experiments, GARP modulation of ^{13}C was used for decoupling.

Solid-state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4-mm DVT probehead. Samples were carefully packed in 4-mm diameter cylindrical zirconia rotors with Kel-F end-caps. Operating conditions involved 3.2 µs, 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by two-pulse phase modulation (TPPM) sequence. The non quaternary suppression (NQS) technique to observe only the quaternary C-atoms was employed. ^{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. The typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 5–60 s; acquisition time, 30 ms; contact time, 2–5 ms; and spin rate, 12 kHz. And for ^{15}N CPMAS were: spectral width, 40 kHz; recycle delay, 5–60 s; acquisition time, 35 ms; contact time, 7–9 ms; and spin rate, 6 kHz.

Computational details

The geometry of the systems have been optimized at the B3LYP/6-31G(d) computational level[44] and the energetic minimum character has been confirmed by frequency calculation at the same computational level.[45] A further geometry optimization has been

performed at the B3LYP/6-311++G(d,p) level.[46] These geometries has been used to obtain the absolute chemical shielding using the GIAO method[47] at the B3LYP/6-311++G(d,p) level. All the calculations have been performed within the G03 package.[48] The energies and absolute shieldings are given in the Supporting Information.

Supporting information

Supporting information may be found in the online version of this article.

Acknowledgements

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This paper is dedicated to Professor Daniel Belluš in the occasion of his 70th birthday.

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