

## STRUCTURE AND BASICITY OF 2-GUANIDINOBENZIMIDAZOLES

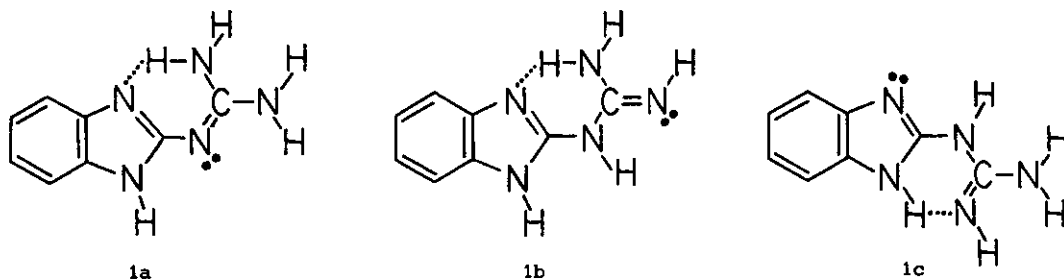
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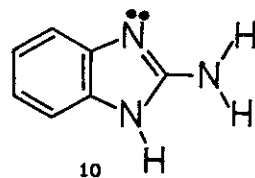
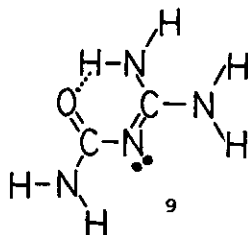
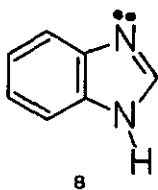
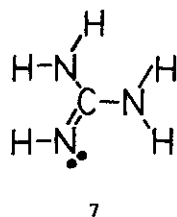
**Abstract** - A theoretical and experimental study of the basicity of three 2-guanidinobenzimidazoles has been carried out. The most abundant tautomer, the structure of the protonated molecule, and the reason of the relatively low  $pK_a$  are discussed. In addition, a careful  $^1H$  and  $^{13}C$  nmr study provides information about the influence of intramolecular hydrogen bonds on annular tautomeric rates.

2-Guanidino benzimidazole 1 is a complex molecule for which, at least, three intramolecular hydrogen-bonded structures can be written:

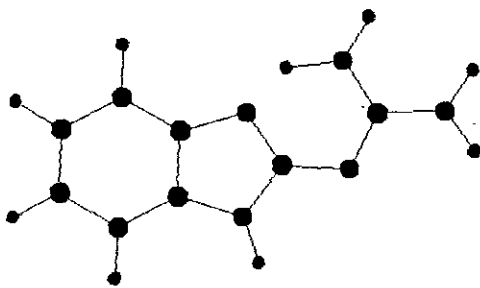


The first one, 1a, is a tautomer different from 1b and 1c, whereas 1b and 1c are isomers interconvertible by rotations about C-N single bonds. In each structure there are two  $sp^2$  nitrogen lone pairs, but one of them is involved in an intramolecular hydrogen-bond. The remaining one is susceptible of being protonated: in 1a and 1b it is a guanidine nitrogen whereas in 1c it is a benzimidazole nitrogen. The  $pK_a$  of 1 is 7.09.<sup>1</sup>

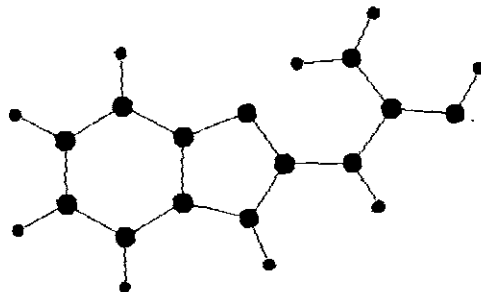
Guanidine itself 7 is a much stronger base ( $pK_a = 14.38$ ,<sup>2</sup>  $14.63$ <sup>3</sup>) than the parent benzimidazole 8 ( $pK_a = 5.56$ ).<sup>4</sup> Thus, the 7.09 value can correspond either to a guanidine weakened by the benzimidazole substituent or to a benzimidazole strengthened by the guanidino substituent effect. For instance, carbamoylguanidine 9, which protonates in the guanidine nitrogen, has a  $pK_a = 7.85$ <sup>3</sup> and 2-aminobenzimidazole 10 which, in turn, protonates in the benzimidazole nitrogen, has a  $pK_a = 7.39$ .<sup>4</sup>



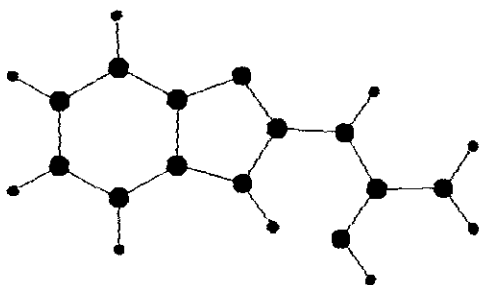
The first problem that must be solved is the structure of the cations obtained by protonation of **1a**, **1b** and **1c**. Within the INDO framework<sup>5</sup> and using the Rinaldi and Rivail<sup>6</sup> technique of optimization, the geometries of the neutral molecules and those of the corresponding cations have been calculated. These planar molecules have been drawn with the CHEM-X software:<sup>7</sup>



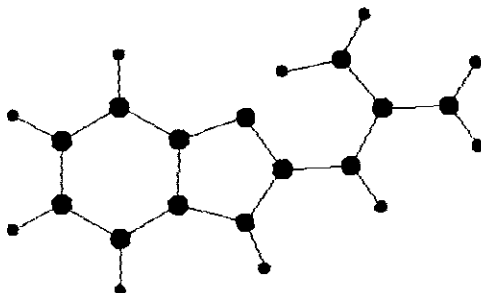
1a



1b



1c



2

The most interesting feature is that the same cation **2** is always obtained when the protonated forms are optimized. This is an important result with which it is possible to discuss the basicity of guanidinobenzimidazoles considering only the structural characteristics of the three neutral forms. The results are gathered in Tables 1 and 2. Table 1 also contains the calculated dipole moments in Debyes and Table 2, the experimental  $pK_a$  values in water. The  $-\Delta E_p$  values of Table 2 are calculated from the energy values of Table 1. For instance,  $-\Delta E_p(\mathbf{1a}) = -73789.1 + 74180.2 = 391.1$  kcal/mole. These protonation energies are linearly related to the experimental proton affinities.<sup>5</sup> In the case of benzimidazole itself **8**,  $-\Delta E_p(\text{INDO}) = 375.6$  kcal/mole whereas its PA = 225.6 kcal/mole.<sup>8</sup>

Table 1. Theoretical properties of 2-guanidinobenzimidazoles

Compound	Energies (kcal/mole)	$\Delta E$	$\mu$ (D)
1a	-73789.1	0	2.80
1b	-73773.1	16.0	3.18
1c	-73774.7	14.4	7.93
2	-74180.2	-----	-----
3a	-84396.1	0	3.01
3b	-84380.5	15.6	3.10
3c	-84382.7	13.4	8.15
4	-84788.9	-----	-----
5a	-79092.3	0	2.71
5b	-79076.7	15.6	3.01
6	-79483.7	-----	-----

Table 2. Theoretical protonation energies (kcal/mole) and  $pK_a$ 's in water at 25°C

Compound	$-\Delta E_p$	$pK_a$
1a	391.1	7.09
1b	407.1	
1c	405.5	
3a	392.8	7.32
3b	408.4	
3c	406.3	
5a	391.4	7.30
5b	407.0	

Compound 3 is the 5,6-dimethyl derivative with its corresponding common cation 4. Compound 5 is the 1-methyl derivative (common cation 6); due to the N-methylation, there is no 5c chelated structure, for this reason 5 was synthesized and studied.

### Tautomerism

The  $\Delta E$  values (Table 1) show that tautomer a is largely favoured in the gas-phase. Isomers b and c are of comparable energy. Since nothing is known about this problem from an experimental point of view, we must consider that the large  $\Delta E$  values are a guarantee of the predominance of tautomer a. Water will stabilize the tautomer with the higher dipole moment, c, but not to the point to overcome the 15 kcal/mole of difference in energy.

A careful  $^1H$  and  $^{13}C$  nmr study has been carried out on compounds 1, 3 and 5 in order to get some insight on their structures (Tables 3 and 4).

Table 3.  $^1H$  N.M.R. results ( $\delta$ , ppm) at room temperature

Compound	Solvent	Frequency	4	5	6	7	1	$NH_2$
1	DMSO- $d_6$	300 MHz	7.14(b)	6.90	6.90	7.14(b)	← 6.7 (v.b) →	
3	DMSO- $d_6$	200 MHz	6.97	2.23	2.23	6.97	← 6.5 (v.b) →	
5	$CDCl_3$	200 MHz	7.1	7.1	7.1	7.4	3.58	6.1 (b)

Table 4.  $^{13}\text{C}$  N.M.R. results ( $\delta$ , ppm; J, Hz) (Solvent: DMSO- $d_6$ )

Compound	Freq.	Temp.	2	4	5	6	7	3a	7a	Guan.	Others
1	75 MHz	24°C	159.1 <sup>a</sup>	113.5(b)	119.6	119.6	110.6(b)	141.7(vb)	133.2(vb)	159.0 <sup>a</sup>	
	50 MHz	24°C	159.1 <sup>a</sup>	112.5(b)	119.6 <sup>a</sup>	119.6 <sup>a</sup>	112.5(b)	141(vb)	135(vb)	159.0 <sup>a</sup>	
	50 MHz	80°C	159.1 <sup>a</sup>	111.9(b) <sup>b</sup>	119.4 <sup>c</sup>	119.4 <sup>c</sup>	111.9(b) <sup>b</sup>	135.7(b)	135.7(b)	159.0 <sup>a</sup>	
3	50 MHz	24°C	158.4	112.5(b)	126.8 <sup>d</sup>	126.8 <sup>d</sup>	112.5(b)	not obs.	not obs.	158.4	e
	50 MHz	80°C	158.4	112.7 <sup>f</sup>	126.8 <sup>g</sup>	126.8 <sup>g</sup>	112.7 <sup>f</sup>	139.6	139.6	158.4	h
5	50 MHz	24°C	158.1 <sup>i</sup>	115.0 <sup>j</sup>	119.0 <sup>k</sup>	120.1 <sup>l</sup>	107.6 <sup>m</sup>	141.4 <sup>n</sup>	133.6 <sup>o</sup>	158.4	p

<sup>a</sup><sub>1</sub>J = 159.0, <sup>3</sup><sub>J</sub> = 7.3; <sup>b</sup><sub>1</sub>J = 159.9; <sup>c</sup><sub>1</sub>J = 159.0, <sup>3</sup><sub>J</sub> = 7.4; <sup>d</sup><sub>2</sub>J = 4.4 (Me); <sup>e</sup><sub>1</sub>J = 125.4, <sup>3</sup><sub>J</sub> = 5.1 (H<sub>4</sub>)(C-Me,  $\delta$  = 19.8); <sup>f</sup><sub>1</sub>J = 153.1; <sup>g</sup><sub>2</sub>J = 4.3 (Me); <sup>h</sup><sub>1</sub>J = 125.4, <sup>3</sup><sub>J</sub> = 5.1 (H<sub>4</sub>)(C-Me,  $\delta$  = 19.6); <sup>i</sup><sub>3</sub>J = 2.0 (N-Me); <sup>j</sup><sub>1</sub>J = 159.9, <sup>3</sup><sub>J</sub> = 6.6, <sup>2</sup><sub>J</sub> = 2.6; <sup>k</sup><sub>1</sub>J = 159.6, <sup>3</sup><sub>J</sub> = 7.6; <sup>l</sup><sub>1</sub>J = 158.4, <sup>3</sup><sub>J</sub> = 7.2; <sup>m</sup><sub>1</sub>J = 159.7, <sup>3</sup><sub>J</sub> = 6.2, <sup>2</sup><sub>J</sub> = 2.5; <sup>n</sup><sub>3</sub>J = 7.9, <sup>3</sup><sub>J</sub> = 5.9; <sup>o</sup>Complex multiplet due to couplings with the N-Me; <sup>p</sup><sub>1</sub>J = 138.9 (N-methyl,  $\delta$  = 27.9).

All the N-H protons give rise to a very broad signal at about 6.5 ppm, thus preventing  $^1\text{H}$  nmr to be used to discuss the tautomerism of these guanidines. However, compounds 1 and 2 show in  $^1\text{H}$  but particularly in  $^{13}\text{C}$  nmr broad signals for "prototropic nuclei" (i.e., nuclei that became isochronous by rapid prototropic exchange). This fact has been observed for other 2-substituted benzimidazoles<sup>9</sup> and has been explained by the existence of an intramolecular hydrogen bond between the substituent and the benzimidazole ring. As the three structures, a, b and c, have this type of bond, it cannot be used to decide between them.

#### Basicity

As can be seen in Table 2, compounds 1, 3 and 5, have similar  $\text{pK}_a$  values. This proves that c structures play a minor role in aqueous solution too. These structures, with their high dipole moments (about 8 D) would produce an extra-stabilization of the neutral forms of guanidinobenzimidazoles 1 and 3 in water with regard to that of 5. This stabilization would result in a significant lowering of the  $\text{pK}_a$ 's of 1 and 3 compared to 5, a fact which is not observed.

Based on the effect of 5,6-dimethyl and 1-methyl substituents on the  $\text{pK}_a$  values (Table 2), it is possible to discuss qualitatively the protonation position in aqueous solution. It is important to note that if one assumes that cations 2, 4 and 6 lead, by deprotonation, to structures 1a, 3a and 5a, their  $\text{pK}_a$ 's can be directly compared, without statistical correction<sup>4</sup> since, in all cases, only one proton is involved.

Two methyl groups in 5,6-positions produce an increase in the basicity of 0.23  $\text{pK}_a$  units, which is lower than that found when the  $\text{pK}_a$ 's of benzimidazole 8 and 5,6-dimethylbenzimidazole 11 ( $\text{pK}_a = 5.98$ )<sup>4</sup> are compared ( $\Delta\text{pK}_a = 0.42$ ). On the other hand, the N-methylation effect in these guanidinobenzimidazoles ( $\Delta\text{pK}_a = 0.21$ ) is significantly larger than that observed for the couple benzimidazole 8/1-methylbenzimidazole 12 ( $\text{pK}_a = 5.55$ ;  $\Delta\text{pK}_a = -0.31$  taking into account the statistical factor).<sup>4</sup> We consider these differences as a clear indication that guanidinobenzimidazoles do not protonate in the benzimidazole nitrogen.

In conclusion, the measured  $\text{pK}_a$ 's correspond to the basicity of guanidines 1a, 3a and 5a. To compare them to the  $-\Delta E_p$  values (Table 2) it would be necessary to calculate theoretically a large collection of guanidines including most of those studied by Charton<sup>3</sup> and by Taylor.<sup>2</sup> This work is now in

progress.<sup>10</sup> From an empirical point of view, the Charton-Taylor equation,  $pK_a = 14.18 - 22.58 \sigma_I$  provides an explanation of the substituent effect of benzimidazole: its base-weakening effect is due to its  $\sigma_I$  value ( $\sigma_I = 0.32$ ).<sup>2,11</sup>

## EXPERIMENTAL

*Theoretical Calculations.* All calculations were performed at the UAM/IBM Centre (Madrid).

*Basicity Measurements.* The  $pK_a$  measurements were carried out in a Metrohm Herisan at  $25 \pm 0.2^\circ\text{C}$  under nitrogen atmosphere, by direct titration with 0.1 M HCl. The guanidine concentration was about 5 mM. The ionic strength was maintained constant (0.1 M) with KCl. The  $pK_a$  values are the averaged values of, at least, three determinations. They have been corrected for zero ionic strength by means of the Debye-Hückel equation: 1,  $7.091 \pm 0.003$ ; 3,  $7.324 \pm 0.004$ ; 5,  $7.300 \pm 0.005$ .

*N.M.R. Measurements.* The spectra were recorded in a Bruker AM-200 and a Varian XL-300 superconducting spectrometers (CSIC).

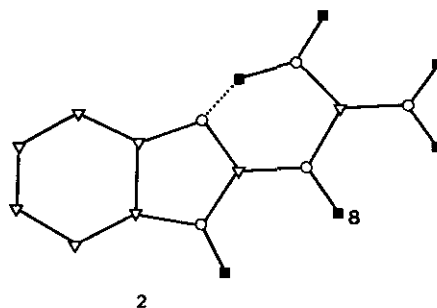
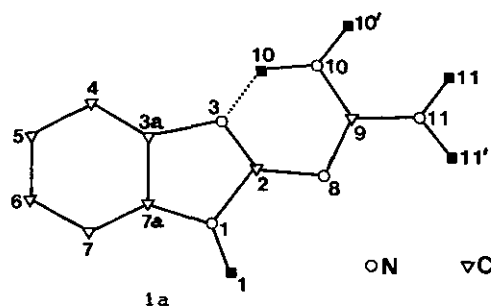
*Synthesis.* 2-Guanidinobenzimidazole 1 (Aldrich G1,180-2) and 5,6-dimethyl-2-guanidinobenzimidazole 3 (ABC S57311-6) are commercial products.

To a mixture of 0.876 g (0.005 moles) of 2-guanidinobenzimidazole, 1.38 g (0.1 mole) of anhydrous potassium carbonate in 10 ml of acetone and 5 ml of water, 0.25 ml (0.0026 moles) of dimethyl sulfate were added and the suspension was stirred for 16 h at room temperature. The acetone was removed under vacuum and the aqueous solution extracted with chloroform. After evaporation of the organic solvent, 0.3 g of crude 1-methyl derivative were obtained (Yield 32%). The product was purified by column chromatography on silica gel and eluted with chloroform-ethanol (9/1). From the aqueous layer, the unreacted initial 2-guanidinobenzimidazole was recovered. 1-Methyl-2-guanidinobenzimidazole, mp  $152-154^\circ\text{C}$  (decomp).

## REFERENCES

- <sup>1</sup>A simultaneous measurement<sup>2</sup> gives  $pK_a = 6.97 \pm 0.05$ .
- <sup>2</sup>P.J. Taylor and A.R. Wait, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1765.
- <sup>3</sup>M. Charton, *J. Org. Chem.*, **1965**, **30**, 969.
- <sup>4</sup>J. Catalán, J.L.M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, **1987**, **41**, 187.
- <sup>5</sup>J. Catalán, J.L.G. de Paz and M. Yañez, *J. Mol. Struct., THEOCHEM*, **1984**, **107**, 257.
- <sup>6</sup>D. Rinaldi and J.L. Rivail, *C.R. Hebd. Seances Acad. Sci., Sér. C.*, **1972**, **274**, 1664.
- <sup>7</sup>We acknowledge Drs P. Goya and I. Rozas for their help. The CHEM-X package is implemented on a Vax 11/750 computer and uses a SIGMEX CDL-6130/20 terminal provided with a hardcopy (Instituto "Rocasolano", CSIC). The Tables of angles and distances for all the optimized guanidinobenzimidazoles, **1a-6**, are available on request. Those of compounds **1a** (most stable tautomer) and **2** (common cation) are given in the Appendix.
- <sup>8</sup>R.W. Taft, personal communication.
- <sup>9</sup>J. Elguero, G. Llouquet and C. Marzin, *Tetrahedron Lett.*, **1975**, 4085.
- <sup>10</sup>J. Catalán, F. Fabero, M. Sánchez-Cabezudo and J. Elguero, unpublished results.
- <sup>11</sup>Our  $pK_a$  values correspond to  $\sigma_I = 0.30$  to  $0.31$ .

Appendix



Distances (Å) and angles (°)

N(1)-C(2)
C(2)-N(3)
N(3)-C(3a)
C(3a)-C(4)
C(4)-C(5)
C(5)-C(6)
C(6)-C(7)
C(7)-C(7a)
C(7a)-C(3a)
C(2)-N(8)
N(8)-C(9)
C(9)-N(10)
C(9)-N(11)
N(1)-H(1)
N(10)-H(10)
N(10)-H(10')
N(11)-H(11)
N(11)-H(11')
N(8)-H(8)
N(3)···H(10)
C(7a)-N(1)-H(1)
H(1)-N(1)-C(2)
C(7a)-N(1)-C(2)
N(1)-C(2)-N(8)
N(8)-C(2)-N(3)
N(3)-C(2)-N(1)
C(2)-N(8)-H(8)
H(8)-N(8)-C(9)
C(9)-N(8)-C(2)
N(8)-C(9)-N(11)
N(11)-C(9)-N(10)
N(10)-C(9)-N(8)
C(9)-N(10)-H(10')
H(10')-N(10)-H(10)
H(10)-N(10)-C(9)
C(9)-N(11)-H(11')
H(11')-N(11)-H(11)
H(11)-N(11)-C(9)
H(10)···N(3)-C(3a)
C(3a)-N(3)-C(2)
C(2)-N(3)···H(10)
N(10)-H(10)···N(3)

1a	2
1.384	1.369
1.360	1.349
1.403	1.409
1.393	1.394
1.387	1.384
1.391	1.394
1.388	1.385
1.389	1.391
1.420	1.416
1.362	1.388
1.352	1.385
1.351	1.332
1.372	1.360
1.065	1.065
1.169	1.216
1.068	1.069
1.064	1.064
1.064	1.064
-----	1.069
1.277	1.229
125.8	127.0
125.9	126.7
108.3	106.3
122.1	126.1
127.1	120.6
110.8	113.3
-----	120.5
-----	120.5
111.2	119.0
117.3	118.3
119.2	125.1
123.5	116.6
119.1	117.0
127.5	128.5
113.4	114.5
122.6	123.3
114.0	114.7
123.4	122.0
146.7	145.7
106.1	105.0
107.2	109.3
137.6	140.0

Received, 22nd January, 1987