STRUCTURE AND BASICITY OF 2-GUANIDINOBENZIMIDAZOLES

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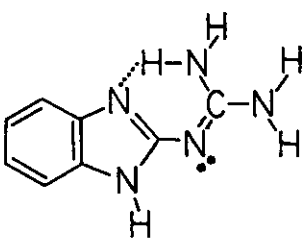
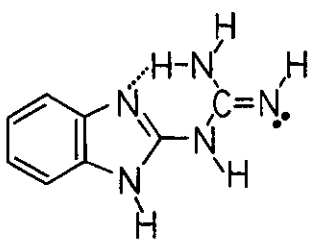
Abstract - A theoretical and experimental study of the basicity of three 2-guanidinobenzimidazoles has been carried out. The most abundant tautomer, the structure of the protonated molecule, and the reason of the relatively low pK_a are discussed. In addition, a careful ^1H and ^{13}C nmr study provides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

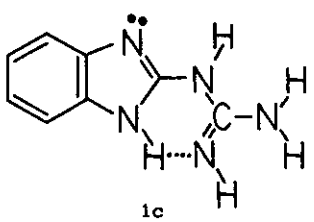
2-Guanidino benzimidazole **1** is a complex molecule for which, at least, three intramolecular hydrogen-bonded structures can be written:



1a



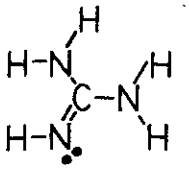
1b



1c

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.[1]

Guanidine itself **7** is a much stronger base (pK_a = 14.38,[2] 14.63[3]) than the parent benzimidazole **8** (pK_a = 5.56).[4] 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[3] and 2-aminobenzimidazole **10** which, in turn, protonates in the benzimidazole nitrogen, has a pK_a = 7.39.[4]



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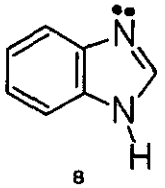

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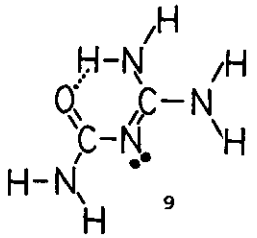
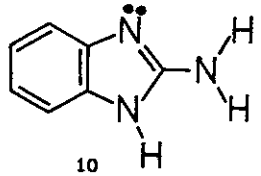
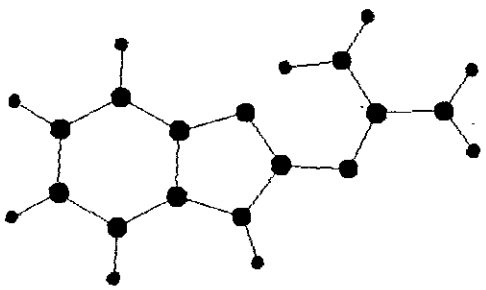


9

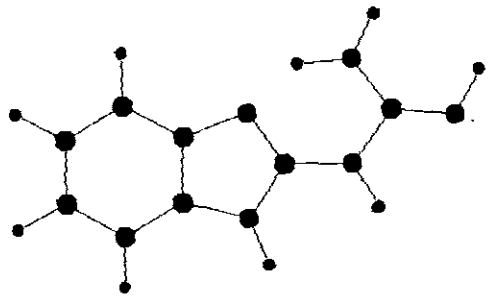


10

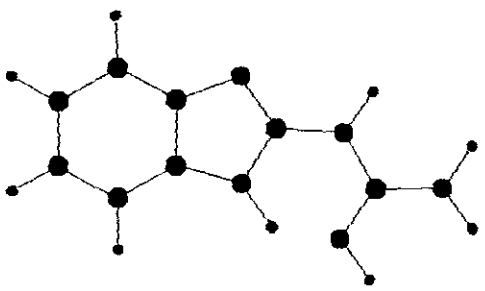
The first problem that must be solved is the structure of the cations obtained by protonation of 1a, **1b** and 1c. Within the INDO framework[5] and using the Rinaldi and Rivail[6] technique of optimization, the geometries of the neutral molecules and those of the corresponding cations have been calculated.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



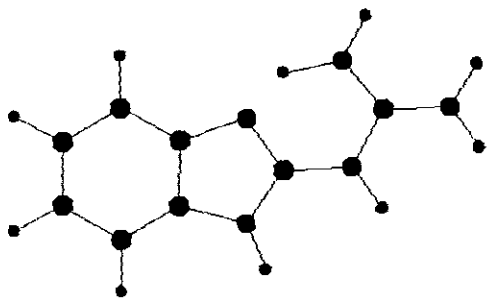
1a



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, $-\Delta E_p$(**1a**) = -73789.1 + 74180.2 = 391.1 kcal/mole. These protonation energies are linearly related to the experimental proton affinities.[5] In the case of benzimidazole itself **8**, $-\Delta E_p$(INDO) = 375.6 kcal/mole whereas its PA = 225.6 kcal/mole.[8]

Table 1. Theoretical properties of 2-guanidinobenzimidazoles

Compound	Energies (Kcal/mole)	ΔE	μ(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 ΔE 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 ΔE 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 (δ, 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}C N.M.R. results (δ, 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*	113.5(b)	119.6	119.6	110.6(b)	141.7(vb)	133.2(vb)	159.0*	
	50 MHz	24°C	159.1*	112.5(b)	119.6[a]	119.6[a]	112.5(b)	141(vb)	135(vb)	159.0*	
	50 MHz	80°C	159.1*	111.9(b)[b]	119.4[c]	119.4[c]	111.9(b)[b]	135.7(b)	135.7(b)	159.0*	
3	50 MHz	24°C	158.4	112.5(b)	126.8[d]	126.8[d]	112.5(b)	not obs.	not obs.	158.4	e
	50 MHz	80°C	158.4	112.7[f]	126.8[g]	126.8[g]	112.7[f]	139.6	139.6	158.4	h
5	50 MHz	24°C	158.1[i]	115.0[j]	119.0[k]	120.1[l]	107.6[m]	141.4[n]	133.6[o]	158.4	p

[a] ^1J = 159.0, ^3J = 7.3; [b] ^1J = 159.9; [c] ^1J = 159.0, ^3J = 7.4; [d] ^2J = 4.4 (Me); [e] ^1J = 125.4, ^3J = 5.1 (H_4)(C-Me, δ = 19.8); [f] ^1J = 153.1; [g] ^2J = 4.3 (Me); [h] ^1J = 125.4, ^3J = 5.1 (H_4)(C-Me, δ = 19.6); [i] ^3J = 2.0 (N-Me); [j] ^1J = 159.9, ^3J = 6.6, ^2J = 2.6; [k] ^1J = 159.6, ^3J = 7.6; [l] ^1J = 158.4, ^3J = 7.2; [m] ^1J = 159.7, ^3J = 6.2, ^2J = 2.5; [n] ^3J = 7.9, ^3J = 5.9; [o] Complex multiplet due to couplings with the N-Me; [p] ^1J = 138.9 (N-methyl, δ = 27.9).

All the N-H protons give rise to a very broad signal at about 6.5 ppm, thus preventing ^1H nmr to be used to discuss the tautomerism of these guanidines. However, compounds **1** and **2** show in ^1H but particularly in ^{13}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[9] 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 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 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 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 pK_a's can be directly compared, without statistical correction[4] 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 pK_a units, which is lower than that found when the pK_a's of benzimidazole **8** and 5,6-dimethylbenzimidazole **11** (pK_a = 5.98)[4] are compared (ΔpK_a = 0.42). On the other hand, the N-methylation effect in these guanidinobenzimidazoles (ΔpK_a = 0.21) is significantly larger than that observed for the couple benzimidazole **8**/1-methylbenzimidazole **12** (pK_a = 5.55; ΔpK_a = -0.31 taking into account the statistical factor).[4] We consider these differences as a clear indication that guanidinobenzimidazoles do not protonate in the benzimidazole nitrogen.

In conclusion, the measured 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[3] and by Taylor.[2] This work is now in

progress.[10] 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 σ_I value ($\sigma_I = 0.32$).[2,11]

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 ± 0.2°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 ± 0.003; **3**, 7.324 ± 0.004; **5**, 7.300 ± 0.005.

N.M.R. Measurements. The spectra were recorded in a Bruker AM-200 and a Varian XL-300 supraconducting 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°C (decomp).

REFERENCES

[1] A simultaneous measurement[2] gives $pK_a = 6.97 \pm 0.05$.

[2] P.J. Taylor and A.R. Wait, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 1765.

[3] M. Charton, *J. Org. Chem.*, 1965, **30**, 969.

[4] J. Catalán, J.L.M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, 1987, **41**, 187.

[5] J. Catalán, J.L.G. de Paz and M. Yañez, *J. Mol. Struct., THEOCHEM*, 1984, **107**, 257.

[6] D. Rinaldi and J.L. Rivail, *C.R. Hebd. Seances Acad. Sci., Sér. C.*, 1972, **274**, 1664.

[7] 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.

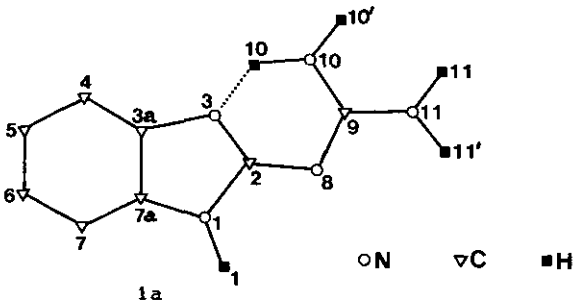
[8] R.W. Taft, personal communication.

[9] J. Elguero, G. LLouquet and C. Marzin, *Tetrahedron Lett.*, **1975**, 4085.

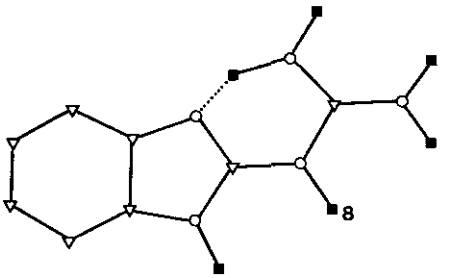
[10] J. Catalán, F. Fabero, M. Sánchez-Cabezudo and J. Elguero, unpublished results.

[11] Our pK_a values correspond to $\sigma_I = 0.30$ to 0.31.

Appendix



1a



2

Distances (Å) and angles (°)	1a	2
N(1)-C(2)	1.384	1.369
C(2)-N(3)	1.360	1.349
N(3)-C(3a)	1.403	1.409
C(3a)-C(4)	1.393	1.394
C(4)-C(5)	1.387	1.384
C(5)-C(6)	1.391	1.394
C(6)-C(7)	1.388	1.385
C(7)-C(7a)	1.389	1.391
C(7a)-C(3a)	1.420	1.416
C(2)-N(8)	1.362	1.388
N(8)-C(9)	1.352	1.385
C(9)-N(10)	1.351	1.332
C(9)-N(11)	1.372	1.360
N(1)-H(1)	1.065	1.065
N(10)-H(10)	1.169	1.216
N(10)-H(10')	1.068	1.069
N(11)-H(11)	1.064	1.064
N(11)-H(11')	1.064	1.064
N(8)-H(8)	-----	1.069
N(3)···H(10)	1.277	1.229
C(7a)-N(1)-H(1)	125.8	127.0
H(1)-N(1)-C(2)	125.9	126.7
C(7a)-N(1)-C(2)	108.3	106.3
N(1)-C(2)-N(8)	122.1	126.1
N(8)-C(2)-N(3)	127.1	120.6
N(3)-C(2)-N(1)	110.8	113.3
C(2)-N(8)-H(8)	-----	120.5
H(8)-N(8)-C(9)	-----	120.5
C(9)-N(8)-C(2)	111.2	119.0
N(8)-C(9)-N(11)	117.3	118.3
N(11)-C(9)-N(10)	119.2	125.1
N(10)-C(9)-N(8)	123.5	116.6
C(9)-N(10)-H(10')	119.1	117.0
H(10')-N(10)-H(10)	127.5	128.5
H(10)-N(10)C(9)	113.4	114.5
C(9)-N(11)-H(11')	122.6	123.3
H(11')-N(11)-H(11)	114.0	114.7
H(11)-N(11)-C(9)	123.4	122.0
H(10)···N(3)-C(3a)	146.7	145.7
C(3a)-N(3)-C(2)	106.1	105.0
C(2)-N(3)···H(10)	107.2	109.3
N(10)-H(10)···N(3)	137.6	140.0

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