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THE STRUCTURE OF NH-BENZAZOLES (1*H*-BENZIMIDAZOLES, 1*H*- AND 2*H*-INDAZOLES, 1*H*- AND 2*H*-BENZOTRIAZOLES)

The structure and properties (crystallography, NMR, theoretical calculations) of the three *N*-unsubstituted benzazoles (1*H*-benzimidazoles, 1*H*- and 2*H*-indazoles, 1*H*- and 2*H*-benzotriazoles) have been reviewed for the period 2000–2012 with some results from previous years. The study of these compounds will greatly increase in the coming years and it is expected that the present review will contribute to it.

Keywords: benzimidazoles, benzotriazoles, indazoles, tautomerism, DFT calculations, NMR spectroscopy, X-ray crystallography.

In 1974 we published a paper entitled "The benzazoles (benzimidazole, indazole, benzotriazole): molecular structure and fundamental properties" [1] where the three stable parent compounds **1**, **6**, and **12** were compared (Figs. 1–3, the possible tautomers of compounds **1**, **6**, and **12** were not reported in the solid state). Nearly forty years later the situation has much changed and thousands of papers and several books have been published on these heterocycles. This review will be limited to: 1) compounds bearing protons on the nitrogen atoms, NH-benzazoles (Figs. 1–3); 2) structural and theoretically calculated physico-chemical properties (synthetic aspects, reactivity, and biological properties will not be discussed); 3) the literature will cover mainly the 2000–2012 period, and 4) all our main contributions, published or in press, will be reported.

The results will be presented in the following order: general considerations, including calculations of the parent compounds, then benzimidazole, indazole, benzotriazole, and within each group, in the order gas-phase, solution and solid-state. Since in several publications there are topics belonging to different sections, and to avoid repetitions, they will be discussed in the section where their more interesting properties belong.

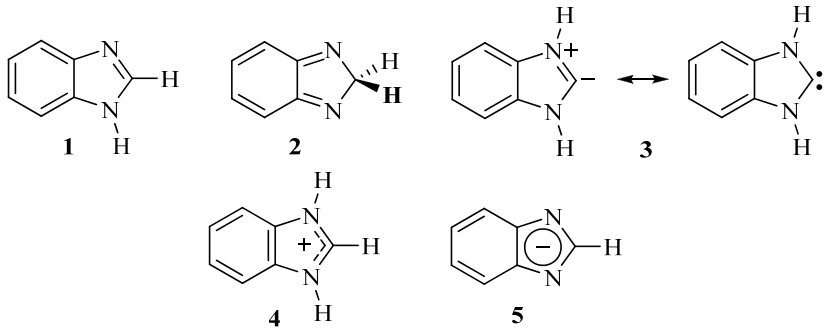


Fig. 1. Benzimidazoles: 1*H*-isomer **1**, 2*H*-isomer **2**, carbene **3**, benzimidazolium cation **4** and benzimidazolate anion **5**

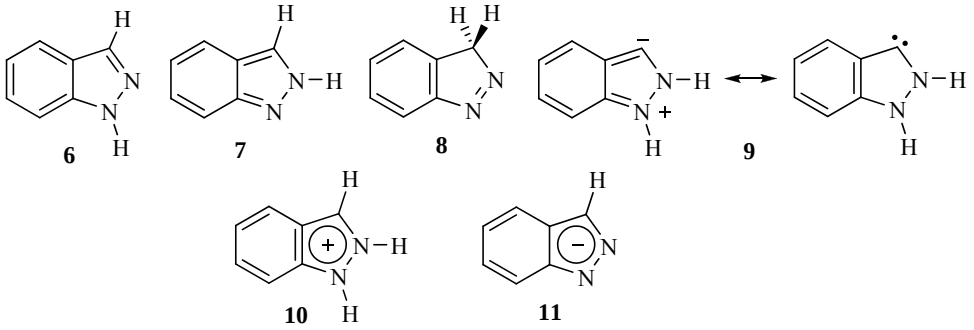


Fig. 2. Indazoles: 1*H*-isomer **6**, 2*H*-isomer **7**, 3*H*-isomer **8**, carbene **9**, indazolium cation **10** and indazolate anion **11**

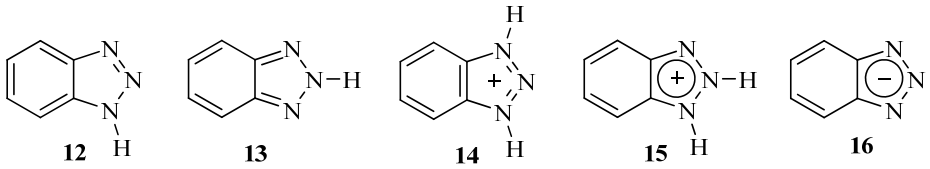
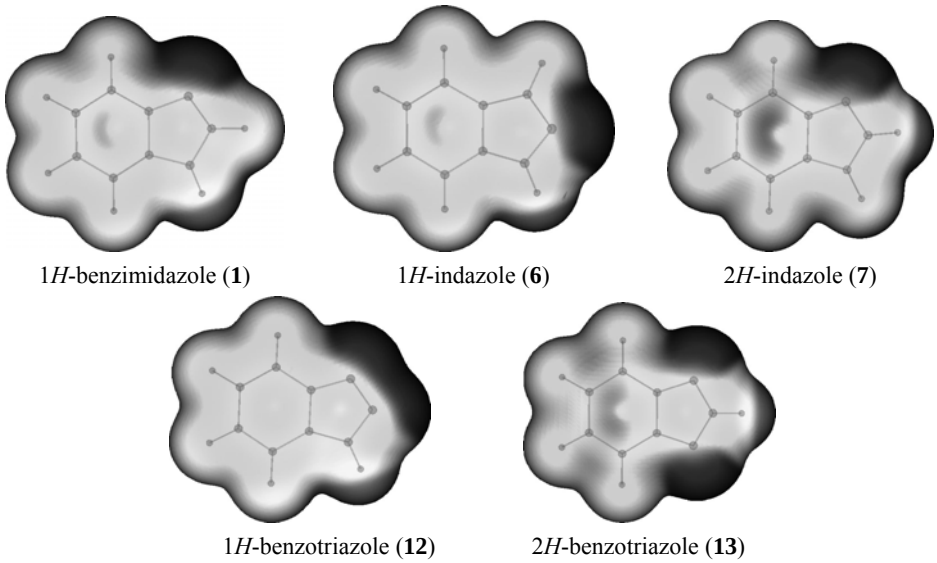


Fig. 3. Benzotriazoles: 1*H*-isomer **12**, 2*H*-isomer **13**, 1,3-di*H* benzotriazolium cation **14**, 1,2-di*H* benzotriazolium cation **15** and benzotriazolate anion **16**

In some cases, mainly related to theoretical calculations, we will discuss high energy tautomers, such as CH compounds **2** and **8** and heterocyclic carbenes **3** and **9**. For indazole-derived carbenes (much less common than those derived from benzimidazole [2–4]), see reference [5].

Generalities, computational aspects, and methodological considerations for the three heterocycles

The maps of electrostatic potential (MEP) of compounds **1**, **6**, **7**, **12**, **13** have been calculated at the B3LYP/6-311++G(d,p) level (Fig. 4) [6].



1*H*-benzimidazole (**1**) 1*H*-indazole (**6**) 2*H*-indazole (**7**)

1*H*-benzotriazole (**12**) 2*H*-benzotriazole (**13**)

Fig. 4. MEPs of benzazoles: the NH part and the N lone pairs appear darker

Benzazoles bearing no substituents on the N atoms have been the subject of a large number of theoretical papers covering a wide range of levels, see for benzimidazoles [7–13], indazoles [14–23], and benzotriazoles [18, 24–36], the more recent articles using higher levels. None of these publications covers all three heterocycles although some of them include substituted derivatives. There is also a great deal of experimental information about benzazoles that will be reported when comparing calculations and experiments. This section will describe the results of the study of the sixteen compounds reported in Figures 1 (benzimidazoles), 2 (indazoles) and 3 (benzotriazoles).

We have included, along with the neutral molecules, the non-aromatic tautomers **2** and **8**, as well as the Arduengo's heterocyclic carbenes **3** (benzimidazol-2-ylidene) and **9** (indazol-3-ylidene) [37–40]. Cations and anions were studied to evaluate basicity and acidity of the respective heterocycles.

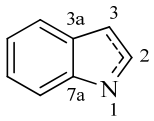
Geometries

First we will compare the calculated geometries (Table 1) [6] with those reported in the Cambridge Structural Database (CSD) [41]. The structures and the corresponding Refcodes are reported in Figure 5.

We will limit the discussion to the 5-membered ring (the azole moiety) and only to non-hydrogen atoms (C and N) since the distances involving H atoms are underestimated in X-ray crystallography [42]. For compounds **4**, **14** and **16**, with C_{2v} symmetry, the experimental values have been averaged.

Table 1

Comparison between calculated (top) and average experimental X-ray geometries (bottom)



Com-pound	Distances, Å					Angles, deg.				
	1–2	2–3	3–3a	3a–7a	7a–1	1–2–3	2–3–3a	3–3a–7a	3a–7a–1	7a–1–2
Benzimidazoles										
1	1.377	1.304	1.389	1.414	1.385	113.5	105.0	110.3	104.5	106.8
	1.345	1.315	1.395	1.396	1.378	114.1	104.1	109.6	105.5	106.0
4	1.333	1.333	1.398	1.404	1.398	109.0	109.6	105.9	105.9	109.6
	1.327	1.327	1.382	1.398	1.382	109.0	109.4	106.0	106.0	109.4
Indazoles										
6*	1.358	1.318	1.429	1.416	1.367	106.1	111.5	104.3	105.6	112.5
	1.375	1.304	1.414	1.404	1.355	106.0	112.4	103.6	107.4	110.8
10	1.358	1.334	1.403	1.426	1.364	110.6	107.9	106.0	107.1	108.5
	1.342	1.321	1.408	1.414	1.356	111.8	107.2	105.4	108.0	107.6
Benzotriazoles										
12	1.362	1.287	1.380	1.408	1.364	108.8	108.7	108.6	103.0	110.8
	1.343	1.309	1.370	1.386	1.355	108.5	108.2	108.5	104.2	110.7
14	1.309	1.309	1.376	1.408	1.376	105.1	113.4	104.1	104.1	113.4
	1.312	1.312	1.362	1.391	1.362	105.3	112.6	104.8	104.8	112.6
15	1.351	1.291	1.353	1.426	1.359	113.7	105.6	109.4	104.3	106.9
	1.317	1.311	1.387	1.378	1.364	106.8	110.4	105.9	104.9	112.0
16	1.338	1.338	1.361	1.422	1.361	113.1	106.1	107.3	107.3	106.1
	1.330	1.330	1.360	1.389	1.360	111.8	106.7	107.4	107.4	106.7

* Including a recent determination of the structure of indazole still not part of the CSD [23].

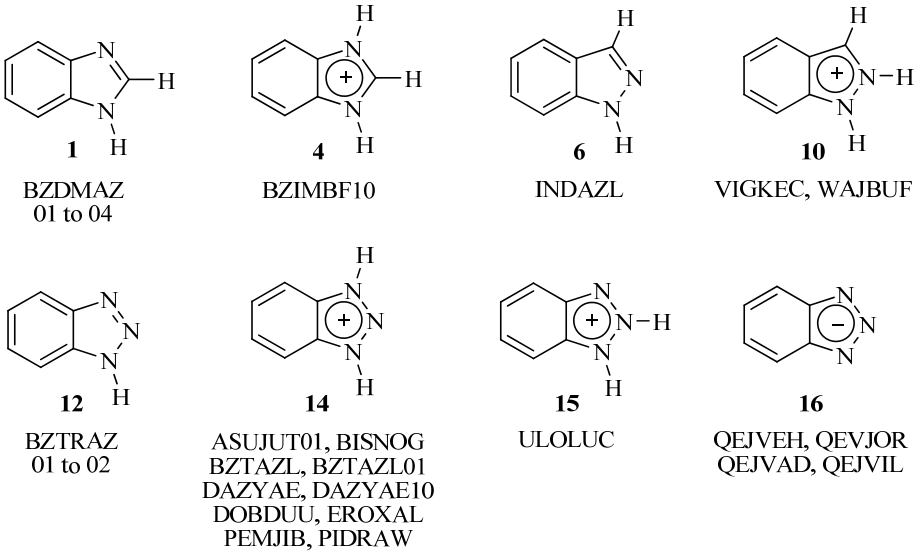


Fig. 5. Structures determined by X-ray crystallography
(Refcodes of Cambridge Structural Database are given)

Excluding the experimental structure **15** (ULOLUC) for the reasons explained below, the following relationships have been found between the experimental and calculated values of the distances (eq. 1) and angles (eq. 2) in Table 1 (n – number of points, R^2 – square correlation coefficient):

$$\text{Exp. (Å)} = (0.22\pm0.06) + (0.83\pm0.04)\ \text{calc. (Å)},\ n = 35,\ R^2 = 0.91 \qquad (1)$$

$$\text{Exp. (°)} = (11.5\pm4.5) + (0.89\pm0.04)\ \text{calc. (°)},\ n = 35,\ R^2 = 0.93 \qquad (2)$$

The worst agreement is observed for the 1–2 distances in benzimidazole (**1**) (–0.022 Å) and in indazole (**6**) (+0.024 Å), the 2–3–3a angle in benzimidazole (**1**) (–1.2°), and the 3a–7a–1 angle in indazole (**6**) (+1.6°).

The structure **15** appears to be an exception, since benzotriazole (**12**) upon protonation thus would form a 1*H*,2*H*-cation. A simple examination of Table 1 data reveals that the published structure was wrong and that the cation should have the structure **14**. According to equations 1 and 2, the 1*H*,2*H*-cation **15** should have the following geometry: distances 1.345 (1–2), 1.296 (2–3), 1.347 (3–3a), 1.408 (3a–7a), and 1.352 Å (7a–1), angles 113.1 (1–2–3), 105.8 (2–3–3a), 109.2 (3–3a–7a), 104.7 (3a–7a–1), and 107.0° (7a–1–2), very different from the ones measured [43]. The structure of ULOLUC contains seven benzotriazolium cations, which is a strange number, two molecules of ethanol and five molecules of water; besides, the two anions are very bulky, $Mo_{12}O_{40}P^{3-}$ and $Mo_{12}O_{40}P^{4-}$, all of this can explain the error in locating the proton.

Two compounds show polymorphism [44, 45]: benzimidazole (**1**) and benzotriazole (**12**). The same year, 2005, Krawczyk and Gdaniec described the structure of two additional polymorphs of benzimidazole [46] and benzotriazole [47]. Previous structures of these compounds were solved in 1974 [48, 49]. Old benzimidazole polymorph (α) is stable while the new polymorph (β) is metastable at room temperature. In both polymorphs, benzimidazole molecules are connected

into polymeric chains *via* N–H···N hydrogen bonds (HBs). However, the mode of aromatic ring interactions differs significantly in the two crystalline forms. In the α form, the molecules show edge-to-face interactions, whereas in the new β form, a sandwich–herringbone arrangement of the aromatic molecules is observed.

The α polymorph of compound **12** consists of 1*H*-tautomers. Three out of the four symmetry-independent molecules are connected into polymeric chains *via* N–H···N HBs, whereas the fourth molecule is attached to the chain *via* N–H···N and C–H···N interactions. In the β polymorph all molecules also correspond to the 1*H*-tautomer **12**. A cyclic decamer (a centrosymmetric 10-membered ring) is formed *via* N–H···N HBs, but the HBs in eight molecules use the N(3) lone pair and in two – the N(2) lone pair.

The structure of indazole (**6**) deserves further comments. The structure published by Escande and Lapasset has the hydrogen atom of the NH group out of plane with respect to the remaining atoms and, therefore, a diastereogenic center on the N-1 atom (at least, in the crystal, where no N inversion occurs) [50]. This point was verified recently [23] searching for a possible explanation of the fact that **6** crystallizes in a non-centrosymmetric group ($P2_1$); note that **6** shows spontaneous resolution (conglomerate).

Concerning the geometries without experimental counterparts, the most interesting are those of the carbenes (Fig. 6). Dihedral angle (θ) is defined as the H–N···N–H angle for carbene **3** and H–N–N–H angle for carbene **9**.

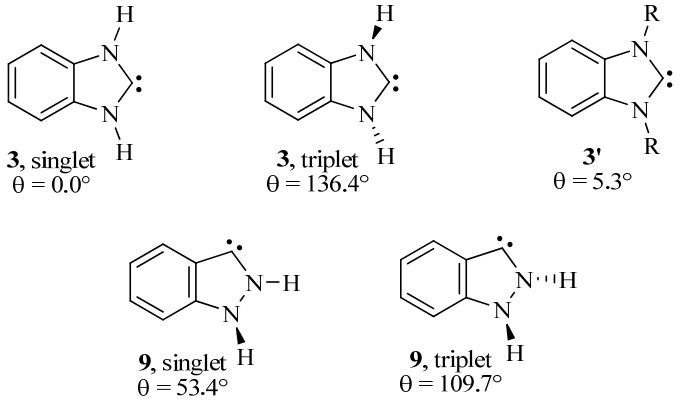


Fig. 6. Structures of the carbenes **3** and **9**. That of carbene **3'** was determined by X-ray crystallography (the value of θ = 5.3° corresponds to the average)

The following structures of type **3'** are found in the CSD (some of them having several independent benzimidazol-2-ylidene molecules, in all ten different geometries) [41]: LOGVUY, POYKOE, RENYEP, RENYIT, RENZEQ, SIRJIN and YUXJUX. The average value of θ is 5.3° with one of the structures being planar (θ = 0.0°). These geometries clearly belong to singlet carbenes. No data are available for indazol-3-ylidenes related to carbene **9**.

Energies

Table 2 summarizes the energies corresponding to compounds **1**–**16** [6]. These energies will be discussed in relation to tautomerism and to acid-base properties.

Table 2

Energies (*E*, absolute in hartree, relative in kJ·mol^{-1}) and dipole moments (*D*) of the minima (ZPE – zero-point energy)

Compound	E_{total}	E_{total} + ZPE	*D*	E_{rel}	E_{rel} + ZPE
			Benzimidazoles		
1	–379.96728	–379.84964	3.54	0.0	0.0
2	–379.91699	–379.80081	2.19	132.0	128.2
3 singlet	–379.92849	–379.81028	2.46	101.8	103.3
3 triplet	–379.80386	–379.68895	0.88	429.1	421.9
4	–380.34313	–380.21144	4.89		PA (kJ·mol^{-1}) = –949.9
5	–379.41226	–379.30831	3.34		ΔH° (acidity) = 1421.2
			Indazoles		
6	–379.94402	–379.82632	1.84	0.0	0.0
7	–379.93619	–379.81831	2.55	20.5	21.0
8	–379.91226	–379.79611	3.86	83.4	79.3
9 singlet	–379.87267	–379.75568	3.88	187.3	185.5
9 triplet	–379.79570	–379.68033	1.19	389.4	383.3
10	–380.30077	–380.17048	5.05		PA (kJ·mol^{-1}) = –903.6
11	–379.37684	–379.27401	5.59		ΔH° (acidity) = 1450.1
			Benzotriazoles		
12	–395.97098	–395.86564	4.20	0.8	0.0
13	–395.97129	–395.86472	0.28	0.0	2.4
14	–396.33225	–396.21243	1.19	0.0	PA (kJ·mol^{-1}) = –910.5
15	–396.31146	–396.19314	4.67	50.7	PA (kJ·mol^{-1}) = –859.8
16	–395.42371	–395.33214	6.45		ΔH° (acidity) = 1400.7

Tautomerism

For neutral molecules, the stability decreases in the order **1** > **3** (singlet) > **2** > **3** (triplet) (benzimidazole); **6** > **7** > **8** > **9** (singlet) > **9** (triplet) (indazole); **12** ≈ **13** (benzotriazole). For benzotriazolium cations, the order is **14** > **15**.

Although triplet carbenes are known [51] in all reported heterocyclic derivatives, triplet carbenes are appreciably less stable than singlet carbenes [2, 4, 52].

Experimental results concern only the NH-tautomers, and they confirm that **6** > **7**, **12** ≈ **13**. In the case of indazole, the pair of compounds **6**/**7** has been known for a long time [53]. The case of the tautomer pair **12**/**13** although discussed in Minkin's review [53], has been revisited many times with the conclusion that both tautomers have similar stabilities and that the actual result depends on the environment [24–36].

A less studied case involves benzotriazolium cations **14**/**15**. Catalán *et al*. favored the 1*H*,3*H*-tautomer **14** based on thermodynamic considerations [24]. Others authors have written the cation with the 1*H*,3*H*-structure **14** or with the 1*H*,2*H*-structure **15**, but without any experimental back-up [54, 55]. In the solid state (see "Geometries" section), only cations **14** have been reported.

Tautomerism of indazoles and benzotriazoles is related to aromaticity and to lone pair / lone pair repulsion in adjacent N atoms (for instance in compound **12**) [15, 24, 25, 56, 57].

Acid-base equilibria

For this part of our review we have found relevant data in two sources. The following values are reported in NIST [58]: PA (benzimidazole) = –953.8 kJ·mol^{-1}; PA (indazole) = –900.8 kJ·mol^{-1}; $\Delta H°$ (indazole) = 1457 kJ·mol^{-1}; $\Delta H°$ (benzotriazole) = 1415 kJ·mol^{-1}. In our review of 1987 concerning the acid-base properties of azoles, the following pK_a values are reported [59]: basicity – benzimidazole 5.56, indazole 1.04, benzotriazole 1.6; acidity – benzimidazole 12.86, indazole 13.86, benzotriazole 8.38. Comparing these numbers with the calculated ones reported in Table 2, equations 3–5 are obtained.

$$PA_{exp} = (3.8\pm2.6) + (1.005\pm0.002)\ PA_{calc}, \quad n = 4,\ R^2 = 0.999991 \qquad (3)$$

$$pK_a\ (basic) = -(88.1\pm2.2) - (0.099\pm0.002)\ PA_{calc},\ n = 3,\ R^2 = 0.9994 \qquad (4)$$

$$pK_a\ (acid) = -(139.1\pm72.7) + (0.106\pm0.002)\ \Delta H°,\ n = 3,\ R^2 = 0.811 \qquad (5)$$

Equations (3) and (4) are excellent, however, equation (5) is far from acceptable. The pK_a values determined in water that correspond to deprotonation (from neutral to anion) are probably influenced by solvent and counterion effects. The problem of basicity and acidity of azoles and benzazoles has been discussed by Catalán, Palomar, and de Paz [60].

Chemical shifts

All the calculated absolute shieldings, as well as all the known chemical shifts [6] are reported in Table 3. Due to fast prototropic exchange between the N atoms, some values of compounds **1**, **12** and **15** in solution have been averaged.

T a b l e 3

Calculated absolute shieldings (σ, ppm) and experimental chemical shifts (δ, ppm)

Compound	Atom	σ	Average σ solution (300 K)	Exp. δ solid (300 K)	Exp. δ CD_3OD (178 K)	Exp. δ another value
1	2	3	4	5	6	7
			Benzimidazoles			
1	N-1	100.50			–	–232.6 [61]
	N-3	–28.04	36.23	–185.0 [62]	–	–153.5
	C-2	40.90		141.5 [63]	142.6 [63, 64]	143.0
	C-3a	32.46			143.0	143.0
	C-7a	44.62	38.54	137.9	136.1	134.4
	C-4	56.06			119.9	119.7
	C-7	70.03	63.04	115.4	112.2	113.7
	C-5	56.06			122.1	123.9
	C-6	54.87	55.46	122.9	123.0	124.7
4	N-1(3)	85.54				
	C-2	45.11		137.0 [65]		
	C-3a/C-7a	48.29		128.4		
	C-4/C-7	64.10		113.3		
	C-5/C-6	44.00		126.3		

Table 3 (continued)

1	2	3	4	5	6	7
			Indazoles			
6	N-1	62.04		–200.6 [66]	–196.6 [61]	
	N-2	–90.90		–65.1	–77.5	
	C-3	43.71		133.4 [67]	134.4 [61, 64]	
	C-3a	53.02		122.8	123.3	
	C-4	57.27		120.4	121.8	
	C-5	57.58		120.1	121.8	
	C-6	51.89		125.8	126.6	
	C-7	70.92		110.0	111.6	
	C-7a	37.49		139.9	140.9	
10	N-1	87.53				
	N-2	65.29				
	C-3	45.18		129.8 [65, 67]		
	C-3a	57.50		118.4		
	C-4	52.37		121.4		
	C-5	46.51		124.7		
	C-6	34.49		140.2		
	C-7	68.97		109.9		
	C-7a	37.30		138.1		
			Benzotriazoles			
12	N-1	25.34			–157.6 [61, 68]	
	N-3	–130.58	–52.62	–96.7 [62]	–56.4	
	N-2	–157.44		–7.5	–24.5	
	C-3a	31.73			142.5 [64]	
	C-7a	45.29	38.51	139.8 [68]	132.7	
	C-4	56.53			115.5	
	C-7	71.42	63.98	115.4	110.7	
	C-5	56.33			123.4	
	C-6	50.66	53.50	125.9	123.4	
14	N-1(3)	20.11		–158.0 [68]		
	N-2	–129.32		–29.4		
	C-3a/C-7a	44.00		133.8 [68]	135.0 [54]	
	C-4/C-7	65.43		113.2	115.1	
	C-5/C-6	42.20		131.9	131.8	

No experimental data (only σ values in ppm):

Compound	Atom	σ, ppm	Atom	σ, ppm	Atom	σ, ppm
1	2	3	4	5	6	7
2	N-1(3)	–168.54	C-2	83.84	C-3a/C-7a	13.06
	C-4/C-7	48.76	C-5/C-6	43.78		
3 singlet	N-1(3)	68.59	C-2	–55.68	C-3a/C-7a	43.69
	C-4/C-7	69.43	C-5/C-6	56.45		
3 triplet	N-1(3)	144.55	C-2	66.23	C-3a/C-7a	40.54
	C-4/C-7	65.47	C-5/C-6	54.40		
5	N-1(3)	–11.10	C-2	22.38	C-3a/C-7a	26.59
	C-4/C-7	63.32	C-5/C-6	67.28		
7	N-1	–62.24	N-2	26.88	C-3	59.49
	C-3a	55.42	C-4	57.95	C-5	55.35
	C-6	52.20	C-7	58.00	C-7a	27.54
8	N-1	–279.24	N-2	–282.41	C-3	98.90
	C-3a	38.28	C-4	56.72	C-5	49.21
	C-6	49.90	C-7	55.78	C-7a	17.70

Table 3 (end)

1	2	3	4	5	6	7
9 singlet	N-1	70.11	N-2	49.01	C-3	–75.62
	C-3a	38.96	C-4	42.07	C-5	56.23
	C-6	46.55	C-7	69.94	C-7a	36.11
9 triplet	N-1	121.33	N-2	113.72	C-3	26.76
	C-3a	56.78	C-4	67.36	C-5	51.73
	C-6	58.71	C-7	70.88	C-7a	25.95
11	N-1	–98.53	N-2	–154.82	C-3	50.83
	C-3a	51.66	C-4	62.82	C-5	68.98
	C-6	66.10	C-7	62.56	C-7a	25.00
13	N-1(3)	–90.75	N-2	–17.10	C-3a/C-7a	33.04
	C-4/C-7	58.30	C-5/C-6	51.43		
15	N-1	50.30	N-3	–119.91	N-2	21.91
	C-3a	34.63	C-7a	45.57	C-4	51.81
	C-7	69.26	C-5	42.64	C-6	32.26
16	N-1(3)	–112.96	N-2	–212.55	C-3a/C-7a	29.68
	C-4/C-7	63.32	C-5/C-6	65.62		

The data from Table 3 when analyzed afford the following equations:

$$\delta^{15}\text{N (solid)} = -(145.7\pm3.8) - (0.740\pm0.036)\ \sigma^{15}\text{N},\ n = 5,\ R^2 = 0.993 \quad (6)$$

$$\delta^{15}\text{N (solution, average)} = -(145.8\pm1.8) - (0.891\pm0.020)\ \sigma^{15}\text{N},\ n = 7,\ R^2 = 0.997 \quad (7)$$

$$\delta^{13}\text{C (solid)} = (172.1\pm2.7) - (0.872\pm0.047)\ \sigma^{13}\text{C},\ n = 23,\ R^2 = 0.932 \quad (8)$$

$$\delta^{13}\text{C (solid)} = (170.4\pm2.4) - (0.854\pm0.046)\ \sigma^{13}\text{C} + (7.1\pm2.5)\ \text{C-2},\ n = 23,\ R^2 = 0.952 \quad (9)$$

$$\delta^{13}\text{C (MeOH)} = (174.2\pm5.8) - (0.893\pm0.112)\ \sigma^{13}\text{C},\ n = 27,\ R^2 = 0.927 \quad (10)$$

$$\delta^{13}\text{C (MeOH)} = (169.3\pm4.2) - (0.817\pm0.078)\ \sigma^{13}\text{C} + (7.1\pm2.6)\ \text{C-2},\ n = 7,\ R^2 = 0.975 \quad (11)$$

$$\delta^{13}\text{C (solution, average)} = (172.6\pm2.5) - (0.911\pm0.049)\ \sigma^{13}\text{C},\ n = 28,\ R^2 = 0.930 \quad (12)$$

$$\delta^{13}\text{C (solution, average)} = (170.4\pm2.1) - (0.877\pm0.039)\ \sigma^{13}\text{C} + (6.6\pm1.6)\ \text{C-2},\ n = 28,\ R^2 = 0.959 \quad (13)$$

Equations (9), (11) and (13) were calculated to obtain a value for benzimidazole C-2, that systematically deviated by about 7 ppm. It appears that the B3LYP/6-311++G(d,p) method cannot reproduce satisfactorily this atom, perhaps because it is situated between a pyrrole-like N(H) and a pyridine-like nitrogen atom. An attempt to improve the results using GIAO/MP2/6-111++G(d,p) calculations failed [6].

Using equations (7) and (13) the following chemical shift values are predicted for carbenes **3** (benzimidazol-2-ylidene) and **9** (indazol-3-ylidene) in their singlet and triplet states (Fig. 7). The chemical shifts are very different, including some carbons of the benzene ring, particularly in the case of carbene **9**. The ^{13}C chemical shift of carbon C-2 of the diadamantyl derivative **3"** has been reported (223.0 ppm), leaving no doubt about carbene **3** being a singlet [2, 4, 52]. In the case of carbene **9**, its dimethyl derivative **9"** has been characterized by mass spectrometry, but it is too labile to record its ^{13}C NMR spectrum [69–71].

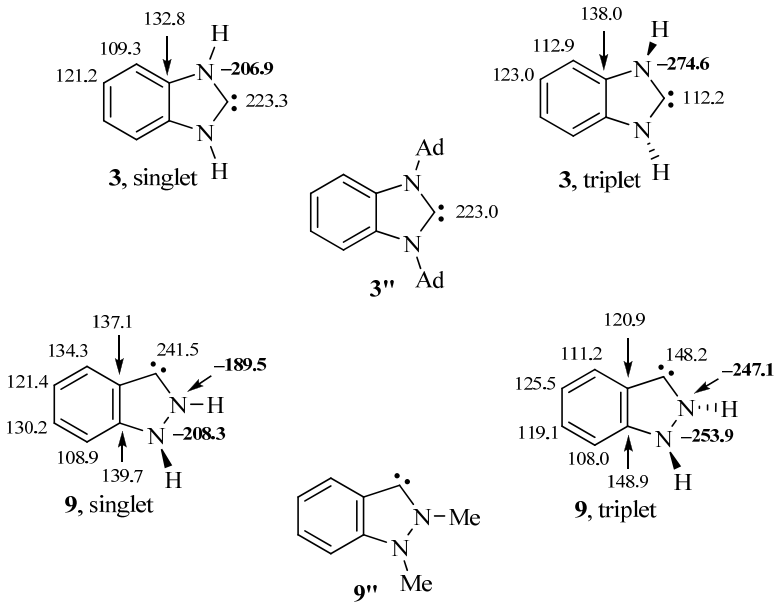


Fig. 7. Predicted (top) and experimental (bottom, only for **3"**) ^{13}C and ^{15}N (bold) chemical shifts of singlet and triplet carbenes

Aromaticity

We will discuss the aromaticity of the studied compounds using Schleyer's nucleus-independent chemical shift (NICS). We have calculated their values at 0, 1, and 2 Å (Table 4), but we will use the NICS(1) values as a good compromise between NICS(0), too close to the sigma frame, and NICS(2), less sensitive. For non-planar compounds, carbenes **3t** (triplet), **9s** (singlet) and **9t** (triplet), we have calculated the NICS above and below the ring plane. However, as the perturbation arises from H atoms, the values are very similar and in Figure 8 we have averaged their values. We have also reported the sum of the NICS of the 6- and the 5-membered rings (Σ, ppm).

Table 4

NICS values on both rings of benzazoles determined in the center of the ring at 0, 1 and 2 Å above the ring plane

Com-pound	6-membered ring			5-membered ring		
	NICS(0)	NICS(1)	NICS(2)	NICS(0)	NICS(1)	NICS(2)
1	2	3	4	5	6	7
			Neutral			
1	–10.1	–11.1	–5.3	–11.4	–10.1	–4.3
6	–9.5	–10.6	–5.2	–12.9	–11.7	–4.7
7	–7.5	–9.2	–4.7	–15.6	–13.4	–5.3
12	–9.8	–11.0	–5.4	–13.0	–12.7	–5.1
13	–8.0	–9.7	–4.9	–15.4	–14.2	–5.5
			Cations			
4	–10.9	–11.8	–5.3	–12.6	–9.1	–3.8
10	–8.5	–10.2	–5.0	–14.9	–11.0	–4.3
14	–10.2	–11.3	–5.4	–14.6	–11.8	–4.6
15	–8.4	–10.2	–5.1	–15.6	–12.5	–4.8
			Anions			
5	–9.4	–10.6	–5.1	–11.2	–12.5	–5.3
11	–8.4	–9.6	–4.9	–13.3	–14.6	–5.9
16	–9.1	–10.3	–5.2	–13.1	–15.2	–6.0

Table 4 (end)

1	2	3	4	5	6	7
			Carbenes			
3s	–10.7	–11.3	–5.2	–10.6	–9.5	–3.9
3t (above)	–7.5	–8.4	–3.7	–3.1	–0.2	–0.4
3t (below)	–7.5	–8.5	–3.6	–3.1	0.0	0.0
9s (above)	–8.7	–10.5	–5.2	–9.3	–9.1	–3.9
9s (below)	–8.7	–10.3	–5.0	–9.3	–9.3	–3.9
9t (above)	–4.4	–6.0	–2.8	–4.7	–1.3	–0.3
9t (below)	–4.4	–5.7	–2.7	–4.7	–1.2	–0.3

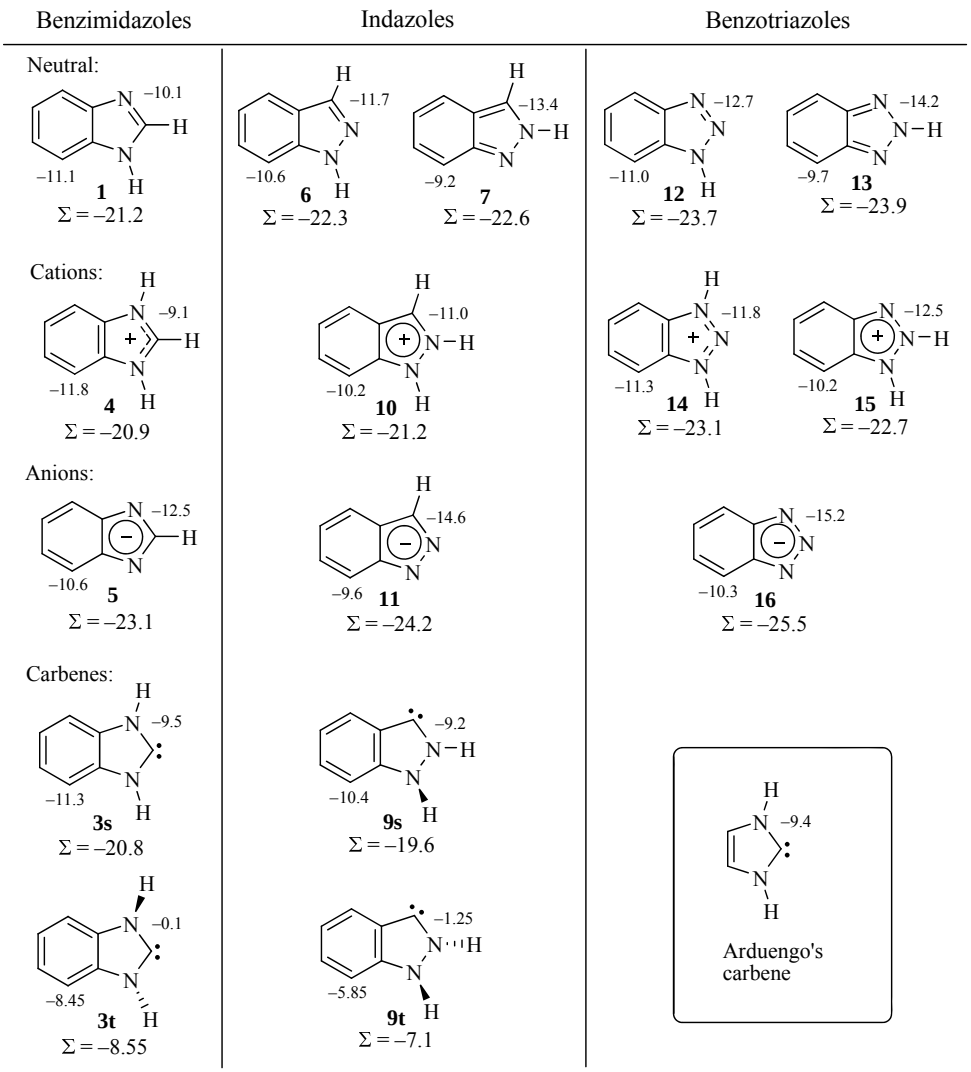


Fig. 8. NICS(1) values (ppm) and sum of the NICS(1) values for both rings (Σ)

The values reported in Figure 8 deserve several comments:

1) If we consider Σ as a descriptor of benzazole aromaticity, Σ increases in absolute value (the compound becomes more aromatic) following the order:

benzimidazole < indazole < benzotriazole and in the order cation < neutral < anion. Thus, the less aromatic is the benzimidazolium cation **4**, and the most aromatic is the benzotriazolate anion **16**. Martin *et al*. reported that, according to NICS approach, indazole is more aromatic than benzimidazole [72]. Novak *et al*. reported that the NICS of the 6-membered ring is lower for structure **13** than for structure **12** [35].

2) The singlet carbenes **3s** and **9s** are aromatic compounds with Σ values about –20 ppm similar to the cations **4** and **10**. Using other aromaticity criteria, imidazol-2-ylidenes appear slightly less aromatic than imidazolium cations [73]. For Arduengo's *N*-heterocyclic carbene (Fig. 8) a NICS(1) value of –9.4 ppm has been recently reported [74].

3) The 6-membered rings are always aromatic, but Σ values vary from –5.85 (carbene **9t**) to –11.8 ppm (cation **4**). Tautomerism affects the NICS of this ring, being higher in the more aromatic tautomer (benzenoid: compounds **6**, **12**) than in the less aromatic tautomer (quinonoid: compounds **7**, **13**). In singlet carbenes, NICS values of the 6-membered rings are similar to those of the corresponding cations. In triplet carbenes, the 6-membered rings suffer a great decrease in aromaticity, more in indazoles than in benzimidazoles; this is probably related to the distance between the carbene center and the benzene ring.

4) Triplet carbenes **3t** and **9t** have non-aromatic 5-membered rings. This is a new and interesting result. It is known that between singlet and triplet states there is an inversion of aromaticity and anti-aromaticity [75–77]. Here, we move from an aromatic singlet to a non-aromatic triplet.

We decided to use a technique we have recently developed to represent the NICS values on one van der Waals isosurface [78] (Table 5). Figure 9 illustrates the NICS values on the electron density isosurface of 0.001 au. The central black part corresponds to regions with NICS values less than –5 ppm, while the grey periphery belong to positive NICS values. For instance, similar distributions can be found in the 6-membered ring when comparing 1*H*-benzimidazole (**1**) and 1*H*-indazole (**6**), but some differences appear in the 5-membered ring. Thus, comparing compounds **6** and **7**, the effect of the position of the NH proton, either on N-2 or on N-1, is observed. When the proton changes from N-2 to N-1, there is an enlargement of the negative area on the 5-membered ring concomitantly with a contraction of that area over the 6-membered ring. These effects are reflected in the minimum values on the van der Waals surface, which suffer an inversion from compound **6** (–6.2, –5.7 ppm, 6- and 5-membered rings, respectively) to compound **7** (–5.6, –6.4 ppm, 6- and 5-membered rings, respectively). The same features can be observed for compounds **12** and **13**.

Cations **4** and **10** show very similar NICS arrangement to those observed in the neutral parent molecules (compounds **1** and **6**) with a main difference, the negative area on the 5-membered ring is considerably smaller than in the neutral ones. The protonation of compound **12** to afford cation **14** is accompanied by a slight decrease (in absolute value) of the minimum NICS value on the 5-membered ring (from –6.5 to –6.0 ppm), while for the 6-membered ring it remains almost constant. The same occurs going from compound **13** to cation **15** introducing slight differences, observable in both rings. In the comparison between cations **14** (1*H*,3*H*-) and **15** (1*H*,2*H*-), the effect of the position of the proton is again apparent, following the same pattern observed in the comparison between compounds **6** and **7** (or between compounds **12** and **13**).

Table 5

NICS minima values on the van der Waals surfaces

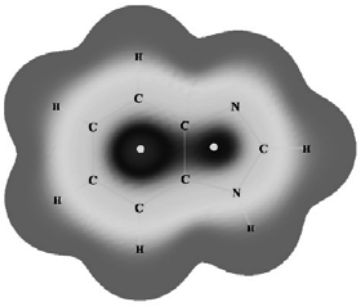
Compound	6-membered ring	5-membered ring
1*H*-benzimidazole (**1**)	–6.3	–5.3
1*H*-indazole (**6**)	–6.2	–5.7
2*H*-indazole (**7**)	–5.6	–6.4
1*H*-benzotriazole (**12**)	–6.4	–6.5
2*H*-benzotriazole (**13**)	–5.8	–7.0
1*H*-benzimidazol-3-ium (**4**)	–6.6	–4.9
1*H*-indazol-2-ium (**10**)	–6.1	–5.3
1*H*-benzotriazol-3-ium (**14**)	–6.6	–6.0
1*H*-benzotriazol-2-ium (**15**)	–6.2	–6.3
Benzimidazolate (**5**)	–6.0	–6.3
Indazolate (**11**)	–5.7	–7.1
Benzotriazolate (**16**)	–6.1	–7.4
Benzimidazol-2-ylidene (**3**) singlet	–6.2	–4.8
Benzimidazol-2-ylidene (**3**) triplet*	–4.5 (–4.4)	–
Indazol-3-ylidene (**9**) singlet*	–6.2 (–6.0)	–4.8 (–4.8)
Indazol-3-ylidene (**9**) triplet*	–3.4 (–3.3)	–

* Values correspond to up (down) positions over the ring.

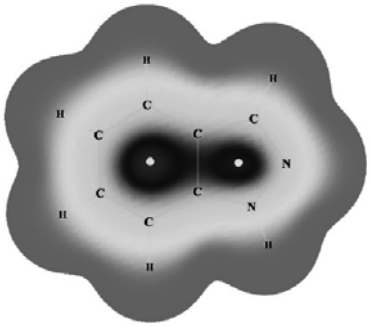
The comparison of the negative zones over the rings in anions **5**, **11**, and **16** shows the increasing negative NICS values on both rings in going from benzimidazolate to indazolate, and to benzotriazolate, this increase larger being for the 5-membered ring than for the 6-membered ring.

In the singlet carbenes **3s** and **9s**, the position of the carbene center corresponds to the light grey region around the C atoms (C-2 and C-3), showing more negative values around it than around the vicinal C atoms. Finally, one interesting observation arises from the comparison between singlet and triplet states. When the surfaces of carbenes **3s** and **3t** are examined the increase of the NICS values is evident. The minimum located on the 6-membered ring becomes less negative (from –6.2 to –4.5 ppm) and that over the 5-membered one completely disappears. Instead of the minima, a large area with positive NICS value is present over the 5-membered ring. Similar, but enhanced features, are observed in the carbenes **9s** *vs*. **9t** comparison, where the variation of the 6-membered ring minimum is more pronounced (from –6.2 to –3.4 ppm). These are in agreement with the non-aromatic nature of the triplet carbenes discussed previously.

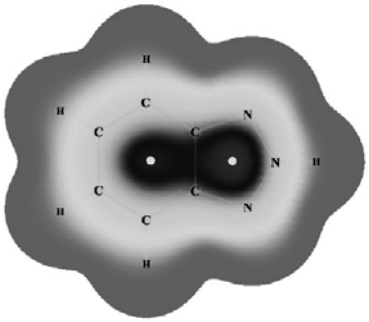
Concerning solution NMR studies, one of the most useful approaches is the comparison of experimental chemical shifts (δ, ppm) with calculated absolute shieldings (σ, ppm) [53, 57, 79, 80]. These were obtained using the GIAO method and a DFT calculated minimum energy structure. To improve the results, the introduction of solvent effects through continuum models, like PCM, and/or specific solvent molecules, have been used. Empirical equations of the type $\delta = a_0 + a_1\sigma$ have been established for several nuclei (Table 6). This approach transforms calculated values for the gas phase into experimental results in solution. Note that a_0 is close, but not identical to the σ value of the reference compound and a_1 is close, but not identical to 1.



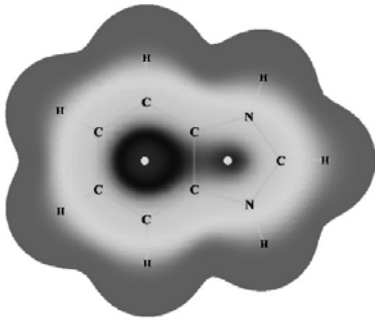
1*H*-benzimidazole (**1**)



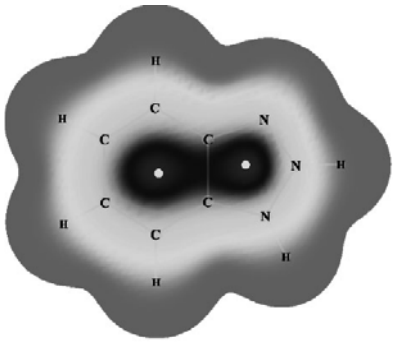
1*H*-indazole (**6**)



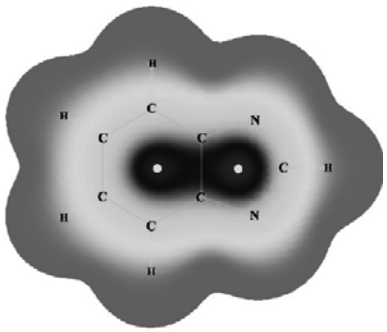
2*H*-benzotriazole (**13**)



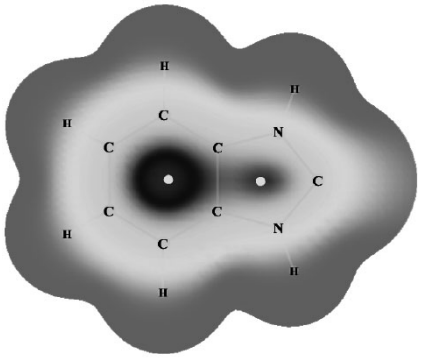
1*H*-benzimidazol-3-ium (**4**)



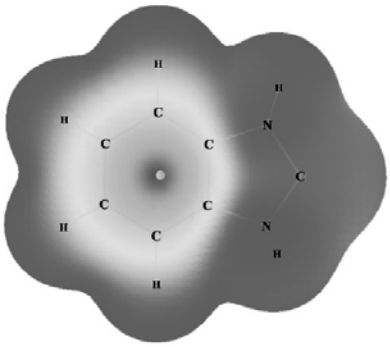
1*H*-benzotriazol-2-ium (**15**)



Benzimidazolate (**5**)

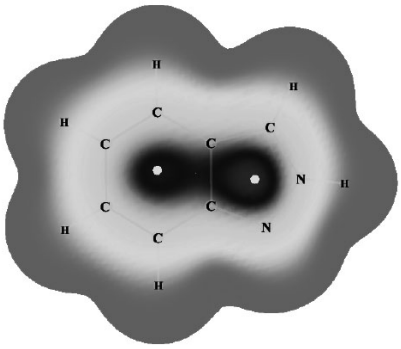


Benzimidazol-2-ylidene (**3s**)

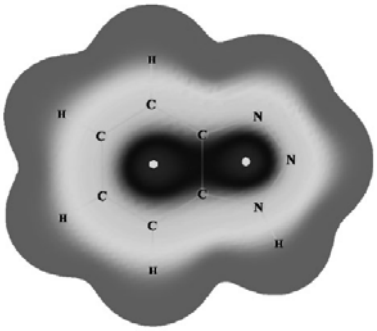


Benzimidazol-2-ylidene (**3t**)

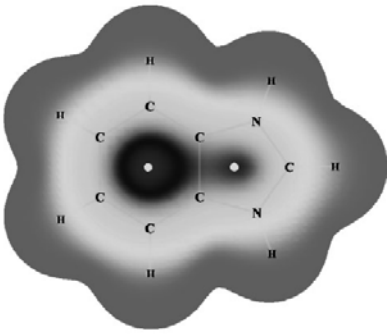
Fig. 9. 3D-representation of the NICS values (ppm)



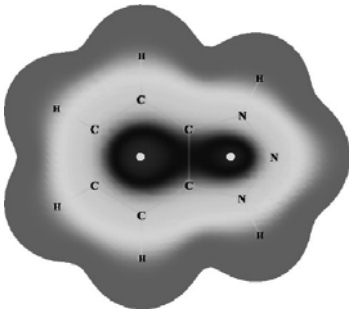
2*H*-indazole (**7**)



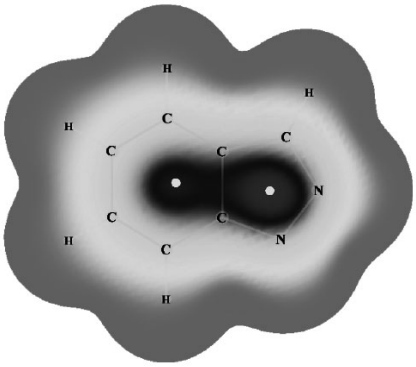
1*H*-benzotriazole (**12**)



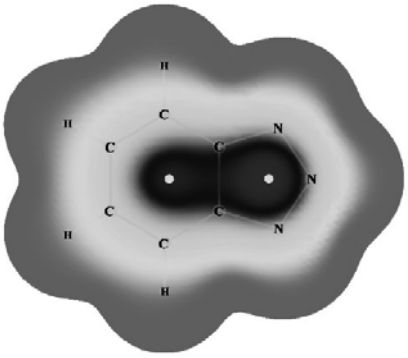
1*H*-indazol-2-ium (**10**)



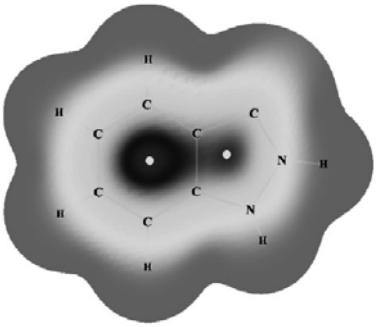
1*H*-benzotriazol-3-ium (**14**)



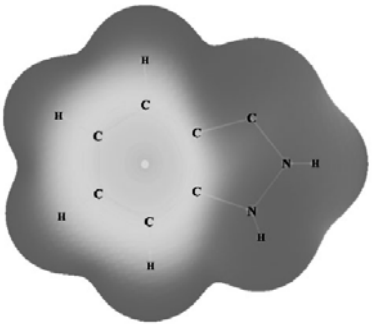
Indazolate (**11)**



Benzotriazolate (**16**)



Indazol-3-ylidene (**9s**)



Indazol-3-ylidene (**9t**)

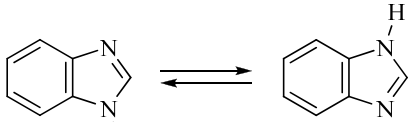
on the van der Waals surface (0.001 a. u.)

Table 6

Empirical equations used to transform absolute shieldings (σ, B3LYP/6-311++G(d,p)) into chemical shifts (δ) (both in ppm); the equations for ^{31}P, ^{29}Si and ^{11}B were established for the present review

$\delta^{1}H = 31.0 - 0.97\sigma^{1}H$	[81]
$\delta^{13}C = 175.7 - 0.963\sigma^{13}C$	[82]
$\delta^{15}N = -152.0 - 0.946\sigma^{15}N$	[82]
$\delta^{19}F = 162.1 - 0.959\sigma^{19}F$	[83]
$\delta^{33}S = 77.8 - 0.884\sigma^{33}S$	[84]
$\delta^{17}O = 250.0 - 0.898\sigma^{17}O$	[85]
$\delta^{31}P = 247.9 - 0.896\sigma^{31}P$	
$\delta^{29}Si = 305.8 - 0.914\sigma^{29}Si$	
$\delta^{11}B = 93.7 - 0.893\sigma^{11}B$	

In the case of benzazoles **1**, **6** and **12**, the method was used to establish the corresponding equations since the X-ray structures were known [61]. In benzimidazole (**1**), the annular tautomerism **1**/**1'** was blocked in CD_3OD at 178 K, thus serving to calculate phase effects.



1, 1*H* **1',** 3*H*

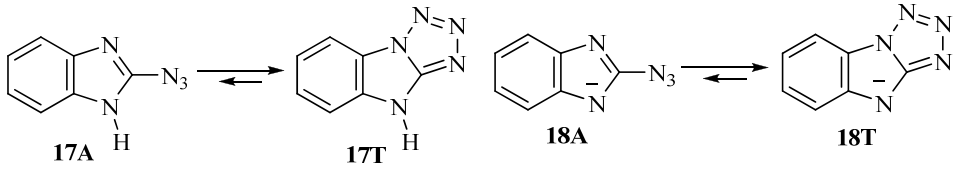
Today, it is possible to carry out theoretical calculations corresponding to the crystal structure [86] using the GIPAW (Gauge Including Projector Augmented Waves) chemical-shift methodology [87, 88].

In the following sections, the case of the C-unsubstituted derivatives will be no longer discussed unless it is needed for comparative purposes. Concerning the X-ray molecular structures of the compounds under review, we will mainly discuss the aspects involving weak interactions, i. e. hydrogen bonds (HB) – both intramolecular hydrogen bonds (IMHB) and intermolecular hydrogen bonds. This is due to the fact that the geometry of the molecule (bond distances, bond angles and torsion angles) is, in general, within the general structural knowledge and, besides, is excellently reproduced by the calculations, except for some torsion angles that are modified by the crystal field.

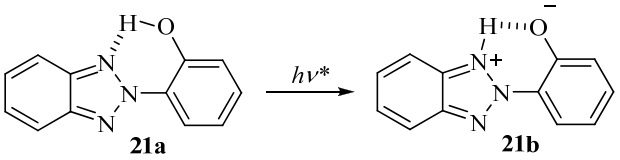
Benzimidazoles

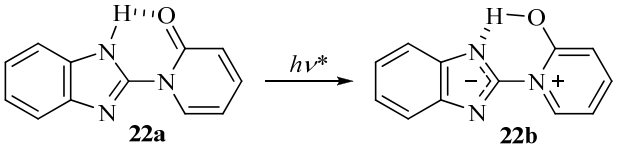
The relationships between the tautomerism and aromaticity of benzimidazoles, including the parent compound **1**, have been discussed in Balaban, Oniciu, and Katritzky's review [89].

The azido/tetrazole tautomerism of a series of azoles including 2-azidobenzimidazole **17A** and 3-azidoindazole **19A** as well as their anions **18A** and **20A** has been studied theoretically at the G3B3 level and compared with experimental values when available [90]. The tautomerization barriers have also been calculated (they are in the order of 100 kJ·mol^{-1}). In three cases, the azides are more stable than the corresponding tetrazoles, i. e., for compounds **17T**, **18T** and **19T** the corresponding values are 33.7, 4.7, and 55.2 kJ·mol^{-1}. However, in the case of compound **20** the opposite is true, for azide **20A** the tautomerization barrier is 36.6 kJ·mol^{-1}.

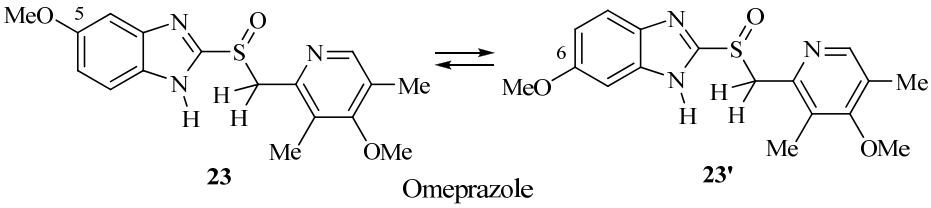


Related to Tinuvin P **21** (Excited state intramolecular protpon transfer (ESIPT) mechanism, compounds **21a**/**21b**) is the 1*H*-benzimidazole **22a**/**22b** that is susceptible of presenting an inverted ESIPT process [91].



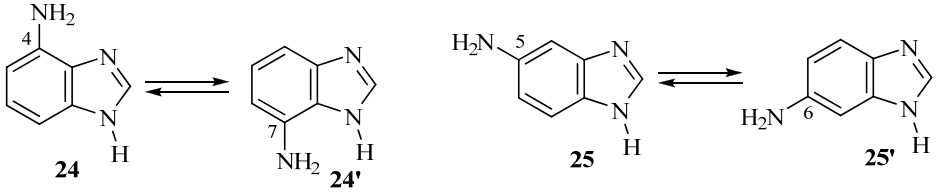


The tautomerism of 5(6)-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)-methyl]sulfinyl-1*H*-benzimidazole (**23**, Omeprazole) was determined in solution, K_T = 0.59 in THF-d_8 at 195 K, in favor of the 6-methoxy tautomer **23'**. The assignment of the ^{13}C and ^{15}N NMR signals was made by comparison with its two *N*-methyl derivatives in acetone-d_6 and through theoretical calculations of the absolute shieldings (GIAO/DFT/6-311++G(d,p)) [92].



The ^{13}C NMR spectra in DMSO-d_6, HMPA-d_{18}, and in solid state, as well as ^{15}N NMR spectra in solid-state of several *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 **24** and the slight preference for the 6-amino tautomer **25**. GIAO-calculated absolute shieldings compare well with experimental chemical shifts [93]. The obtained results correspond to 4(7)-aminobenzimidazole existing in the solid state as the 4-amino tautomer **24**, this being the expected result, and 5(6)-aminobenzimidazole existing in the solid state as a 50/50 mixture of 5-amino tautomer **25** and 6-amino tautomer **25'**. Since the difference in energy is small, this result is not in contradiction with the

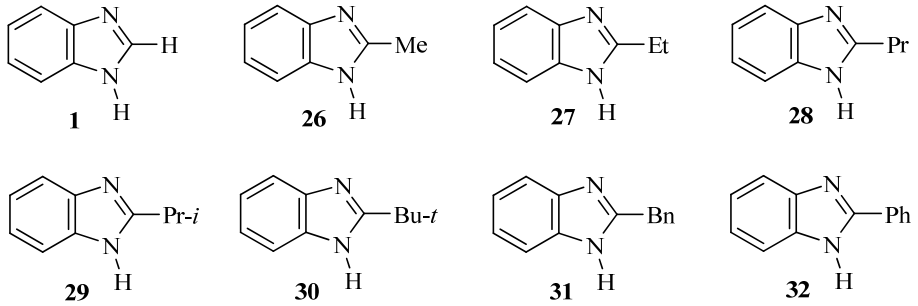
calculations (see below) nor with the results in solution, however, this is the first example of a benzimidazole crystallizing as a mixture of tautomers. A search in the CSD [41] proves that there is no example of the existence of pairs of benzimidazole tautomers in crystals.



24 **24'** **25** **25'**

The tautomerism of Omeprazole (**23**) was also studied in the solid state by ^{13}C and ^{15}N CPMAS NMR [94]. In the solid state, the only tautomer present was **23'**, another example of the rule that the major tautomer in solution coincides with the solid-state tautomer.

In several works the calorimetric study of a series of 2-substituted benzimidazoles **26**–**32** was carried out [9, 95–97]. Unsubstituted benzimidazole (**1**) was also included. Through experiments of combustion calorimetry, vapor pressure, Knudsen effusion method, Calvet microcalorimetry, molar enthalpies of sublimation, and standard molar enthalpies of formation were determined (Table 7). Using Cioslowski scheme and B3LYP/6-311++G(d,p) calculations, the values of Table 1 were discussed.



1 **26** **27** **28**

29 **30** **31** **32**

Table 7

Enthalpies (kJ·mol^{-1}) of sublimation of 2R-benzimidazoles

R	H	Me	Et	Pr	*i*-Pr	*t*-Bu	Bn	Ph
Compound	**1**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
Enthalpy	102.2	102.6	107.6	109.4	109.9	115.1	136.2	123.0

From the experimental and theoretical survey of the substituent effects on the enthalpies of formation of five different families of nitrogen-containing aromatic compounds it is possible to conclude that substituent effects are not strictly transferable from one family to another, as they seem to depend on the nature of the ring to which they are attached. Nevertheless, both calculated and experimental values are internally consistent in the sense that the correlation between enthalpies of formation of the different families is in general reasonably good. Systematically, poorer correlations are found for those cases in which the substituent is attached to a different atom (C or N) of the aromatic moiety, but even in these cases the correlation coefficient is never smaller than 0.97 [9].

The existence of these reasonably good correlations opens the possibility of estimating the enthalpies of formation for other families of closely related

compounds. This has been applied in the present paper for two families of nitrogen containing aromatic systems, namely 1- and 3-susbtituted indazoles [9].

A systematic analysis of the thermochemistry of ureas includes benzimidazolone [98]. The molar enthalpy of formation of this compound has been determined by Liebman *et al.* [99]. Using isodesmic reactions and high-level calculations (B3LYP/6-311++G(3df,2p), MP2, CBS-QB3, G2, G3) the experimental values were rationalized. In the case of benzimidazolinone, it was confirmed that this compound exists in the solid state as the oxo, not 2-hydroxy, tautomer [100–102].

The analysis of these calorimetric results require the structure of the compounds in the solid state to be known, which resulted in several X-ray crystallographic determinations. One of the most interesting was that of 2-phenylbenzimidazole (**32**) [103].

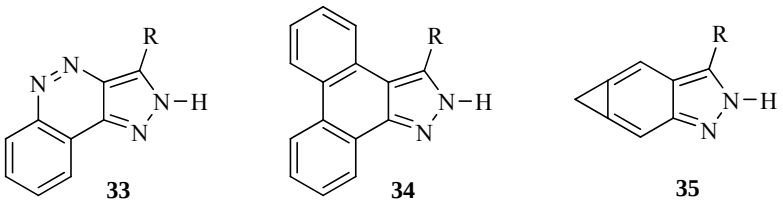
The structural analysis based on single-crystal X-ray diffraction data confirms that compound **32** exhibits a one-dimensional incommensurate structure, stable down to the lowest studied temperature (90 K). The structure was determined using a novel charge flipping method generalized for the treatment of superspace structures. The main structural feature related to the incommensurability is the torsion angle between the phenyl and the benzimidazole rings. Both independent molecules have on average an almost flat configuration, but the twist angles around the C–C bond joining the rings are modulated with amplitudes of ±5 and ±3°. Compared with the configuration of the isolated molecule in the gas phase (171.6°), the crystal packing forces molecules to reduce the twist angle towards an almost planar configuration [103].

Indazoles

Useful information, predating 2000, about indazoles can be found in the following reviews or chapters of books [70, 104, 105].

During the period covered by this review, the tautomerism and the proton affinities of indazole (forms **6**–**8**) and its 3-chloro, 3-bromo, and 3-methyl substituted derivatives were studied by Ögretir *et al.* [16, 17]. Using semi-empirical methods, the best of them was MNDO, they calculated tautomerism of these compounds and their proton affinities in the gas-phase and in aqueous solution, finding linear relationships with the pK_a values. In 2004 a paper with odd results was published [19]; although the level of the calculations was good (MP2/6-311G(2d,2p)) they considered benzimidazole (**1**) as tautomer of indazole! (The name "benzimidazole" never appears in the publication). At the MP2 level, the relative stabilities are 0.0 kJ·mol^{-1} for form **6**, 13.9 kJ·mol^{-1} for form **7**, and 86.1 kJ·mol^{-1} for form **8** (3*H*-indazole). The same year B3LYP/6-311++G(d,p) calculations were reported: 0.0 and 20.5 kJ·mol^{-1} for forms **6** and **7**, respectively [18]. The great instability of form **8** corresponds to synthetic methodologies leading to 3*H*-indazoles that spontaneously tautomerize to 1*H*-indazoles [106, 107].

A theoretical study has been carried out to answer the following question: is it possible to displace the tautomeric equilibrium from 1*H*-indazole (**6**) to 2*H*-indazole (**7**) by means of substituents? [20]. B3LYP/6-31G(d) calculations predict that compounds **33**–**35** (R = NO_2 or CO_2Me) would be more stable as 2*H*-tautomers. Compound **35** was designed taking into account the Mills–Nixon effect. Previous studies on the influence of the presence of an ester group at position 3 were reported [108].



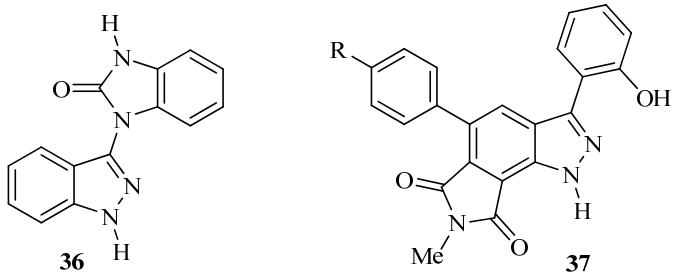
33 **34** **35**

R = NO_2, CO_2Me

Studies concerning the aromaticity of indazoles are also related to tautomerism. Martin *et al.* [72] have calculated the GIAO shielding increment surfaces of a number of heterocycles including benzimidazole (**1**) and 1*H*-indazole (**6**) and compared them with various published measures of aromaticity, including those related to energy (ASE), geometry (HOMA) and magnetic properties (NICS). Cruz-Cabeza, Schreyer, and Pitt [36] apply MP2 quantum mechanical (QM) calculations to the annular tautomerism of indazole (forms **6**/**7**) and benzotriazole (forms **12**/**13**). The calculated relative energies of tautomers were compared to relative abundances within the Cambridge Structural Database (CSD) [41] and the Protein Data Bank (PDB). Particularly interesting is the HBD and HBA distribution of PDB structures containing indazole-like fragments. The role of the substituent on the aromaticity variation of mono- and di-substituted aza analogs of indole was studied by Mohajeri and Shahamirian [109]. Electronically-based indices (ATI and FLU) were used to estimate the aromaticity of 3R-substituted indazoles and 2R-substituted benzimidazoles (R = OCH_3, Cl, CN) bearing the same substituents at positions 4 and 7.

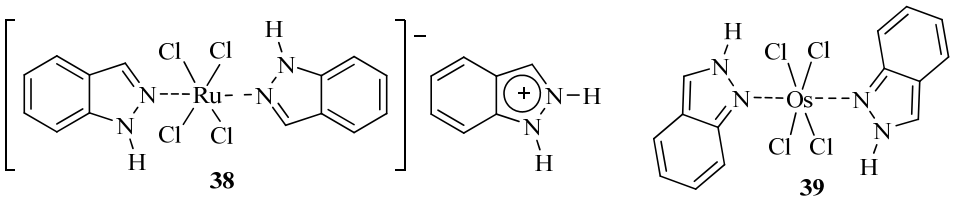
Gas-phase calculations of many molecules, including compounds **6** and **10**, have been carried out to determine the values of hydrogen bond basicity and acidity scales [110]. A complete infrared spectroscopic study of compound **10** has been carried in the gas phase (coupled to B3LYP/D95(d,p) calculations, scaling factor 0.972) [111]. The technique used was free electron laser induced multiple photon dissociation spectroscopy in a quadrupole ion trap. Other scaling factors for different levels of semiempirical calculations were obtained for the Semiglobal Self-consistently Scaled Quantum Mechanical (S4QM//PM6) model [112].

Several publications discussed in section "Chemical shifts" also reported NMR solution studies. Studies in solution of NH-indazoles are very common, so only two examples will be reported, those of compounds **36** [113] and **37** [114]. In both cases, multinuclear magnetic resonance established the tautomers to be of the 1*H*-type.



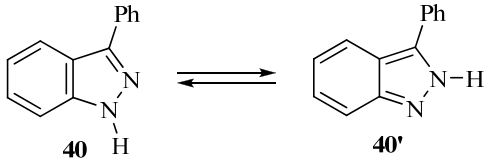
36 **37**

A behavior related to the predominance of 1*H*-tautomers in indazoles means that the lone pair of atom N-2 is used for coordination. A beautiful example is the tumor-inhibiting agent KP1019 (**38**), containing the cation **10** [115, 116]. Much more unexpected is the complex **39** isolated by Arion *et al.* where the 2*H*-tautomer is coordinated to osmium by atom N-1 [117].



38 **39**

According to Karl von Auwers, the pioneer of indazole studies, 3-phenylindazole (**40**) shows desmotropy with two forms – the low melting point (LMP) and the high melting point (HMP). Actually, it is not a case of desmotropy, but a case of polymorphism [45, 118].



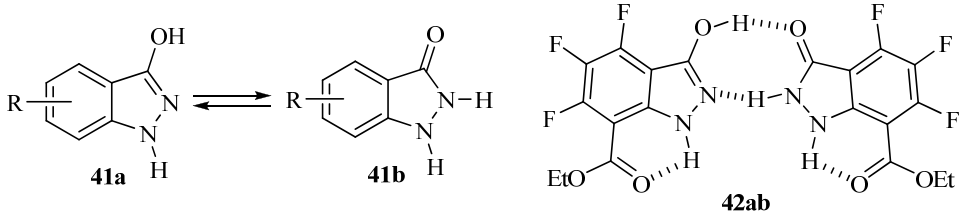
40 **40'**

Desmotropy means two different tautomers of the same compound, i. e. tautomers **40** and **40'** [119], while polymorphism corresponds to two crystalline forms of the same tautomer, for instance, **40**. Both polymorphs contain 1*H*-tautomers crystallizing in trimers through N–H···N HBs; in one case, only a trimer was present in the unit cell, and in the other case, two trimers were present.

One of the fields where 1*H*-indazoles play a major role is as inhibitors of one (or several) of the nitric oxide synthase (NOS) isoforms [120–123]. The modelling of these interactions requires the knowledge of indazole structure, in particular of 7-nitroindazole. This is what we have done in a series of papers [124–126]. Besides, the structures of some 1*H*-indazoles inside the pocket of the receptor have been determined [127–130].

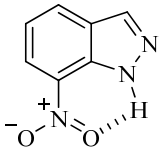
We have devoted several papers to the study of the structure of indazoles: fluorinated indazoles by X-ray crystallography [21], difluoroindazoles by CPMAS NMR [131], nitroindazoles by X-ray crystallography [132], and indazoles forming chiral helices by X-ray crystallography, vibrational circular dichroism (VCD) and DFT calculations [23]. Other authors have reported the X-ray structures of several perfluorinated 1*H*-indazoles [133].

3-Hydroxyindazoles **41a** are tautomers of indazolinones **41b**. In the solid state (crystallography and NMR), these compounds exist in the hydroxy form **41a** that remains predominant in solution [134]. The situation becomes more complex when there are substituents like F or CO_2R [135]: a prominent example is compound **42ab** that forms heterodimers between both hydroxy- and oxo-tautomers **a** and **b**. These studies were extended to other fluorinated indazolinones, where in addition to crystallography and solid state NMR, DFT calculations including solvent effects were carried out [136].



41a **41b** **42ab**

There are also many 1*H*-indazole structures in the CSD [41]. Three of the most interesting structures are shown below. Compounds **43** [137] and **44** [138] are important for their NOS inhibition properties. In the paper reporting the structure of compound **45**, Foces-Foces analyzed the hydrogen-bonded networks of 1*H*-indazoles [139].



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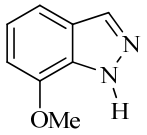

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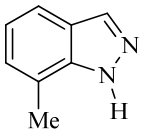


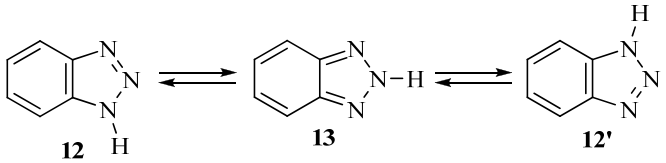
45

The powerful approach of utilizing crystallography and solid-state CPMAS NMR was analyzed in review [80]. Other techniques include the use of calorimetry (to study 5- and 6-nitro-1*H*-indazoles) [140] and the use of vibrational spectroscopy [112, 141].

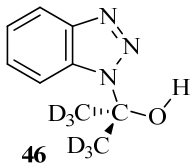
Benzotriazoles

All that concerns the parent compounds, such as tautomerism (isomers **12/13**), has been discussed in detail above. The relationship between tautomerism of benzotriazoles and their aromaticity is reported in Balaban's review [89]. The work of Booker-Milburn *et al.*, although concerning reactivity, deserves mention because it is one of the rare examples where the reactivity of benzotriazole has been related to its tautomerism: the intermolecular [2+2]-photocycloaddition of maleimides on benzotriazole proceeds selectively *via* the 2*H*-tautomer **13** [142]. Few papers report studies of *C*-substituted-*NH*-benzotriazoles [34, 143].

In hexadeuteroacetone solution at low temperatures, besides the adduct **46**, the ^{1}H, ^{13}C and ^{15}N spectra correspond to a degenerate equilibrium (same energy) between tautomers **12** and **12'** [29]. 2*H*-Tautomer **13** was not detected, but it may play a role in the proton transfer mechanism. From the ^{13}C chemical shifts measured between +30 to –90°C, the Eyring equation lead to the following values: $\Delta G^{\neq}_{294}$ = 45.2 kJ·mol^{-1}, $\Delta H^{\neq}$ = 21.3 kJ·mol^{-1}, $\Delta S^{\neq}$ = 80 J·mol^{-1}·K^{-1}. Correlations between $\delta^{15}N$ and $\sigma^{15}N$ (GIAO/B3LYP/6-311++G(d,p)) were shown to depend on the phase (solid-state, CO_2–acetone, benzene).

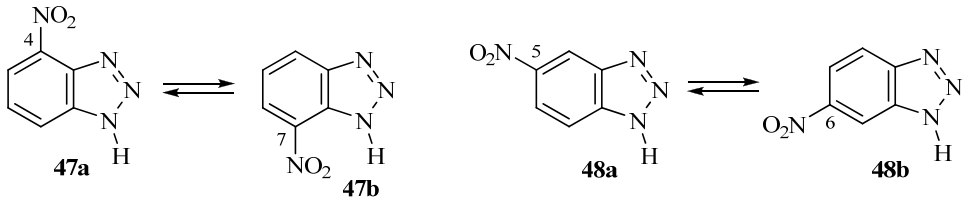


12 **13** **12'**

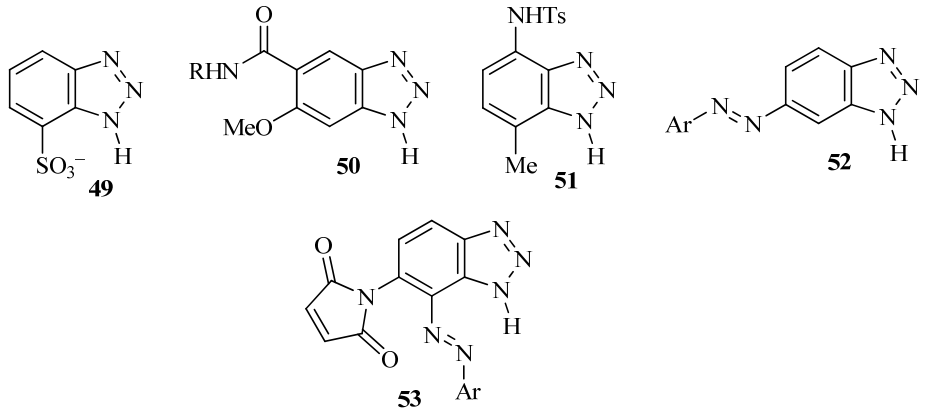


46

Larina and Milata [143] have studied the tautomerism by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy of nitrobenzotriazoles **47** and **48**. They have used the *N*-methyl derivatives as model compounds and have also calculated ^{15}N chemical shifts (B3LYP/6-311+G). Besides excluding the 2*H*-tautomers, they reached the conclusion that the position of a nitro group at the phenylene fragment of benzotriazole cycle does not influence the tautomeric equilibrium significantly. This is a surprising result, since one expects the 7-tautomer to be stabilized by an IMHB while the 4-nitro should be destabilized by LP/LP repulsions.



In addition to BZTRAZ (Fig. 5) the CSD [41] reports several structures including 1*H*-tautomer **12** (none related to 2*H*-tautomer **13**) belonging to different complexes: ASUJUT (contains also a N(3)–Co complex of tautomer **12**), DIWCAO, GEBZOC (contains also a N(3)–Cu complex of tautomer **12**), GEKWUP, GUYQUM, HUHRAD, JAMWEA, MAHYUQ (contains also a N(3)–Zn complex of tautomer **12**) and SUZZOC. There are a few C-derivatives of compound **12**: INEWII (**49**), IDAXAO (**49**, different cation), JECYEV (**50**), JORWOC (**51**), MEXMIL (**52**) and YAPFEB (**53**).



For many years benzazoles were a small and lateral part of azoles, as their names (apart from indazoles) remind us. This is no longer true. Benzazoles have specificities, characteristic properties and individual importance that deserve a separated treatment in books and monographs. We hope that the present review will contribute to this end.

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