Importance of aromaticity on the relative stabilities of indazole annular tautomers: an *ab initio* study

Javier Catalán,*[,a] **José Luis G. de Paz**[a] **and José Elguero**[b]

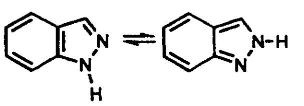
[a] *Departamento de Química Física Aplicada, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid, Spain*
[b] *Instituto de Química Médica, C.S.I.C., Juan de la Cierva, 3, E-28006 Madrid, Spain*

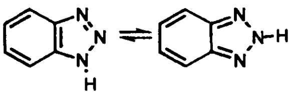
MP2-6-31G calculations on 1*H*- and 2*H*-indazole annular tautomers show that the 1*H* tautomer is more stable than the 2*H* one by 3.6 kcal mol^{-1}. In the case of 1*H*-indazole, the excellence of MP2-6-31G** results is confirmed by the fact that its microwave rotational constants are reproduced with great accuracy. The addition of the thermal energy correction and entropy effects to ΔE(MP2-6-31G**) led to the following thermodynamic values: $\Delta H^{298}(1H \rightarrow 2H)$ = 3.9 kcal mol^{-1} and $\Delta G_0^{298}(1H \rightarrow 2H)$ = 4.1 kcal mol^{-1}. Electronic spectra recorded at 80 °C provided experimental evidence for the clear predominance of 1*H*-indazole in the gas phase.**

Introduction

There is much interest in deducing the prototropic tautomeric equilibria of heterocyclic compounds for several reasons: (*i*) because they influence their chemical and biological properties; (*ii*) because they are related to such important questions as aromaticity and lone pair–lone pair repulsions and (*iii*) because they are still a challenge to theory.[1,2] In the case of indazole annular tautomerism, although studied for a long time,[3,4] all the above topics are still much alive: experimental studies in solution in the ground[5–9] and the excited states,[8,9] biological properties of indazole-derived drugs (indazole derivatives are mainly used as anti-inflammatory and analgesic drugs),[10–13] aromaticity studies[14–16] and lone pair–lone pair interactions have been reported.[17]

Concerning indazole tautomerism in solution, the conclusion from all physicochemical methods is that the 1*H*-tautomer **1a** is predominant,[3,4] for instance in water (from pK_a measurements), K_T = [**1a**]/[**1b**] = 51.4, $\Delta G°_{298}$ = 2.3 kcal mol^{-1}.†[9]

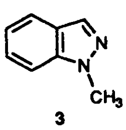

1a **1b**

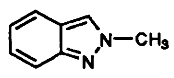

2a **2b**

Concerning indazole tautomerism in the gas-phase, the conclusion is the same. A great variety of techniques have been used: the older ones were mass spectrometry[18] and photoelectron spectroscopy (PES).[19] Recently, a systematic exploration of the gas phase properties of indazole was carried out by Velino *et al.* Thus, a microwave (MW) study of this compound was carried out by these authors.[20] They conclude that the spectrum corresponds to the 1*H*-tautomer. The gas-phase infrared spectrum of indazole has been recorded and the spectrum assigned to tautomer **1a** by the same group.[21] Another publication by the same group, concerns the assignment of the electronic 290 nm band of 1*H*-indazole in the gas phase to a π*–π transition.[22]

Ab initio theoretical results concerning the relative stabilities of 1*H*- and 2*H*-indazole all agree that the 1*H*-tautomer is more stable than the 2*H* one by 10.7 kcal mol^{-1} (LCGO),[19] 10.0 and 12.9 kcal mol^{-1} (STO-3G//STO-3G),[23–25] 8.0 kcal mol^{-1} (4–21G//4-21G)[19] and 9.2 and 10 kcal mol^{-1} (6-31G//6-31G).[9,25] The positive sign of the difference is certainly correct, but the absolute values are without doubt exaggerated since the origin of these differences in stability is their difference in aromaticity which, according to our estimation, should be about 2.5 kcal mol^{-1} in favour of the 1*H*-tautomer.[26] This last value was obtained, at the MP2-6-31G** level for the related case of benzotriazole **2a**/**2b** tautomerism.

Here, we report on the tautomerism of indazoles using the same level of theory and provide experimental evidence of it based on UV spectroscopy studies of indazole **1** and its two *N*-methyl derivatives, **3** and **4**, in the gas phase.


3


4

Experimental

Materials

Compounds **1**, **3** and **4** were previously described.[9]

Measurements

Electronic spectra in the gas phase at 80 °C were measured using a CARY 5 spectrophotometer and a pair of thermostatted cells (10 cm of optical path) for indazole **1** and a Shimadzu 2100 for its much more volatile methyl derivatives **3** and **4**.

Theoretical calculations

All computations were carried out using a standard version of the GAUSSIAN 92 program.[27] The geometry has been fully optimized using Berny's algorithm.[28] The calculations were carried out at the MP2-6-31G** and 6-31G** levels. Over the 6-31G** optimized geometries we have calculated the zero point energy (ZPVE), the H – H° and the entropy contributions using harmonic vibrational frequencies scaled by a factor of 0.89.[29] Finally, the polarizabilty of both tautomers **1a** and **2a** was calculated.

Results and discussion

Molecular structure and spectroscopic properties

The MP2-6-31G** calculated geometries [bond distances (Å) and bond angles (°)] are reported Fig. 1. The only available structural data in the gas phase are the position of the pyrrolic hydrogen on N(1) and the rotational constants of 1*H*-indazole **1a**.[20] The data given in Table 1 show that the MW rotational

---

† 1 cal = 4.184 J.

Table 1 Rotational constants (MHz), dipole moments (μ/D; the X, Y and Z components are given in parentheses) and located positions of the amino hydrogen (r_s/Å) of 1*H*- and 2*H*-indazole

Compound	Rot. const. (MHz) (exp.)[20]	Rot. const. (MHz) (calc.)	Diff.	Ratio	μ/D (exp.)[10]	μ/D (calc.)
1*H*-Indazole **1a**	3977.927	3975.01	2.9	0.9993	1.76 (1.44, 1.01, 0.0)	1.92 (1.66, 0.96, 0.0)
	1633.272	1631.83	1.4	0.9991		
	1158.141	1156.89	1.2	0.9989		
2*H*-Indazole **1b**	—	3934.70	—	—	—	2.72 (1.15, 2.46, 0.0)
	—	1650.75	—	—		
	—	1162.88	—	—		

	r_s/Å (exp.)			r_s/Å (calc.)		
	|*a*|	|*b*|	|*c*|	|*a*|	|*b*|	|*c*|
1*H*-indazole **1a**	1.9251	1.9508	0.0	1.9687	1.9598	0.0
2*H*-indazole **1b**				3.2943	0.1186	0.0

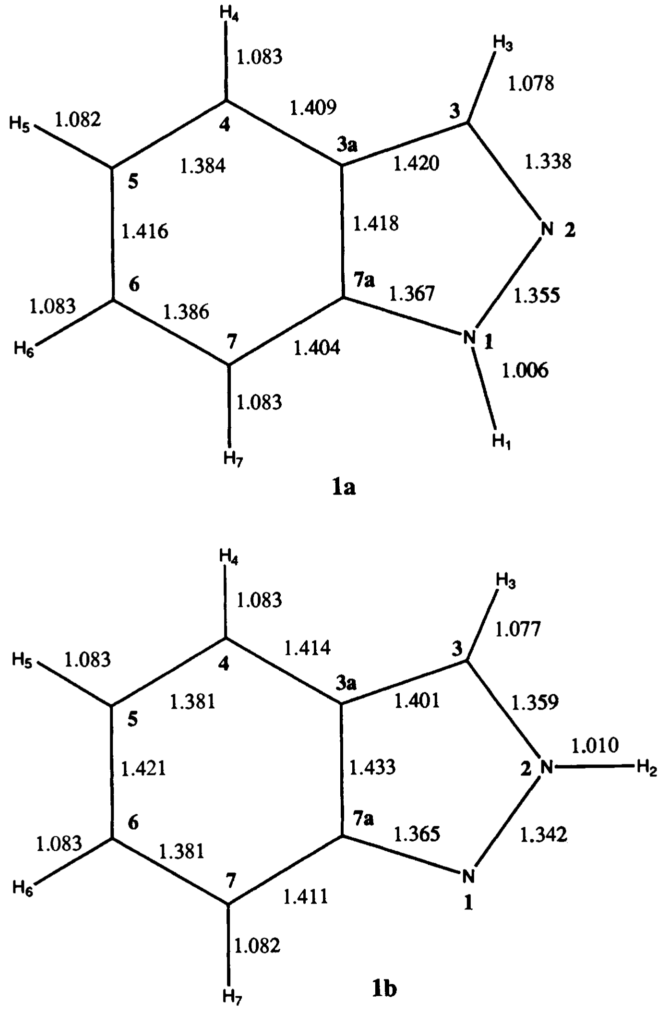


Fig. 1 MP2/6-31G** optimized geometry [bond lengths (Å) and angles (°)] of 1*H*- and 2*H*-indazole

constants are very well reproduced by the MP2-6-31G** calculations proving the quality of the molecular geometries reported in this work.

To compare our geometry with the X-ray geometry of 1*H*-indazole[30] is meaningless since in the crystal compound **1a** is involved in strong intermolecular hydrogen bonds which alter significantly the intrinsic geometry of the isolated molecule. A comparison with the 'plausible' geometry of Velino *et al.*[20] is also of no use since they used a 4-21G geometry rescaled to fit the MW data.

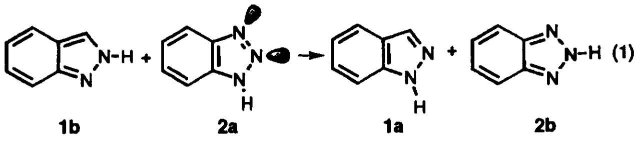
Since no signal corresponding to the 2*H*-tautomer **1b** is observed by either MW, PES or by IR spectroscopy (although it has a dipole moment larger than that of 1*H*-indazole), there is no doubt that the **1a** tautomer is largely predominant in the gas phase. Nevertheless we have carried out a UV study of indazole in the gas phase since all previous work was done in solution.[4,31] In Fig. 2 are reported the electronic spectra, determined in the gas phase at 80 °C, of compounds **1**, **3** and **4**. They are similar to those found in solution.[32,33] Clearly indazole presents a spectrum very similar to that of 1-methylindazole **3** and completely different from that of 2-methylindazole **4**. The only difference between the spectra of 1*H* indazole **1a** and **3** is the normal bathochromic shift of about 10 nm due to the *N*-methylation; in solution the α band at 288 nm is shifted to 294 nm by *N*-methylation[33] (for pyrazoles, the effect is 6.4 nm on average).[34]

Thermochemical data and tautomerism

Although all experimental evidence coherently points to the 1*H* indazole as the most stable tautomer, there is no quantitative estimation of the difference in stability between the two tautomers. The MP2-6-31G** thermochemical data in Table 2 show that 1*H*-indazole is 4.08 kcal mol^{-1} more stable than 2*H*-indazole. Since the calculated entropic contribution is small and negative (at 298 K, $T\Delta S = -0.17$ kcal mol^{-1}), it appears that increasing the temperature would only produce a small extra-stabilization of the most abundant tautomer.

We have now a set of consistent MP2-6-31G** values for pyrazoles, 1,2,3-triazoles, indazoles and benzotriazoles at our disposition. The combination of these theoretical calculations in a series of isodesmic reactions could provide information on the structural effects responsible for tautomeric equilibria.

All other things being equal, the fact that the isodesmic reaction (1) ($\Delta E_{\mathrm{MP2\text{-}6\text{-}31G^{**}}} = -6.2$ kcal mol^{-1}) is shifted to the



(1)

right can be attributed to the repulsion of adjacent lone pairs in 1*H*-benzotriazole **2a**. The value 6.2 kcal mol^{-1} is very close to our previous estimation, 6.5 kcal mol^{-1}, of lone pair–lone pair repulsion in azoles.[35]

Another interesting comparison is shown in reaction (2) (in this case pyrazole **5** is on both sides of the equation): the difference in energy ($\Delta E_{\mathrm{MP2\text{-}6\text{-}31G^{**}}} = 3.64$ kcal mol^{-1}) between the two indazole tautomers is mainly due to their difference in aromaticity: the benzenoid 1*H*-indazole tautomer is 3.6 kcal mol^{-1} more stabilized than the quinonoid 2*H*-tautomer. This

Table 2 Thermochemistry of indazole[a]

Comp.	E_T/kcal mol^{-1}	ZPVE/kcal mol^{-1}	$H - H_0$/kcal mol^{-1}	S/cal mol^{-1} k^{-1}	Polarizability (α/J^{-1} C^2 m^2)
1*H*-Indazole **1a**	−237 642.18	79.75	3.57	77.08	72.9
2*H*-Indazole **1b**	−237 638.54	80.11	3.47	87.51	74.9
Equilibrium **1a**$\rightleftharpoons$**1b**	ΔH^{298}(1*H*→2*H*)/kcal mol^{-1}		$T\Delta S^{298}$(1*H*→2*H*)/kcal mol^{-1}	ΔG^{298}(1*H*→2*H*)/kcal mol^{-1}	
	3.91		−0.17	4.08	

[a] $H - H^{\circ}$ is the thermal correction.[2]

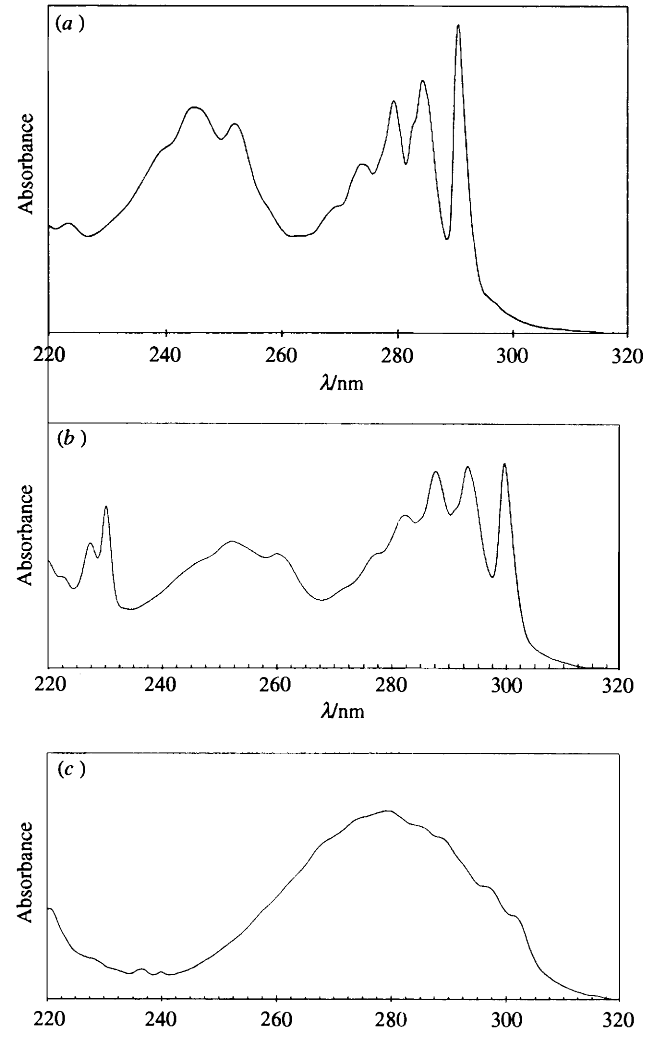
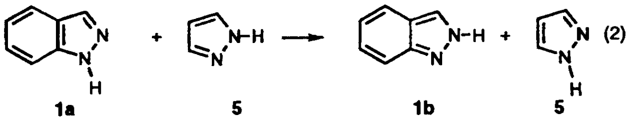
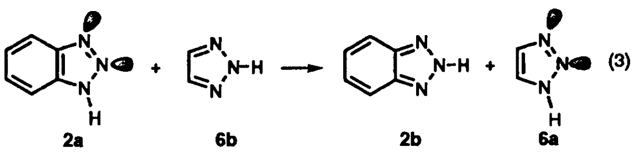


Fig. 2 UV spectra at 80 °C in the gas phase of (*a*) indazole, (*b*) 1-methylindazole, (*c*) 2-methylindazole



value is slightly larger than that of reaction (3) ($\Delta E_{\mathrm{MP2\text{-}6\text{-}31G^{**}}}$ = 2.5 kcal mol^{-1}).[26]

Since in reaction (3) lone pair effects cancel (they are the same in **2a** and **6a**), either 1*H*-indazole **1a** is more 'aromatic' than 1*H*-benzotriazole **2a** or 2*H*-indazole **1b** is more 'quinonoid' than 2*H*-benzotriazole **2b**. According to Bird[15] 1*H*-indazole has a unified aromaticity index, I_A, larger than that of 1*H*-benzotriazole (144 and 140, respectively) (see also ref. 16).



Solvent effects

We have no calculated quantitative values of solvent effects. However, since the polarizabilities (Table 2) are similar and since the dipole moments (Table 1) are not very different for the two tautomers, no important solvent effects are expected for indazole annular tautomerism. Assuming that the 4.1 kcal mol^{-1} value of Table 2 exactly reflects the difference in stability between the two tautomers in the gas phase and, taking into acount the fact reported in the introduction, that in water ΔG°_{298} = 2.3 kcal mol^{-1}, it can be estimated that water solvation reduces the difference in stability by 1.8 kcal mol^{-1}; a possible explanation for this attenuation is specific solvent effects of water on the basic (–N=) and acid (–NH–) centres of indazole.[9]

Conclusions

The two publications on benzotriazoles,[26,36] together with the two on indazoles (including the present one)[9] provide a comprehensive view of the tautomerism of benzazoles (the two tautomers of benzimidazole are identical). A series of general principles (aromaticity, lone pair–lone pair repulsion) has been used to explain qualitatively the energies obtained using high level theoretical methods which, otherwise, explain satisfactorily the spectroscopic results.

Acknowledgements

We are greatly indebted to Professor F. Tomás (University of Valencia) for his help and to CICYT of Spain for financial support (Project no. PB93-0280). J. C. acknowledges the support of CICYT (JN93-0056).

References

1 O. G. Parchment, D. V. S. Green, P. J. Taylor and I. H. Hillier, *J. Am. Chem. Soc.*, 1993, **115**, 2352.
2 M. Cao, B. J. Teppen, D. M. Miller, J. Pranata and L. Schäfer, *J. Phys. Chem.*, 1994, **98**, 11353.
3 J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, *The Tautomerism of Heterocycles*, Academic Press, New York, 1976.
4 J. Elguero, *Pyrazoles and Their Benzo Derivatives*, in *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984, pp. 291–297.
5 W. Schilf, L. Stefaniak, M. Witanowski and G. A. Webb, *Bull. Pol. Acad. Sci. Chem.*, 1985, **33**, 437.
6 M. Witanowski and L. Stefaniak, *Bull. Pol. Acad. Sci.*, 1987, **35**, 305.
7 C. López, R. M. Claramunt, S. Trofimenko and J. Elguero, *Can. J. Chem.*, 1992, **71**, 678.
8 I. Janic and M. Kakas, *Vestn. Slov. Kem. Drus.*, 1986, **33** (*Suppl.*), 171 (*Chem. Abstr.*, 1987, **107**, 235951c).

9 J. Catalán, J. C. del Valle, R. M. Claramunt, G. Boyer, J. Laynez, J. Gómez, P. Jiménez, F. Tomás and J. Elguero, *J. Phys. Chem.*, 1994, **98**, 10 606.

10 J. W. Longworth, R. O. Rahn and R. G. Shulman, *J. Chem. Phys.*, 1966, **45**, 2930.

11 Z. Kazimerczuk, H. Lönnberg, J. Vilpo and W. Pfleiderer, *Nucleosides Nucleotides*, 1989, **8**, 599.

12 F. Seela and W. Bourgeois, *Helv. Chim. Acta*, 1991, **74**, 315.

13 L. Mosti, G. Menozzi, P. Fossa, P. Schenone, E. Lampa, C. Parrillo, M. D'Amico and F. Rossi, *Il Farmaco*, 1992, **47**, 567.

14 A. R. Katritzky, V. Feygelman, G. Musumarra, P. Barczynski and M. Szafran, *J. Prakt. Chem.*, 1990, **332**, 870.

15 C. W. Bird, *Tetrahedron*, 1992, **48**, 335.

16 L. Caruso, G. Musumarra and A. R. Katritzky, *Quant. Struct.-Act. Relat.*, 1993, **12**, 146.

17 W. M. F. Fabian, *Z. Naturforsch., A: Phys. Sci.*, 1990, **45**, 1328.

18 A. Maquestiau, Y. Van Haverbeke, R. Flammang, M. C. P. Pardo and J. Elguero, *Org. Mass Spectrom.*, 1975, **10**, 558.

19 M. H. Palmer and S. M. F. Kennedy, *J. Mol. Struct.*, 1978, **43**, 33 and 203.

20 B. Velino, E. Cané, A. Trombetti, G. Corbelli, F. Zerbetto and W. Caminati, *J. Mol. Spectrosc.*, 1992, **155**, 1.

21 E. Cané, P. Palmieri, A. Tarroni and A. Trombetti, *J. Chem. Soc., Faraday Trans.*, 1993, **89**, 4005.

22 E. Cané, A. Trombetti, B. Velino and W. Caminati, *J. Mol. Spectrosc.*, 1992, **155**, 307.

23 J. Catalán, O. Mó, P. Pérez and M. Yáñez, *J. Mol. Struct.*, 1983, **94**, 143.

24 D. Kocjan, M. Hodoscek and D. Hadzi, *J. Mol. Struct.* (*THEOCHEM*), 1987, **152**, 331.

25 M. Hodoscek, D. Kojcan and D. Hadzi, *J. Mol. Struct.* (*THEOCHEM*), 1988, **165**, 115.

26 F. Tomás, J. Catalán, P. Pérez and J. Elguero, *J. Org. Chem.*, 1994, **59**, 2799.

27 M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. André, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, GAUSSIAN 92, Revision C, Gaussian Inc., Pittsburgh PA, 1992.

28 H. B. Schlegel, *J. Comput. Chem.*, 1982, **3**, 214.

29 J. A. Pople, H. B. Schlegel, K. Raghavachari, D. J. Defrees, J. S. Binkley, M. J. Frisch, R. F. Whitesides, R. F. Hout and W. J. Hehre, *Int. J. Quantum Chem., Symp.*, 1981, **15**, 269; D. J. Defrees and A. D. McLean, *J. Chem. Phys.*, 1985, **82**, 333.

30 A. Escande, J. Lapasset, R. Faure, E. J. Vincent and J. Elguero, *Tetrahedron*, 1974, **30**, 2903; erratum 1975, **31**, 2.

31 J. Elguero, *Pyrazoles and Their Benzo Derivatives*, in *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 2nd edn., 1996, in the press.

32 V. Rousseau and H. G. Lindwall, *J. Am. Chem. Soc.*, 1950, **72**, 3047.

33 J. Derkosch, O. E. Polansky, E. Rieger and G. Derflinger, *Monatsh. Chem.*, 1961, **92**, 1131.

34 C. Cativiela, J. A. Gálvez, J. I. García and J. Elguero, *Gazz. Chim. Ital.*, 1989, **119**, 41.

35 J. Catalán, J. L. G. de Paz, J. Elguero, A. Martínez, R. W. Taft and F. Anvia, *J. Mol. Struct.* (*THEOCHEM*), 1990, **205**, 367.

36 J. Catalán, P. Pérez and J. Elguero, *J. Org. Chem.*, 1993, **58**, 5276.

Paper 5/03802B
Received 13*th June* 1995
Accepted 21*st July* 1995