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BASICITY OF AZOLES: COMPLEXES OF DIIODINE WITH IMIDAZOLES, PYRAZOLES AND TRIAZOLES

M. J. EL GHOMARI,[1] R. MOKHLISSE[1], C. LAURENCE[2]* J.-Y. LE QUESTEL[2] and M. BERTHELOT[2]

[1] *Laboratoire de Spectroscopie Moléculaire, Faculté des Sciences Semlalia, Université Cadi Ayyad, Marrakesh, Morocco*
[2] *Laboratoire de Spectrochimie, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France*

The diiodine basicity (a soft Lewis basicity) of 15 azoles (imidazoles, pyrazoles and triazoles) was measured by means of the formation constant of the diiodine–azole complexes in heptane at 298 K. The preferred sites of diiodine fixation are the nitrogens N-3 in imidazoles, N-2 in pyrazoles and N-4 in 1,2,4-triazoles. The diiodine basicity decreases with (i) the number of ring nitrogens, (ii) benzofusion, (iii) field electron-withdrawing effects of substituents on N-1 and (iv) for pyrazoles only, steric effect of substituents on N-1. In imidazoles and 1,2,4-triazoles, the lengthening and branching of alkyl groups on N-1 increase significantly the basicity, and 1-(adamant-1-yl)imidazole is the most basic of the azoles studied. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

The Brønsted basicity of azoles has been the subject of many studies,[1] both in aqueous solution (the pK_a scale) and in the gas phase (the GB and PA scales). They are also well represented (16 compounds) in the log K_β scale[2] of hydrogen-bond basicity, constructed towards 4-nitrophenol. Other values have been obtained[3] for *N*-unsubstituted pyrazoles towards 3,4-dinitrophenol. However, the Lewis basicity of azoles seems to have been little studied.

This work was aimed at measuring the Lewis basicity of azoles **1**–**15** towards the Lewis acid I_2. We obtained equilibrium constants, *K*, for 1:1 molecular complexes of these azoles and diiodine [equation (1)].

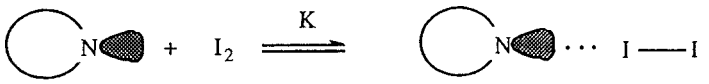
Diiodine constitutes a reference Lewis acid of choice for measuring the soft character of Lewis bases since its absolute hardness parameter[4] η is among the weakest known. Moreover, there is a good correlation between the formation constants *K* of diiodine complexes and the anti-thyroid activity *in vivo* of organic molecules.[5] In fact, 2-mercapto-1-methylimidazole (methimazole), which gives[6] a *K* value of 23 194 l mol^{-1}, among the highest known, is the most potent synthetic anti-thyroid drug[7] currently used.

A number of constants *K* are available[8] for the formation of azole–diiodine complexes, but they refer to different temperatures and solvents of various kinds (heptane, CCl_4, $ClCH_2CH_2Cl$, CH_2Cl_2 and $CHCl_3$) and do not allow the construction of a coherent basicity scale. On our part, we have studied equilibrium (1) at a given temperature (298 K) and in the same solvent (heptane) every time the solubility of azoles permitted us to do so. For these solubility reasons we were obliged to study azoles **5**, **11** and **15** in CH_2Cl_2 and compound **12** in chlorobenzene. However, we have referred the *K* values in these solvents to heptane, in order to obtain a homogeneous basicity scale.

Since azoles possess several potentially basic nitrogen atoms, we shall look for the most basic nitrogen on which diiodine is bonded. Then we shall be able to discuss the relationships between structure and diiodine basicity.

EXPERIMENTAL

Materials. Heptane, dichloromethane and chlorobenzene were solvents of spectroscopic grade and were dried over molecular sieves. Diiodine was sublimed twice. Azoles **1**, **2**, **5**, **7**, **10**, **11** and **15** were commercial products



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* Correspondence to: C. Laurence.

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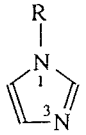
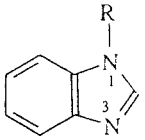
Imidazoles

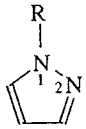


1 R=Me
2 R=n-Bu
3 R=t-Bu
4 R=Ad

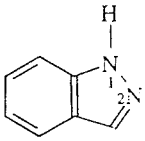


5 R=H
6 R=n-Bu

Pyrazoles

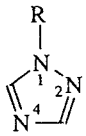


7 R=H
8 R=Me
9 R= Ad
10 R=Ph

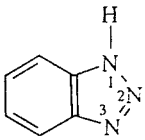


11

Triazoles



12 R=Me
13 R=Ad
14 R= CH_2Ph



15

(Aldrich). The other azoles were supplied by Professor J. Elguero (CSIC, Madrid, Spain).

Equilibrium constant determinations. Equilibrium constants at 298 K were obtained by the spectrometric method of Rose and Drago[9] [equation (2)] from absorbance measurements on the visible transition of diiodine:

$$\frac{1}{K}=\frac{A-A_0}{\varepsilon_c-\varepsilon_I}-C_D^0-C_I^0+\frac{C_D^0C_I^0(\varepsilon_c-\varepsilon_I)}{A-A_0} \qquad (2)$$

where $A-A_0$ is the difference in absorbance between a sample cell (l=1 cm) containing diiodine at a concentration C_I^0 and an electron donor (azole) at a concentration C_D^0 and a reference cell of the same optical path containing diiodine at the same concentration as the sample cell; $\varepsilon_c-\varepsilon_I$ is the difference between the molar extinction coefficients of complexed and free diiodine. The unknown quantities K_c and $\varepsilon_c-\varepsilon_I$ were calculated from the $A-A_0$ values measured at the maximum of the curve $A-A_0=f(\lambda)$ for a series of solutions with varying C_I^0 (*ca* 10^{-3} mol l^{-1}) and C_D^0 (10^{-2}–10^{-4} mol l^{-1} depending on the strength of the base). The error in K was calculated from the standard deviation of the mean at the 90% confidence level.

Apparatus. Absorbances were measured on a Cary 219 instrument. The 1 cm cells were thermostated to within ±0·2 K by means of a Lauda K 2R cryostat.

Calculations. All calculations were performed using the Spartan 4·0 molecular modeling program[10] running on a Silicon Graphics Indy workstation. Calculations of electrostatic potential surfaces were performed on azoles using geometry-optimized structures. These surfaces were mapped on to the electron density surface (0·002 e/au isosurface) at high resolution. The geometries of the azole–dichlorine complexes were fully optimized. The starting geometry of complexation was chosen such that dichlorine stands along the conventional sp^2 nitrogen lone pair, with respective values of 180° and 2·730 Å for the N · · ·Cl—Cl angle and the N · · · Cldistance according to the microwave results for the $H_3N\cdots Cl_2$ complex.[11]

RESULTS AND DISCUSSION

Diiodine basicity scale of azoles

Table 1 lists the formation constants K=[complex]/[I_2][azole] for 1:1 diiodine complexes with azoles at 298 K in heptane, CH_2Cl_2 and chlorobenzene. Since the formation constant of diiodine complexes is strongly solvent dependent,[12] it is crucial to refer the C_6H_5Cl value for **12** and the CH_2Cl_2 values for **5**, **11** and **15** to one solvent, and we chose heptane, the most commonly used and the most apolar. Fortunately, for structurally related compounds, log K values determined in two different solvents are generally related.[12b] From literature data[12b, 13] on N(sp^2) bases and our own data in Table 1, we can establish the linear free energy

Table 1. Formation constants (l mol^{-1}) for 1:1 diiodine complexes with azoles at 298 K

No	Compound	Solvent	K	Log K[a]	pK_a[b]
Imidazoles:					
3	1-Methylimidazole	Heptane	725±23	2·86	7·12
		C_6H_5Cl	1247±74		
		CH_2Cl_2	448±36		
2	1-*n*-Butylimidazole	Heptane	1094±35	3·04	7·16
3	1-*t*-Butylimidazole	Heptane	1194±53	3·08	7·30
		C_6H_5Cl	1955±95		
		CH_2Cl_2	682±22		
4	1-(Adamant-1-yl)imidazole	Heptane	2561±117	3·41	
5	Benzimidazole	CH_2Cl_2	164±7	2·49[c]	5·56
6	1-*n*-Butylbenzimidazole	Heptane	612±36	2·79	5·31
Pyrazoles:					
7	Pyrazole	Heptane	78±6	1·89	2·48
8	1-Methylpyrazole	Heptane	138±11	2·14	2·06
9	1-(Adamant-1-yl)pyrazole	Heptane	37±9	1·57	
10	1-Phenylpyrazole	Heptane	10±1	1·00	0·43
11	Indazole	CH_2Cl_2	16±1	1·65[c]	1·04
Triazoles:					
12	1-Methyl-1,2,4-triazole	C_6H_5Cl	99±15	1·71[d]	3·20
13	1-(Adamant-1-yl)-1,2,4-triazole	C_6H_5Cl	156±17		
		Heptane	79±10	1·90	
14	1-Benzyl-1,2,4-triazole	Heptane	23±1	1·36	
15	Benzotriazole	CH_2Cl_2	4±0·2	1·15	~1·6

[a] 1 log$K$ unit = 1·36 kcal mol^{-1} = 5·69 kJ mol^{-1}. All values refer to heptane.
[b] Brønsted basicity in water.[1c]
[c] Obtained through equation (4).
[d] Obtained through equation (3).

relationships in equations (3) and (4) for azoles and calculate log K values for **5**, **11**, **12** and **15** in heptane through these correlations, where n is the number of data points and r the correlation coefficient.

$$\log K(n\text{-}C_7H_{16}) = -0{\cdot}44 + 1{\cdot}07 \log K(C_6H_5Cl) \quad (3)$$
$$n = 3; \quad r^2 = 0{\cdot}998$$

$$\log K(n\text{-}C_7H_{16}) = 0{\cdot}65 + 0{\cdot}83 \log K(CH_2Cl_2) \quad (4)$$
$$n = 9; \quad r^2 = 0{\cdot}996$$

The fifth column in Table 1 constitutes a diiodine basicity scale of azoles in heptane at 298 K. This soft Lewis basicity scale is only roughly related to the pK_a scale[1c] of azoles [equation (5)].

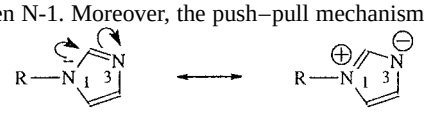
$$\log K(I_2) = 1{\cdot}12 + 0{\cdot}265\ pK_a(H^+_{aq}) \quad (5)$$
$$n = 11; \quad r^2 = 0{\cdot}876$$

Site of fixation of diiodine

The existence of two nitrogens in imidazoles and pyrazoles, three nitrogens in triazoles and a benzene π ring in **5**, **6**, **10**, **11**, **14** and **15** raises the question of the fixation site(s) of diiodine. We first note that all the visible spectra of free diiodine in equilibrium with complexed diiodine show an isosbestic point, which excludes the presence of a 1:2 complex but not of two 1:1 complexes.[14]

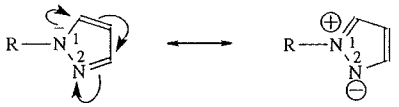
In compounds **5**, **6**, **10**, **11**, **14** and **15**, the fixation of diiodine on the benzene π ring is considered negligible when we compare the very low formation constant ($\log K = -0{\cdot}62$)[15] of the benzene–diiodine complex with the constants in Table 1.

In imidazoles **1**–**6**, the low formation constant ($\log K = 0{\cdot}78$)[16] of the diiodine–*N*-methylpyrrole complex, compared with the values in Table 1 ranging from 2·50 to 3·41, is also indicative of halogen bonding [halogen bonding (cf. hydrogen bonding) refers to the intermolecular bond between the halogen atom and the basic atom of the Lewis base] to the imino nitrogen N-3 and not to the amino nitrogen N-1. Moreover, the push–pull mechanism



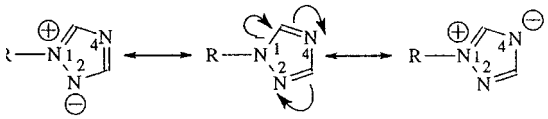
still decreases the basicity of nitrogen N-1 at the benefit of N-3. In fact, imidazoles behave as all other amidines where protonation[17] and hydrogen bonding[18] occur on the imino nitrogen.

If we consider pyrazoles as imidazole vinylogues (amidine vinylogues):



the same arguments apply to pyrazoles **7**–**11** and allow us to conclude that diiodine is halogen bonded to nitrogen N-2 in these compounds.

In triazoles, diiodine can be halogen bonded to either nitrogen N-2 or N-4, as shown by the resonance limit forms **a** and **b**:



a **b**

The respective importance of forms **a** and **b** will determine the major site. Three arguments allow us to conclude that the preferred site is N-4.

The first argument in favour of an I—I· · ·N-4 complex comes from the fact that the bulky 1-adamant-1-yl substituent does not give a steric effect in triazoles. In fact, if diiodine were to fix on nitrogen N-2, the formation constant of **13** with diiodine should decrease compared with **12**, as for pyrazoles (see below). Since, on the contrary, the adamantyl substitution increases *K*, as for imidazoles (see below), we conclude that the diiodine is halogen bonded to N-4.

The second argument comes from the calculation of the minimum electrostatic potential on the molecular surface, $V_{s,\,min}$. *Stricto sensu*, V_s corresponds to the electrostatic interaction energy with a proton located on the molecular surface, but it also reflects the orientational-dependent electron density and $V_{s,\,min}$ should design the most basic nitrogen lone pair. In fact, the electrostatic interaction energy is dominant in the complexes of dihalogens[19, 20] with nitrogen bases. Calculations of $V_{s,\,min}$ at the PM3, HF/3–21G* and HF/6–31G* levels (Table 2) confirm clearly that the nitrogen N-3 of imidazoles and N-2 of pyrazoles are the basic ones and show that the nitrogens N-4 of 1,2,4-triazoles and N-3 of the 1,2,3-triazole **15** are more basic than N-2. There is a rough relationship between log *K* and $V_{s,\,min}$ and the energy of the highest occupied orbital, ε_{HOMO}, calculated, for economic reasons, at the PM3 level:

$$\log K = 1{\cdot}19 + 0{\cdot}109(-V_{s,\,min}/\text{kcal mol}^{-1}) + 0{\cdot}771\,(\varepsilon_{HOMO}/\text{eV}) \quad (5)$$

(1 kcal = 4·184 kJ). In equation (5), the number of data points is 15 and the multiple correlation coefficient is 0·910; the normalized regression coefficients (not given) show that the leading term is the *V* term. The importance of the *V* term is also shown by the significant partial correlation coefficient of log *K* vs $V_{s,\,min}$ ($r = 0{\cdot}80$) compared with the non-significant one ($r = 0{\cdot}24$) for log *K* vs ε_{HOMO}. Equation (5) allows the estimation of $\delta\log K$, the difference in basicity between nitrogens [equation (6)], from the difference δV between $V_{s,\,min}$ (N-*i*) and V_s(N-*j*) [equation (7)].

$$\delta \log K = \log K(\text{N-}i) - \log K(\text{N-}j) = \log \frac{K(\text{N-}i)}{K(\text{N-}j)} \quad (6)$$

$$\delta\log K = 0{\cdot}109\ \delta V \quad (7)$$

For 1-methyl-1,2,4-triazole, $\delta V = 8{\cdot}1$ kcal mol^{-1} predicts that K(N-4) is about eight times greater than *K*(N-2), and for benzotriazole $\delta V = 10{\cdot}4$ kcal mol^{-1} gives K(N-3) ≈ 14*K*(N-2). These ratios *K*(N-*i*)/*K*(N-*j*) are only orders of magnitude, since equation (7) is very approximate, but they indicate how much the imidazolic nitrogens are more basic than the pyrazolic nitrogens in triazoles.

A last argument is given by the *ab initio* study of the complexes of azoles with dihalogens. Few *ab initio* calculations have been devoted to diiodine complexes and, in any case, they have been performed on simple molecules (e.g. ammonia,[19] methylamine[19] or acetone[21]). For economic reasons, (i) we replaced diiodine with dichlorine, (ii) we studied only triazoles **12** and **13**, and for comparison imidazole **1** and pyrazole **8**, and (iii) we chose the HF/3–21G* basis set (3–21G*//3–21G* calculations). Being interested only in the relative basicity of two nitrogens in the same molecule, we assume that the errors induced by the finite character of the basis and the neglect of electron correlation are about the same for each nitrogen. To judge

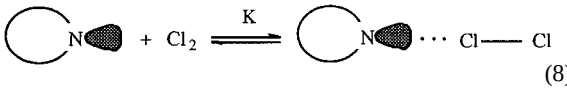
Table 2. Electrostatic potentials (kcal mol^{-1}) on the 0·002 e/au isosurface for azoles

		HF/6–31G*			HF/3–21G*	PM3
No.	Compound	$-V_{s,\,min}$ (N-*i*)[a]	$-V_s$ (N-*j*)[b]	δV[c]	δV[c]	δV[c]
1	1-Methylimidazole	59·2 (N-3)	—[d] (N1)	—[e]	—[e]	—[e]
8	1-Methylpyrazole	49·1 (N-2)	—[d] (N-1)	—[e]	—[e]	—[e]
12	1-Methyl-1,2,4-triazole	50·5 (N-4)	44·1 (N-2)	6·4	10·2	8·1
15	Benzimidazole	50·4 (N-3)	41·2 (N-2)	9·2	8·8	10·4

[a] Minimum electrostatic potential, on nitrogen numbered *i*.
[b] Electrostatic potential on nitrogen numbered *j*.
[c] Difference between $-V_{s,\,min}$ (N-*i*) and $-V_s$ (N-*j*).
[d] Not negative enough to be determined.
[e] Very large.

the interaction strength of the complex, we focused on three properties:

(i) the electronic energy change, ΔE_0, for the reaction (8):



(8)

$$\Delta E_0 = E_0\,(\text{complex}) - [E_0\,(\text{azole}) + E_0\,(\text{Cl}_2)] \qquad (9)$$

(ii) the length of the intermolecular bond, $r(N\cdots Cl)$;

(iii) the change in the Cl—Cl bond distance upon complex formation, Δr (Cl—Cl).

The results are summarized in Table 3. We note that the 3–21G* basis set gives a fairly good prediction of the Cl_2 bond length (calc. 1·9964 Å; exp.[11] 1·9915 Å) and predicts a geometry of the complexes which seems reasonable, compared with the geometry of $Cl—Cl\cdots NH_3$:[11] the complexation leads to a lengthening of the Cl—Cl bond distance, Cl_2 lies along the axis of the nitrogen sp^2 lone pair (as conventionally envisaged) and the $Cl—Cl\cdots N$ arrangement is quasi-linear. We see that the most negative ΔE_0, the shortest halogen bond and the longest dichlorine bond are found when dichlorine is bonded to N-4 in triazoles **12** and **13**. If we make the reasonable assumptions that $\delta\Delta H_{298} \approx \delta\Delta E_0$ and $\delta\Delta S_{298} \approx 0$ (the operator δ is for the difference between the complexes on N-4 and N-2), $\delta\Delta E_0 = 1{\cdot}45$ kcal mol^{-1} allows us to estimate that, for triazole **12**, K(N-4) is 12 times greater than K(N-2). This order of magnitude (for the dichlorine complex) agrees with that found previously from the correlation (7) between $\delta\log K$ and electrostatic potentials. We conclude that the imidazolic nitrogen N-4 of 1,2,4-triazoles is the major site of diiodine fixation.

Influence of structure on the diiodine basicity

The inequalities 1-Me-imidazole > 1-Me-pyrazole > 1-Me-1,2,4-triazole (where > means 'more basic than') show that the basicity of azoles decreases when the number of imino nitrogens increases. This extends to tetrazoles which are very weakly basic ($\log K \approx 0{\cdot}5$).[8] The inequalities 1-*n*-Bu-imidazole > 1-*n*-Bu-benzimidazole and pyrazole > indazole show that the benzofusion decreases the basicity. The same was found for thiazole and benzothiazole.[22]

The inductive-field electron-withdrawing effect of $PhCH_2$ ($\sigma_F = +0{\cdot}05$)[23] explains why 1-benzyl-1,2,4-triazole is less basic than 1-methyl-1,2,4-triazole. Both the σ_F value of phenyl ($\sigma_F = +0{\cdot}10$)[23] and an electron-withdrawing resonance effect (**10b** and two other similar forms compete with **10a**) cause 1-phenylpyrazole to be the least basic of the azoles of this study.

The influence of alkyl substituents on the amino nitrogen N-1 is similar for the families of imidazoles and 1,2,4-triazoles, but differs for pyrazoles. For imidazoles and triazoles, the alkyl substituents on N-1 increase the basicity in the order of chain lengthening and branching: adamant-1-yl > *tert*-butyl ≈ *n*-butyl > methyl > hydrogen.

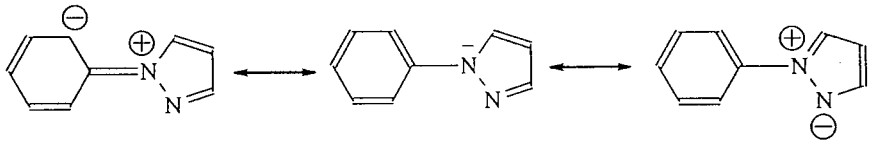
The electronic effects of alkyl groups are the subject of an old controversy. Our findings support the historical point of view of Taft[24] that the electron-donating effect of alkyl groups increases with increasing chain length and branching, and not the alternative view[25] that this effect remains almost constant. In fact, compared with methyl the adamant-1-yl substituent increases the basicity of imidazoles, compared with methyl, by 0·55 log K unit (i.e. 0·75 kcal mol^{-1} in free energy, to be compared with the enthalpy of formation of the diiodine–nitrogen sp^2 bases,[26] 8 kcal mol^{-1}). However, the mechanism(s) of electron donation remain(s) to be established.

In the pyrazole family, the hydrogen/methyl substitution *increases* log K by 0·25 unit, but the methyl/adamant-1-yl substitution *decreases* log K by 0·57 unit. This reflects the front strain between the bulky adamant-1-yl substituent and the diiodine molecule bonded to N-2: the upsilon steric parameter[27] of adamant-1-yl is 1·33, compared with only 0·52 for methyl and zero for hydrogen. It seems clear that,

Table 3. Some properties of the azoles–dichlorine complexes calculated at the HF/3–21G* level

No.	Compound	N[a]	$-\Delta E_0$[b, c]	$r(N\cdots Cl)$ (Å)	$\Delta r(Cl_2)$[d] (Å)
1	1-Methylimidazole ($\log K = 2{\cdot}86$)	N-3	7·90	2·559	0·036
8	1-Methylpyrazole ($\log K = 2{\cdot}14$)	N-2	6·18	2·661	0·023
12	1-methyl-1,2,4-triazole ($\log K = 1{\cdot}69$)	N-2	5·34	2·715	0·017
		N-4	6·79	2·621	0·026
13	(1-Adamant-1-yl)-1,2,4-triazole ($\log K = 1{\cdot}90$)	N-2	6·48	2·759	0·014
		N-4	8·84	2·603	0·029
—	Ammonia($\log K = 1{\cdot}76$)[e]	N	—	2·730[f]	0·010[f]

[a] Nitrogen to which Cl_2 is bonded.
[b] Electronic energy change in kcal mol^{-1} at 0 K, without zero-point correction.
[c] The 3–21G* basis can overestimate these values. A 6–31G*//6–31G* calculation gives $\Delta E_0 = -3{\cdot}42$ kcal mol^{-1} for the complex of 1-methylimidazole.
[d] $\Delta r(Cl_2) = r$ (complexed Cl_2) $- r$ (free Cl_2).
[e] Ref. 28.
[f] Experimental results from Ref. 11 for comparison.



10 b **10 a**

in the pyrazole series, the electron-donating effect of bulkyl alkyl substituents on N-1 can be overcome by their steric effect.

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