

SIMILARITY IN PHYSICAL ORGANIC CHEMISTRY: SUBSTITUENT EFFECTS ON THE INTRINSIC BASICITY OF 4-SUBSTITUTED PYRAZOLES

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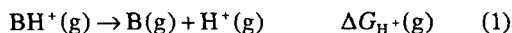
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The gas-phase basicities of eight pyrazoles substituted only at position 4 ($R^4 = H, NO_2, F, Cl, CO_2C_2H_5, CH_3, NH_2, 1\text{-adamantyl}$) were measured by Fourier transform ion cyclotron resonance. The experimental values were treated in two ways, first by comparing these values with the AM1-calculated proton affinities. Since the correlation was reasonably good [$PA(\text{calc.}) = -11.3 + 1.063PA(\text{exp.})$, $n=8$, $r=0.984$], a set of 17 further 4-substituted pyrazoles and their cations were calculated using the AM1 approximation and their gas-phase basicities were estimated. Second, both the experimental and the AM1-calculated values were considered within the framework of the Taft-Topsom analysis of substituent effects. Comparison of the analyses for pyrazoles and pyridines led to the unexpected result that, in spite of differences in ring size and number of heteroatoms, both systems behave remarkably alike.

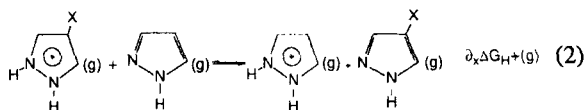
INTRODUCTION

The empirical observation of similarities¹ in substituent effects on reactivity (very often appearing as 'linear free energy relationships' (LFER)² has played a key role in the development of physical organic chemistry. Great strides have been made in this field owing to new experimental techniques³ that allow (inter alia) the determination of the proton basicity of a species B in the gas phase, $GB(B)$. $GB(B)$ is defined as the standard Gibbs energy change for the reaction



[the proton affinity of B, $PA(B)$, is defined as $PA(B) = \Delta H_{H^+}(g)$].

Consider, for example, reaction (2), the proton exchange between pyrazole and a 4-X-substituted derivative:



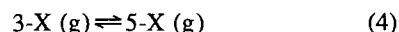
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The link between reactions (1) and (2) is obvious. Physically, $\delta_x \Delta G_{H^+}(g)$ is a measure of the 'substituent effect' (SE) of X on the intrinsic basicity of pyrazole. These SEs can be studied on a quantitative basis by means of quantum-mechanical methods⁴ or by correlation analysis techniques.² Noteworthy among the latter are the Taft-Topsom⁵ and Tsuno and co-workers⁶ treatments. In the particular case of the Taft-Topsom approach, an SE, such as $\delta_x \Delta G_{H^+}(g)$, is divided into three main components, according to the equation

$$\delta_x \Delta G_{H^+}(g) = \rho_\alpha \sigma_\alpha + \rho_F \sigma_F + \rho_R \sigma_R \quad (3)$$

where σ_α , σ_F and σ_R are descriptors of polarizability, field and resonance contributions, respectively.

Although extensive quantitative studies of SEs on GBs have been carried out,^{4d,5a,7} the information available on heterocyclic substrates is fairly scarce, the main exceptions being pyridines^{5a,8} and 3(5)-substituted pyrazoles.⁹ For the latter, we have determined⁹ SEs on their intrinsic basicities and on the position of the equilibrium



Here we present new experimental data on the GBs of

4-X-substituted pyrazoles [reaction (2)]. Our interest in these SEs is twofold. First, we feel it necessary to broaden the database for heterocyclic compounds. Second, we wish to explore the scope of similarity principles and LFERs derived therefrom, the pyrazolic substrate being an interesting target. Thus, in the case of 3-X (or 5-X) derivatives, we drew attention to the fact that the pattern of SEs on the GBs of these compounds was closely related to that of 2-X-substituted pyridines, the analogy extending up to protonation in aqueous solution. The present results should provide a more comprehensive picture.

In parallel with the experimental work, a quantum-mechanical study of the energetics of reaction (2) was carried out using the AM1 semi-empirical method.¹⁰ This technique is particularly useful for the study of medium- to large-sized systems.^{7,11}

EXPERIMENTAL METHODS AND COMPUTATIONAL TECHNIQUES

Materials

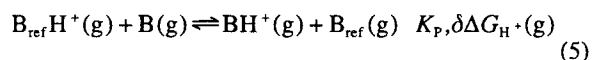
With the exception of the 4-(adamant-1-yl) derivative, all the other pyrazoles, namely 4-chloro-,¹²⁻¹⁴ 4-phenyl-,^{15,16} 4-ethoxycarbonyl-,¹⁷⁻¹⁹ 4-amino-²⁰⁻²² and 4-nitro-,²³⁻²⁵ were obtained according to well known procedures. 4(Adamant-1-yl)pyrazole was obtained as follows:²⁶

A mixture of unsubstituted pyrazole (20 mmol) and 1-bromoadamantane (10 mmol) in a high-pressure stainless-steel autoclave of 250 ml (maximum working pressure 200 atm) was heated in an oven at 230 °C for 4 h. When the heating was completed, the reactor was allowed to cool to room temperature and then the

autoclave was opened and the crude reaction product was mixed with 5 ml of ethanol and 500 ml of water. The acidic solution was neutralized with 1 M NaOH. The precipitate that formed was filtered, dried and column chromatographed on MerckSi 60 silica gel (230–400 mesh) with dichloromethane–ethanol as eluent. The reaction yields a mixture of 1-(adamant-1-yl)pyrazole (relative amount 13%) and 4-(adamant-1-yl)pyrazole (relative amount 87%). Pure 4-(adamant-1-yl)pyrazole was obtained with a yield of 78%, m.p. 200–202 °C (lit.,²⁷ 198–199 °C). A mixture of the compound thus prepared with a sample obtained according to the lengthier procedure of Reichardt and Würthwein²⁷ gave no depression of the melting point (melting points were determined in a capillary tube and are uncorrected). These materials were purified by repeated crystallization and their purity (always higher than 99%) was assessed by mass and ¹H NMR spectroscopy, high-performance liquid chromatography and differential scanning calorimetry. Pyrazole and its 4-methyl- and 4-fluoro-derivatives have already been studied.⁹

Gas-phase basicities

GBs were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS-47 Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer under conditions similar to those already described.^{7,9} Table 1 presents the results of proton-transfer equilibria (5) obtained in this study along with the standard bases used (B_{ref}).



In this equilibrium, B is a neutral pyrazole. The

Table 1. Gas-phase basicities of 4-X-substituted pyrazoles obtained with reference bases^a

X	Reference base	$\delta\Delta G_{H^+}(g)$	$\Delta\Delta G_{H^+}(std)^b$	$\Delta\Delta G$	$\Delta\Delta G_{H^+}(g)$
NO ₂	(CH ₃) ₂ CO	-1.15	8.3	7.1 ₅	7.0 ± 0.2
	(CH ₂) ₄ O	1.28	5.6	6.8 ₈	
Cl	(<i>n</i> -C ₄ H ₉) ₂ S	1.72	-5.6	-3.8 ₈	-3.7 ± 0.2
	(CH ₃ CO) ₂ CH ₂	0.39	-4.0	-3.6 ₁	
CO ₂ Et	(<i>n</i> -C ₄ H ₉) ₂ S	-0.90	-5.6	-6.5 ₀	-6.5 ± 0.2
	2-Fluoropyridine	1.50	-7.9	-6.4 ₀	
	HC≡CCH ₂ NH ₂	1.79	-8.5	-6.7 ₁	
C ₆ H ₅	<i>c</i> -C ₃ H ₅ NH ₂	-0.36	-12.0	-12.3 ₆	-12.5 ± 0.1
	H ₂ C=CHCH ₂ NH ₂	0.75	-13.3	-12.5 ₅	
NH ₂	H ₂ C=CHCH ₂ NH ₂	0.40	-13.3	-12.8 ₇	-12.9 ± 0.1
	Pyridazine	0.62	-13.6	-12.9 ₉	
	4-Methylpyrazole	0.09	-12.7	-12.8 ₃	
1-Adamantyl	H ₂ C=CHCH ₂ NH ₂	-0.79	-13.3	-14.0 ₀	-14.0 ± 0.1
	<i>n</i> -C ₃ H ₇ NH ₂	1.20	-15.1	-13.9 ₀	
	Pyridazine	-0.28	-13.6	-13.8 ₈	

^a All values in kcal mol⁻¹.

^b From Ref. 28 and with the correction indicated in the text.

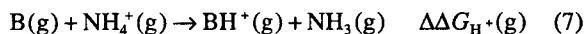
reversibility of reaction (5) was systematically confirmed by means of double-resonance experiments. At least two reference bases were used in each case. Their *GBs* are mostly published values²⁸ from Taft's laboratory. These values were compared with those given in the most recent HPMS determination of *GBs* and *PAs*, carried out under extremely careful conditions of temperature monitoring.²⁹ The correlation between *GBs* at 333 K (our nominal working temperature) obtained from Ref. 29 for 18 bases ranging from water to dimethylamine and Taft's data is exceptionally good: $r = 0.9997$, $s.d. = 0.34 \text{ kcal mol}^{-1}$ ($1 \text{ kcal} = 4.184 \text{ kJ}$). The slope is 1.068 ± 0.021 at the 99% level. Taft's values were therefore multiplied by this factor throughout (for a precedent, see, e.g., Ref. 7). The AM1 calculations¹⁰ were carried out using the MOPAC³⁰ package of programs and the keyword PRECISE. The proton affinities obtained at this level were calculated taking for the heat of formation of the proton the experimental value ($367.2 \text{ kcal mol}^{-1}$).³¹ No restrictions whatsoever were imposed in the optimization of the geometries of the various species.

EXPERIMENTAL RESULTS

The values of $\delta\Delta G_{\text{H}^+}(\text{g})$ given in Table 1 are defined as

$$\delta\Delta G_{\text{H}^+}(\text{g}) = -RT \ln K_p \quad (6)$$

All *GBs* are referred to ammonia. Thus, with respect to this reference, $GB(\text{B}) = -\Delta\Delta G_{\text{H}^+}(\text{g})$ for the reaction



$\Delta\Delta G_{\text{H}^+}(\text{g})$ is the average of the $\Delta\Delta G$ values obtained through the equation

$$\Delta\Delta G = \delta\Delta G_{\text{H}^+}(\text{g}) + \Delta\Delta G_{\text{H}^+}(\text{std}) \quad (8)$$

where $\Delta\Delta G_{\text{H}^+}(\text{std})$ pertains to the reaction



Table 2. Experimental (FT-ICR) and calculated (AM1) proton affinities (*PA*) of 4-*X*-substituted pyrazoles relative to ammonia

<i>X</i>	<i>PA</i> (exp.) ^a	<i>PA</i> (calc.) ^{a,b}
NO ₂	-7.5 ^b	-19.9
F	1.8 ^c	-8.9
Cl	3.2 ^b	-5.6
CO ₂ Et	6.0 ^b	-7.2
H	9.2 ^c	-1.1
C ₆ H ₅	12.0 ^b	0.8
CH ₃	12.1 ^c	0.4
NH ₂	12.4 ^b	3.2
1-Adamantyl	13.5 ^b	3.1

^a All values in kcal mol^{-1} .

^b This work.

^c From Ref. 9.

The corresponding *PA* values relative to ammonia and presented in Table 2 were obtained using entropy changes $\Delta\Delta S$ for reaction (7) estimated by means of the appropriate changes in symmetry numbers σ involved in this reaction:³²

$$\Delta\Delta S = R \ln 4 + R \ln[\sigma(\text{B})/\sigma(\text{BH}^+)] \quad (10)$$

Equation (10) reflects the fact that $\sigma(\text{NH}_3) = 3$ and $\sigma(\text{NH}_4^+) = 12$. Since for pyrazole and its 4-substituted derivatives $\sigma(\text{B}) = 1$ and $\sigma(\text{BH}^+) = 2$, we obtain $T\Delta\Delta S = 0.46 \text{ kcal mol}^{-1}$ at 333 K.

COMPUTATIONAL RESULTS AND DISCUSSION

Table 2 presents the experimental *PAs* relative to ammonia and the corresponding values calculated at the AM1 level (and referred to ammonia by subtracting its experimental *PA*,³³ $204.0 \text{ kcal mol}^{-1}$). From this database, the following are deduced.

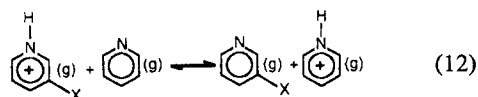
(1) The correlation between the experimental and calculated *PA* values relative to ammonia is fairly satisfactory:

$$PA(\text{calc.}) = -11.3(0.7) + 1.063(0.075)PA(\text{exp.}) \quad (11)$$

$n = 9$; $r = 0.984$; standard deviation of fit, $s.d. = 1.5 \text{ kcal mol}^{-1}$. The standard deviations for the regression coefficients are given in parentheses.

The SEs described by equation (11) span $20.9 \text{ kcal mol}^{-1}$ and involve a variety of substituents covering a wide range of polarizability, field and resonance effects. This lends credence to the calculated values of differential structural effects on *PAs* to be discussed below.

(2) As in previous work,⁹ we compare SEs for 4-substituted pyrazoles with those for 2-, 3- and 4-substituted pyridines. The best correlation involves $\delta_x\Delta G_{\text{H}^+}(\text{g})$ values for reactions (2) and (12) (data for the latter are given in Table 3).



$$\delta_x\Delta G_{\text{H}^+}[\text{g, reaction (12)}] = -0.18(0.60) + 0.903(0.083)\delta_x\Delta G_{\text{H}^+}[\text{g, reaction (2)}] \quad (13)$$

$n = 8$; $r = 0.975$; $s.d. = 1.6 \text{ kcal mol}^{-1}$.

Correlations involving $\delta_x\Delta G_{\text{H}^+}[\text{g, reaction (2)}]$ and $\delta_x\Delta G_{\text{H}^+}(\text{g})$ values for 2- and 4-substituted pyridines are poorer ($r = 0.968$ and 0.85 , respectively). Equation (13) defines an essentially direct proportionality of effects. We believe that the origin of these results lies in the absence of direct conjugation between the basic centers and the substituents in the protonated forms.

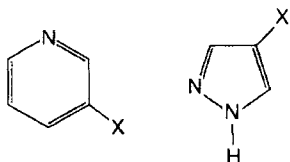
Table 3. Differential substituent effects on the G_B s of 4-X-substituted pyrazoles and 3-X-substituted pyridines, $\delta_X \Delta G_{H^+}(g)^a$

X	$\delta_X \Delta G_{H^+}(g)$				
	4-X-pyrazoles	3-X-pyridines ^b	σ_a^c	σ_F^c	$\sigma_{R^+}^c$
H	0	0	0	0	0
NO ₂	-16.7	-14.4	-0.26	0.65	0.0
F	-7.4	-7.5	0.13	0.44	-0.25
Cl	-6.0	-6.6	-0.43	0.45	-0.17
CO ₂ Et	-3.2	-3.0	-0.52	0.24	0.0
C ₆ H ₅	2.8	—	-0.81	0.10	-0.22
CH ₃	2.9	3.1	-0.35	0.0	-0.08
NH ₂	3.2	0.2	-0.16	0.14	-0.52
1-Adamantyl	4.2	6.0	-0.95	0.0	-0.06

^a All values in kcal mol⁻¹.

^b From Ref. 8 and using the correction factor 1.068 as indicated in the text.

^c From Ref. 5 and personal communication from R. W. Taft.



It is also clear that equation (13), a 'bona fide' LFER, is of only moderate quality, thus indicating a limited similarity (see below).

(3) The analysis of structural effects on $\delta_X \Delta G_{H^+}(g)$ for reaction (2) requires that the sets of explanatory variables $\{\sigma_a\}$, $\{\sigma_F\}$ and $\{\sigma_{R^+}\}$ be orthogonal for the set of substituents. This condition is not far from being fulfilled, the r^2 values for the correlations between the various sets, namely $\{\sigma_a\}/\{\sigma_F\}$, $\{\sigma_a\}/\{\sigma_{R^+}\}$ and $\{\sigma_F\}/\{\sigma_{R^+}\}$, being equal to 0.14, 2×10^{-3} and 3×10^{-3} , respectively. The range of variation of each of these variables is substantial. This makes the correlation more 'robust.' We find

$$\delta_X \Delta G_{H^+}(g) = -3.74(0.78)\sigma_a - 24.8(1.3)\sigma_F - 12.9(1.9)\sigma_{R^+} \quad (14)$$

$n = 9$; $r = 0.991$; s.d. = 1.0 kcal mol⁻¹.

The σ_{R^+} used in this work and in Ref. 7 are those defined by Taft and co-workers^{5a,b} as ' σ_{R^+} values for electron-acceptor systems.' They are extremely close to the σ_R^0 values defined by Bromilow *et al.*,^{5c} with the only (and important) difference that $\sigma_{R^+} = 0$ for all +R substituents. The correlation coefficients for the correlations involving σ_{R^+} and σ_R^0 are virtually identical. The correlation with σ_R^0 , however, shows a significant skewness and so σ_{R^+} is a more appropriate descriptor. A referee has rightly pointed out that in the neutral pyrazoles the lone pair of the NH nitrogen and the +R substituents are conjugated and so, a dependence on σ_{R^-} rather than on σ_{R^+} is to be expected. This is certainly

true as far as substituent effects on properties of the neutral species are concerned. However, as indicated previously,⁷ differential substituent effects on $\Delta G_{H^+}(g)$ values for the protonation of 3(5)-substituted pyrazoles and pyridines^{5a} essentially reflect differences in interactions between the substituents and the positive charge borne by the ring. These interactions are best described by σ_{R^+} . In our case, the correlation of the experimental data with σ_{R^-} instead of σ_{R^+} leads to a poorer correlation coefficient (0.977 instead of 0.991) and substantially larger standard deviation of the fit (1.7 vs 1.0 kcal mol⁻¹).

We summarize in Table 4 the coefficients ρ_a , ρ_F and ρ_{R^+} pertaining to analogous correlations for 3- and 5-substituted pyrazoles and for 2-, 3- and 4-substituted pyridines (whenever necessary, values have been corrected by the factor 1.068 indicated in the Experimental section). The similarity between the patterns for 3- and 5-substituted pyrazoles and 2-substituted pyridines is clear and has been discussed.⁹

Direct comparison has indicated important similarities between SEs on 4-substituted pyrazoles and 3- and to a lesser extent, 2-substituted pyridines. The data in Table 4 shows the origin of these similarities: the absolute values of ρ_a are relatively small and of comparable size. The ρ_F values are large (in absolute value) and remarkably close in all cases.

Hence analogies and differences can be traced to ρ_{R^+} values. The smallest absolute value is for 4-substituted pyrazoles and is appreciably lower (30%) than that for 3-substituted pyridines. This explains why the statistical quality of equation (13) is only fair. This seems to indicate a quantitative difference in the stabilization through resonance effects in pyrazolium and pyridinium ions. Interestingly, in our previous work, the similarity in size of ρ_{R^+} values for 3- and 5-substituted pyrazoles and 2-substituted pyridines was rationalized in terms of

Table 4. Study of structural effects on the GBs of pyrazoles and pyridines

Compounds	$-\rho_a^{a,b}$	$-\rho_F^{a,b}$	$-\rho_R^{a,b}$
Substituted pyrazoles			
3-X ^c	8.9 (1.6)	26.7 (1.6)	16.5 (2.0)
4-X	3.74 (0.78)	24.8 (1.3)	12.9 (1.9)
5-X ^c	7.3 (1.0)	26.0 (1.0)	21.0 (1.4)
Substituted pyridines ^d			
2-X	6.8 (0.8)	28.9 (2.0)	15.3 (2.0)
3-X	4.5 (1.4)	24.4 (1.4)	17.4 (1.6)
4-X	5.1 (2.2)	23.0 (1.2)	27.6 (1.7)

^a All values in kcal mol⁻¹.^b Standard deviation in parentheses.^c From Ref. 9 corrected with the factor 1.068 as indicated in the text.^d From Ref. 8, with the same correction.Table 5. Calculated (AM1) proton affinities (PA) of selected 4-X-substituted pyrazoles relative to ammonia^{a,b}

X	PA^c	σ_a^d	σ_F^d	σ_R^d
N(CH ₃) ₂	3.5	-0.44	0.10	-0.64
<i>t</i> -C ₄ H ₉	2.0	-0.75	0	-0.07
<i>i</i> -C ₃ H ₇	1.4	-0.62	0	-0.07
C ₂ H ₅	1.0	-0.49	0	-0.07
OCH ₃	-1.6	-0.17	0.25	-0.42
OH	-4.1	-0.03	0.30	-0.38
Br	-6.1	-0.59	0.45	-0.15
COCH ₃	-7.2	-0.55	0.26	0
CO ₂ CH ₃	-8.0	-0.49	0.24	0
CHO	-8.6	-0.46	0.31	0
NO	-10.3	-0.25	0.41	0
CN	-11.5	-0.46	0.60	0
CF ₃	-13.4	-0.25	0.44	0
COCF ₃	-15.6	-0.51	0.50	0
<i>t</i> -C ₄ F ₉	-15.8	-0.68	0.61	0
SO ₂ CF ₃	-24.4	-0.58	0.84	0
SOCF ₃ (=NSO ₂ CF ₃)	-30.9	(—)	(1.17) ^e	(0)

^a All values in kcal mol⁻¹.^b This work.^c Defined in the text.^d From Ref. 5.^e From Ref. 35.

repulsions between the NH⁺ groups and -R substituents. While these repulsions certainly exist, we are now led to question whether they are the only reason behind the relatively small $|\rho_R^+|$ values in the case of pyrazoles. We suspect that these facts are related to the lower aromaticity of pyrazole relative to pyridine and benzene³⁴ and to the fact that pyrazole and pyridine are π -excessive and π -deficient heterocycles, respectively, but more information is needed.

(4) The satisfactory performance of the AM1 method [see equation (11)] has prompted us to extent

our theoretical calculations to a large set of substituents for which no experimental data are available. The calculated PA s relative to ammonia are given in Table 5.

A stringent test of the quality of these predictions is provided by the Taft-Topsom treatment. On account of the essentially constant value of $\Delta\Delta S$ for reaction (2), $\delta_x\Delta G_{H^+}(g) = \delta_x PA$. It follows that equation (14) should also apply to $\delta_x PA$. This is indeed the case: for the set of 25 'usual' substituents presented in Tables 2 and 5 and for which σ_a , σ_F and σ_R^+ are available, we find

$$\delta_x PA = -2.4 (1.0)\sigma_a - 26.5 (1.3)\sigma_F - 13.5 (1.9)\sigma_R^+ \quad (15)$$

$n = 25$; $r = 0.971$; s.d. = 1.9 kcal mol⁻¹. The coefficients of this regression equation agree within the limits of uncertainty with those of equation (14).

Recently, a number of compounds have been synthesized (notably by Yagupolskii and co-workers³⁵) that are endowed with an extremely high intrinsic protonic acidity.³⁶ This acidity originates in unusual substituents such as SOCF₃(=NSO₂CF₃). It seems reasonable to infer that these substituents will greatly reduce the basicity of 4-substituted pyrazoles. Indeed, for SOCF₃(=NSO₂CF₃) we compute $\delta_x PA = -29.8$ kcal mol⁻¹, an enormous base-weakening effect. For this +R substituent, $\sigma_R^+ = 0$. We can estimate its σ_a at ca -0.58, the value for SO₂Me. Then, by means of equation (15), we deduce $\sigma_F = 1.15$. The value obtained by means of ¹⁹F NMR³⁷ is 1.17.^{35a} This value also accounts for the intrinsic protonic acidity of the superacids containing this group.³⁸

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from CSIC. One of us (I.F.) is indebted to the Ministère de la Recherche et de la Technologie, France, for a postdoctoral fellowship. This work is dedicated to Professor Robert W. Taft on his 70th birthday. It illustrates some applications of his concepts and methods. They are endowed with a considerable heuristic power and, most important, they stimulate new experimental and theoretical studies.

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