

are in a similar quandary with respect to the transition state. In the end, what we know is that the nitro group increases the energy of activation over what it is in thiophene.

It is, however, meaningful to ask the question "Does this increase in activation energy arise because 2-nitrothiophene has a charge distribution that is different from that of thiophene, or does it arise because 2-nitrothiophene, is less able to delocalize the added charge than is thiophene?" This question can be given precise definition in both theory and experiment. It is simplest to think of these in terms of adding or removing a proton,<sup>3a</sup> but the ideas can be generalized to more complex systems.

The effect of the reactant charge distribution on the energy to add a proton is the potential energy of a proton at the site of addition. The nitro group at the 2-position makes the potential at sulfur and at C(5) more positive and, hence, less attractive to the proton; therefore, the activation energy is increased. This potential is well-defined quantum mechanically.<sup>3a</sup>

The effect of the charge delocalization, or relaxation, is to lower the energy of the transition state when the electrons rearrange from the reactant charge distribution to the distribution appropriate to the transition state. This relaxation energy is also well defined.<sup>3a</sup> It is conceivable that the nitro group, being electron withdrawing, inhibits the flow of electrons toward the electrophile. In the language of organic chemistry, the transition state would, in this case, be less stabilized<sup>49</sup> by delocalization for 2-

nitrothiophene than it is for thiophene. However, both experiment and theory indicate that the degree of stabilization of the transition state due to delocalization is nearly the same for both molecules and is nearly the same for electron-withdrawing substituents as for electron-donating substituents.

One cannot say from a measurement of a shift in activation energy between 2-nitrothiophene and thiophene which of these effects is the more important. One needs either a theoretical calculation or a pair of measurements, such as we have presented, that are sensitive to these effects in different ways.

Traditionally, substituent effects have been explained by the ability of the substituent to delocalize charge in the transition state, whereas the initial-state effects have been largely ignored. Our results clearly indicate that the variation in substituent effect is predominantly determined by the ground-state charge distribution and that the charge rearrangement is very little influenced by the nature of the substituent. Our results thus challenge not only the current theory of electrophilic attack, but that of substituent effects as a whole.

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**Supplementary Material Available:** Calculated total energies of the initial closed-shell ground state and the sulfur 2p core-hole state for all of the molecules, cartesian coordinates for all of the molecules (3 pages). Ordering information is given on any current masthead page.

(48) One might try to get around this problem by some construction of isodesmic reactions. These will, however, typically involve 4 species rather than 2, and it is still impossible to say what has been stabilized with respect to what. We have shown in ref 3e that consideration of isodesmic reactions does not provide a useful approach to these problems.

(49) Or, more loosely, "destabilized". However, since the charge rearrangement is always stabilizing, it is more accurate to speak of substituents being "less stabilizing" or "more stabilizing" in their effect on the transition state.

## Effect of the Replacement of a Methyl by a Trifluoromethyl Group on the Acid-Base Properties of Pyrazoles

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Experimental determinations have been carried out of the thermodynamic basicities and acidities in the gas phase and in aqueous solution of pyrazoles substituted at positions 3 and 5 with methyl and trifluoromethyl groups. Corresponding theoretical calculations at the STO-3G level have also been done. The results are highly consistent both between relative gas-phase properties and theoretical calculations (including STO-3G calculations of anions) and between gas-phase and aqueous solution values. The trifluoromethyl group is found to considerably decrease the basicity (more in position 3 than in position 5) and increase the acidity (more in position 5 than in position 3).

Pyrazoles, due to the close proximity of an acid center (>N-H) and a basic center (≥N): in their structure and also

to the simplicity of the pentagonal aromatic ring, are very useful substrates for the study of acid-base properties in

Table I. Gas-Phase Basicity (kcal mol<sup>-1</sup>)

pyrazole	standard base	$\Delta G^\circ$ (std) <sup>a</sup>	$\Delta G^\circ$ (obs) <sup>b</sup>	$\Delta G^\circ$ <sup>c</sup>	$\Delta H^\circ$ <sup>d</sup>
unsubstituted 4	from ref 3	-	-	204.7 ± 0.2	212.7
3,5-dimethyl 1	from ref 3	-	-	213.9 ± 0.1	221.9
3(5)-(trifluoromethyl)-5(3)-methyl 2	3-chloro-5,5-dimethylcyclohexen-2-one	199.4	-0.7 ± 0.1	200.1 ± 0.2	207.9
	di- <i>n</i> -butyl sulfide	200.8	+0.7 ± 0.1		
3,5-bis(trifluoromethyl) 3	<i>n</i> -propylformiate	185.8	-1.0 ± 0.1	186.9 ± 0.1	194.9
	benzotrile	187.6	+0.7 ± 0.1		

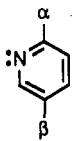
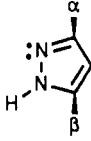
<sup>a</sup>BrefH<sup>+</sup> → Bref + H<sup>+</sup>. <sup>b</sup>B + BrefH<sup>+</sup> = BH<sup>+</sup> + Bref. <sup>c</sup>Ammonia at 195.6 kcal mol<sup>-1</sup>. <sup>d</sup>Sackur-Tetrode correction,  $\Delta H^\circ = \Delta G^\circ + T\Delta S$ ,  $T\Delta S = 8.0$  kcal mol<sup>-1</sup> for symmetrical molecules 4, 1, and 3,  $T\Delta S = 7.8$  kcal mol<sup>-1</sup> for the asymmetrical molecule 2.

Table II. Gas-Phase Acidity Results (kcal mol<sup>-1</sup>)

pyrazole	standard acid	$\Delta G^\circ$ (std) <sup>a</sup>	$\Delta G^\circ$ (obs) <sup>b</sup>	$\Delta G^\circ$ <sup>c</sup>	$\Delta H^\circ$ <sup>d</sup>
unsubstituted 4	from ref 3	-	-	346.5	353.9
3,5-dimethyl 1	ethanethiol	348.9	-0.6 ± 0.1	348.1 ± 0.2	355.5
	3(5)-methylpyrazole	347.1 <sup>13</sup>	+0.8 ± 0.2		
3(5)-(trifluoromethyl)-5(3)-methyl 2	<i>m</i> -(trifluoromethyl)phenol	332.4	+1.2 ± 0.1	333.6 ± 0.1	341.4
	benzenethiol	333.8	-0.2 ± 0.1		
3,5-bis(trifluoromethyl) +3	hydrogen bromide	318.2	-1.0 ± 0.2	317.4 ± 0.2	324.8
	trifluoroacetic acid	316.3	+1.2 ± 0.2		

<sup>a</sup>AH(ref) → A<sup>-</sup> + H<sup>+</sup>. <sup>b</sup>AH + A<sup>-</sup>(ref) = A<sup>-</sup> + AH(ref). <sup>c</sup>Pyrrrole at 350.9 kcal mol<sup>-1</sup>. <sup>d</sup>Sackur-Tetrode correction,  $\Delta H^\circ = \Delta G^\circ + T\Delta S$ ,  $T\Delta S = 7.4$  kcal mol<sup>-1</sup> for symmetrical molecules 4, 1, and 3,  $T\Delta S = 7.8$  kcal mol<sup>-1</sup> for the asymmetric molecule 3.

Table III. Comparison of Substituent Effects on the Intrinsic Basicity of Pyridines and Pyrazoles

	$\rho_\alpha$	$\rho_F$	$\rho_R$		$\sigma_\alpha$	$\sigma_F$	$\sigma_R$
$\alpha$	-6.4	-27.0	-14.3	CH <sub>3</sub>	-0.35	0	-0.08
$\beta$	-4.2	-22.8	-16.3	CF <sub>3</sub>	-0.25	0.44	0.07

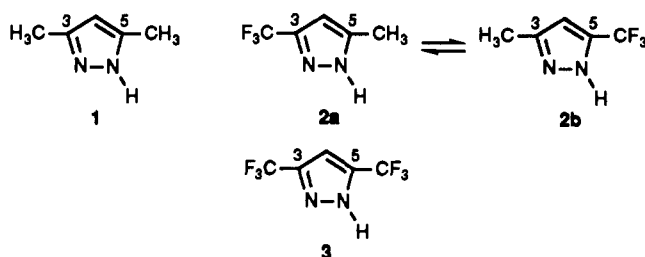
	$\rho_\alpha\sigma_\alpha$	$\rho_F\sigma_F$	$\rho_R\sigma_R$	total
$\alpha$ -CH <sub>3</sub>	2.24	0	1.15	3.39
$\beta$ -CH <sub>3</sub>	1.47	0	1.30	2.77
$\alpha$ -CF <sub>3</sub>	1.60	-11.88	-1.00	-11.28
$\beta$ -CF <sub>3</sub>	1.05	-10.03	-1.14	-10.12
3,5-dimethyl 1	3.39 + 2.77 = 6.16, exp: 9.2 <sup>a</sup>			
3,5-bis(trifluoromethyl) 3	-11.28 - 10.12 = -21.40, exp: -17.8 <sup>a</sup>			
3-CF <sub>3</sub> , 5-CH <sub>3</sub> 2a	-11.28 + 2.77 = -8.51 exp: -4.6 <sup>a</sup>			
3-CH <sub>3</sub> , 5-CF <sub>3</sub> 2b	3.39 - 10.12 = -6.73 exp: -4.6 <sup>a</sup>			

<sup>a</sup> $\Delta G^\circ$ , Table I.

the gas phase by ICR,<sup>1-3</sup> acid-base properties in solution,<sup>2,4</sup> and hydrogen bonds both in pyrazole crystals<sup>5,6</sup> and in solution.<sup>7</sup> Theoretical calculations have been used to rationalize the experimental observations.<sup>3,8-11</sup> From these studies and from others in progress, the importance of

C-substituents on the acid-base properties of pyrazoles is shown. We report here a comparative study in the gas phase and in solution of three 3,5-disubstituted pyrazoles, one of them existing in two tautomeric forms.

The preliminary observations are that compound 3 has a strong, pungent odor (as indicated when prepared for the first time)<sup>12</sup> that diminishes for 2 and almost disappears for 1. These observations are related to the fact that compound 3 is an extraordinary volatile compound and that this property strongly depends on the presence of CF<sub>3</sub> groups.



This work also represents a first attempt to obtain very strong organic acids using C-substituted azoles; for this purpose the substituents should have a strong electron-attracting character without rendering the azole too involatile.

### Gas Phase

The experimental results obtained by ICR (see the Experimental Section) are collected in Tables I and II.

Without taking into account the tautomerism problem of pyrazole 2, the  $\Delta H^\circ$  values of Tables I and II correspond to the following averaged effects (kcal mol<sup>-1</sup>):

	basicity	acidity
methyl group at positions 3 or 5	+4.6	+0.8
trifluoromethyl group at positions 3 or 5	-8.9	-14.5

(note that the positive sign corresponds to a basicity increase and an acidity decrease).

It is not possible to separate the contributions of positions 3 and 5, which can be quite different and even of opposite sign. Nevertheless, it is clear that methyl and trifluoromethyl groups have strong effects on the basicity

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but that only the latter affects the acidity, i.e. the presence of a trifluoromethyl group increases the acidity of the pyrazoles to the point that compound **3** is, in the gas phase, an acid of comparable strength to hydrogen bromide or trifluoroacetic acid (Table I). Since the  $\text{SO}_2\text{CF}_3$  substituent is known to produce at least twice the enhanced acidity of a  $\text{CF}_3$  substituent in similar kinds of aromatic systems it can be estimated that 3,5- $(\text{CF}_3\text{SO}_2)_2$ -pyrazole will have a gas-phase superacidity of  $\Delta G_{\text{acid}} = \text{ca. } 290 \text{ kcal mol}^{-1}$ .

Compound **2** shows properties intermediate between compounds **1** and **3** but does not give exactly the average values (basicity,  $-8.9 + 4.6 = -4.3$ ; obsd,  $-4.8$ ; acidity,  $0.9 - 14.5 = -13.6$ ; obsd,  $-12.5$ ). This is the first indication that  $[\mathbf{2a}]/[\mathbf{2b}] \neq 1$ .

It is of interest to compare corresponding substituent effects for pyrazoles and pyridines. With regard to the basic center, a substituent in position 3 of a pyrazole ring is like a pyridine  $\alpha$ -substituent, and a substituent in position 5 like a  $\beta$ -substituent. We have shown<sup>14</sup> that gas-phase basicities of pyridines follow eq 1. The values

$$\delta \Delta G_{\text{g}}^{\circ} = \rho_{\alpha} \sigma_{\alpha} + \rho_{\text{F}} \sigma_{\text{F}} + \rho_{\text{R}} \sigma_{\text{R}} \quad (1)$$

of  $\rho$  are collected in Table III together with the  $\sigma_{\alpha}$ ,  $\sigma_{\text{F}}$ , and  $\sigma_{\text{R}}$  values for methyl and trifluoromethyl groups.<sup>15</sup> Adding the contribution of each substituent, the calculated values given in Table III were obtained for the four compounds.

Considering only compounds **1** and **3** (both of which have two identical tautomers), then  $\delta \Delta G_{\text{g}}^{\circ} = 316 + 0.98 \delta \Delta G_{\text{g}}^{\circ} \text{calc}$ . With this equation,  $\delta \Delta G_{\text{g}}^{\circ}$  values for tautomers **2a** and **2b** would be  $-5.17$  and  $3.43$  which corresponds to 80% **2a** and 20% **2b**.

Another way to consider the problem is to suppose that  $\rho_{\alpha}$  (polarizability) and  $\rho_{\text{R}}$  (resonance) are not the same in pyridines and in pyrazoles. Using the three compounds (100% of **2a** tautomer) it can be calculated that  $\rho_{\alpha}$  in pyrazoles is 1.5 times larger than in pyridines ( $-13.6$  compared to  $-8.9$ ) whereas  $\rho_{\text{R}}$  is 1.1 times smaller ( $-9.0$  compared to  $-10.2$ ).

### Theoretical Calculations

**Computational Details.** An IBM VM/CMS version of GAUSSIAN 80<sup>16</sup> using gradient method<sup>17</sup> to optimize the geometries was used. Ab initio methods STO-3G<sup>18</sup> and 4-31G<sup>19</sup> were selected, since they gave acceptable results in similar cases.<sup>2,20</sup>

The only geometrical constraint was the planarity of the pyrazole ring. The methyl and trifluoromethyl groups were free to rotate in all forms (neutral, cation, and anion). Due to limitations to 120 base functions in our version of the GAUSSIAN 80 series of programs, the calculations always corresponded to STO-3G optimized geometries. The notation STO-3G//STO-3G and 4-31G//STO-3G means STO-3G and 4-31G energy calculations on STO-3G optimized geometries, respectively. Even 4-31G//STO-3G

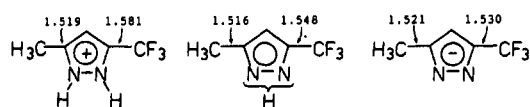


Figure 1. C-C bond lengths (in angstroms).

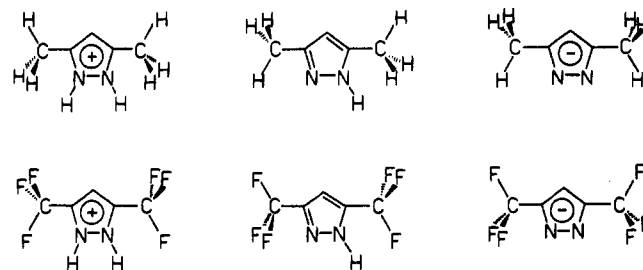


Figure 2. Schematic representation of the minimum energy conformations.

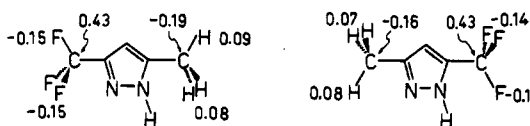


Figure 3. STO-3G charges.

calculations cannot be carried out on bis(trifluoromethyl)pyrazole **3** due to limitations in base functions. The main possible criticism of this approach concerns the anions, where the level of calculation should be, at least, split-valence plus diffuse functions or split-valence plus polarization.<sup>21</sup> However, this is only true for absolute acidities, i.e. deprotonation energies. For relative acidities, even the minimal basis calculations reproduce the majority of experimental data accurately.<sup>21</sup>

**Geometries.** Pyrazole optimized geometries and the effect of the charge on bond lengths and bond angles have been discussed in previous papers.<sup>3,8-11</sup> We will comment on only the differences between the methyl and trifluoromethyl groups. The most noteworthy difference concerns the C-C bond length between the substituent and the ring (see Figure 1, where the formula does not represent compound **2** but an average of the three compounds). Not only is the C-CF<sub>3</sub> bond much longer than the C-CH<sub>3</sub> bond but it is also much more sensitive to the ring charge. This is, probably, a consequence of the total charge densities of the C-methyl group (cation,  $-0.18$ ; neutral,  $-0.19$ ; anion,  $-0.44 \text{ e}$ ) and the C-trifluoromethyl group (cation,  $+0.46$ ; neutral,  $+0.43$ ; anion,  $+1.15 \text{ e}$ ).

Another difference between these two substituents concerns their minimum energy conformation. Although this difference never amounts to more than  $1 \text{ kcal mol}^{-1}$ , it is significant that in all cases the conformations are just opposite (Figure 2, in some minimum energy conformations, one of the H or F atoms is not exactly in the plane defined by the pyrazole ring but slightly out of it).

These conformations result from attractive terms, C-H/lone pair and C-F/N-H, and from repulsive terms, C-H/N-H and C-F/lone pair, corresponding to differences in polarization between C-H and C-F bonds.

**Charges and Dipole Moments.** In the case of STO-3G//STO-3G calculations, where all the necessary information is available, the main difference observed regarding charge distribution concerns the sp<sup>3</sup> carbon. Depending on its substituents, H or F, it can be negatively or positively charged. To illustrate this observation, Figure 3 represents

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Table IV. Energies (Hartrees) and Difference of Energies (kcal mol<sup>-1</sup>)

		4	1	2a	2b	3
neutral	STO-3G//STO-3G	-221.97726	-299.15316	-591.53307 <sup>c</sup>	-591.52980 <sup>c</sup>	-883.90770
	4-31G//STO-3G	-224.44665	-302.41704	-598.61692 <sup>d</sup>	-598.61257 <sup>d</sup>	-
cation	STO-3G//STO-3G	-222.39962	-299.59442	-591.95152	-598.96453	-884.30657
	4-31G//STO-3G	-224.81681	-302.80418	-598.96453	-598.96453	-
anion	STO-3G//STO-3G	-221.27544	-298.44772	-590.85261	-590.85261	-883.25436
	4-31G//STO-3G	-223.84234	-301.80844	-598.04564	-598.04564	-894.27527
$\Delta E_p^a$	STO-3G//STO-3G	265.1	277.0	262.7	264.7	250.7
	4-31G//STO-3G	232.4	243.0	218.2	220.9	-
$\Delta E_{dp}^b$	STO-3G//STO-3G	440.5	442.8	427.1	425.1	410.1
	4-31G//STO-3G	379.3	382.0	358.6	355.9	-

<sup>a</sup> Protonation energy:  $E(\text{neutral}) - E(\text{cation})$ . <sup>b</sup> Deprotonation energy:  $E(\text{anion}) - E(\text{neutral})$ . <sup>c</sup> Tautomer 2a more stable by 2.05 kcal mol<sup>-1</sup> (STO-3G//STO-3G). <sup>d</sup> Tautomer 2a more stable by 2.73 kcal mol<sup>-1</sup> (4-31G//STO-3G).

Table V. Thermodynamic Data for Pyrazoles 1-5 (Water Solution at 298.15 K,  $\Delta H$  in kcal mol<sup>-1</sup>)

pyrazole	basic $pK_a$	acid $pK_a$	$\Delta H_{sol}^\circ$	$\Delta H_{sub}^\circ$	$\Delta H_{solv}^\circ$	$\Delta H_{aq}^\circ$
unsubstituted 4	2.64 ± 0.02 <sup>2</sup>	14.18 ± 0.08 <sup>2</sup>	3.73 ± 0.04 <sup>4</sup>	17.68 ± 0.05 <sup>4</sup>	-13.95 ± 0.09 <sup>4</sup>	13.91 ± 0.14 <sup>2</sup>
3,5-dimethyl 1	4.06 ± 0.03 <sup>23</sup>	15.00 ± 0.03 <sup>24</sup>	2.42 ± 0.04	19.91 ± 0.05	-17.49 ± 0.07	15.9 ± 0.4
3(5)-(trifluoromethyl)-5(3)-methyl 2	-0.5 ± 0.1	12.33 ± 0.04	1.63 ± 0.12	18.69 ± 0.19	-17.06 ± 0.23	<i>d</i>
3,5-bis(trifluoromethyl) 3	(-8.23) <sup>a</sup>	7.51 ± 0.04	1.30 ± 0.05	16.23 ± 0.14	-14.93 ± 0.17	6.87 ± 0.04
3,5-dimethyl-4-nitro 5	-0.22 ± 0.03 <sup>b</sup>	10.27 ± 0.04 <sup>c</sup>	-	-	-	-

<sup>a</sup> Too weak to be measured, see text. <sup>b</sup> Literature reports -0.45 ± 0.05.<sup>23</sup> <sup>c</sup> Literature reports 10.65.<sup>24</sup> <sup>d</sup> At the concentrations used for calorimetric measurements, the compound does not dissolve in the strong basic media.

both tautomers of 3(5)-(trifluoromethyl)-5(3)-methylpyrazole.

The STO-3G calculated dipole moments are as follows: 4, 2.15; 1, 2.27; 2a, 4.28; 2b, 0.26; 3, 2.24 D (those obtained with the 4-31G basis set are systematically larger). The experimental dipole moment of pyrazole (Stark effect, microwave spectroscopy) is 2.21 D.<sup>22</sup>

STO-3G//STO-3G results on 3-methyl- and 5-methylpyrazole,<sup>11</sup> and the values of Table IV, show that the contribution of methyl and trifluoromethyl substituents to the dipole moment of pyrazole are exactly additive: 3-CH<sub>3</sub>, -0.28; 5-CH<sub>3</sub>, 0.40; 3-CF<sub>3</sub>, 1.72; 5-CF<sub>3</sub>, -1.62 D.

**Energies: Intrinsic Basicity and Intrinsic Acidity.** The values of the energies are collected in Table IV. Using the data of the STO-3G//STO-3G calculations of 3-methyl- and 5-methylpyrazole<sup>11</sup> it is possible to estimate statistically (multiple linear regression using indicator variables, 1 = presence of group, 0 = absence of group,  $n = 7$ ,  $r^2 = 0.9996$ ) the contribution of methyl and trifluoromethyl substituents to the calculated basicity (all values in kcal mol<sup>-1</sup>)

$$3\text{-CH}_3: 6.09$$

$$5\text{-CH}_3: 5.87$$

$$3\text{-CF}_3: -8.17$$

$$5\text{-CF}_3: -6.57$$

To do the same with the acidities we have calculated the STO-3G//STO-3G energy of the anion of 3(5)-methylpyrazole ( $E = -259.86158$  hartrees). With this result, those of the corresponding neutral pyrazoles and the data in Table IV, the following contributions to  $\Delta E_{dp}$  (kcal mol<sup>-1</sup>) can be calculated ( $n = 7$ ,  $r^2 = 0.9998$ )

$$3\text{-CH}_3: 0.87$$

$$5\text{-CH}_3: 1.27$$

$$3\text{-CF}_3: -14.43$$

$$5\text{-CF}_3: -16.03$$

Comparison with experimental results ( $\Delta H^\circ$ , Tables I and II) shows that for relative values, the STO-3G minimal basis set performs remarkably well. Compounds 4, 1, and 3 were used to establish the linear relationships given in eqs 2 and 3 and to predict the calculated value corresponding to pyrazole 2

$$\Delta E_p(\text{STO-3G//STO-3G}) = 64.56 + 0.952\Delta H^\circ(\text{exp}) \quad (2)$$

$$r^2 = 0.984$$

$$2: 207.9 \rightarrow 262.4 \text{ kcal mol}^{-1}$$

$$\Delta E_{dp}(\text{STO-3G//STO-3G}) = 67.09 + 1.056\Delta H^\circ(\text{exp}) \quad (3)$$

$$r^2 = 0.997$$

$$2: 341.4 \rightarrow 427.6 \text{ kcal mol}^{-1}$$

The predicted values for compound 2 agree perfectly with the calculated values for tautomer 2a (262.7 and 427.1 kcal mol<sup>-1</sup>, respectively, Table IV), which suggests that, in the experimental conditions of ICR, probably only tautomer 2a is present.

### Aqueous Solution

In addition to the previously discussed pyrazoles 1-4, Table V also contains information about a fifth derivative, 3,5-dimethyl-4-nitropyrazole, 5, which we will need for the discussion.

The basicity of 3,5-bis(trifluoromethyl)pyrazole 3 is too weak to be measured experimentally with the technique we have used (see the Experimental Section). However, we have shown<sup>7,24</sup> that, for a family of azoles, acid and basic  $pK_a$  values are linearly related, i.e., substituent effects on acidity and basicity are proportional. There exist 14 pyrazoles whose thermodynamic acid and basic  $pK_a$  values are known, the first four of Table VI and the following:<sup>7</sup> 3(5)-methylpyrazole (3.27; 14.54), 4-methylpyrazole (3.04; 14.66), 3,4,5-trimethylpyrazole (4.56; 15.49), 3(5)-phenylpyrazole (2.09; 13.84), 4-phenylpyrazole (1.64; 13.64), 3(5)-phenyl-5-(3)methylpyrazole (2.87; 14.33), 4-bromopyrazole (0.63; 12.69), 3(5)-nitropyrazole (-4.66; 9.81), 4-nitropyrazole (-2.0; 9.64), 3(5)-methyl-4 nitropyrazole (-1.23; 10.06) and 3,5-dimethyl-4-nitropyrazole (-0.45; 10.65)

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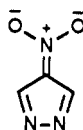
Table VI. Thermodynamic Quantities (kcal mol<sup>-1</sup>) Derived from Tables I, II, and V

pyrazole	basicity					acidity				
	$\Delta G^\circ_{\text{aq}}^a$	$\Delta H^\circ_{\text{aq}}^b$	$\frac{\Delta H^\circ_{\text{g}} - \Delta H^\circ_{\text{aq}}}{\Delta H^\circ_{\text{aq}}}$ <sup>c</sup>	$\Delta H^\circ_{\text{soliv}}(\text{cat.})^d$	$\frac{\Delta H^\circ_{\text{soliv}}(\text{cat.}) - \Delta H^\circ_{\text{soliv}}}{\Delta H^\circ_{\text{soliv}}}$ <sup>e</sup>	$\Delta G^\circ_{\text{aq}}^a$	$\Delta H^\circ_{\text{aq}}^b$	$\frac{\Delta H^\circ_{\text{g}} - \Delta H^\circ_{\text{aq}}}{\Delta H^\circ_{\text{aq}}}$ <sup>f</sup>	$\Delta H^\circ_{\text{soliv}}(\text{anion})^h$	$\frac{\Delta H^\circ_{\text{soliv}}(\text{anion}) - \Delta H^\circ_{\text{soliv}}}{\Delta H^\circ_{\text{soliv}}}$ <sup>i</sup>
4	3.60	3.22	209.5	-74.5	-60.5	19.34	13.91 <sup>2</sup>	339.3	-83.9	-69.9
1	5.54	4.89	217.0	-70.5	-53.0	20.46	15.9	340.0	-87.1	-69.6
2	-0.68	-0.47	208.4	-78.7	-61.6	16.82	12.51 <sup>f</sup>	328.8	-76.0	-59.0
3	-11.23	-9.57	204.9	-80.5	-65.5	10.24	6.87	317.8	-62.9	-47.8

<sup>a</sup>  $\Delta G^\circ_{\text{aq}} = 1.3642pK_a$  (Table V). <sup>b</sup>  $\Delta H^\circ_{\text{aq}} = 0.112 + 0.862\Delta G^\circ_{\text{aq}}$  (from the equation on p 207, ref 7). <sup>c</sup> From  $\Delta H^\circ_{\text{g}}$  of Table I and  $\Delta H^\circ_{\text{aq}}$  of the preceding column. <sup>d</sup> From the thermodynamic cycle taking into account that  $\Delta H^\circ_{\text{soliv}}(\text{H}^+) = -270 \text{ kcal mol}^{-1}$  (ref 25);  $\Delta H^\circ_{\text{soliv}}(\text{cation}) = \Delta H^\circ_{\text{g}} - \Delta H^\circ_{\text{soliv}}(\text{H}^+) - \Delta H^\circ_{\text{aq}} + \Delta H^\circ_{\text{soliv}}$  (the last one from Table V). <sup>e</sup> From the preceding column and  $\Delta H^\circ_{\text{soliv}}$  (Table V), it corresponds to  $\frac{\Delta H^\circ_{\text{soliv}}(\text{cat.}) - \Delta H^\circ_{\text{soliv}}}{\Delta H^\circ_{\text{soliv}}}$ . <sup>f</sup>  $\Delta H^\circ_{\text{aq}} = -1.622 + 0.840\Delta G^\circ_{\text{aq}}$  (from the equation on p 207, ref 7). <sup>g</sup> From  $\Delta H^\circ_{\text{g}}$  of Table II and  $\Delta H^\circ_{\text{aq}}$  of the preceding column. <sup>h</sup> From the thermodynamic cycle and the value of  $\Delta H^\circ_{\text{soliv}}(\text{H}^+) = -270 \text{ kcal mol}^{-1}$  (ref 25);  $\Delta H^\circ_{\text{soliv}}(\text{anion}) = -\Delta H^\circ_{\text{g}} - \Delta H^\circ_{\text{soliv}}(\text{H}^+) + \Delta H^\circ_{\text{aq}} + \Delta H^\circ_{\text{soliv}}$  (the last one from Table V). <sup>i</sup> From the preceding column and  $\Delta H^\circ_{\text{soliv}}$  (Table V), it corresponds to  $\frac{\Delta H^\circ_{\text{soliv}}(\text{anion}) - \Delta H^\circ_{\text{soliv}}}{\Delta H^\circ_{\text{soliv}}}$ .

(for internal consistency reasons, we prefer to use the value of ref 24, rather than that given in Table V).

If these values are represented graphically it appears that the last three compounds belong to a separate group [ $pK_a(\text{basic}) = -16.61 + 1.52pK_a(\text{acid})$ ,  $n = 3$ ,  $r^2 = 0.991$ ]. All of them are 4-nitropyrazole derivatives; the last one, 5, was measured again, searching for a possible error. Table V values are similar to those previously reported.<sup>7</sup> Compared to the other pyrazoles, they are either too acid, too basic, or both. Probably, they are abnormally acidic due to the stability of the fulvene-like anion:



The 11 remaining pyrazoles have  $pK_a$ s related by eq 4, which allows an estimation of the basicity of bis(trifluoromethyl)pyrazole, a very weak base indeed.

$$pK_a(\text{basic}) = -20.41 + 1.62pK_a(\text{acid}) \quad r^2 = 0.993 \quad (4)$$

$$3: 7.51 \rightarrow -8.23 \text{ (basic } pK_a)$$

Now we have all the data necessary for the discussion. First, a series of simple calculations has to be carried out, known as the thermodynamic cycle,<sup>4,7</sup> the results of which are summarized in Table VI.

To avoid errors, we preferred to calculate  $\Delta H^\circ_{\text{aq}}$  from the corresponding  $pK_a$ s. Of the eight values in Table VI, three have been determined experimentally (Table V, last column).

Arnett et al.<sup>26a</sup> observed, in the case of pyridinium cations, a linear correlation between the difference of solvation enthalpies of the cationic and neutral forms,  $\Delta H^\circ_{\text{soliv}}(\text{charged}) - \Delta H^\circ_{\text{soliv}}(\text{neutral})$ , and the gas-phase acidity,  $\Delta H^\circ_{\text{g}}$ . This occurs because the difference in the heats of transfer from the gas phase to aqueous solution for pyridines and pyridinium ions are essentially free of general solvent effects and depend only on specific interactions which vary linearly with  $\Delta H^\circ_{\text{g}}$ .

In the case of pyrazoles 1–4 analogous relationships to that described by Arnett et al.<sup>26a</sup> are found, for both the basicity [(5) pyrazoles and pyrazolium ions] and the acidity [(6) pyrazoles and pyrazolate anions].

$$\Delta H^\circ_{\text{g}} = 332.6 + 2.05[\Delta H^\circ_{\text{soliv}}(\text{cat.}) - \Delta H^\circ_{\text{soliv}}] \quad (5)$$

$$n = 4 \quad r^2 = 0.91$$

$$\Delta H^\circ_{\text{g}} = 261.0 - 1.34[\Delta H^\circ_{\text{soliv}}(\text{anion}) - \Delta H^\circ_{\text{soliv}}] \quad (6)$$

$$n = 4 \quad r^2 = 0.995$$

In pyridines, the attenuation effect of water (the slope) is equal to 1.55.<sup>26a</sup> The values we have found (eqs 5 and 6) are larger in the case of the basicity and smaller in the case of the acidity of pyrazoles.

### Conclusions

(i) There exists a very coherent picture between gas-phase measurements and theoretical calculations, on one hand, and between gas-phase and aqueous solution measurements on the other. Ab initio calculations at the STO-3G level provide a rationale for the relative basicities and acidities of methyl and trifluoromethyl pyrazoles.

(ii) Concerning the tautomeric equilibrium  $2a \rightleftharpoons 2b$ , it is clear that the former is more stable (see Table IV). This confirms the qualitative evidence gained from NMR and coordination behavior.<sup>27</sup>

(iii) In a homogeneous series of compounds, volatility should decrease with the molecular weight. However, in the case of compounds 1 ( $M = 96$ ), 2 ( $M = 150$ ), and 3 ( $M = 204$ ), the enthalpy of sublimation,  $\Delta H^\circ_{\text{sub}}$ , decreases as the molecular weight increases [19.9, 18.7, and 16.2 kcal mol<sup>-1</sup>, respectively (Table V)]. A possible explanation of this anomaly is to assume that  $\Delta H^\circ_{\text{sub}}$  decreases with weakening of the hydrogen bonds, which maintain the crystal lattice of pyrazoles.<sup>6</sup> The strength of hydrogen bonds in pyrazoles results from a delicate balance on N<sub>2</sub> basicity and N<sub>1</sub>-H acidity. Since intrinsic basicity (Table I) and intrinsic acidity (Table II) of pyrazoles 1, 2, and 3 are highly correlated ( $r^2 = 0.998$ ), it is not possible to test a biparametric model. Taking 1 as reference, the following equations relate the enthalpy of sublimation to the acid-base properties of the gas phase:

$$\delta\Delta H^\circ_{\text{sub}} = 0.18 + 0.12\delta\Delta H^\circ_{\text{g}}(\text{bas}) \quad (7)$$

$$n = 3 \quad r^2 = 0.97$$

$$\delta\Delta H^\circ_{\text{sub}} = 0.22 + 0.136\delta\Delta H^\circ_{\text{g}}(\text{ac}) \quad (8)$$

$$n = 3 \quad r^2 = 0.96$$

$$\delta\Delta H^\circ_{\text{sub}} = -0.25 + 0.943[\delta\Delta H^\circ_{\text{g}}(\text{bas}) - \delta\Delta H^\circ_{\text{g}}(\text{ac})] \quad (9)$$

$$n = 3 \quad r^2 = 0.98$$

$$\delta\Delta H^\circ_{\text{sub}} = -0.15 - 0.0043[\delta\Delta H^\circ_{\text{g}}(\text{bas})][\delta\Delta H^\circ_{\text{g}}(\text{ac})] \quad (10)$$

$$n = 3 \quad r^2 = 0.99$$

Even if these models need further development, the question of the extraordinary volatility of 3,5-bis(trifluoromethyl)pyrazole seems, at least partially, to be related to its very low basicity. Another contributing factor to the relatively high vapor pressure of 3 may be intermolecular electrostatic and steric repulsion between trifluoromethyl groups which would seriously destabilize the

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hydrogen trimer observed in the crystal structure of 1.<sup>5,6</sup> While the crystal structure of 3 is not available, intramolecular NH...N hydrogen bonds observed in 1 are probably replaced with weaker NH...F<sub>3</sub>C hydrogen bonds. Even in this arrangement, "spectator" trifluoromethyl groups would further weaken this type of hydrogen bonding through unfavorable secondary electrostatic interactions.<sup>27</sup>

### Experimental Section

**Preparation of 3(5)-(Trifluoromethyl)-5(3)-methylpyrazole (2) and 3,5-Bis(trifluoromethyl)pyrazole (3).** Both compounds were prepared by reaction of hydrazine with the corresponding  $\beta$ -diketones (commercially available). In these reactions, the intermediate hydroxypyrazoline and dihydroxypyrazolidine were isolated<sup>28</sup> and then subsequently dehydrated to the corresponding pyrazoles.

3(5)-(Trifluoromethyl)-5(3)-methylpyrazole, 2: mp 87–88 °C [lit. mp 89–90 °C].<sup>29</sup> Atwood et al.<sup>30</sup> does not report the melting point (nor quoted Nishiwaki)<sup>29</sup> but described the <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F spectra of compound 2. MS  $m/z$  160 (M<sup>+</sup>).

3,5-Bis(trifluoromethyl)pyrazole, 3: mp 83–84 °C [lit. 84 °C,<sup>11</sup> 57–60 °C];<sup>31</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) 6.86 (H<sub>4</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) 102.6 (<sup>1</sup>J = 267.9) (CF<sub>3</sub>), 104.7 (<sup>3</sup>J = 1.7) (C<sub>4</sub>), 138.2 (<sup>2</sup>J = 38.6) (C<sub>3,5</sub>); MS  $m/z$  204 (M<sup>+</sup>).

Compounds 1, 2, and 3 were purified by repeated sublimations. The purity of the samples was determined by DSC: 1 (99.91%), 2 (99.73%), and 3 (98.97%).

**Gas-Phase Acidities and Basicities.** The gas-phase acidities and basicities have been obtained as given in ref 1 or as cited therein. Modifications of the ICR spectrometer and calculations leading to values in Tables I and II are described in ref 2.

**pK<sub>a</sub> Measurements.** pK<sub>a</sub> values (Table V) were determined spectrophotometrically according to a method described by Ernst and Menashi.<sup>32</sup> A Cary 210 spectrophotometer fitted with a thermostated (25.0 ± 0.1 °C) cell compartment was used. In a first series of measurements, the spectrum of each compound was recorded at different hydroxide or proton concentrations in order to determine the best wavelength for pK<sub>a</sub> determination and to check that a simple equilibrium took place [2,  $\lambda$  = 232 nm (acidity) or  $\lambda$  = 235 nm (basicity); 3,  $\lambda$  = 230 nm; 5,  $\lambda$  = 280 nm (acidity) or  $\lambda$  = 290 (basicity)]. A second series of measurements was then performed for a large number of buffered solutions with different pH's or proton concentrations for acid ( $\mu$  = 0.01) or basic pK<sub>a</sub> determination (compounds 2 and 3), respectively. In the case of the acidity of compound 2, Yagil's acidity scale<sup>33</sup> was used for NaOH concentrated solutions.

**Enthalpies of Sublimation.** The enthalpies of sublimation were obtained from vapor pressures determined by the Knudsen effusion method, using the technique and procedure described previously.<sup>34,36</sup> The apparatus consisted, essentially, of a stainless-steel sublimation chamber immersed in a jacket and connected to a high-vacuum system (1 × 10<sup>-4</sup> Pa). The temperature of the jacket was maintained constant to within ±0.005 K for each vapor-pressure experiment, and was measured with a calibrated platinum resistance thermometer. The enthalpies of sublimation were computed from the relationship between pressure and temperature. The details of the two orifices employed in the sublimation experiments carried out for the three compounds were

Table VIII. Molar Enthalpies of Sublimation

pyrazole	$\theta$ , K	A	B	$\Delta H_{\text{sub}}^{\circ}$ , kcal mol <sup>-1</sup>
3,5-dimethyl 1	300.92	14.64 ± 0.03	-4350.9 ± 8.0	19.91 ± 0.05
3(5)-(tri- fluoro- methyl)-5- (3)-methyl 2	297.02	13.93 ± 0.14	-4082.2 ± 40.7	18.69 ± 0.19
3,5-bis(tri- fluoro- methyl) 3	266.06	13.89 ± 0.12	-3602.6 ± 30.9	16.49 ± 0.14

as follows: orifice area, (7.99 ± 0.03) × 10<sup>-4</sup> cm<sup>2</sup>, and Clausing coefficient,  $W_a = 0.958 \pm 0.009$  for 3,5-dimethyl pyrazole; orifice area, (4.44 ± 0.02) × 10<sup>-4</sup> cm<sup>2</sup>, and Clausing coefficient,  $W_a = 0.943 \pm 0.012$  for 3(5)-(trifluoromethyl)-5(3)-methylpyrazole and 3,5-bis(trifluoromethyl)pyrazole.

The results of the Knudsen effusion experiments with the three compounds are summarized in Table VII (supplementary material), in which values of temperature, time, and mass of sublimed substance are collected.

The vapor pressures were calculated by means of the equation

$$p = (m/W_a at)(2\pi RT/M)^{1/2} \quad (13)$$

The symbols of eq 13 have the same meaning as in ref 35. The highest percentage of error for the vapor pressure in Table VII is 0.1 and has been computed as the sum of the estimated error of all quantities in eq 13.

An equation of the type  $\log(p, \text{Pa}) = -B(T, \text{K})^{-1} + A$  was fitted to the results of Table VII by the least-squares method. The values  $10^2 \delta p/p$  are the fractional deviations of the experimental vapor pressures from those computed using the preceding equation. The coefficients A and B of the equation concerning the three studied compounds are shown in Table VIII. The uncertainties assigned to the values of  $\Delta H_{\text{sub}}^{\circ}$  are based on the standard deviations of B values.

The sublimation enthalpy of 3,5-bis(trifluoromethyl)pyrazole at 298.15 K has been computed using the same equation as in ref 36. The  $C_{p,m}^{\circ}(\text{cr})$  values have been determined by dsc whereas the  $C_{p,m}^{\circ}(\text{g})$  values were calculated using the group-contribution scheme of Rihany and Doraiswamy.<sup>37</sup> The  $\Delta H_{\text{sub}}^{\circ}(298.15 \text{ K})$  of compound 3 is 16.23 ± 0.14 kcal mol<sup>-1</sup>.

**Enthalpies of Solution.** The enthalpies of solution of the three compounds 1–3 have been measured using a new calorimetric system.<sup>38</sup> For each series of experiments, 1 to 5 mg of solute were dissolved in 9 ml of water. At least three series of 4 experiments were performed for each substance. The solvation enthalpies,  $\Delta H_{\text{sol}}^{\circ}$ , were obtained as the difference  $\Delta H_{\text{sol}}^{\circ} - \Delta H_{\text{sub}}^{\circ}$ . The results are gathered in Table V.

**Acidic Ionization Enthalpies.** Dissociation enthalpies of compounds 1 and 3 were determined following the procedures described in ref 2.

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**Supplementary Material Available:** Table VII with vapor pressures of compounds 1, 2, and 3 (1 page). Ordering information is given on any current masthead page.

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