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Protonated Forms of 2-(2-Furyl)pyrroles and Their Interconversion: ^{1}H NMR and Quantum-Chemical (MNDO) Study

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The 2-(2-furyl)pyrroles and vinylpyrroles are protonated by various acids (HSO_3F, CF_3CO_2H, HCl, HBr) at C_5 of either the pyrrole or furan ring depending on reaction conditions (temperature and acid nature). At −80 °C only the pyrrole ring protonation is observed; at −40 °C (the reaction with HCl and HBr) an equilibrium mixture of pyrrolium (A) and furanium (B) ions is formed, with the hydrogen halides being added to the vinyl group. At 0 °C the HBr molecule adds to the protonated furane ring with the formation of 2-(2-pyrrolyl)-4-bromo-4,5-dihydrofuranium cations, which upon further heating (20 °C) are transformed to 2-(2-furyl)-4-bromo-4,5-dihydropyrrolium cations. The heats of formation (ΔH), atomic charges, and characteristics of the frontier molecular orbitals in the 2-(2-furyl)pyrrole molecule (1) and its protonated forms (1A) and (1B) have been calculated by MNDO method. The ΔE values for 1A and 1B are in close agreement with their experimental ratio. The protonation of 1 is likely to proceed under orbital control. The internal rotational potentials in 1, 1A, and 1B have been calculated and discussed.

Introduction

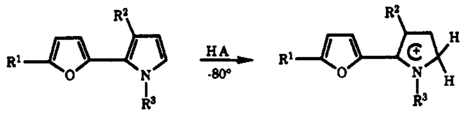
The reactivity of the simplest five-membered aromatic heterocycles (pyrrole, furan, and thiophene) has been the subject of many investigations.[1,2] The decreasing sensitivity to electrophilic attack in the order pyrrole > furan > thiophene is well-documented.[2] For instance, the rate of acid-catalyzed hydrogen isotope exchange in pyrrole is about 6 powers of 10 higher than in furan.[3] The stability of the protonated forms of pyrrole derivatives usually greatly exceeds that of furan compounds. Stable furanium cations were observed only in superacids,[4,5] whereas the protonated forms of pyrrole derivatives are quite stable in less acidic media.[6–9]

Linked five-membered aromatic heterocycles are attracting growing attention not only as intermediates having unexplored synthetic possibilities,[10] but also as suitable objects for study of the mutual influence of heteroaromatic systems, particularly in the course of electrophilic reactions where the interannular stabilizing p,π- and π,π-conjugation effects should be most pronounced. In order to further examine these problems, we have studied, by ^{1}H NMR, protonation of 2-(2-furyl)pyrroles (1 and 3) and their *N*-vinyl and *N*-ethyl derivatives (2 and 4–6).

Results

At −80 °C, all the pyrroles studied are protonated at C_5 of the pyrrole ring to form **A** regardless of the acid nature, and for 2, 4, and 5 the vinyl group remains intact.

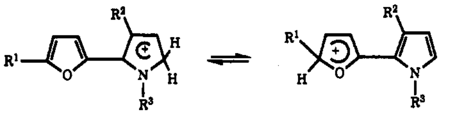
Heating of the sample up to 20 °C (in the case of trifluoroacetic acid) and to 50 °C (in the case of fluorosulfonic acid) does not alter the patterns of the NMR spectra of the protonated forms for any of the compounds.



A

1 (R^1, R^2, R^3 = H); 2 (R^1, R^2 = H, R^3 = CH=CH$_2$); 3 (R^1, R^3 = H, R^2 = CH$_3$); 4 (R^1 = H, R^2 = CH$_3$, R^3 = CH=CH$_2$); 5 (R^1 = CH$_3$, R^2 = H, R^3 = CH=CH$_2$); 6 (R^1, R^2 = H, R^3 = Et).

The interaction of pyrroles 1–4 and 6 with HCl or HBr at −30 °C leads to the formation of the mixture of pyrrolium (**A**) and furanium (**B**) cations. The same result is observed upon gradual heating from −80 to −30 °C. The only exception is 2-(5-methyl-2-furyl)-1-vinylpyrrole (5), for which the furanium cation was not detected. Thus, at least formally, proton transfer from the protonated pyrrole moiety to the furan ring takes place. In the case of the vinyl compounds addition of HX to the double bond also occurs (eq 1).



(1)

A **B**

With larger excesses of HX the rate of the **A** ⇌ **B** equilibration and of the HX addition to the vinyl group decreases. The ratio of cations **A** and **B** does not depend upon R^3, and for the molecules 1, 2, and 6 is ca. 1:1 (for protonation by HCl) and 2:1 (for protonation by HBr). In the case of the 3-methyl derivatives 3 and 4 the corresponding pyrrolium cations predominate (2:1 for HCl). The cation **5A**, where the α-position of the furan ring is occupied, adds the hydrogen halide to the double bond only upon heating (−80 to −30 °C).

Further heating of the furylpyrroles (1–4, 6) with HBr to 0 °C leads to a gradual decrease of the signal intensity of the **A** and **B** group cations (their intensity being diminished synchronously, confirming the existence of the equilibrium of **A** and **B**). Concurrently, there appear the signals of new cations: 2-(2-pyrrolyl)-4-bromo-4,5-dihydrofuranium ions (**C**), which are formed by the addition of HBr molecule to the protonated furan ring of cations **B**.

If the temperature is increased further to 20 °C, the ions **C** are transformed completely to 2-(2-furyl)-4-bromo-4,5-

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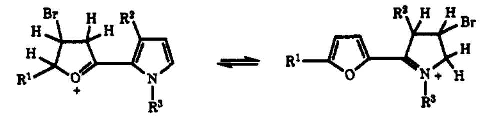
dihydropyrrolium ions **D**, with the retroaromatization of the furan moiety. This evidently occurs via the cation **A** (eq 2).



(2)

C **D**

The cations **D** are formed from **2** and **5** only. In the case of 1-vinyl-2-(5-methyl-2-furyl)pyrrole **5**, the cations **B** and **C** are not observed, and the precursor of the cation **5D** is evidently the pyrrolium cation **5A**. For 2-(2-furyl)pyrrole **1**, the 3-methyl-substituted pyrroles (**3**, **4**) and 1-ethyl-2-(2-furyl)pyrrole (**6**), the ultimate products of the reaction with HBr are dihydrofuranium cations **1C**, **3C**, **4C**, and **6C**, respectively.

When the interaction with hydrogen halogenides is carried out in the presence of $AlCl_3$ or $AlBr_3$, the rates of the above processes sharply drop, and the major reaction products are the pyrrolium cations **A**. However, the addition of Me_4NBr to the sample of 1-vinyl-2-(2-furyl)pyrrole (**2**) facilitates the interaction with HBr, resulting in the decrease of the formation temperature of the cations **C** and **D** by 15–20 °C.

All the above transformations were observed by ^1H NMR. Spectra of the pyrrolium cations generated by interaction of furylpyrroles **1**–**6** with HSO_3F, CF_3COOH, HCl, and HBr at −80 °C show the $5\text{-}CH_2$ group signal at 4.97–5.38 ppm (Table I, supplementary material). The signals of the vinyl group protons (for the cations from pyrroles **2**, **4**, and **5**) are shifted downfield to a great extent (about 1.5 ppm) in comparison with unprotonated molecules.[10] The vicinal coupling constants $^3J_{AC}$ and $^3J_{BC}$ are not changed relative to the corresponding values of *N*-vinylpyrroles, (−15.0 and 9.0 Hz, respectively), but the geminal coupling $^2J_{AB}$ is substantially decreased (from −0.8 to −3.0 Hz).

The spectra of pyrrolium cations (**2A**, **4A**, **5A**) with the HX molecule added to their vinyl group have an important feature: the $5\text{-}CH_2$ protons are nonequivalent due to the asymmetric carbon atom in the α-haloethyl moiety and have the unusually high geminal coupling constant ^2J = 27 Hz.

The structure of the cations **1B**–**5B** is strongly supported by the protonated furan ring signals in their spectra (Table II (supplementary material), δ, ppm): 5.96–6.16 (bs, CH_2-5), 7.35–7.52 (dt, H_3, ^3J = 6 Hz, ^4J = 1.5 Hz), 8.28–8.32 (dt, H_4, ^3J = 1.0 Hz).

The spectra of the cations **C** and **D** (Tables III and IV, supplementary material) contain the signals of the five-spin proton system in the range of 3.5–6.0 ppm, which relate to 4-bromo-4,5-dihydropyrrolium and -furanium rings. In the cases of cations **2C** and **4C** for which the precursors were the 1-vinylpyrroles, all the signals are doubled. This may be caused by both the diastereomerism due to the two asymmetric carbon atoms and by the hindered rotation of the heterocycles around the C_2–C_2' bond. When the 1-bromoethyl radical is replaced by ethyl (the cation **6C**), the doubling of signals disappears.

The spectra of the cations **2D** and **5D** are distinguished from those of the cations **C** by the absence of the signal doubling, despite the fact that in these cations there are also two asymmetric carbon atoms.

Discussion

The 2-(2-furyl)pyrrolium cations **A** formed by α-protonation of the pyrrole ring undergo upon heating the transformations indicated, which depend on the acid nature. The principal cause of this is a higher stability of these cations in HSO_3F and CF_3CO_2H media and lower stability in the presence of HCl and HBr.

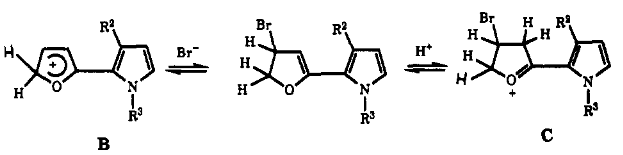
It is well-known[11,12] that carbocation stability depends on both the cation structure and the acidity and nucleophilicity of the medium. In the case of HSO_3F, owing to their super acid character, the equilibrium is well shifted toward the cations; therefore, the substituent nature is not very important for the reversible processes, which proceed through the deprotonation step. It is evident that the substituent influence on such processes might be revealed in less acidic media. Recently[13] approximately the same acidity of CF_3COOH, HCl, and HBr in chloroform solution was evaluated. A fairly high stability of 1-vinyl-2-(2-furyl)pyrrolium cations in CF_3COOH (unlike 2-alkyl- and 2-phenylpyrrolium ions, which undergo dimerization in this medium)[8] is caused by the furyl substituent effect. The dependence of 1-vinylpyrrolium cation dimerization rate on the substituents at C_2 (Ph > Me ≫ 2-furyl) roughly correlates to their σ_p^+ values (0.08, 0.26, and −0.86, respectively).

The existence in solution of nucleophilic anions Cl^-, Br^-, and also HCl_2^- and HBr_2^-,[14] which can abstract the proton from a pyrrolium α-complex, results in the protonation reaction becoming reversible. Under these conditions the direction of furylpyrrole molecule protonation should be determined by activation barriers (kinetic control) and by the relative stability of the cations formed (thermodynamic control). One can assume, in agreement with σ_p^+ values (−0.86 for 2-furyl and −1.7 for 2-pyrrolyl[3]) that the pyrrole ring stabilizes the furanium cation more effectively than vice versa.

Thus, the selective pyrrole ring protonation at a low temperature (−80 °C) can be considered as a kinetic result, leading to the thermodynamically nonequilibrium state with the predominance of pyrrolium ions **A**, the latter being comparable in energy with furanium isomers **B**. As the temperature increases (−30 °C) the system reaches the equilibrium state, and the concentrations of both isomers become equal in agreement with their energies (see below).

The addition of $AlCl_3$ or $AlBr_3$ sharply increases the medium acidity and reduces its nucleophilicity by the formation of complex acids HAl_2X_7 (X = Cl, Br), thereby it makes difficult not only proton transfer, but also the addition of hydrogen halide to vinyl group. Also, this finding excludes the diprotonated form (simultaneously at pyrrole and furan rings) as an intermediate between pyrrolium and furanium σ-complexes, since its concentration (if it is formed) should be increased in more acidic medium.

The formation of 2-(2-pyrrolyl)-4-bromo-4,5-dihydrofuranium bromide (**C**) from **B** occurs as a result of the attack of the Br^- anion at the C_4 atom with the subsequent protonation of the dihydrofurane intermediate. This



B **C**

assumption is confirmed by the fact that in the presence of $AlBr_3$ which incorporates the bromide ion into the complex anion $Al_2Br_7^-$ this interaction is sharply sup-

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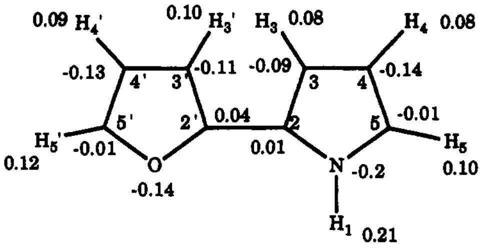
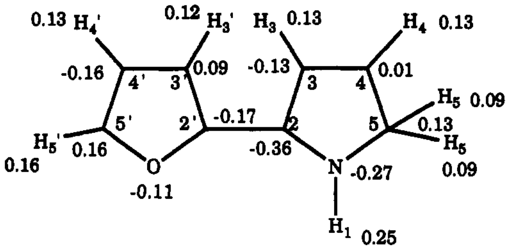


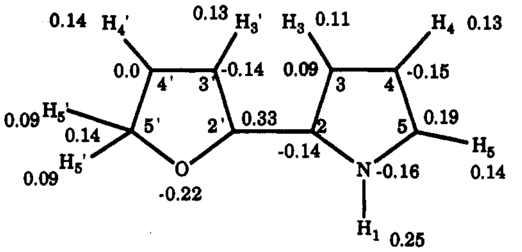
ΔH = 87.32 kJ mol^{-1}

1A



ΔH = 739.72 (745.75) kJ mol^{-1}

1C



ΔH = 740.53 (748.56) kJ mol^{-1}

Figure 1. The values of full atomic charges and heats of formation (ΔH) for 2-(2-furyl)pyrrole (1) and its protonated forms (1A, 1B). The corresponding ΔH values for trans conformers are given in parentheses.

pressed. On the contrary, the introduction of bromide ions, in a form of Me_4NBr, catalyzes the reaction. In the case of HCl the attack by the less nucleophilic chloride ion does not occur at all.

The transformations of **C** to **D**, resulting in furan ring rearomatization and the migration of the covalently-bonded bromine atom from the furan ring to the pyrrole, may be interpreted as a kinetic preference for Br^- attack at C_4 of the furanium atom **B** to form **C** initially. However, the cation **D** is thermodynamically more stable because of the higher charge stabilization by the nitrogen atom as compared with that of the oxygen atom, and also because of somewhat greater stability of the furan aromatic system.

The absence of the **C** to **D** transformation for the 2-(2-furyl)pyrrole (**1**) and the 1-ethyl-2-(2-furyl)pyrrole (**6**) is explained by the decreased electrophilicity of the pyrrole ring in the cations **1A** and **6A** relative to that of **2A** due to a stronger electron-withdrawing character of the CHBrMe moiety.

MNDO Calculations. For the theoretical rationalization of the transformations observed we have carried out the quantum-chemical calculations (MNDO) of 2-(2-furyl)pyrrole (**1**) and its protonated forms (**1A** and **1B**) with full geometry optimization. The computed values for the net charges and the heats of formation (ΔH) are shown in the molecular diagrams (Figure 1).

From the comparison of the charges and HOMO electron densities on rates of the unprotonated molecule **1** (Figure 1; Table V, supplementary material) with the results observed (the initial protonation addition to C_5 of the pyrrole ring), it may be supposed that the regioselectivity of the first reaction stages is determined by the HOMO electron densities rather than by the charge distribution (the charges on C_3, C_4, C_3', and C_4' are substantially higher than that on C_5). Indeed, as seen from Table V, the p_z atomic orbital contributions to the HOMO from C_2 and C_5 of pyrrole ring are largest (0.21), and they are much larger than those from C_2' and C_5' of furan ring (0.10 and 0.12, respectively). Since the carbon atom C_2 is sterically hindered, the proton preferentially attacks the C_5 of pyrrole ring to form the ion **1A**. This suggestion of the orbital control of these reactions implies the participation of the softer (in comparison with proton) electrophiles, namely the nondissociated acid molecules.

What is the cause of the subsequent furan ring protonation with the partial deprotonation of the pyrrole (the formation of the equimolar mixture of ions **1A** and **1B** mixture upon temperature rise)? Apparently, this can happen only if the energies of protonated forms **1A** and **1B** are near to degeneracy, but that a priori seems to be improbable. However, the computed ΔH values (Figure 1) are completely in keeping with this suggestion which therefore seems to be the main reason of the unprecedented case of the approximately equal pyrrole and furan ring reactivity in the thermodynamically controlled electrophilic process.

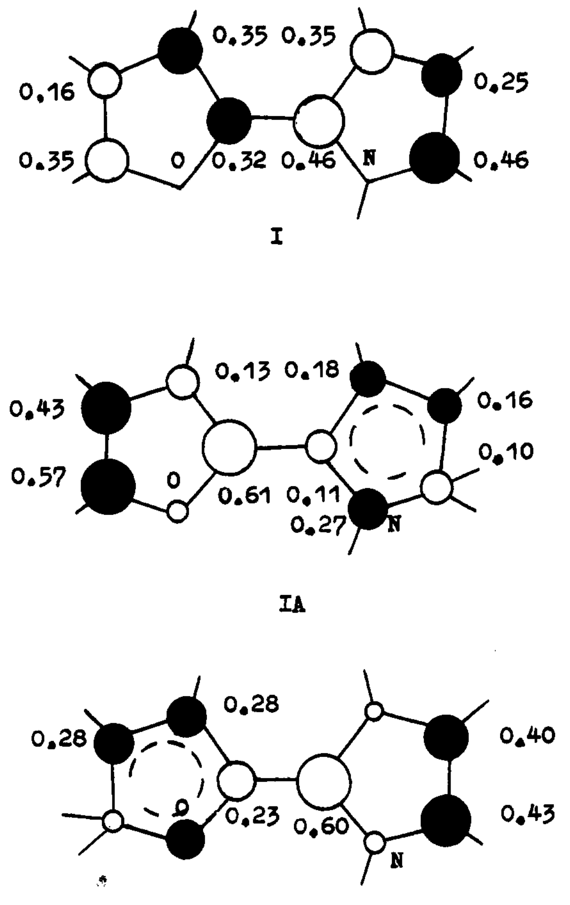
This fact deserves more attention, as being connected with the general mechanism of the substituent effect transmission and stabilization in the protonated forms of compounds with conjugated heteroaromatic moieties of different nature, including similarly constructed polymer systems, such as polypyrroles, polythiophenes, and the like.

In order to elucidate the details of this mechanism and to estimate the degree of pyrrole and furan ring mutual influence upon protonation of one of them, we have performed the detailed MNDO calculations of the conformers of 2-(2-furyl)pyrrole and its protonated forms with the evaluation of the internal rotation potentials.

Protonation induces a major change of the geometry of the neutral 2-(2-furyl)pyrrole molecule (Table VI, supplementary material). The C_2–C_2' bond length (1.45 Å in the neutral molecule) shortens to 1.43 Å upon the pyrrole ring protonation (**1A**) and to 1.40 Å upon the furan ring protonation (**1B**). In the protonated ring the C_2–C_3 (C_2'–C_3') and C_4–C_5 (C_4'–C_5') bonds lengthen, whereas the C_3–C_4 (C_3'–C_4') bond shortens, and the C_4–C_5–N (C_4'–C_5'–O) angle decreases. It should be noted that the changes occurring in one of the rings essentially do not affect the adjacent unprotonated ring. The furylpyrrole protonated forms, both cis (**1A** and **1B**) and trans (**1A** and **1B**) conformers, are found to be the planar species, whereas the unprotonated molecule (**1**) is nonplanar: the angle between planes of furan and pyrrole rings (according to calculation with the full geometry optimization) is about 13°.

The observed change of the furylpyrrole geometric parameters upon protonation corresponds to the increase of interannular conjugation, which stabilizes the cations formed.

The reinforcement of π-π conjugation between the cycles in the protonated forms is revealed also in the change of furylpyrrole HOMO symmetry as a result of protonation. In the neutral molecule (**1**, Figure 2) the HOMO has antibonding character toward the C_2–C_2' bond (p_z orbitals of C_2 and C_2' atoms introduce the opposite sign contributions). In the protonated molecules, this fragment of



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IA

IB

Figure 2. Absolute values of p_z AO contributions to HOMO.

Table VII. The Principal Parameters Characterizing the Conjugation between Pyrrole and Furan Rings in 2-(2-Furyl)pyrrole (1-cis) and Its Protonated Forms (1A-cis, 1B-cis)[a]

structure	bond order	bond length, Å	barrier height, kJ mol^{-1}	V_2, kJ mol^{-1}
1-cis	1.02	1.45	0.00	2.51
1A-cis	1.17	1.43	31.05	34.39
1B-cis	1.38	1.40	80.84	85.48

[a] Trans conformers have close values of parameters.

HOMO becomes bonding (**1A**, **1B**, Figure 2) and thereby the electron transfer between the rings is facilitated. The increase of electron density on the C_2–C_2' bond corresponds to the increase of its order (Table VII).

Apparently, for the clarification of the question about pyrrole and furan ring stabilizing effect on the corresponding cation it is necessary to determine the energy of the protonated forms **1A**-cis and **1B**-cis (**1A**-trans and **1B**-trans) without conjugation. For this reason we have calculated for both protonated forms the potential functions of internal rotation around the C_2–C_2' bond (Figure 3). The angle ψ was varied in the range 0–180° by a step of 30°. From the p_z atomic orbitals symmetries it follows that in the vicinity of point $\psi = 90°$ the conjugation between pyrrole and furan rings is minimal. In other words, the heights of internal rotation barriers of the two furylpyrrole protonated forms can be considered in the first approximation as a measure of their full energy differences when the conjugation between the pyrrole and furan cycles is switched off. As seen from Table VII, the internal rotation barrier for the cation **1B** is about 2.5 times higher than the corresponding value for the cation **1A** (80.8 and 31.1 kJ/mol, respectively). A more detailed analysis of the π-π conjugation can be performed with the help of analytical expansion of the rotational potential in terms of Fourier series

$$\Delta E = E(\psi) - E(O) = \int_{i=1}^{6} \tfrac{1}{2} V_i[1 - \cos(i\psi)]$$

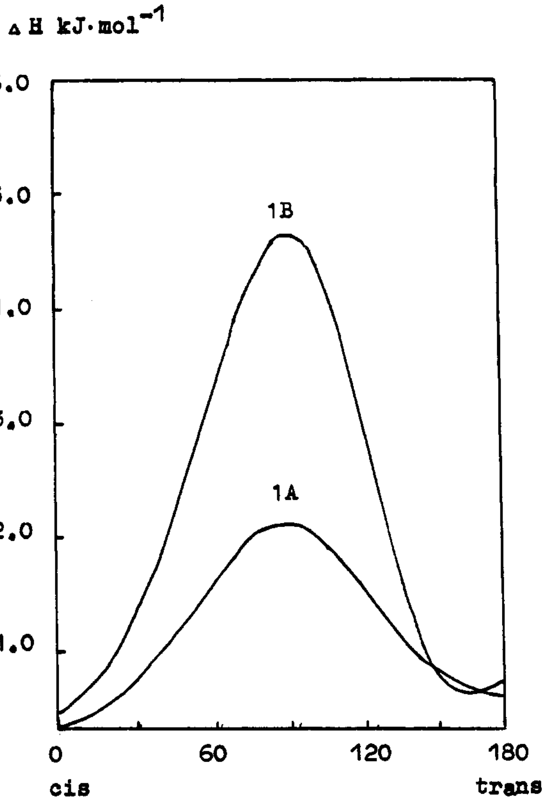

Figure 3. The potential functions of internal rotation around C_2–C_2' bond for **1A** and **1B**.

The π-π conjugation value is characterized by the V_2 potential constant.[15,16] This term dominates in the expansion of the rotation potential of the furylpyrrole protonated forms (Table VIII, supplementary material). In addition, the V_2 value for **1B** is about 2.5 times larger than for **1A**, in good agreement with the ratio of the internal rotation barriers heights for these species.

The results obtained show that the internal rotation barriers for the furylpyrrole protonated forms observed in the framework of MNDO are caused almost entirely by the π-π conjugation based on π-electron donation by the unprotonated ring into the protonated one. This leads to stabilization of the whole system by positive charge delocalization and formation of the π-bond between the rings. The heights of internal rotation barriers appears to be proportional to the π-π conjugation efficacy, i.e., to the π-electron donation. Thus, the stabilizing power of the pyrrole ring toward the protonated furan ring (cation **1B**) is about 2.5 times larger than that of the furan ring toward the protonated pyrrole ring (cation **1A**). The stronger conjugation in cation **1B** also results in the shortened C_2–C_2' bond and in its higher order (Table VII).

Experimental Section

The ^{1}H NMR spectra were recorded on Tesla BS 567A (100 MHz) and Bruker WP-200SY (200 MHz) spectrometers.

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The interaction of 2-(2-furyl)pyrroles 1–6 with HSO_3F and CF_3COOH was carried out at −80 °C by mixing in the NMR tube 0.02 g of pyrrole with 5–10-fold acid excess in equal (0.2 mL) volumes of CD_2Cl_2. The reactions with hydrogen halides were also performed in the NMR tube, by passing dry HCl (or HBr) through the pyrrole solution in CD_2Cl_2 at −80 or −30 °C.

The methods of synthesis of the compounds studied have been described.[10]

Quantum-chemical (MNDO) calculations of 2-(2-furyl)pyrrole and its protonated forms were performed on an EC-1061 computer.

Registry No. 1, 126476-04-8; **1a**·SO_3F, 126475-81-8; **1b**, 138667-36-4; **1c**, 138667-41-1; **2**, 126475-82-9; **2a**·SO_3F, 126475-83-0; **2a**·Cl, 126475-89-6; **2a**·Br, 126475-90-9; **2b** (R^3 = CHClMe), 138667-37-5; **2b** (R^3 = CHBrMe), 138667-38-6; **2c**, 138667-42-2; **2d**, 138667-45-5; **3**, 138693-70-6; **3a**·SO_3F, 126475-85-2; **3b**, 138667-39-7; **4**, 126475-86-3; **4a**·SO_3F, 126475-87-4; **4a**·Cl, 126545-35-5; **4b**, 138667-40-0; **4c**, 138667-43-3; **5**, 138667-34-2; **5a**·Cl, 126475-88-5; **5a**·Cl (R^3 = CHClMe), 126475-91-0; **5a**·Br (R^3 = CHBrMe), 126475-90-9; **5d**, 138667-46-6; **6**, 138667-35-3; **6a**·Br, 126475-93-2; **6c**, 138667-44-4.

Supplementary Material Available: Tables I–VI and VIII (8 pages). Ordering information is given on any current masthead page.

Basicity of C-Substituted Pyrazoles in the Gas Phase: An Experimental (ICR) and Theoretical Study

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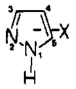
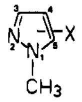
The experimental gas-phase proton affinities (PAs) of 32 *N*-H and *N*-methyl pyrazoles have been determined by means of Fourier transform ion cyclotron resonance spectroscopy (FTICR). Together with the previously reported PAs for 12 *C*-methyl-substituted pyrazoles, they provide a set of 57 data (counting each tautomer separately). The remarkably large spread of PAs, ca. 55 kcal·mol^{-1}, makes this set most suitable for structural analyses. In a few cases, ab initio 6-31G//6-31G protonation energies were calculated and found to be linearly related to the experimental PAs to a very high degree of precision. A simple additive model of substituent effects on PAs (including substitutions at positions 3, 4, and 5) was found to hold, even for very crowded derivatives such as 1,4-dimethyl-3,5-di-*tert*-butylpyrazole (**27**). The only significant interaction appears between phenyl groups at positions 3 and 5. The statistically averaged substituent effects on PAs were successfully analyzed in terms of polarizability and field and resonance contributions, according to the Taft–Topsom model. Both positions 3 and 5 behave in a way similar to that of position 2 in the pyridines. From this interesting result it follows that, with the exception of 3-aminopyrazole, the tautomerism of pyrazoles is not very dependent of the nature of the 3(5)-substituent.

1. Introduction

To understand the nature of substituent effects, it is necessary to use intrinsic properties, i.e., properties of the isolated molecules. A comparison with the same properties in solution will shed light on solvent effects. In this way, two of the main topics in physical organic chemistry, namely, substituent and solvent effects, can be approached. We have chosen to study the effects of seven substituents (X) on the basicity of NH and *N*-methylpyrazoles.





We expected, through the determination of the effect of X on the basicity of pyrazoles, to attain the position of the tautomeric equilibrium 3-X ⇄ 5-X, for which only solution data are available (the case of 3(5)-methylpyrazole, X = CH_3, has already been discussed).[1]

Differences in energy between 3- and 5-tautomers are often small, and so these kinds of studies need a careful theoretical determination of the protonation energies, ΔE_P. As we have shown previously,[2] linear correlations between ΔE_P and proton affinities, PA, need ab initio calculations of a relatively high level. Although INDO,[3a,3b] AM1,[3c] STO-3G,[3d] and 3-21G[3e] calculations were previously carried out, in this discussion we will use exclusively 6-31G data. At this level, we can calculate only monosubstituted molecules. Even then, the best one can expect is a linear relationship between ΔE_P and PA. To obtain absolute values, calculations at much higher levels are necessary; this has been done only on pyrazole itself.[4]

Substituent effects (SEs) in a six-membered heteroaromatic ring, e.g., pyridine, can be compared to those in

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