215. Gas-Phase Basicities of Furan Compounds

The Role of Alkyl Substitution on Proton Affinity and on the Site of Protonation

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Dedicated to Prof. *Tino Gäumann* on the occasion of his 60th birthday

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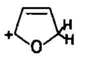
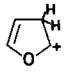
The gas-phase protonation of alkyl-substituted furan compounds is investigated in equilibrium proton-transfer reactions conducted in an ion cyclotron resonance (ICR) spectrometer. From the effects of substituents on the stability of protonated species, it is concluded that protonation of the majority of these systems occurs specifically on the C(α)-atom to form carbenium ions. Parallel MO calculations performed on different structures of the products reinforce the experimental conclusions and provide energy values for the less stable structures. The solution reactivity of these compounds towards electrophilic agents and NMR spectra of protonated species obtained in strong acidic media have been investigated.

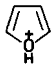
Introduction. – The behaviour of reacting systems in the gas phase constitutes a useful reference frame for the understanding of the chemical reactivity free of medium interactions. Quantitative evaluation of the fundamental molecular properties may be achieved in a straightforward manner. Recent experimental and theoretical results [1] show that, in the gas phase, protonation of furan occurs on the C(α)-atom to form the thermodynamically favoured cation $\mathbf{1H}_a^+$:



$\mathbf{1H}_a^+$



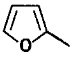
$\mathbf{1H}_b^+$



$\mathbf{1H}_c^+$

It has been also demonstrated that the products resulting from protonation at C(β) ($\mathbf{1H}_b^+$) or on the O-atom ($\mathbf{1H}_c^+$) are less stable than $\mathbf{1H}_a^+$ by 16 [1a] and 149 [1c] kJ·mol^{-1}, respectively. These results were in agreement with the observations made in solution where the electrophilic substitutions on furan preferentially occurs at C(α) [2]; *e.g.* acylation of furan with Ac_2O produces an α/β ratio > 800 [3].

It can be anticipated that the behaviour in alkyl substituted furans may be quite different since the stabilizing effects of alkyl substituents can direct the site of protonation. Whereas electrophilic attack at C(β) seems to be generally negligible in solution [2b], no information as to the gas-phase behaviour is available. We have thus used the substituted furans **2**–**8** to investigate the influence of alkyl substituents on the preferred site of protonation and on the resulting basicities.



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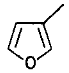

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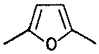

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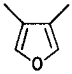

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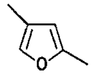

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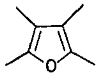

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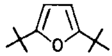

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Our approach involves the experimental determination of gas-phase basicities using ion cyclotron resonance (ICR) techniques. Parallel semi-empirical MO calculations are performed on the protonated species **2**H^+–**6**H^+ to support and extend the experimental conclusions.

Experimental. – The ICR measurements were carried out under conditions similar to those described in [4]. The gas-phase basicities (GB) were determined from equilibrium proton-transfer reactions $MH^+ + B \rightleftarrows M + BH^+$ yielding the change in free energy $\Delta G_r = -RT \cdot \ln K_{eq} = GB(M) - GB(B)$. At least three series of independent measurements were performed for earch couple M (furan compound)/B (reference base) at the temp. of 313 K; care was taken to change the ratio of neutral pressure over a range of *ca.* 3. The pressures of neutral M and B were obtained, after correction owing to ionization cross section, from measurement with an ionization gauge [5]. *Table 1* summarizes the basicity data determined for compounds **2**–**8**.

Table 1. *Experimental* ΔG_r° *Values for the Reaction* $MH^+ + B \rightleftarrows M + BH^+$ *and Resulting Gas-Phase Basicities* $GB(M)$[a])

M	Reference base B	ΔG_r°	GB(B)	GB(M)
2	$(i\text{-}Pr)_2O$	0.0	831[b])	831
3	Di-pentylether	−2.1	826[b])	823
	Bu_2O	0.8	822[b])	
4	2,4-Pentanedione	1.3	837[c])	838
5	2,4-Pentanedione	1.7	837	839
6	$MeNH_2$	−2.1	861[b])	859
7	$i\text{-}PrNH_2$	−3.3	883[b])	879
	$BuNH_2$	−1.7	881[b])	
	$PrNH_2$	0.4	879[b])	
8	$MeNH_2$	−0.4	861	860

[a]) All values in kJ · mol^{-1}, standard exper. deviation on ΔG_r° is 0.8 kJ · mol^{-1}. [b]) [6]. [c]) [7].

The proton affinities (PA) may be deduced from GB values using a $T\Delta S$ correction equal to 31 kJ · mol^{-1} for the symmetrical furans (**4**, **5**, **7**, and **8**) and 33 kJ · mol^{-1} otherwise [6]. These values, combined with the heats of formation of the neutral molecule yield $\Delta H_f^\circ(MH)^+$. These data are reported in *Table 2*.

Table 2. *Experimental PA*(M) *and* ΔH_f° *Values of* M *and* MH^+ *for* **1**–**8**[a])

M	PA(M)	$\Delta H_f^\circ(M)$[b])	$\Delta H_f^\circ(MH^+)$[c])	M	PA(M)	$\Delta H_f^\circ(M)$[b])	$\Delta H_f^\circ(MH^+)$[c])
1	822[d])	−34	674	**5**	870	−101	559
2	864	−69	597	**6**	892	−103	535
3	856	−68	606	**7**	910	−171	449
4	869	−105	556	**8**	891	−355	284

[a]) All values in kJ · mol^{-1}. [b]) ΔH_f° of neutrals estimated by the additivity method of *Benson* [8]. [c]) Calculated using $\Delta H_f^\circ(H^+) = 1530$ kJ · mol^{-1} [6]. [d]) For the determination of GB (**1**), see [1b].

MO Calculations. – Calculations were performed for the plausible structures resulting from protonation of mono- and dimethylfurans **2**–**6**. In view of their large number of

Table 3. *Calculated Heats of Formation* [kJ · mol^{-1}] *of Protonated Methylfurans* $C_5H_7O^+$ *Using MNDO Method*

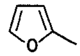
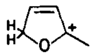
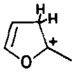
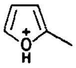
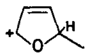
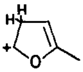
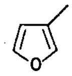
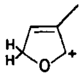
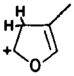
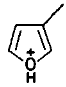
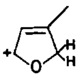
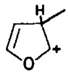
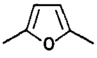
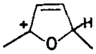
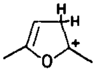
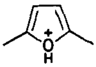
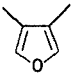
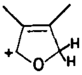
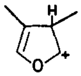
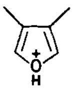
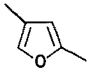
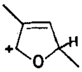
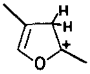
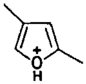
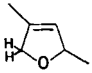
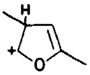
M	*M*H$^+$		
 **2**	 2H$_a^+$: 651 (0)	 2H$_b^+$: 672 (21)	 2H$_c^+$: 758 (107)
	 2H$_{a'}^+$: 683 (32)	 2H$_{b'}^+$: 683 (32)	
 **3**	 3H$_a^+$: 661 (5)	 3H$_b^+$: 683 (27)	 3H$_c^+$: 759 (103)
	 3H$_{a'}^+$: 656 (0)	 3H$_{b'}^+$: 714 (58)	

Table 4. *Calculated Heats of Formation* [kJ · mol^{-1}] *of Protonated Dimethylfurans* $C_6H_9O^+$ *Using MNDO Method*

M	*M*H$^+$		
 **4**	 4H$_a^+$: 625 (2)	 4H$_b^+$: 623 (0)	 4H$_c^+$: 706 (83)
 **5**	 5H$_a^+$: 610 (0)	 5H$_b^+$: 661 (51)	 5H$_c^+$: 718 (95)
 **6**	 6H$_{a'}^+$: 634 (36)	 6H$_{b'}^+$: 622 (24)	 6H$_c^+$: 708 (110)
	 6H$_a^+$: 598 (0)	 6H$_b^+$: 657 (59)	

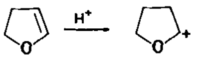
atoms and of their expected similarities with furan itself and 2,5-dimethylfuran (**4**), compounds **7** and **8** were not included in these calculations.

The semi-empirical MNDO method [9] was selected for this study. In the case of the protonated furan, it has been demonstrated that enthalpy differences between isomeric structures given by MNDO agree well with experiment [1a] and also with *ab initio* calculations carried out with a polarized basis set and with inclusion of the correlation effect [1c].

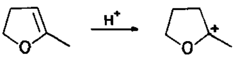
The heats of formation presented in *Table 3* and *4* were obtained after complete geometry optimisation of the 21 protonated structures of the three kinds of basic sites in **2**–**6**. Note that only relative values are significant; absolute ΔH_f° calculated by MNDO are greater than experimentally determined values by *ca.* 50 and 70 kJ · mol^{-1} for the $C_5H_7O^+$ and $C_6H_5O^+$ systems, respectively. A shift of *ca.* 33 kJ · mol^{-1} has been determined earlier for protonated furan [1a]. The detailed geometrical parameters may be requested from the authors.

Discussion. – *Site of Protonation.* In a recent investigation of the gas-phase electrophilic reactions of furan and analogous compounds, *Speranza* and coworkers have determined the reactivity of the various positions (heteroatom, C(α)- and C(β)-atoms) towards protonation [10]. Under their experimental conditions, all basic sites can lead to formation of protonated products because of the strong *Brønsted* acid used, HeT^+ (PA(He) = 188 kJ · mol^{-1}). Under the present conditions of thermodynamic equilibrium, only the most stable protonated species can be formed as unambiguously shown by previous experiments using specifically D-labelled furans [1b]. On this basis, we can exclude protonation of **1**–**8** on the O-atom. Moreover, the incidence of Me substitution on the GB observed in *Table 1* can hardly be accounted for by a protonation on the heteroatom. The MNDO results (*Tables 3* and *4*) show equally that *O*-protonated species are less stable than the C(α)-protonated ones by 80–110 kJ · mol^{-1}. It is too large a difference to consider reasonably the *O*-protonated forms in the forecoming discussion which is restricted to the thermodynamically stable species formed under equilibrium proton transfer conditions.

The protonation of **1**–**8** is thus discussed further in terms of the Me-substituent effects on the stability of the resulting carbenium ions. The changes in basicity properties caused by these effects are documented in [6]: an increase in stabilization of the protonated species is observed with increasing substitution on the cationic center. This is exemplified by the proton affinity values for ethylene, propylene and 2-methylpropylene: PA($CH_2{=}CH_2$) = 684 kJ · mol^{-1}; PA($CH_3CH{=}CH_2$) = 733 kJ · mol^{-1} and PA($(CH_3)_2C{=}CH_2$) = 824 kJ · mol^{-1} [6]. We note that the effect of a Me group on proton affinity in the related 2,3-dihydrofuran system is less pronounced: a difference in proton affinity, PA (**10**) – PA(**9**) of 34 kJ · mol^{-1} was recently determined [11].

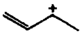


9 **9H$^+$**

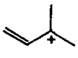


10 **10H$^+$**

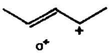
Similar effects were found in the allylic cation series **m**$^+$–**q**$^+$:



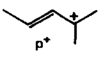
m$^+$



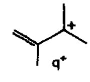
n$^+$



o$^+$



p$^+$

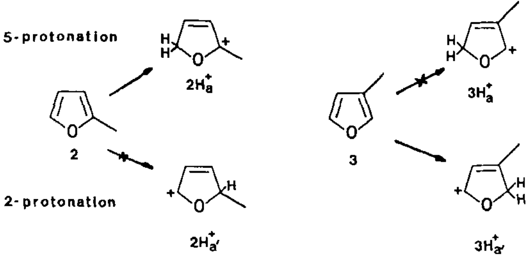


q$^+$

an increase in the PA of their corresponding olefins of *ca.* 27 kJ·mol^{-1} is observed in going from **m**$^+$ to **n**$^+$ and from **o**$^+$ to **q**$^+$, whereas a difference of only 7 kJ·mol^{-1} occurs from **n**$^+$ to **q**$^+$ indicating that no appreciable stabilization is brought about by a Me group in position 3 (all PA values are from [6]).

Basicity of 2- and 3-Methylfurans. The present results indicate that introduction of a Me group in position 2, or in position 3, increases the proton affinity by 42 or by 34 kJ·mol^{-1}, respectively *(Table 2)*. It can be anticipated that protonation of **2** in positions 5 or 2 leads to the most stable structures with a preference for the former since it forms a tertiary carbocation. Similarly, protonation of **3** in position 2 should be preferred according to the larger stabilizing effect of the Me group in the β-position of the allylic system than in the α-position. These reactions are exemplified in *Scheme 1*.

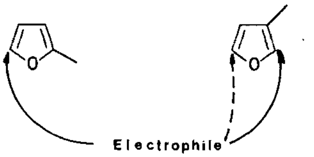
Scheme 1



The MNDO calculations performed on the different protonated products of **2** indicate that **2H**$_a^+$ is the most stable structure, in accordance with the above expectations; the other species are seen to be less stable by at least 20 kJ·mol^{-1} *(Table 3)*. The MNDO results on the protonation of **3** confirm the preferred protonation in position 2 to form the allylic cation **3H**$_{a'}^+$. However, a difference of 5 kJ·mol^{-1} only is found with **3H**$_a^+$: this is clearly less than the difference in PA of the olefins corresponding to ions **p**$^+$ and **q**$^+$ *(vide supra)*, ΔPA = 27 kJ·mol^{-1}. Furthermore, we can rationalize the above results by considering the positional effects of Me substituents: it is known from NMR spectra [12] that it is possible to compare the 3-, 4-, and 5-positions in 2-alkyl substituted heterocycles (furan, thiophene) with the *ortho*- *meta*- and *para*-positions of alkylbenzene, respectively. Similarly, the 2- and 5-positions in 3-alkyl substituted heterocycles can be compared to the *ortho*- and *meta*-positions of alkylbenzene, respectively, whereas the 4-position shows properties that deviate from the *ortho*-position [12]. On the other hand, the positional effect of Me substituent on the proton affinity of toluene have been rationalized by *Devlin et al.* [13] as follows: with respect to benzene, one Me group increases the PA of toluene by 25 in *ortho*-, 10 in *meta*-, 30 in *para*- and less than 5 kJ·mol^{-1} in the *ipso*-position relative to the proton.

In the present systems, we observe that introducing a Me group in positions 2 or 3 on furan increases its proton affinity by 42 and 34 kJ·mol^{-1}, respectively. From these considerations it is expected that protonation of **2** should occur in position 5 (*'para'*-position). This is in agreement with the conclusions drawn from the GB measurements and from the MNDO calculations. In line with this reasoning, compound **3** is protonated in position 2 (*'ortho'*-position) to form **3H**$_{a'}^+$. In summary, all the above considerations agree with the exclusive formation of structures **2H**$_a^+$ and **3H**$_{a'}^+$ upon gas-phase protonation of

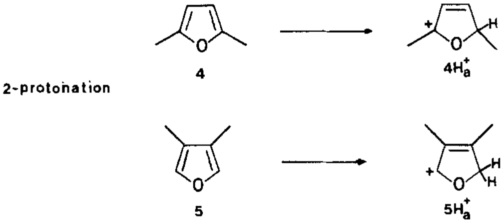
2- and 3-methylfuran, under thermodynamically controlled conditions. It is remarkable that in solution electrophilic substitution of **2** gives exclusively the 5-substituted product [14]: moreover, the acid-catalyzed hydrolysis of **2** starts with protonation in position 5 as indicated by NMR spectroscopy [15].



In contrast, acylation of **3** leads to a mixture of products, however, the substitution is predominantly oriented towards position 2 [16]. Finally, it is of interest to observe that the NMR spectra of protonated 2- and 3-methylthiophenes determined in strong acidic media [17] have pointed out to protonation in positions 5 and 2, respectively, to form carbocations analogous to structures **$2H_a^+$** and **$3H_a^+$**, in agreement with our conclusions.

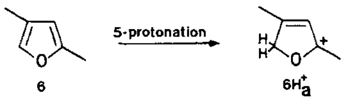
Basicities of 2,5-, 3,4- and 2,4-Dimethylfuran (**4**, **5**, *and* **6**). The symmetrical compounds **4** and **5** give identical GB values. This can be interpreted by formation of two protonated structures similarly stabilized. The ions **$4H_a^+$** and **$5H_a^+$** *(Scheme 2)* are both characterized by an allylic system bearing a Me group at one extremity.

Scheme 2



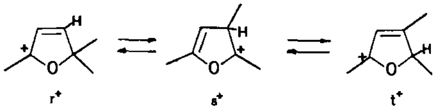
We thus conclude that protonation of **4** and **5** also occurs in the α-position to form allylic cations homologous to **$2H_a^+$** and **$3H_a^+$**. The 2,4-dimethyl derivative **6**, shows a quite enhanced basicity (by 22 kJ·mol^{-1}) relative to **4** and **5**. This probably results from protonation in position 5: in that case an allylic cation **$6H_a^+$** is formed in which the two resonance structures bear a tertiary carbocation structure *(Scheme 3)*.

Scheme 3

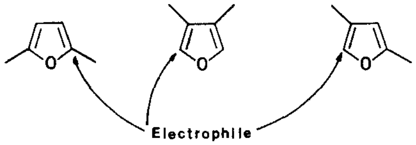


The results of MNDO calculations on the protonation of **4**–**6** are reported in *Table 4*. The most stable ionic products are unambiguously the α-protonated species **$5H_a^+$** and **$6H_a^+$**. Surprisingly MNDO predicts that **$4H_a^+$** and **$4H_b^+$** are of comparable stability. This observation may be complemented by the following; in strong acid medium the occur-

Scheme 4



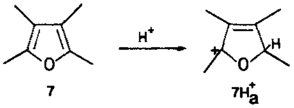
rence of the rearrangement of the 2,5,5-trimethyldihydrofuryl ion **r**$^+$ into **t**$^+$ points to the stability of the intermediate **s**$^+$ a β-protonated structure analog to **4H**$_b^+$ *(Scheme 4)*. Moreover, only **r**$^+$ and **t**$^+$ are experimentally detected (in the ratio **t**$^+$/**r**$^+$ > 20) thus indicating a better stability of the α-protonated form **t**$^+$ [14]. In solution, electrophilic substitution on **4**–**6** occurs in α-positions [2].



The protonation of **4** and **6** in solution was described by *Brouwer et al.* [16]. The unique formation of **4H**$_a^+$ and **6H**$_a^+$ *(Table 4)* was attested by NMR spectra. Moreover, no interconversion **4H**$_a^+ \rightleftarrows$ **6H**$_a^+$ is occurring thus demonstrating the unstability of the β-protonated structure in the isomerization process [14]. It may be added that the behaviour of sulfur analogs is also dominated by the exclusive protonation in the α-position [17].

Basicities of Tetramethylfuran (**7**) *and 2,5-Di(*tert*-butyl)furan* (**8**). The behaviour of **7** can be obviously deduced from that of furan itself. The α-protonation is certainly the most probable process from a thermodynamic point of view *(Scheme 5)*. Accordingly, the GB(**7**) may be estimated by the incremental method presented later (see *Conclusion*). Assuming formation of **7H**$_a^+$, one obtains GB(**7**) – GB(**1**) = 92 kJ · mol^{-1}, the corresponding experimental difference is 87 kJ · mol^{-1}.

Scheme 5



Protonation of **8** in strong acidic conditions occurs in the α-position as established from NMR [18]. Owing to the discussion concerning the 2,5-dimethylfuran, the question of the α/β protonation in the gas phase is raised again. The influence of the *t*-Bu groups on gas-phase basicity can be disclosed from compound by reference to the unsubstituted furan. A stabilization effect approximated by GB(**8**) – GB(**1**), of 68 kJ · mol^{-1} is observed. This value is greater than that corresponding to the dimethyl analog **4** by 22 kJ · mol^{-1}. This is much more than the difference in GB between toluene and (*tert*-butyl)benzene, *i.e.* 8 kJ · mol^{-1} [6]. A clear interpretation of this phenomena will be proposed after further experimental investigation of 2,5-disubstituted dihydrofuryl ions.

Conclusion. – The present study has demonstrated that, with the possible exception of 2,5-derivatives, protonation of alkyl-substituted furans under equilibrium conditions occurs in the α-position. However, other protonation sites on the C-atoms yield cations which lie no more than 60 kJ·mol^{-1} above the most stable structure. The participation of these latter to the unimolecular dissociation of protonated furans has to be taken into consideration. For example, it was recently observed that the mass-analyzed ion kinetic energy (MIKE) spectra of protonated **2**–**6** are dominated by the loss of CO [19]. These eliminations are endothermic by as much as 120 kJ·mol^{-1} approximately, thus this energy requirement allows the occurrence of most of the structures quoted in *Tables 3* and *4*.

Additivity Rules. Interesting conclusions as to the effect of Me substituents can be drawn from the PA of **1**–**5** by considering the positional Me stabilization. For polysubstituted furans, it is assumed that the global stabilization is the sum of the individual effects (additivity rule). Thus, **1**–**5** provide the incremental values on PA as a function of the position of the Me group with respect to the site of protonation, *i.e.* the C(α)-atom. For example, **3** is protonated in the *ortho*-position with respect to the Me group, yielding: ΔPA(*ortho*) = PA(**3**) – PA(**1**) = 33 kJ·mol^{-1}. Similarly, **5** is protonated in *ortho*- and *meta*-position with respect to the Me groups thus giving: ΔPA(*meta*) = PA(**5**) – PA(**1**) – ΔPA(*ortho*) = 13 kJ·mol^{-1}. The resulting incremental values are compared below with those deduced from the protonation of benzene derivatives:

ΔPA [kJ·mol^{-1}]

	ortho	*meta*	*para*	*ipso*
Benzene [13]	25	10	30	5
Furan	33	13	41	5

The effects of Me substituents are greater in the furan compounds, but the ordering and the relative magnitude of the increments are similar for both series. We can also note that in both cases ΔPA(*ortho*) + ΔPA(*meta*) = ΔPA(*ipso*) + ΔPA(*para*). Using these increments calculated values for PA(**6**) = 896 and PA(**7**) = 914 kJ·mol^{-1} were obtained, in agreement with the experimental values (892 and 910 kJ·mol^{-1}, respectively). Furthermore, comparable stability for $\mathbf{4H_a^+}$ and $\mathbf{4H_b^+}$ is predicted by this additivity procedure, in accordance with the MNDO calculations *(Table 4)*.

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