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Experimental and Theoretical Evaluation of Proton Affinities of Furan, the Methylphenols, and the Related Anisoles

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The proton affinities of furan, 2-, 3-, and 4-methylphenol, and the related anisoles have been determined with Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry. The proton affinity of furan is redetermined to be 812 kJ mol^{-1} on the basis of the experimental equilibrium constant for the proton transfer to acetone. The present value is significantly higher than that recommended in the literature (803 kJ mol^{-1}), but in agreement with ab initio G3(MP2) calculations, which suggest a proton affinity of 814 kJ mol^{-1} for the 2-position in furan. The determination of the equilibrium constant for the reaction between a protonated methylphenol or methylanisole and a suitable reference base results in the following proton affinities: 2-methylphenol, 832 kJ mol^{-1}; 3-methylphenol, 841 kJ mol^{-1}; 4-methylphenol, 814 kJ mol^{-1}; 2-methylanisole, 850 kJ mol^{-1}; 3-methylanisole, 860 kJ mol^{-1}; and 4-methylanisole, 841 kJ mol^{-1}. Calculations at the G3(MP2) level indicate that the 4-position is the most basic site in the 2- and 3-methyl-substituted phenols, whereas almost the same proton affinity is obtained for the 2- and 4-position in 4-methylphenol. The G3(MP2) proton affinity for the most basic site in a given methylphenol is in agreement with the present experimental values.

Introduction

The occurrence of proton transfer to organic and biological molecules in the gas phase is of fundamental importance from both an experimental and a theoretical point of view.[1,2] The interest in gas-phase proton-transfer reactions is to a large extent motivated by the importance of understanding the kinetic and thermodynamic properties that determine the preferred site of protonation of polyfunctional molecules.[3,4] In particular, a number of studies concerned with proton transfer to substituted aromatic species[5] have revealed that protonation of a heteroatom-containing substituent is often preferred kinetically, whereas proton transfer to the aromatic ring is thermodynamically favorable.[6,7] For example, protonation at the oxygen atom in phenol is known to occur in the strongly exothermic gas-phase reaction with CH_5^+ as the Brønsted acid irrespective of the fact that proton transfer to the 4-position of the ring is thermodynamically favored by 60 kJ mol^{-1} over protonation at the hydroxy group.[8] Similar results are reported for other substituted aromatic compounds, such as anisole,[9] fluorobenzenes,[10,11] fluorophenols,[12] and phenyl propyl ethers.[13,14]

Knowledge of the preferred site of protonation is also of significance for structure elucidation of polyfunctional molecules with the use of mass spectrometry.[15] Notably, the site of protonation under chemical ionization (CI) conditions is often reflected directly in the mechanism of the ensuing dissociation reactions as discussed in a number of studies concerned with propene loss from the metastable $[M + D]^+$ ions of a series of aryl propyl ethers[14,16,17] and—more recently—for isomeric propoxypyridines.[18] The mechanism proposed involves competing deuteron transfer to the oxygen atom and the aromatic ring, and the low extent of deuterium incorporation in the propene eliminated from the $[M + D]^+$ ions of 3-methylphenyl *n*-propyl ether was considered to reflect a preference for deuteron transfer to the ring for this isomer. By contrast, deuteron transfer to the oxygen atom is quite pronounced when the methyl group is situated at the 4-position in the parent ether. A more complete interpretation of these findings requires well-determined proton affinities of the aromatic ethers and the methyl-substituted phenols related to the product ions of propene loss from the $[M + D]^+$ ions of the parent ethers. To address this limitation, we decided to study the thermodynamics of proton transfer to 2-, 3-, and 4-methylphenol and the related methylanisoles with the Fourier transform ion cyclotron resonance (FT-ICR) method.[19] The proton affinity of furan was included in this study in order to examine the reliability of our experimental strategy for obtaining proton affinities. In addition, ab initio calculations[20,21] were performed with the G3 and G3(MP2) procedures[22,23] in order to obtain the proton affinity of each ring position of the aromatic compounds as well as of the oxygen atom of the methylphenols. The computational results allowed us also to examine the influence of a methyl group on the proton affinity of the various sites and compare the results with our previous study of protonation of the fluorophenols and fluoroanisoles.[12]

Experimental Section

Instruments. Experiments were performed with two Fourier transform ion cyclotron resonance mass spectrometers. The proton affinities of the methyl-substituted phenols and anisoles were measured with an instrument that was constructed at the University of Amsterdam.[24] The general operating procedure of this instrument has been described in detail elsewhere.[25] The

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total pressure in the instrument was in most experiments less than 4 × 10^{-7} mbar as measured with an uncalibrated ionization gauge placed in a sidearm of the main vacuum system. In the present series of experiments, the ratio between the partial pressures of a methyl-substituted phenol or anisole and the reference base was varied between 1:1 and 3:1 or 1:3 in order to determine the equilibrium constant for the proton transfer reactions as precisely as possible. The proton affinity of furan was also measured with this instrument, and the experiments were repeated with a Bruker Daltonics Apex II FT-ICR mass spectrometer. A description of the general operating procedures for ion manipulation with this instrument has been given previously.[26] The total pressure in the Apex II instrument was in most experiments (1−3) × 10^{-8} mbar as measured with an uncalibrated ionization gauge placed in a sidearm of the main vacuum system. The ratio between the partial pressures of furan and the reference base acetone was varied from 1:1 to 1:2 or 2:1.

Pressure Correction. The equilibrium constant (K) is obtained from the gas-phase reaction between a protonated reference base (B in eq 1) and a molecule M as indicated in eq 2:

$$BH^+ + M \rightleftharpoons B + MH^+ \tag{1}$$

$$K = \frac{I(MH^+)\,P(B)}{I(BH^+)\,P(M)} \tag{2}$$

In eq 2, $I(MH^+)$ and $I(BH^+)$ represent intensities of the peaks (in arbitrary units) corresponding to the MH^+ and BH^+ ions, respectively; P(B) and P(M) are the partial pressures of the neutral species. The measured partial pressures were corrected for the sensitivity of the ionization gauge for the neutral species according to a reported procedure.[27] In brief, the measured partial pressure of a given compound involved in the proton-transfer reactions was corrected with the use of eq 3, in which R is the sensitivity relative to N_2 ($R(N_2)$ is arbitrarily set to 1) and α is the molecular polarizability.

$$R = 0.36\alpha + 0.30 \tag{3}$$

Calculations. The G3 and G3(MP2) calculations[22,23] were performed with the Gaussian 98 suite of programs.[28] In brief, the G3(MP2) procedure involves calculation of the equilibrium structure at the Hartree−Fock (HF) level with the 6-31G(d) basis set. The HF-6-31G(d) method is used to calculate harmonic frequencies that are scaled by a factor of 0.8929 and used to evaluate zero-point vibrational energies and to estimate thermodynamic properties, such as the third law entropy of the species. Refinement of the equilibrium geometry is achieved at the MP2(full)/6-31G(d) level prior to the calculation of single point energies with MP2 and QCISD(T) methods.[23]

Materials. All chemicals were obtained commercially and used without purification.

Results

Experimental Determination of Proton Affinities. The thermodynamic proton affinity (PA) of a molecule M is defined as the negative of the enthalpy change, $-\Delta_rH°$, of the hypothetical gas-phase reaction at a temperature of 298 K (eq 4):[29]

$$M^+ + H \rightarrow MH^+ \tag{4}$$

The proton affinity of a gaseous molecule is commonly obtained by studying ion−molecule equilibria either under the low-pressure conditions characteristic of FT-ICR instruments[1,30,12] or with the use of high-pressure mass spectrometry (HPMS).[4,31] The experimental determination of proton affinities is also achieved frequently by the so-called kinetic method that is based upon an examination of the dissociation reactions of proton bound dimers or heterodimers in the gas phase.[32] In the present study, the FT-ICR method is used in order to study the proton-transfer reactions from protonated reference bases to furan and the 2-, 3-, and 4-methylphenols and the related anisoles (Table 1).

TABLE 1: Occurrence/Nonoccurrence of Proton Transfer in the Reactions of the Protonated Reference Bases with Furan, 2-, 3-, and 4-Methylphenol and the Related Anisoles

molecule	reference base	gas-phase basicity[a]	proton transfer
furan	2-methylpropene	776	complete
	acetone	782	reversible
	methyl acetate	791	no
2-$CH_3C_6H_4OH$	dimethyl ether	801	reversible
3-$CH_3C_6H_4OH$	dimethyl ether	801	complete
	3-pentanone	807	reversible
4-$CH_3C_6H_4OH$	cyclopropyl cyanide	778	complete
	acetone	782	reversible
2-$CH_3C_6H_4OCH_3$	di-*n*-butyl ether	818	reversible
3-$CH_3C_6H_4OCH_3$	diisopropyl ether	828	reversible
4-$CH_3C_6H_4OCH_3$	dimethyl ether	801	reversible

[a] The values are in kJ mol^{-1} and are taken from ref 29. The average uncertainty on the values is ±8 kJ mol^{-1}.

In a typical experiment, the aromatic compound of interest (M) and the reference base (B) are admitted to the FT-ICR cell and ionized by electron ionization (eq 5). The ionization of B is followed by ion−molecule reactions leading to the formation of protonated species (eq 6).

$$B + e \rightarrow B^{\bullet +} \tag{5}$$

$$B^{\bullet +} + B \rightarrow BH^+ + [B-H]^{\bullet} \tag{6}$$

The protonated molecules are subsequently isolated by ejection of all other ions from the cell by suitable radio-frequency pulses.[26] The ions are then allowed to react by proton transfer with the neutral molecules present in the cell. For furan, proton transfer from the $C_4H_9^+$ ion generated from 2-methylpropene is irreversible (Table 1), whereas proton transfer is not observed in the reaction with the protonated methyl acetate. Reversible proton transfer is observed, however, in the reaction with protonated acetone, in agreement with a previous ICR study.[33]

The system was allowed to reach equilibrium starting either with protonated acetone or protonated furan as the primary reactant species (see Figure 1). With the FT-ICR instrument constructed at the University of Amsterdam, the average equilibrium constant for the proton-transfer reaction between protonated acetone and furan is determined to be 0.54 ± 0.03. A similar value (0.78 ± 0.10) is obtained with Apex II FT-ICR instrument (Table 2, see also Experimental Section).

The determination of the equilibrium constants for the proton transfer to the methylphenols and anisoles is achieved by the same procedure as followed in the experiments with furan (see Tables 1 and 2). The average value of the equilibrium constant leads to the change in Gibbs energy, $\Delta_rG°$, for the proton-transfer reaction in eq 1. According to the definition of the gas-phase basicity GB ($-\Delta_rG°$(298 K) for the reaction in eq 4),[29] the $\Delta_rG°$ value is equal to the difference between the GB value of a given reference base and the molecule, M (eq 7). The values of ΔGB are given in Table 2 and are based upon the assumption

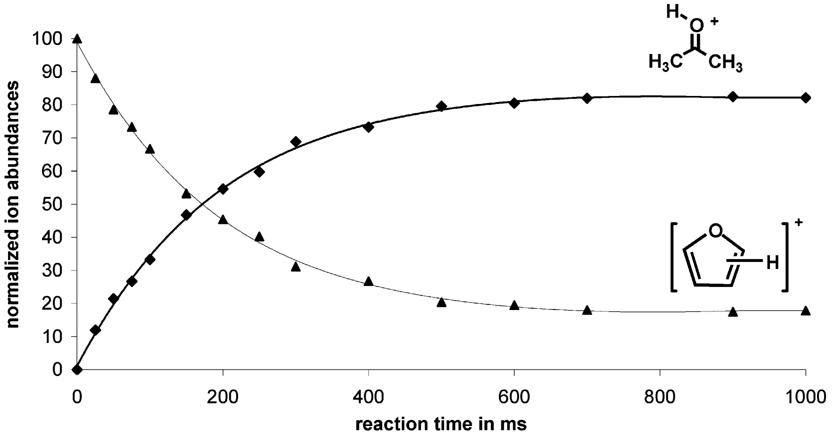


Figure 1. Relative abundance of protonated acetone and protonated furan as a function of reaction time. The corrected partial pressures are P(acetone) = 17 × 10^{-6} Pa and P(furan) = 6.3 × 10^{-6} Pa (see also Experimental Section).

TABLE 2: Equilibrium Constants for the Proton Transfer Reactions between a Methylphenol or Methylanisole with a Reference Base Together with the Difference in Gas-Phase Basicity, Δ(ΔGB), between the Species of Interest

molecule	ref base	GB(ref base)[a]	K[b]	Δ(ΔGB)
furan[d]	acetone	782	0.54 ± 0.03	1.1
furan[e]	acetone	782	0.78 ± 0.10	0.2
2-$CH_3C_6H_4OH$[d]	dimethyl ether	801	0.74 ± 0.04	0.8
3-$CH_3C_6H_4OH$[d]	3-pentanone	807	2.23 ± 0.30	−2.0
4-$CH_3C_6H_4OH$[d]	acetone	782	1.14 ± 0.02	−0.3
2-$CH_3C_6H_4OCH_3$[d]	di-*n*-butyl ether	818	0.80 ± 0.2	0.6
3-$CH_3C_6H_4OCH_3$[d]	diisopropyl ether	828	1.0 ± 0.1	−0.1
4-$CH_3C_6H_4OCH_3$[d]	dimethyl ether	801	23.4 ± 2.3	−7.8

[a] The values are in kJ mol^{-1} and taken from ref 29. [b] Average values of 3−4 measurements (see text). [c] Δ(ΔGB) = Δ(GB) (reference) − Δ(GB) (compound). [d] Values obtained from experiments with the FT-ICR instrument constructed at the University of Amsterdam. [e] Values obtained from experiments with the Apex II FT-ICR mass spectrometer.

TABLE 3: Gas-Phase Basicities (GB) and Proton Affinities (PA) of the Methylphenols and Methylanisoles[a]

molecule	GB	PA[b]	molecule	GB	PA[b]
furan[c]	781	812	4-$CH_3C_6H_4OH$[c]	782	814
furan[d]	782	813	2-$CH_3C_6H_4OCH_3$[c]	818	850
2-$CH_3C_6H_4OH$[c]	800	832	3-$CH_3C_6H_4OCH_3$[c]	828	860
3-$CH_3C_6H_4OH$[c]	809	841	4-$CH_3C_6H_4OCH_3$[c]	809	841

[a] The values are in kJ mol^{-1}. The average uncertainty is ±8 kJ mol^{-1}. [b] Estimated with a $T\Delta_rS°$ term of −30.7 J mol^{-1} K^{-1} for furan and a $T\Delta_rS°$ term of −32 J mol^{-1} K^{-1} for the methylphenols and methylanisoles (see text). [c] Values obtained from experiments with the FT-ICR instrument constructed at the University of Amsterdam. [d] Values obtained from experiments with the Apex II FT-ICR mass spectrometer.

that the temperature of the reactant chemical system in the FT-ICR instrument is 298 K (see also ref 25).

$$-RT\ln(K) = \Delta_r G° = \Delta GB = GB(B) - GB(M) \quad (7)$$

The ΔGB values in Table 3 are used to obtain the proton affinities on the basis of an estimated entropy change for the protonation reaction (eq 4). The estimation of the entropy of protonation of a gaseous molecule ($\Delta_rS°$(M)) is realized commonly with the use of eq 8 in which σ(M) is the rotational symmetry number of the molecule, $\sigma(MH^+)$ is the symmetry number of the protonated species, and $S°(H^+)$ is the entropy of the free proton (108.95 J mol^{-1} K^{-1}).[29]

$$\Delta_rS°(M) = S°(MH^+) - S°(M) - S°(H^+) \approx R\ln[\sigma(M)/\sigma(MH^+)] - S°(H^+) \quad (8)$$

For furan the rotational symmetry number changes from 2 to 1 if the protonation occurs on the 2- or 3-position, which yields an $\Delta_rS°$ term of −103 J mol^{-1} K^{-1} and a $T\Delta_rS°$ value of −30.7 kJ mol^{-1} with T set to 298 K. With the use of this $T\Delta_rS°$ term the experimental GB value of 781 kJ mol^{-1} for furan leads to a proton affinity of 812 kJ mol^{-1} (eq 9 and Table 3). For the M and MH^+ species of the substituted phenols or anisoles, the symmetry numbers are the same, and as a result, the entropy for the protonation reaction can be considered to be close to the entropy of the free proton in the gas phase. Provided this assumption is correct, the value of the $T\Delta_rS°$ term in eq 9 becomes −32 kJ mol^{-1} if the temperature is assumed to be 298 K. This $T\Delta_rS°$ term leads subsequently to the proton affinities collected in Table 3.

$$PA(M) = GB(M) - T\Delta_rS° \quad (9)$$

Theoretically Obtained Proton Affinities. The calculated proton affinities at 0 K are obtained from the electronic energies and the zero-point vibrational energies (eq 10). Subsequently, the 298 K values are determined with the use of the integrated constant pressure heat capacities for the molecule and the protonated species (eq 11). For the proton, the value of the constant pressure heat capacity is assumed to be the same as that of an ideal gas ($^5/_2RT$).

$$PA(M, 0\ K) = E(M) + ZPE(M) - [E(MH^+) + ZPE(MH^+)] \quad (10)$$

$$PA(M, 298\ K) = PA(M, 0\ K) + \int_0^{298} C_P(M)\,dT + \frac{5}{2}RT - \int_0^{298} C_P(MH^+)\,dT \quad (11)$$

The calculated proton affinities of the various positions within furan, phenol, and the methylphenols are collected in Table 4 together with the values for toluene. For furan, the calculations with the G3 procedure[23,34] yielded the following proton affinities at 298 K: 699 kJ mol^{-1} for the oxygen atom, 815 kJ mol^{-1} for the 2-position, and 771 kJ mol^{-1} for the 3-position. Essentially the same proton affinities are obtained with the G3(MP2)

TABLE 4: Overview of the Calculated Proton Affinities of Furan, Phenol, Toluene, and the 2-, 3-, and 4-Methylphenols[a]

		protonation site						
molecule	method	O	C1	C2	C3	C4	C5	C6
furan	G3	699		815	771			
	G3(MP2)	699		814	771			
C_6H_5OH[b]	G3(MP2)	745	688	797	747	811		
$C_6H_5CH_3$	G3(MP2)		743	773	760	780		
2-$CH_3C_6H_4OH$	G3(MP2)	753	723	795	775	824	782	810
3-$CH_3C_6H_4OH$	G3(MP2)	754	705	819	744	835	761	827
4-$CH_3C_6H_4OH$	G3(MP2)	756	723	811	775	810		

[a] Values in kJ mol^{-1}. [b] Values taken from ref 12.

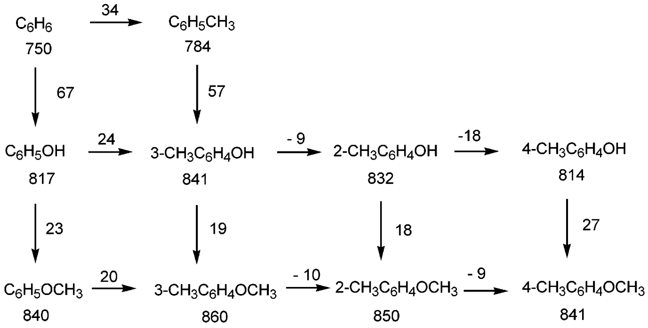
procedure (Table 4), and accordingly, the calculations for the other aromatic species were performed only at this level.

Discussion

Proton Affinity of Furan. The recommended literature value of the gas-phase basicity of furan is 771 kJ mol^{-1}.[29] This value leads to the anticipation that proton transfer from the $C_4H_9^+$ ion (GB(2-methylpropene) = 776 kJ mol^{-1}) to furan should be reversible in keeping with the common observation that equilibrium in proton-transfer reactions will be established in an FT-ICR instrument[25] if the GB values differ less than about 8 kJ mol^{-1} (except if substantial energy barriers prevent proton transfer). Reversibility in the proton transfer from the $C_4H_9^+$ ion to furan is not observed, however, in the present experiments (Table 1), indicating that the gas-phase basicity is considerably higher than 771 kJ mol^{-1}. Furthermore, proton transfer does not take place in the reactions of the $[M + H]^+$ ion of methyl acetate with furan, indicating that the GB of furan is lower than that of this reference base (GB(methyl acetate) = 791 kJ mol^{-1}; see also Table 1). By contrast, proton transfer occurs in both directions in the reaction with acetone (GB = 782 kJ mol^{-1}), and equilibrium is attained readily (Figure 1).

Clearly, the present results disagree with the average value of the gas-phase basicity value as obtained on the basis of a number of experiments with high-pressure mass spectrometry and the ICR method. The high-pressure experiments are reported to yield GB values of 775 and 767 kJ mol^{-1},[35] whereas the first series of ICR experiments based on the occurrence/nonoccurrence of proton transfer to furan indicated that the GB value should be between 756 and 765 kJ mol^{-1}.[36] In a later ICR study,[33] the proton transfer between furan and protonated acetone was reported to be reversible and lead to a GB value of 780 kJ mol^{-1}. The latter value is supported by our FT-ICR experiments, which result in a GB value of 781 kJ mol^{-1} and a proton affinity of 812 kJ mol^{-1} with the use of a $T\Delta_rS°$ value of -30.7 kJ mol^{-1} (see Results). It should be emphasized that the present $T\Delta_rS°$ value is based upon a change in symmetry number upon protonation of furan, whereas the recommended value of $T\Delta_rS°$ (-32 kJ mol^{-1})[29] rests upon the assumption that the entropy of furan and the protonated species is the same. Such a slight modification of the $T\Delta_rS°$ value would not change the recommended proton affinity to any significant extent, and as a conclusion, the present results strongly indicate that the value of 803 kJ mol^{-1} for the proton affinity of furan is too low. This is further substantiated by the results of G3(MP2) calculations; that is, G3(MP2) predicts a proton affinity of the 2-position of 814 kJ mol^{-1} and lower values of the 3-position (771 kJ mol^{-1}) as well as of the oxygen atom (699 kJ mol^{-1}). It can be noted here that the present G3(MP2) values for furan agree with recent G2(MP2) calculations that are reported to yield a proton affinity of 816 kJ mol^{-1} for C-2, 774 kJ mol^{-1} for C-3, and 700 kJ mol^{-1} for the oxygen atom.[37]

SCHEME 1: Trends in the Experimentally Obtained Proton Affinities of the Methylphenols and Methylanisoles



In conclusion, the reason for the discrepancy between the high-pressure mass spectrometry measurements and the (FT)-ICR experiments is unclear to us, but the consistency between the present value and the theoretical results indicates that the proton affinity of furan should be adjusted to 812 kJ mol^{-1}. The agreement between our experiments and the previous ICR study in combination with the outcome of the calculations also validates the present experimental strategy to determine the proton affinities of the methylphenols and related anisoles.

Proton Affinities of 2-, 3-, and 4-Methylphenols and Related Anisoles. The trend in the experimental proton affinities is shown in Scheme 1. The same order of proton affinities is obtained for the phenols and anisoles: that is PA(3-$CH_3C_6H_4$-$OH(OCH_3)$) > PA(2-$CH_3C_6H_4OH(OCH_3)$) > PA(4-$CH_3C_6H_4$-$OH(OCH_3)$). A similar relative order was obtained in the previous study of fluorophenols and fluoroanisoles even though the presence of a fluorine atom on the aromatic ring leads to a decrease in the proton affinity compared to the parent phenol or anisole.[12] Also, in a recent study of dihydroxybenzenes the order of proton affinities was reported to be PA(3-isomer) > PA(2-isomer) > PA (4-isomer).[38]

With respect to the influence of a methyl group, the increase in the experimental proton affinity going from benzene to toluene[39] is 34 kJ mol^{-1}, and a somewhat smaller increase in proton affinity (24 kJ mol^{-1}) is obtained if a methyl group is introduced at the 3-position in phenol (Scheme 1). The presence of a methyl group at the 2-position results in a small increase in proton affinity (15 kJ mol^{-1}) with respect to phenol, and an insignificant effect (3 kJ mol^{-1}) is observed when a methyl is placed at the 4-position. A similar trend is obtained for the methylanisoles; that is, a methyl group at the 3-position causes an increase in proton affinity of 20 kJ mol^{-1} with respect to anisole. A methyl group at the 2-position changes the proton affinity by 10 kJ mol^{-1}, whereas a negligible effect is observed if the methyl is introduced at the 4-position (PA(anisole) = 840 kJ mol^{-1} and PA(4-methylanisole) = 841 kJ mol^{-1}). In other words, the effect on the proton affinity of changing the $-OH$ group into $-OCH_3$ is almost independent of the position of the

TABLE 5: Overview of the Calculated HF-6-31(d) and B3LYP/6-31G(d) Entropies of Protonation ($-\Delta_rS°$ in J mol^{-1} K^{-1}) of Furan, Phenol, Toluene, and the 2-, 3-, and 4-Methylphenols (T = 298 K)′

species	reported or assumed value	method	protonation site O	C1	C2	C3	C4	C5	C6
furan	109[a]/103[b]	G3(MP2)	102.3		104.0	102.8			
C_6H_5OH	104[a]	G3(MP2)	100.2	95.2	101.9	97.7	103.0		
		B3LYP					102.9		
$C_6H_5CH_3$	93[a]/103[b]	G3(MP2)		118.8	103.5	113.5	108.1		
		B3LYP					103.6		
2-$CH_3C_6H_4OH$	109[b]	G3(MP2)	97.5	96.9	104.6	91.0	104.1	98.2	102.2
		B3LYP					104.4		
3-$CH_3C_6H_4OH$	109[b]	G3(MP2)	112.3	113.4	119.8	121.4	120.1	114.7	120.3
		B3LYP					106.9		
4-$CH_3C_6H_4OH$	109[b]	G3(MP2)	93.8	96.0	112.0	102.4	116.9		
		B3LYP			120.2				

[a] Values taken from ref 29; see also text. [b] Values obtained as outlined in the text.

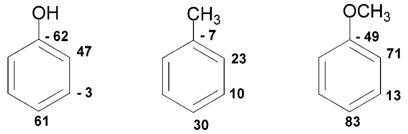


Figure 2. Differences in proton affinity between the value of benzene (750 kJ mol^{-1}) and that calculated by the G3(MP2) method for the indicated position in phenol, toluene, and anisole.

methyl group on the aromatic ring. In terms of values, the increase in proton affinity going from a methylphenol to the methylanisole is between 18 and 27 kJ mol^{-1} and thus comparable to the difference in proton affinity between the parent phenol and anisole (23 kJ mol^{-1}, see Scheme 1).

The G3(MP2) calculations substantiate the expectation that the 4-position in 2- and 3-methylphenol is the thermodynamically preferred protonation site. The calculated value for the 4-position in the 2-methyl isomer is 824 kJ mol^{-1} (Table 4), slightly lower than the experimental value of 832 kJ mol^{-1}. For 3-methylphenol, the theoretical value for the 4-position is only 6 kJ mol^{-1} lower than the experimental value of 841 kJ mol^{-1}, and for the 4-methyl isomer, the calculated value of the 2-position is 3 kJ mol^{-1} lower the experimental result (PA = 814 kJ mol^{-1}). Overall, the G3(MP2) proton affinities agree very well with the present FT-ICR results for the methylphenols, in line with the conclusion reached for furan (vide supra) and for 2-, 3-, and 4-fluorophenol.[12]

In terms of the proton affinities of the different sites within a methylphenol, the G3(MP2) results reveal that the same order is obtained for the 2- and 3-isomers; that is, the PA deceases in the order 4-, 6-, 2-, 5-, 3-, and 1-position (see Table 4). For the 4-isomer, the proton affinity of the 2- and 4-position is essentially the same, whereas the 3-position is associated with a higher PA value than the 1-position. The preference for protonation at the 4-position in the methylphenols is in line with the expected strong stabilization of the positive charge by the oxygen atom and a weaker influence of the methyl group. This effect is also manifested in the fact that the PA of the 4-position in phenol is calculated to be 61 kJ mol^{-1} higher than of benzene (PA = 750 kJ mol^{-1}), whereas the introduction of a methyl group increases the proton affinity by 30 kJ mol^{-1} (as based on the G3(MP2) value for the 4-position in toluene; see Table 4).

A methyl group exerts only a minor change of the PA value of the *ipso*-C atom according to the G3(MP2) calculations (see also ref 40). For toluene, the PA value of the 1-position is 743 kJ mol^{-1}, only 7 kJ mol^{-1} lower than the PA of benzene. The small effect of the methyl group on the PA of the *ipso*-C atom is also manifested in the values for this particular site in the methylphenols. For example, the PA of the 2-position in 2-methylphenol is 795 kJ mol^{-1}, and the PA of the same position in unsubstituted phenol is 797 kJ mol^{-1}. Likewise, the methyl-bearing C atom in 3-methylphenol is calculated to have a PA (744 kJ mol^{-1}) that is essentially the same as the 3-position in phenol (747 kJ mol^{-1}). With respect to the C atom connected to the −OH group, the calculations show that the PA of this position is higher than in phenol (688 kJ mol^{-1}). For the 2- and 4-methyl-substituted phenols the value is the same (723 kJ mol^{-1}) and—as expected—larger than in the 3-isomer (705 kJ mol^{-1}). This trend is in keeping with the fact that a methyl group stabilizes the positive charge in the ions formed by protonation at the C atom connected to the −OH group and that this stabilization is greater when the methyl is situated at the 2- or 4-position.

The calculated PA of the oxygen atom is lower than the value of the ring positions with the exception of the C atom connected directly to the −OH group. The calculations reveal that the PA of the oxygen atom in the methyl-substituted species is 8−11 kJ mol^{-1} higher than the value obtained for this site in phenol (745 kJ mol^{-1}). In addition, the PA value of the oxygen atom in the methylphenols is almost independent of the position of the methyl group (Table 4).

Additivity Scheme. The site specific proton affinities of substituted aromatic molecules has been discussed in a number of instances on the basis of an additivity scheme based upon the proton affinity of the parent arene and a series of increments.[10,12,39−42] For substituted benzenes, these increments are given as the difference between the proton affinity of benzene and the calculated value for a specific position in the species containing one or more substituents (eq 12, x indicates a substituent).

$$\mathrm{PA(M)} = \mathrm{PA(benzene)} + I_{1,x} + I_{2,x} + I_{3,x} + I_{4,x} + I_{5,x} + I_{6,x} \tag{12}$$

For toluene, phenol, and anisole the G3(MP2) calculations result in the increments given in Figure 2. With these increments, the estimated proton affinity of the 4-position in 3-methylphenol (834 kJ mol^{-1}) is close to the experimental value of 841 kJ mol^{-1} (Table 3). For the related 3-methylanisole the additivity scheme yields a value of 856 kJ mol^{-1} for the 4-position (experiment 860 kJ mol^{-1}). Similar small differences between the estimated values and the experimental results are obtained for the other methylphenols and methylanisoles in line with the findings reported for the fluorophenols and fluoroanisoles.[12]

Entropies of Protonation. The entropies of protonation ($\Delta_rS°$ of eq 1) obtained from the vibrational frequencies calculated at the HF 6-31G(d) level are summarized in Table 5 (see also ref

43 for ab initio calculations of third law entropies). For furan, the calculated entropy change upon protonation at the 2-position (-104.0 J mol^{-1} K^{-1}) is in agreement with the value of -103 J mol^{-1} K^{-1} obtained by a consideration of the change in symmetry number (see eq 8). A similar situation applies to phenol as noted in a previous report;[12] that is, the calculated value for protonation at the 4-position (-103.0 J mol^{-1} K^{-1}) agrees with the experimental value of -104 J mol^{-1} K^{-1} as determined by high-pressure mass spectrometry.[44] For toluene, the recommended average value for the entropy change is -93 J mol^{-1} K^{-1}, based upon the temperature dependence of the equilibrium constant for a number of proton-transfer reactions.[31,45] Protonation at the 4-position of toluene is predicted by the calculations to be associated with an entropy change of -108.1 J mol^{-1} K^{-1}. This value is in line with symmetry considerations (-103 J mol^{-1} K^{-1}) but significantly different from the reported experimental value. For the isomeric methylphenols, the assumed value is -109 J mol^{-1} K^{-1} (see Results). This value is not in serious disagreement with the calculated value of -104.1 J mol^{-1} K^{-1} for protonation at the most basic site in 2-methylphenol (the 4-position), and a similar situation applies to the calculated value of -112.0 J mol^{-1} K^{-1} for protonation at the 2-position in 4-methylphenol. With respect to protonation at the 4-position in the 3-methylphenol, the calculations suggest a value of -120.1 J mol^{-1} K^{-1}. This value deviates significantly from the value obtained from considerations of symmetry changes and also from the values for protonation at the most basic sites in the 2- and 4-methylphenols.

In terms of structural changes, a $-\Delta_r S°$ value that is close to the absolute value of the entropy of the free proton in the gas phase indicates that the entropy of the molecule is not significantly changed upon protonation. Such a situation applies to furan and phenol as indicated by the results in Table 5. In addition, the G3(MP2) calculations for protonation at the most basic sites in furan and phenol indicate that the entropy of the protonated species (MH$^+$) is somewhat larger than that of the molecule (M), in line with a number of observations for protonation of aromatic molecules.[29] For the methylphenols, a less clear-cut picture emerges with respect to the calculated changes in the entropy upon protonation. For 2-methylphenol, the calculations predict an increase in entropy of the species upon protonation at the 4-position, whereas they suggest that protonation at the most basic site in 3- and 4-methylphenol results in a decrease in entropy. To examine whether similar results are obtained by other types of theoretical methods, a few DFT calculations were performed with the B3LYP hybrid method and the 6-31G(d) basis set.[21] For phenol, the DFT and G3(MP2) calculations give essentially the same entropy change for protonation at the most basic site. For toluene the DFT calculations lead to a $\Delta_r S°$ value (-103.6 J mol^{-1} K^{-1}) for protonation at the 4-position that is somewhat higher than the G3(MP2) value. The DFT value for the entropy change upon protonation at the 4-position in 2-methylphenol (-104.4 J mol^{-1} K^{-1}) is also very close to the G3(M2) result (-104.1 J mol^{-1} K^{-1}). A distinct situation applies to protonation at the 4-position in 3-methylphenol. For this isomer, the DFT calculation give a $T\Delta_r S°$ value of -106.9 J mol^{-1} K^{-1} for protonation at the 4-position, whereas the G3(MP2) procedure yielded a value of -120.1 J mol^{-1} K^{-1}. The opposite holds for the entropy change upon protonation at the 2-position in 4-methylphenol in the sense that the DFT calculations predict a $T\Delta_r S°$ value of -120.2 J mol^{-1} K^{-1} that is significantly lower than the G3(MP2) result (-112.0 J mol^{-1} K^{-1}).

The inconsistencies in the different calculations of the protonation entropies of toluene and the methylphenols are likely to be associated with difficulties in the determination of the frequency for the hindered rotation involving the methyl group. The hindered rotation of the methyl group in toluene is known to be associated with a low frequency[46] as manifested also in the present G3(MP2) and DFT calculations.[47] For 3-methylphenol, the former calculations give a particularly low vibrational frequency for the hindered rotation involving the methyl group, whereas the DFT calculation of the neutral 3-methylphenol predicts a higher frequency for this mode. A more detailed analysis, however, of the calculation of the frequencies of the hindered rotation in the methylphenols is not within the scope of the present study. In addition, it should be noted that the absence of reported values for the 2-, 3-, and 4-methylphenols hampers a comparison between theory and experiment. In conclusion, the difficulties associated with obtaining a consistent picture for the calculations of the entropy of protonation warrant further studies.

Conclusions

The present study shows that the average literature value for the proton affinity of furan of 803 kJ mol^{-1} is too low. It is recommended to alter the value to 812 kJ mol^{-1} in keeping with the experimental results obtained in this study and the outcome of the G3(MP2) calculations. The experimental proton affinities of the methylphenols and methylanisoles reveal that for both series of compounds the 3-isomer is more basic than the 2-isomer, which in turn is more basic than the 4-isomer. The results of the G3(MP3) calculations of the proton affinity of the most basic site within a methylphenol are in good agreement with the experimental values. The calculations reveal that the 4-position is the most basic site of the 2- and 3-methylphenols, whereas the 2- and 4-position 4-methylphenols are equally basic. The replacement of the phenolic hydrogen with a methyl group in the methylphenols lead to an increase in the proton affinity of about 20 kJ mol^{-1}, irrespective of the position of the methyl group on the aromatic ring.

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(47) Supporting Information is available upon request.