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The proton affinities of saturated and unsaturated heterocyclic molecules

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Dedicated to the memory of Chava Lifshitz, an inspired scientist and an inspiring colleague.

Abstract

The proton affinities derived from G3-calculations of 23 five-membered ring heteroaromatic molecules agree well with the experimentally determined values available in the literature. The calculated local proton affinities show that the principal site of protonation of the heteroaromatic compounds examined is an atom of the ring, carbon when there is only one heteroatom in the ring, and nitrogen where there are two or more heteroatoms. The experimental proton affinities of non-aromatic cyclic ethers, amines and thioethers are also in excellent agreement with the calculated values, with two exceptions (oxetane, *N*-methylazetidine). The literature proton affinities of the four simple cyclic ethers, oxetane, tetrahydrofuran, tetrahydropyran and oxepane were confirmed by Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry, in order to examine the disagreement between the values predicted by extrapolation or additivity for tetrahydrofuran and tetrahydropyran and those determined by experiment and by calculation. The proton affinity differences between the pairs tetrahydropyran/1,4-dioxane, piperidine/morpholine and related compounds show that introduction of an additional oxygen atom in the ring considerably lowers the basicity.

Keywords: Proton affinity; Heteroaromatic compound; Cyclic ether; G3 calculation; Fourier Transform Ion Cyclotron Resonance mass spectrometry

1. Introduction

Enthalpies of formation and proton affinities are important thermodynamic quantities that can be derived from a variety of experimental measurements. Modern composite computational methods provide the means to reliably estimate the same quantities with an accuracy that often rivals that of experiment. In addition, these methods can provide information to complement results obtained experimentally and to examine problems that are not easily approached directly, such as site-specific proton affinities. A case in point is the protonation of unsaturated molecules, which often can take place at more than one position. Computational studies can provide a reliable estimate of the proton affinity of the molecule [1–7] as well as a measure of the thermodynamic difference between the various possible points of attachment of the proton [8–13]. An example is the protonation of pyridine and aniline, which in both cases could take place on nitrogen or on any of the carbon atoms. The proton affinities of the two molecules can be measured as well as calculated, with excellent correspondence. The calculations provide the additional information that it is more than 200 kJ mol^{-1} more favorable to protonate pyridine on nitrogen than on carbon, whereas it is slightly (4 kJ mol^{-1}) more favorable for aniline to be protonated on C4 than on nitrogen [14–24]. Furthermore, systematic high-level computational studies can provide internally consistent results that make it possible to discover systematic trends in the properties of a series of compounds, and results that support contested experimental observations or, occasionally, that suggest reexamination of experimental data.

The present paper examines the proton affinities of two sets of heterocyclic compounds, five-membered ring heteroaromatic

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molecules, and cyclic ethers, amines and thioethers. The purpose is to examine the agreement between experimentally obtained and calculated values, to determine the preferred site(s) of protonation, to reexamine contested experimental proton affinities, and to study the influence of ring size and additional heteroatoms on the proton affinities. The main body of results are derived from G3-calculations [25], complemented by FT-ICR redeterminations of a number of critical proton affinities of cyclic ethers.

2. Methods

2.1. Computational studies

The 298 K proton affinities (PA) were derived from total energies calculated with the G3 composite ab initio method [25], slightly modified in that geometry optimization was performed at the MP2(full)/6–31 + G(d,p) level. The G3-type methods have been shown to yield accurate estimates of the thermochemical properties of neutral molecules and ions [7,26,27]. The energies (E) were obtained with the Gaussian 03 suite of programs [28] and the G3 enthalpies of formation were calculated as described previously [29]. Disregarding heat capacity differences between the molecules and the protonated molecules (these differences are often small [29]), $PA = E(M) - E(MH^+) + 5/2RT$. Proton affinities obtained in this manner from G3-energies may suffer from small systematic imperfections compared to G3 enthalpies of formation, in part because the calculation of the proton affinities does not benefit from the correction of residual error that application of the HLC brings about [7]. There is in turn an average difference of about 4 kJ mol^{-1} between proton affinities derived from the G3 total energies and from G3 enthalpies of formation.

A number of studies of the compounds included in the present investigation have concerned calculated proton affinities derived from computational results obtained at the MP2-level. These results nearly always agree with the results of G3-calculations (and with experiment) with regard to determining the more favored site of protonation of polyfunctional molecules, but the absolute PA values derived from calculation at this level are quite dependent on the choice of basis set, and the results can differ considerably from the experimental values [10,30].

2.2. FT-ICR studies

A Fourier Transform Ion Cyclotron Resonance Bruker Daltonics Apex II instrument was used to determine the experimental proton affinities as described previously [31]. The total pressure in the instrument was in most experiments (1–3) × 10^{-6} Pa as measured with an ionization gauge placed in a side arm of the main vacuum system. The ratio of the partial pressures of the ether and the reference base was varied from 1:1 to 1:2 or 2:1. The measured partial pressures were corrected for the sensitivity of the ionization gauge for the neutral species as described in the literature [32]. The ethers and the reference bases were all commercially available and used without further purification.

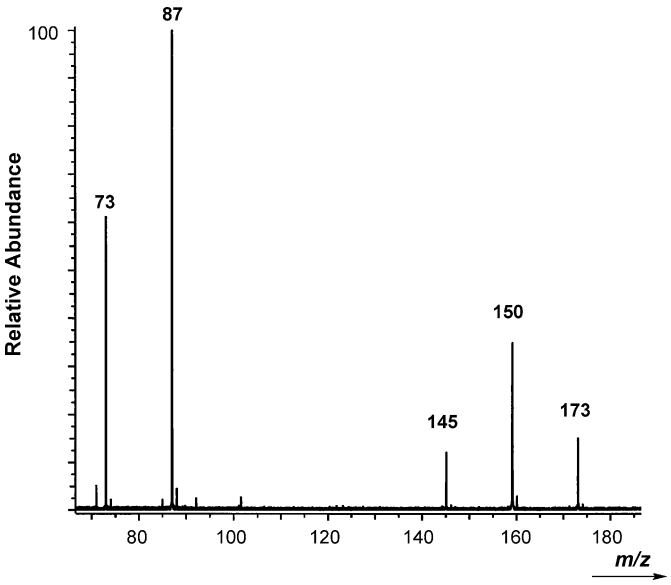


Fig. 1. Overall spectrum of the ions present in the FT-ICR cell after protonated tetrahydropyran has reacted with its own parent compound and tetrahydrofuran for a period of 10 s. The following ions are present: m/z 73 (protonated tetrahydrofuran), m/z 87 (protonated tetrahydropyran), m/z 143 (proton bound adduct of tetrahydrofuran), m/z 159 (proton bound adduct composed of tetrahydrofuran and tetrahydropyran) and 173 (proton bound adduct of tetrahydropyran). The corrected partial pressures were: P(tetrahydrofuran) = P(tetrahydropyran) = 0.8 × 10^{-6} Pa.

The determination of the proton affinities of the cyclic ethers involved electron ionization of the species of interest and the reference base (B) in the FT-ICR cell with 15–30 eV electrons; subsequent ion–molecule reactions led to the formation of the protonated ether and the protonated reference base. The proton transfer reaction was studied by ejecting all ions except the protonated reference base (BH^+) or the protonated ether (MH^+) from the ICR cell and monitoring the subsequent ion–molecule reactions for a period of 10–30 s. In addition to proton transfer, formation of proton bound adducts was observed even at the low pressure in the FT-ICR cell (see Fig. 1). In the experiments with oxetane, the protonated ether reacts with the neutral parent and with the reference bases to give stable proton bound adducts as well as ions that arise by competing losses of water, ethene or acetaldehyde from the adducts.

Irrespective of the occurrence of competing processes, the proton transfer reactions readily reach an equilibrium situation, as exemplified in Fig. 2 for the reaction between protonated tetrahydropyran and cyclopentanone.

The average values of the measured equilibrium constants given in Table 1 refer to Eq. (1); the difference in gas phase basicity, GB, between the selected reference base and the ether is derived from Eq. (2).

$$BH^+ + M \rightleftharpoons B + MH^+ \quad (1)$$

$$-RT\ln(K) = \Delta_r G^\circ = \Delta GB = GB(B) - GB(M) \quad (2)$$

In addition to the experiments summarized in Table 1, the equilibrium constant for the proton transfer reaction between tetrahydrofuran and tetrahydropyran (Eq. (3)) was measured to

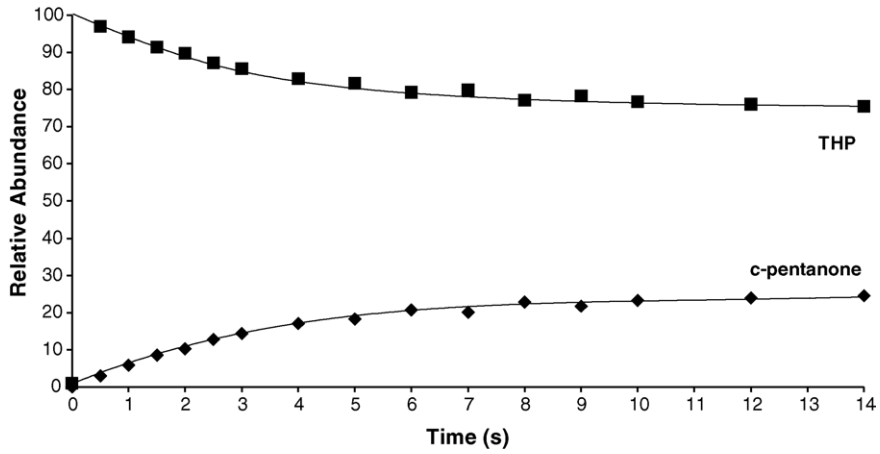


Fig. 2. Relative abundance of protonated tetrahydropyran and protonated cyclopentanone as a function of reaction time. The corrected partial pressures were: P(tetrahydropyran) = 1.0×10^{-6} Pa and P(cyclopentanone) = 1.2×10^{-6} Pa (see also text).

Table 1
Average values of the equilibrium constants for the proton transfer reactions, the difference in gas-phase basicity, Δ(ΔGB), between the species of interest, the gas-phase basicities (GB) and proton affinities (PA) of the cyclic ethers (T = 298 K)

Molecule	Reference base	GB (reference base)[a]	K[b]	Δ(ΔGB)[c]	GB_{exp}[d]	$PA_{exp}(1)$[e]	$PA_{exp}(2)$[f]
Oxetane	Butyronitrile	768	1.2 ± 0.3	−0.45	769	796	801
	Cyclobutanone	773	0.3 ± 0.2	3.0			
Tetrahydrofuran	Cyclopentanone	794	1.6 ± 0.2	−1.6	797	824	829
	Diethyl ether	801	0.2 ± 0.04	4.0			
Tetrahydropyran	Cyclopentanone	794	2.9 ± 1.3	−2.6	798	825	830
	Diethyl ether	801	0.54 ± 0.2	1.5			
Oxepane	3-Pentanone	807	0.36 ± 0.1	2.5	802	829	834
	Diethyl ether	801	0.7 ± 0.2	0.9			

[a] The values are in kJ mol^{-1} and taken from Ref. [37].
[b] Average values of 2–4 measurements.
[c] Δ(ΔGB) = Δ(GB) (reference) − Δ(GB) (compound).
[d] The value (in kJ mol^{-1}) for a given ether is the mean of the two series of measurements. The average uncertainty is ±8 kJ mol^{-1}.
[e] Estimated with a $T\Delta_r S^\circ$ term of −27.4 kJ mol^{-1} (see text and Ref. [37]).
[f] Estimated with a $T\Delta_r S^\circ$ term of −32 kJ mol^{-1} (see text).

be 0.74, which indicates a difference in gas-phase basicity of about 0.7 kJ mol^{-1} in favor of tetrahydropyran.

(3)

The proton affinity of the ethers can be derived from the measured gas phase basicity together with the entropy of protonation given in the literature; that is, $T\Delta_r S^\circ = -27.4$ kJ/mol at an assumed temperature of 298 K. Alternatively, the $T\Delta_r S^\circ$ term can be estimated from Eq. (4) in which σ(M) is the rotational symmetry number of the molecule, $\sigma(MH^+)$ is the symmetry number of the protonated species and $S^\circ(H^+)$ is the entropy of the free proton (108.95 J mol^{-1} K^{-1}).

$$\Delta_r S^\circ(M) = S^\circ(MH^+) - S^\circ(M) - S^\circ(H^+) \approx R \ln\left[\frac{\sigma(M)}{\sigma(MH^+)}\right] - S^\circ(H^+) \quad (4)$$

For the M and MH^+ species of the cyclic ethers, the symmetry numbers are the same, and the entropy of the protonation reaction will in turn be close to the entropy of the free proton in the gas phase. The value of the $T\Delta_r S^\circ$ term then becomes −32 kJ mol^{-1} (T = 298 K), which leads to slightly larger PA values (see Table 1) than those obtained with the $T\Delta_r S^\circ$ value given in the literature.

3. Results and discussion

3.1. Five-membered heteroaromatic compounds

The G3 proton affinities of the most basic site in the five-membered heteroaromatic molecules are in excellent agreement with those derived from experiment (Table 2). Protonation of those with only one heteroatom, furan, pyrrole and thiophene, occurs preferentially on carbon, in contrast to most other heteroaromatic compounds. Houriet et al. [33] used ICR results to demonstrate that the site of protonation of furan was C2, the carbon atom adjacent to the heteroatom, and similar results were

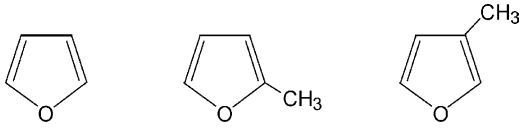
Table 2
Enthalpies of formation, proton affinities and sites of protonation for five-membered heteroaromatic molecules (T = 298 K)[a]

Molecule	$\Delta_f H^\circ$(M)	$\Delta_f H^\circ$(MH^+)	1	2	3	4	5	Exp.
Furan	−33	686	699	815	771	771	815	812[b]
2-Methylfuran	−78	596	722	824	819	796	861	866
3-Methylfuran	−66	617	719	851	774	792	835	854
Pyrrole	113	772	797	874	855	855	874	875
Thiophene	118	836	733	815	784	784	815	815
Pyrazole	183	822	761	896	759	805	764	894
3-Aminopyrazole[c]	187	796	828	925	736	875	792	922[c,d]
4-Aminopyrazole	213	832	816	915	841	791	869	908[e]
5-Aminopyrazole[c]	198	796	800	936	786	902	756	922[c,f]
3-Methylpyrazole	144	761	791	917	763	833	784	906[c]
4-Methylpyrazole	153	776	788	911	788	810	797	907
5-Methylpyrazole	145	761	786	918	782	843	770	906[c]
N-Methylpyrazole	168	784	788	917	801	841	800	912
4-Fluoropyrazole	16	682	745	868	745	746	757	863
Imidazole	137	724	740	806	945	806	820	943
2-Methylimidazole	93	658	768	814	968	834	862	963
4-Methylimidazole[c]	97	669	765	832	961	809	857	953[c]
5-Methylimidazole[c]	99	669	762	848	964	848	828	953[c]
N-Methylimidazole	128	695	766	838	966	840	849	960
Oxazole	−13	644	652	735	876	757	729	876
Isoxazole	84	771	678	846	673	730	628	849
Thiazole	154	785	685	754	902	767	744	904
Isothiazole	162	816	701	880	719	745	701	–[g]
1H-1,2,3-triazole	272		–[h]	843	894	–[h]	713	879[i]
2H-1,2,3-triazole	255	911[j]	827	722	827	713	723	879[i]
1,2,4-Triazole	199	844	699	844	697	888	691	886

[a] Values obtained with the G3 method. The enthalpy of formation of the MH^+ ions refer to the species formed by protonation at the most basic site. Experimental proton affinities from Ref. [37] unless otherwise noted.
[b] Value from Refs. [13,31].
[c] 3- and 5-substituted pyrazoles normally cannot be distinguished experimentally because of tautomerization, nor can 4- and 5-substituted imidazoles.
[d] PA of the NH_2 group: 883 kJ mol^{-1}.
[e] PA of the NH_2 group: 874 kJ mol^{-1}.
[f] PA of the NH_2 group: 826 kJ mol^{-1}.
[g] Experimental value not available.
[h] The calculations suggest that protonation in this position would result in ring opening and possibly decomposition.
[i] See the discussion in the text.
[j] 1,2,3-Triazolium with hydrogens on N1 and N3; the $\Delta_f H^\circ$ value of the isomer with hydrogens on N1 and N2 is 961 kJ mol^{-1}.

obtained for pyrrole [11,34,35] and thiophene [34]. In terms of values, the G3 proton affinity of pyrrole (874 kJ mol^{-1}) is essentially identical to the experimental value (875 kJ mol^{-1}) and a comparable result is obtained for thiophene; that is, a proton affinity of 815 kJ mol^{-1} is obtained by theory as well as experiment.

The protonation of furan and substituted furans has been studied by several authors [10,13,33,34,36]. The calculated proton affinity of furan itself (815 kJ mol^{-1}) is slightly higher than that given in the NIST tables (803 kJ mol^{-1}) [37], but agrees well with the value determined by Houriet [33] and confirmed recently (812 kJ mol^{-1}) [13]. The introduction of methyl groups increases the proton affinity by 40–50 kJ mol^{-1} (Table 2), but the preferred site of protonation continues to be one of the carbon atoms adjacent to the ring oxygen, C5 in 2-methylfuran (calc. 861 kJ mol^{-1}) and C2 in 3-methylfuran (calc. 851 kJ mol^{-1}) [36], in good agreement with expectation based on conventional resonance considerations. The calculations also reveal that the methyl group enhances the proton affinity of the oxygen atom in furan (699 kJ mol^{-1}) with 23 kJ mol^{-1} if situated at the 2-position and somewhat less (20 kJ mol^{-1}) if present at the 3-position (Table 2).



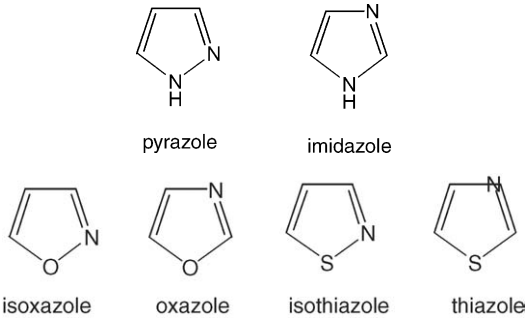
furan 2-methylfuran 3-methylfuran

The introduction of an alkyl group in pyrrole and thiophene leads also to an increase in basicity as exemplified by the proton affinity of 2-methylthiophene (859 kJ mol^{-1} [37]) which is 44 kJ mol^{-1} higher than of thiophene itself; it reflects that alkyl groups particularly stabilize the carbocations formed by protonation of a ring carbon atom. Alkyl substituents tend to stabilize nitrogen protonated heteroaromatic compounds to a smaller extent e.g. the proton affinity of pyridine is 930 kJ mol^{-1} and of 2-methylpyridine 949 kJ mol^{-1} [37].

The five-membered heteroaromatic compounds with more than one heteroatom all possess a pyridine-type nitrogen atom. The calculations show that this atom is the more basic site in the oxazoles, thiazoles, diazoles and triazoles and that the energy difference between protonation at the pyridine-type nitrogen and

the other ring sites is in excess of 100 kJ mol^{-1} in most cases (Table 2). These compounds are considerably more basic than furan, pyrrole and thiophene, which reflects that protonation on pyridine-type ring nitrogen atoms does not disrupt the aromatic system. They are, however, less basic than pyridine, with the exception of imidazole (PA = 943 kJ mol^{-1}).

The thermochemical properties of substituted pyrazoles and imidazoles have been studied extensively [38–43], and the experimentally derived proton affinities in most cases agree well with our calculated values (Table 2). For the parent compounds, the G3 calculations result in a PA value for pyrazole (896 kJ mol^{-1}) that is indistinguishable from the experimental value of 894 kJ mol^{-1} and for imidazole the G3 value of 945 kJ mol^{-1} is also very close to that given in Ref. [37] (943 kJ mol^{-1}). The lower proton affinity of pyrazole than of imidazole has been ascribed to electrostatic interactions between the lone-pair at N2 and the pyrrole-type nitrogen [44]. A comparable effect may be held responsible for the result that the proton affinity of isoxazole (calc. 846 kJ mol^{-1}) is about 30 kJ mol^{-1} lower than the value for oxazole (calc. 876 kJ mol^{-1}). With respect to the sulfur analogs, an experimental proton affinity has not been reported for the isothiazole isomer. The G3 calculations, however, are in line with results for the related oxygen species as the proton affinity of the nitrogen in isothiazole (880 kJ mol^{-1}) is predicted to be 22 kJ mol^{-1} lower than the value for the same site in thiazole.



The introduction of methyl substituents on the ring increases the proton affinities relative to the parent pyrazole and imidazole compounds, but not nearly to the same degree as was observed for the furans. The calculated proton affinity of the 3- and 5-methylpyrazoles is 10–12 kJ mol^{-1} lower than the reported experimental value. According to the calculations the presence of a methyl group on a ring carbon leads to an increase in the proton affinity of the pyrrole-type nitrogen; for example, the proton affinity of the NH position in pyrazole is 761 and 791 kJ mol^{-1} in 3-methylpyrazole. The effect of the methyl group, however, is nearly independent of its position with respect to the NH site. Similar results are obtained for the protonation at the NH position in the methyl substituted imidazoles (Table 2).

Aminopyrazoles are not very much more basic than pyrazole, consistent with the computational result that the N2 position of the ring is the preferred site of protonation in all examined pyrazoles, regardless of substitution. Protonation at the NH_2 group is more favored than at a ring carbon or the NH position for 3- and 4-aminopyrazole (see Table 2, footnotes d and e), whereas the proton affinity of C4 (902 kJ mol^{-1}) is indicated to be considerably higher than of the NH_2 group (826 kJ mol^{-1}) in 5-aminopyrazole.

The protonation of 1,2,3-triazole is an unusual case. In the gas phase, 2H-1,2,3-triazole is the more stable tautomer of this compound (see Eq. (5)) [45]; we find that the G3 enthalpy of formation is 17 kJ mol^{-1} lower than that of the 1H-tautomer. However, the more stable isomer of protonated 1,2,3-triazole is the N3-protonated 1H-1,2,3-triazole, that is, tautomerization accompanies protonation. It follows that the symmetry number of the neutral is the same as that of the protonated species (Eq. (4)) [46,47]; the proton affinity calculated from the electronic energies of the more stable forms of neutral and protonated 1,2,3-triazole agrees well with that included in the NIST tables [37]. With regard to 1,2,4-triazole, our calculated proton affinities (Table 2) suggest that protonation will involve N4, possibly in contradiction to the assumptions of the NIST table authors [37].

(5)

3.2. Alicyclic compounds

The site of protonation is in most cases not an issue when non-aromatic heterocyclic compounds are considered. However, the proton affinities of some of these compounds vary with ring size in an unexpected manner, and with the presence of an additional heteroatom in the ring.

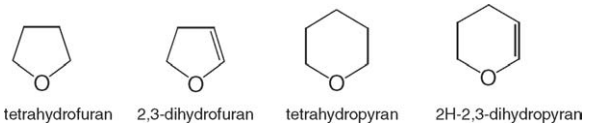
Aubry and Holmes [48] pointed out that the magnitude of the proton affinity of open-chain compounds appears to be related to the size (number of atoms) of the molecule in question [49]. Their results suggest that the proton affinity should increase along a homologous series, approximately linearly related to 1/*n*, where *n* is the number of atoms (see also Ref. [50]). Examining such a relationship for cyclic ethers, these authors noted that two of these, tetrahydrofuran and tetrahydropyran, have about the same literature proton affinity [37] (see Table 3), whereas the expected relationship [48] would suggest a proton affinity difference of approx. 10 kJ mol^{-1}. This led Aubry and Holmes to suggest that the experimental values should be reexamined, and we have now used FT-ICR measurements to (re)determine the proton affinities of the four simple cyclic ethers, oxetane, tetrahydrofuran, tetrahydropyran, and oxepane, and found good agreement with the previous literature values (Table 3). In particular, we find that the PA of tetrahydrofuran and tetrahydropyran are within 1 kJ mol^{-1} of each other; also the calculated proton affinities of these two molecules are within 1 kJ mol^{-1} of each other.

Another pair of five- and six-membered cyclic ethers, 2,3-dihydrofuran and 2H-3,4-dihydropyran, exhibit similar behavior. The literature proton affinities of these two compounds are within 1 kJ mol^{-1} of each other [37,51,52], and the very small difference is also in this case corroborated by the computational results (Table 3).

Table 3
Enthalpies of formation (G3 values) and proton affinities of simple cyclic ethers and open-chain analogs (T = 298 K)

	$\Delta_f H^\circ$(M)	$\Delta_f H^\circ(MH^+)$	G3	Exp[a]
Oxetane	−81	634	819	801[a], 819[b], 796[c]
Tetrahydrofuran	−184	521	829	822[a], 824[c]
2-Methyltetrahydrofuran	−225	468	841	841
Tetrahydropyran	−225	480	829	823[a], 825[c]
Oxepane	−228	467	840	834[a], 829[c]
1,4-Dioxane	−320	415	799	797
Cyclohexanone	−231	462	841	841
Tetrahydropyran-4-one	−329	381	823	–
2,3-Dihydrofuran	−76	591	866	867
2H-3,4-Dihydropyran	−119	549	866	866
2,3-Dihydro-1,4-dioxin	−217	495	822	824
Methyl ethyl ether	−221	502	811	809
Methyl propyl ether	−241	476	817	815
Diethylether	−256	451	827	828
Methyl butyl ether	−262	452	821	820
Ethyl propyl ether	−276	426	832	–
DME (aaa)[d]	−350	383	801	–
DME (agg)[d]	−348	362	822	–
DME (aga)[e]	−349	334	849	858[a], 846[f]

[a] Taken from Ref. [37] unless otherwise indicated.
[b] From Ref. [53].
[c] This work.
[d] No hydrogen bond.
[e] Internal hydrogen bond.



Even though the introduction of an additional ring methylene group into tetrahydrofuran and dihydrofuran is not accompanied by an increase of the proton affinity, the introduction of exocyclic substituents does not have similarly unusual consequences: the proton affinity of 2-methyltetrahydrofuran is 20 kJ mol^{-1} higher than the proton affinity of tetrahydrofuran. This difference agrees well with the change observed when additional substituents are introduced at the α-carbon atoms of open-chain ethers, as illustrated by the PA differences between methyl ethyl ether, diethyl ether, and methyl propyl ether (Table 3): an additional methyl group at the α-carbon atom increases the proton affinity by approx. 20 kJ mol^{-1}, whereas an additional methylene group further removed from the oxygen atom increases the proton affinity by 5–6 kJ mol^{-1}.

The unusual behavior is possibly a peculiarity of five- and six-membered cyclic ethers, possibly the chance accumulation of small effects. The reported experimental proton affinities of the corresponding pairs of saturated cyclic amines and cyclic thioethers (Table 4) are in line with additivity expectations; the six-membered ring compounds are slightly stronger bases than their lower homologs and the differences are of the same order of magnitude as found for the corresponding open-chain compounds, in good agreement with the proton affinities determined by calculation. Furthermore, it may well be that the analogous behavior of the two pairs of cyclic ethers does not reflect that the same effects are behind the slightly unusual observations; the two unsaturated ethers are protonated on carbon [51,52], whereas the two saturated ethers are protonated on oxygen.

One further problem associated with the examination of systematic trends in the proton affinities of cyclic ethers is that the proton affinity of oxetane is not securely established. The value given in the NIST tables [37] is 801 kJ mol^{-1} as based upon a gas-phase basicity of 774 kJ mol^{-1}. However, the report by Bordejé et al. [53] suggests a considerably higher proton affinity, about 819 kJ mol^{-1}. The results of our FT-ICR experiments are in reasonable agreement with the value in the NIST tables (Table 3) if the $T\Delta_r S^\circ$ term is taken to be −27.4 kJ mol^{-1}

Table 4
Enthalpies of formation (G3 values) and proton affinities of simple cyclic amines and sulfides (T = 298 K)

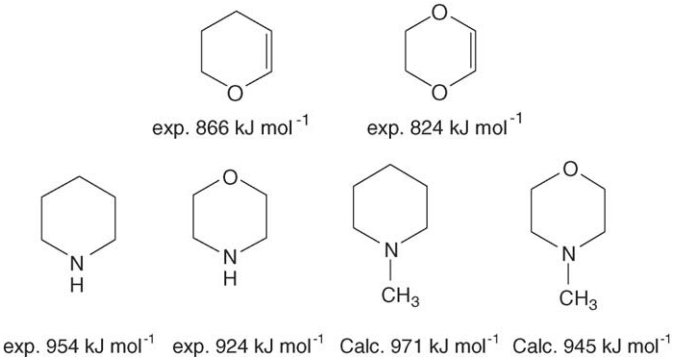
	$\Delta_f H^\circ$(M)	$\Delta_f H^\circ(MH^+)$	G3	Exp[a]
Azetidine	102	694	942	943
N-Methylazetidine	87	661	959	883[b]
Pyrrolidine	−1	580	952	948
N-Methylpyrrolidine	−15	554	964	966
Piperidine	−47	531	955	954
N-Methylpiperidine	−60	502	971	971
4-Trifluoromethylpiperidine[c]	–	–		925
Morpholine (prot on N)	−146	461	926	924
(Prot on O)		566	823	
N-Methylmorpholine (N)	−159	429	945	
Piperazine	31	615	949	944
Thietane	65	767	832	835
Tetrahydrothiophene	−31	655	848	849
Tetrahydrothiapyran	−62	620	852	856

[a] Values taken from Ref. [37].
[b] Presumably misprint in Ref. [37]; see text.
[c] Enthalpies of formation were not obtained.

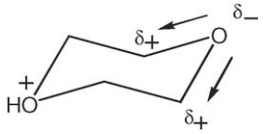
(Table 1). We are unable to determine the reason for the discrepancies between the different experimental determinations of the gas-phase basicity of this compound, but we note that a number of reactions compete actively with proton transfer, which may introduce a significant source of error. Our computational results and those of Bordejé et al. [53] would suggest that the present experimental value represents a lower limit to the true proton affinity of oxetane. For oxepane, our experimental proton affinity agrees reasonably well with the literature value [37] and with the value obtained computationally (Table 3).

We note in passing that the proton affinity of *N*-methylazetidine listed in the NIST tables [37] is in all likelihood a typographical error (cf. Table 4). The value provided is 61 kJ mol^{-1} lower than that of the parent molecule, azetidine, in conspicuous contrast with the expectation that the introduction of an *N*-methyl group would increase the basicity somewhat [49]. The literature reference provided in the NIST tables [37] does not provide data by which to assess the proton affinity of *N*-methylazetidine [54].

The proton affinities of cyclic ethers exhibit an additional interesting feature: the replacement of a CH_2 group by an oxygen atom in position 4 of saturated six-membered heterocycles is accompanied by a lowering of the proton affinity by up to 40 kJ mol^{-1} (Tables 3 and 4). Tetrahydropyran/1,4-dioxane, ΔPA 26 kJ mol^{-1} (calc. 30 kJ mol^{-1}); 2H-3,4-dihydropyran/2,3-dihydro-1,4-dioxin, ΔPA 42 kJ mol^{-1} (calc. 44 kJ mol^{-1}); piperidine/morpholine, ΔPA 30 kJ mol^{-1} (calc. 29 kJ mol^{-1}), *N*-methylpiperidine/*N*-methylmorpholine, ΔPA 26 kJ mol^{-1} (calc.). The cyclohexanone/tetrahydropyran-4-one pair exhibits a similar difference, ΔPA 18 kJ mol^{-1} (calc.). By contrast, replacement of the 4-CH_2 group by an NH group lowers the proton affinity by only 5–10 kJ mol^{-1} (Table 4). The calculated structures of these molecules and their protonated forms show that they all adopt chair-type conformations and that the acidic proton occupies an equatorial position [55].



This lowering of the basicity upon introduction of a ring oxygen also influences the properties of these compounds in solution and is sufficiently widely recognized to be the subject of text-book problems [56]. One possible reason for the gas-phase difference is that the protonated species with oxygen in the 4-position suffers destabilizing interactions between the positive charge and the combined effects of the two remote C–O bond dipoles. This agrees well with the observation that the less electronegative NH group in position 4 exerts a much smaller influence on the proton affinity (the difference is considerably larger for the piperidine/morpholine pair than for the piperidine/piperazine pair).



The difference between the proton affinity of piperidine and 4-trifluoromethylpiperidine affords an additional illustration that the interaction between the charge and a remote bond dipole can significantly influence the stability of the protonated molecule and in turn the proton affinity of the neutral species. Introduction of the 4-trifluoromethyl group causes a 30 kJ mol^{-1} reduction of the piperidine proton affinity (Table 4).

Our interpretation derives support from a comparison with the open-chain compounds that correspond closely to the tetrahydropyran/1,4-dioxane pair, butyl methyl ether and ethylene glycol dimethyl ether (dimethoxyethane, DME). The calculations demonstrate that the proton affinity of the latter is quite dependent upon conformation [57], even when only those rotamers are considered that cannot form intramolecular hydrogen bonds (see Fig. 3). DME in the anti-anti-anti conformation has a calculated proton affinity of 801 kJ mol^{-1}, 20 kJ mol^{-1} lower than that of butyl methyl ether, whose proton affinity we find not to be particularly dependent upon conformation [55]. By contrast, the calculated proton affinity of DME in the anti-gauche-gauche conformation is 822 kJ mol^{-1}. In this conformation DME would appear to resemble 1,4-dioxane (in which by necessity the two oxygen atoms must be gauche), but one of the two C–O dipoles (the O–CH_3 bond) points away from the positive charge, and the unfavorable electrostatic interactions are therefore less pronounced. The DME conformations that allow intramolecular hydrogen bonding have yet higher calculated proton affinity, consistent with the recently measured value of 846 kJ mol^{-1} [58]. We note that the remarkable proton affinity difference between those gauche and anti DME conformers that do not exhibit intramolecular hydrogen bonding reflects differences between the enthalpies of formation of the protonated species almost entirely; the difference between the enthalpies of formation of the various conformers of neutral DME is very small.

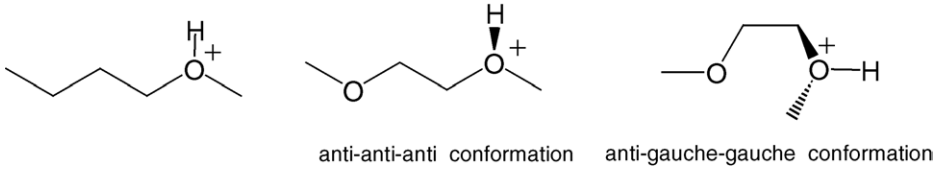


Fig. 3. Schematic drawings of protonated methyl butyl ether and protonated dimethoxyethane in the indicated conformations.

4. Conclusions

The G3 proton affinities of an extended series of five-membered heteroaromatic molecules are in excellent agreement with the experimental values. The calculations confirm that heteroaromatic molecules with a single nitrogen, oxygen or sulfur atom protonate preferentially on a carbon atom adjacent to the heteroatom. Five-membered heteroaromatic molecules with more than one heteroatom and a pyridine-type nitrogen tend to protonate on this site even though the proton affinity of the pyridine-type nitrogen depends on whether it is bonded to directly to another heteroatom (as in isoxazole) or whether is located at the three position (as in oxazole). The presence of a methyl group in the ring of the five-membered heteroaromatic molecules changes the proton affinity of the species without altering the thermochemically preferred site of protonation. The G3 proton affinities of the alicyclic oxygen, nitrogen and sulfur compounds are in agreement with the experimental values with the exception of oxetane whose proton affinity still has to be determined accurately by experiment. In particular, the present study confirms that the proton affinities of tetrahydrofuran and tetrahydropyran are essentially the same. The reduction of the proton affinity observed when oxygen atoms are introduced into the saturated heterocyclic bases can be interpreted in terms of electrostatic effects.

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