Theoretical Study of the Substituent Effects on the S−H Bond Dissociation Energy and Ionization Energy of 3-Pyridinethiol: Prediction of Novel Antioxidant

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The S−H bond dissociation enthalpies [BDE(S−H)] of a set of 5-X- and 6-X-3-pyridinethiols (X = F, Cl, CH_3, OCH_3, NH_2, $N(CH_3)_2$, CF_3, CN, and NO_2) have been computed using the density functional theory based (RO)B3LYP procedure with 6-311++G(2df,2p) basis set. The effects of substituents on the BDE(S−H), proton affinity of the pyridinethiol anion [$PA(S^-)$] and ionization energy (IE) are analyzed and their correlations with Hammett's substituent constants are examined. Subsequently, a series of 6-substituted 3-pyridinethiols have been explored to find out their antioxidant potentials. Finally, a number of 3-pyridinethiol based compounds are theoretically proposed as novel antioxidants.

1. Introduction

Recently there has been great interest in the role of free radicals, especially oxygen and nitrogen centered radicals, in the various fields of chemistry and biology.[1] Phenols are the most widely used antioxidants. The bond dissociation enthalpy (BDE) is one of the most important properties of the antioxidants. Because chain-breaking antioxidants (like substituted phenols) are known to inhibit the chain propagation of peroxyl radicals (ROO•) by transferring their phenolic H-atom (commonly known as hydrogen-atom-transfer (HAT) mechanism) to the radical:

$$ROO^\bullet + ArOH \rightarrow ROOH + Ar\,O^\bullet \qquad (I)$$

The BDE thus influences the effectiveness of the hydrogen-atom-transfer reaction from the antioxidant molecule to the reactive radical intermediates such as hydroxyl, alkoxyl, peroxyl and hydroperoxyl radicals formed during the degradation reactions.[2] Thus, BDE of the phenolic O−H bond is crucial in determining the antioxidant efficacy of a phenolic compound.[3] Phenols with lower O−H BDEs are better antioxidants. We should mention here that the BDE is one of the important factors to be considered for an antioxidant, but there are other conditions that also need to be satisfied before a compound can be taken as an effective and safe antioxidant. Recently, Mulder et al.[4] have clearly pointed out these conditions, like no direct reaction with molecular oxygen, higher ionization energy (IE), radical stability against oxygen, etc. Nevertheless, the BDE, perhaps, is the most important antioxidant index to start with when an antioxidant compound is being designed. Bond dissociation enthalpies can also be considered to obtain quantitative measures of the stabilities of the radicals formed. Although it has been pointed out that the radical stability derived from isodesmic reactions may be a better choice.[5]

Sulfur-centered radicals are also very important to chemistry because of their role in diverse fields such as atmospheric chemistry, biochemistry, organic synthesis, and coal and oil industry.[6] Generally, the antioxidant capacity of thiol compounds is due to the weaker S−H bond. Actually, a sulfur atom can easily accommodate the loss of a single electron resulting from the homolytic cleavage of the S−H bond and provides extra stability to the generated radical species.[7] In addition the lifetime of sulfur radical species thus generated, i.e., a thiyl radical, may be significantly longer than many other radicals.[1] Although BDE is a very important property to understand chemical reactivity and also to design new molecules for specific chemical purposes, the number of available experimental BDEs is still very small, especially for larger organic molecules.[8] Fortunately, reliable BDEs for different types of bonds can now be theoretically calculated within chemical accuracy by using quantum chemical methods. Therefore, theoretical calculations can be used as a tool for predicting the antioxidant property of a compound and also for designing a new potential antioxidant. The ionization energy (IE) of a compound is another important property to determine its effectiveness as an antioxidant,[9] because the lower the IE value of an antioxidant, the more it will be reactive with molecular oxygen through a proton-coupled-electron-transfer reaction.[4] Thus the IE of the antioxidant compound should be high for greater chemical stability in oxygen-rich condition.[4]

Recently, Pratt et al.[10] have reported some novel antioxidants based on 3-pyridinols and 5-pyrimidinols. Their goal was to find a novel class of antioxidants which has a higher inhibition rate constant than that of α-tocopherol. It has been observed from their study that insertion of a nitrogen atom in the benzene ring does not change the BDE of the O−H bond of phenol significantly, but it greatly enhances the IE value of the resulting compound. Subsequently, the substituent effects on BDE(O−H) and IE values for 3-pyridinols were examined to design a molecule with better antioxidant properties.

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In fact, in some cases, the behavior of the aromatic thiophenol is known to be similar to that of phenol. For example, thiophenols have also been used as radical scavengers and antioxidants for a long time, and they are considered good radical scavengers and antioxidants.[6,11] We therefore felt that it would be interesting to study the effect of nitrogen atom incorporation in the phenyl ring of thiophenol (leading to pyridinethiol) on BDE(S−H) and IE values. This effect has not yet been studied for pyridinethiol and thus our study can be useful for understanding the chemistry of pyridinethiols. We have also studied the substituent effects on BDE(S−H) and IE values of pyridinethiols to design potential antioxidants that would have better inhibition property and stability than thiophenol or other widely used antioxidants, like phenol and α-tocopherol. The gas-phase acidity of pyridinethiol has been computed and compared with thiophenol to evaluate the effect of nitrogen atom incorporation in phenolic ring on acidity. Moreover, we have extended our study to examine structure property correlations, such as relation between BDE(S−H) and Hammett's parameters. Furthermore, understanding the behavior of this sulfur radical species can help to rationalize the chemistry of the related compounds with sulfur and oxygen radical species. This work may also encourage synthetic organic chemists to prepare different substituted pyridinethiol and study their chemical behavior.

2. Computational Details

Model density functional theory (DFT) calculations [namely (RO)B3LYP/6-311++G(2df,2p)//6-311G(d,p)] were used for estimating BDE values. The model was originally proposed by DiLabio et al.[12] and later it was extended and extensively used in our group to estimate reliable BDE values for various types of bonds, such as BDE(X−H), (X = C, O, S, and P).[13−16] We chose to use the same model chemistry [(RO)B3LYP] here, because the reliability and consistency of this method has been demonstrated amply from those earlier calculations. The geometries of a set of substituted pyridinethiol (mentioned as X−C$_5$NH$_3$-SH) were fully optimized first by using the B3LYP method in conjunction with the 6-311G(d,p) basis set. The UB3LYP procedure was used for the geometry optimization of the substituted pyridinethiol radicals. The harmonic vibrational frequencies were then computed at the optimized geometry using the same level of theory. A thermal correction to enthalpy was obtained at this level. Single point B3LYP calculations were then carried out with an extended basis set of 6-311++(2df,-2p). The restricted open shell formalism (ROB3LYP) with the large basis set was applied for the open shell radicals at the UB3LYP/6-311G(d,p) optimized geometry. The energies obtained from the extended basis set calculations were used for enthalpy estimation. All calculations were performed by using GAUSSIAN-03 suite of programs.[17]

The homolytic S−H bond dissociation enthalpy [BDE(S−H)] value at 298.15 K for the molecule X−C$_5$NH$_3$−SH was estimated from the expression

$$\text{BDE(S−H)} = H(\text{X−C}_5\text{NH}_3\text{−S}^\bullet) + H(\text{H}^\bullet) - H(\text{X−C}_5\text{NH}_3\text{−SH}) \quad (1)$$

where H's are the enthalpies of different species at 298.15 K. The enthalpies were estimated from the usual expression: $H(298.15\ \text{K}) = E_0 + \text{ZPE} + H_{\text{trans}} + H_{\text{rot}} + H_{\text{vib}} + RT$. H_{trans}, H_{rot}, and H_{vib} are the translational, rotational, and vibrational contributions to enthalpy, respectively. The ZPE and H_{vib} were estimated from the unscaled vibrational frequencies, because

CHART 1
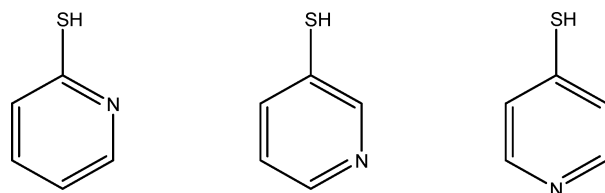
the scaling factor for the B3LYP/6-311G(d,p) method is close to unity (0.9877 for ZPE and 0.9679 for frequencies)[18] and also does not change the BDE values significantly.[13a] The enthalpy of the H-atom was estimated by taking its exact energy of −0.5 Hartree.

The adiabatic ionization energy (IE) of X−C$_5$NH$_3$−SH is defined as the amount of energy required to remove an electron from substituted 3-pyridinethiol. It was computed as the energy difference between its radical cation and the neutral molecule (eq 2). For both neutral molecule and its radical cation the

$$\text{IE} = \Delta E_0 = E_0(\text{X−C}_5\text{NH}_3\text{−SH}^{\bullet+}) - E_0(\text{X−C}_5\text{NH}_3\text{−SH}) \quad (2)$$

electronic energies and the unscaled zero point vibrational energies were taken at the B3LYP/6-311G(d,p) level for IE calculation. The unrestricted open shell method (UB3LYP) was applied for the radical cation species. The ZPE was added to the electronic energy to obtain E_0 at 0 K.

The PAs of the sulfur atom of substituted 3-pyridinethiol anion (X−C$_5$NH$_3$−S$^-$) at 298.15 K were estimated from eq 3.

$$\text{PA(S}^-) = H(\text{X−C}_5\text{NH}_3\text{−S}^-) + H(\text{H}^+) - H(\text{X−C}_5\text{NH}_3\text{−SH}) \quad (3)$$
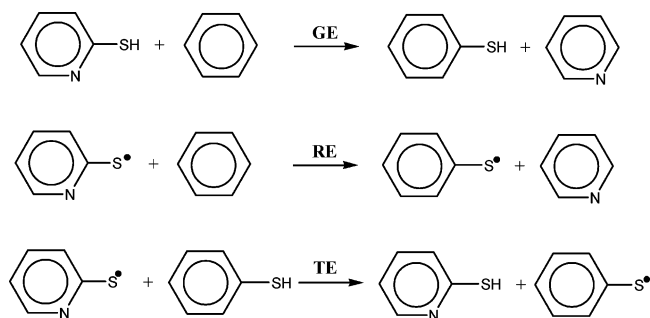
3. Results and Discussion

3.1. Bond Dissociation Enthalpies of 2-, 3-, and 4-Pyridinethiol. First, we have chosen the three compounds shown in Chart 1 to study the effect of nitrogen atom incorporation in the phenolic ring on the BDE(S−H) value. Nitrogen atom incorporation at ortho, meta, and para positions of the phenolic ring are considered to understand the effect of nitrogen atom incorporation at different positions on BDE(S−H). This knowledge will be useful later to measure their antioxidant activity.

Our (RO)B3LYP calculated BDE(S−H) values of 2-, 3-, and 4-pyridinethiol are 361.4, 333.0, and 349.8 kJ/mol, respectively. To the best of our knowledge, experimental BDE(S−H) values for these compounds are not yet reported. But our earlier study shows that the (RO)B3LYP method provides reliable BDE(S−H) values for various systems including thiophenol.[15] For example, our calculated BDE(S−H) value (332.6 kJ/mol)[15] of thiophenol is quite close to the most recent experimental value of 331 kJ/mol.[19] In this context, we like to point out that the reported experimental BDE(S−H) value for thiophenol varies within a wide range of (331−349) ± 8 kJ/mol.[19,20] In a very recent paper, Simoes et al.[21] have obtained a BDE(S−H) value of 347.2 kJ/mol for thiophenol at the CCSD(T) level. However, from the results of our earlier (RO)B3LYP calculations to estimate BDE values of different types of bonds including the S−H bond,[15] we believe that our calculated BDE values should be very close (within ±6.0 kJ/mol) to the exact values. To support the reliability of this procedure further, we calculated the BDE(C−H) of pyridine at the C$_4$-position. Our calculated BDE value of 468.4 kJ/mol is found to be quite close to the experimental data of 468.6 ± 8.4 kJ/mol.[22] In fact, our result is found to be much better than those obtained from the much
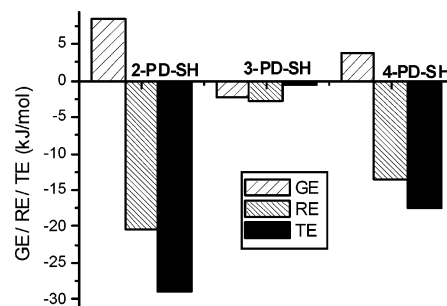
SCHEME 1

Figure 1. Plot of ground-state effect (GE), radical effect (RE) and total effect (TE = RE − GE) on BDE(S−H) for 2-, 3- and 4-pyridinethiol (PD-SH) as calculated from the isodesmic reaction shown in Scheme 1.

more expensive ab initio methods G3 (480.7 kJ/mol) and G3B3 (476.1 kJ/mol).[23]

It is clear from our results that the incorporation of nitrogen atom at the ortho and para positions of the phenolic ring increases the BDE(S−H) in comparison to thiophenol by an amount of 28.8 and 17.2 kJ/mol, respectively. On the other hand, incorporation of a nitrogen atom at the meta position enhances the BDE(S−H) value by only 0.4 kJ/mol. Similar observation was made by Pratt et al. in going from phenols to pyridinols.[10]

To understand the effect of the nitrogen atom incorporation in the phenyl ring on the strength of the S−H bond, we have calculated the ground-state effect (GE), radical effect (RE) and total effect (TE = RE − GE) from the reaction enthalpies of the isodesmic reactions shown in Scheme 1.

This analysis is already known to provide a better understanding of substituent effects on BDE.[5,24] The GE effectively tells us how the ground-state stability of thiophenol changes with nitrogen atom insertion in the phenyl ring, whereas the RE indicates the effect of the same on the stability of thiophenoxyl radical. These two effects together determine how BDE(S−H) will change when going from thiophenol to pyridinethiol. These effects are shown in Figure 1. It can be seen that placing a nitrogen atom in the phenyl ring stabilizes (positive GE) the ground state for 2- and 4-pyridinethiol, whereas it has a small destabilizing effect on 3-pyridinethiol. In the case of the radical, nitrogen atom incorporation in the phenyl ring has a destabilizing effect (negative RE) for all the three pyridinethiol radicals, but the effect is large for 2- and 4-pyridinethiol radicals. As a result, the BDE(S−H) value increases significantly when going from thiophenol to 2- and 4-pyridinethiol. On the other hand, the BDE(S−H) value of 3-pyridinethiol is almost similar to that for thiophenol because of the small GE and RE and their mutual cancellation. On the basis of this analysis, it is expected that 2- and 4-pyridinethiol will not have good inhibition property to act as an antioxidant because of their higher BDE-(S−H) values. We therefore concentrate mainly on the substituent effects upon BDE(S−H) values of 3-pyridinethiol (X−C$_5$NH$_3$−SH) for the purpose of predicting a novel class of antioxidant.

3.2. Substituent Effect on BDE(S−H) of 5-X- and 6-X-3-Pyridinethiol. We have studied a series of substituted 3-pyridinethiol (X−C$_5$NH$_3$−SH), where X includes both the electron donating and withdrawing groups such as X = F, Cl, CH$_3$, NH$_2$, OCH$_3$, N(CH$_3$)$_2$, CN, CF$_3$, and NO$_2$. Substituent effects are considered for both the 5- (meta position with respect to −SH group) and 6-position (para position with respect to the −SH group) of 3-pyridinethiol. Before discussing our data on BDEs of substituted thiophenols, we mention briefly one important structural aspect of substituted 3-pyridinethiols. Mulder et al.[25] have recently pointed out that in the most stable conformer of *p*-OCH$_3$- and *p*-NH$_2$-substituted thiophenols the position of the

S−H bond is almost perpendicular to the plane of the phenyl ring (i.e., the HSCC dihedral angle is close to 90°). On the other hand, for thiophenol and *p*-nitrothiophenol the S−H bond remains in the plane of the ring (the HSCC dihedral angle is close to 0°). We observed from our calculated optimized structures of 5- and 6-substituted 3-pyridinethiols that for 5-X-3-pyridinethiols the S−H bond is always coplanar with the phenyl ring. But for 6-X-3-pyridinethiols the position of the S−H bond depends on the nature of the substituent (X). For electron donating groups (EDGs), such as CH$_3$, OCH$_3$, and NH$_2$, the S−H bond is almost perpendicular to the phenyl ring in the most stable conformer, whereas for electron withdrawing groups (EWGs), like CN, CF$_3$, and NO$_2$, the S−H bond is found to be coplanar to the phenyl ring. The energy difference between the planar and perpendicular conformation is found to be small (∼1 kJ/mol).

The calculated bond dissociation energies for a set of these substituted 3-pyridinethiol molecules are shown in Table 1. The results in Table 1 show that the effects of substitution at the 5-position of 3-pyridinethiol (5-X−C$_5$NH$_3$−SH) is not very significant. Here, EDGs, such as CH$_3$, NH$_2$, and N(CH$_3$)$_2$, have hardly any effect on the BDE(S−H) value of the parent 3-pyridinethiol. Meanwhile EWGs, like CN, CF$_3$, and NO$_2$, tend to increase the BDE(S−H) value from the parent molecule by 5−8 kJ/mol.

It can also be seen from Table 1 that substitution effects are much stronger when the substituent is placed at the 6-position of 3-pyridinethiol. Here, the ED substituent is found to reduce the BDE(S−H) value from the parent 3-pyridinethiol molecule. The largest decrease in BDE(S−H) value amounts to −21.7 and −26.1 kJ/mol for NH$_2$ and N(CH$_3$)$_2$, respectively. On the other hand, the EW substituent can be seen to strengthen the S−H bond of 3-pyridinethiol. Generally, it is believed that EDG stabilizes the radical (known as radical effect, RE) and as a result BDE decreases; whereas EWG stabilizes the ground state of the molecule (known as ground-state effect, GE) more due to dipolar interaction and thus increases the BDE value from the parent molecule. The difference of BDE(S−H) values between the 6-substituted-3-pyridinethiol and 5-substituted 3-pyridinethiol is shown in Table 1. It can be stated that generally the EDGs at the 6-position always reduce the BDE(S−H) much more than what it does at the 5-position, whereas the effect of EWGs are found to be more or less the same at both positions. The effect of substituents on BDE(S−H) of 6-X-3-pyridinethiol is found to be similar to that observed for thiophenol. This is in line with the similar observation made first by Pratt and co-workers[10] while studying the substituent effects on the BDE-(O−H) of pyridinol and pyrimidinols. This observation is important and useful for exploring some novel antioxidants that we discuss later.

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TABLE 1: (RO)B3LYP Calculated BDE(S−H) Values (kJ/mol) at 298.15 K of 5-Susbtituted- and 6-Substituted 3-Pyridinethiol Molecules[a]
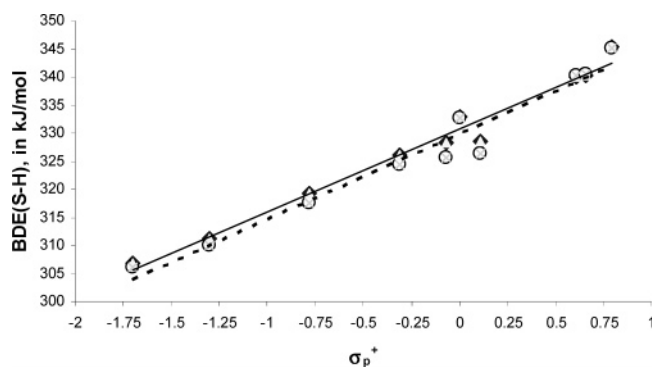
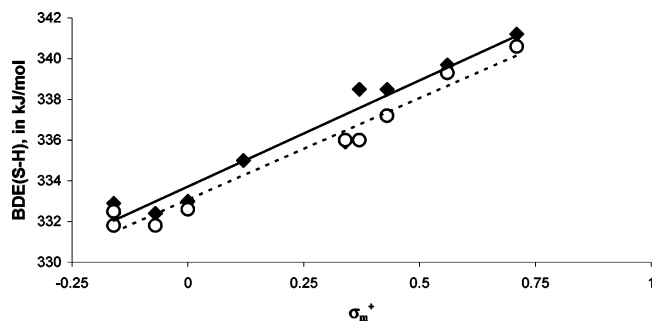|	5-X-3-pyridinethiol		6-X-3-pyridinethiol			
X	BDE_{5X}	ΔBDE^{b}	BDE_{6X}	ΔBDE^{b}	$\Delta BDE_{6X-5X}{}^{c}$	$X-C_6H_5-SH^{d}$
H	333.0	0	333.0	0	0	332.6
F	335.9	2.9	328.3	−4.7	−7.6	325.5
Cl	338.5	5.5	328.6	−4.4	−9.9	326.4
CH_3	332.4	−0.6	326.2	−6.8	−6.2	324.3
OCH_3	335.0	2.0	320.0	−13.0	−15.0	317.6
NH_2	332.9	−0.1	311.3	−21.7	−21.6	310.0
$N(CH_3)_2$	332.4	−0.6	306.9	−26.1	−25.5	306.3
CF_3	338.5	5.5	340.2	7.2	1.7	340.2
CN	339.7	6.7	340.2	7.2	0.5	340.6
NO_2	341.2	8.2	344.3	11.3	3.1	345.2

[a] The BDE(S−H) values of para-substituted thiophenols calculated at the same level of theory are given in the last column for comparison. [b] ΔBDE_{5X} or ΔBDE_{6X} is the difference of the BDE(S−H) value between the substituted compound and the parent one. [c] ΔBDE_{6X-5X} is the difference of the BDE(S−H) values between the 6-substituted 3-pyridinethiol and 5-substituted 3-pyridinethiol. [d] Taken from ref 15.

TABLE 2: B3LYP/6-311++G(2df,2p)//6-311G(d,p) Calculated Proton Affinities [[PA(S⁻), kJ/mol] for 5-X- and 6-X-3-Pyridinethiols

	5-X-3-pyridinethiol		6-X-3-pyridinethiol		
X	PA_{5X}	ΔPA_{5X}	PA_{6X}	ΔPA_{6X}	ΔPA_{6X-5X}
H	1395.6	0.0	1395.6	0.0	0.0
F	1375.1	−20.5	1382.6	−13.0	7.5
Cl	1372.1	−23.5	1369.7	−25.9	−2.4
CH_3	1399.3	3.7	1400.6	5.0	1.3
OCH_3	1399.0	3.4	1406.5	10.9	7.5
NH_2	1412.9	17.3	1420.9	25.3	8.0
$N(CH_3)_2$	1414.7	19.1	1422.6	27.0	7.9
CF_3	1359.2	−36.4	1352.6	−43.0	−6.6
CN	1345.5	−50.6	1334.1	−61.5	−10.9
NO_2	1341.9	−53.7	1318.7	−76.9	−23.2

3.3. Acidities of Substituted 3-Pyridinethiol. We thought that it would be worthwhile in this context to study also the effect of nitrogen atom insertion in the phenolic ring (producing 3-pyridinethiol) on the gas-phase acidity of thiophenol and also the effect of substituents on the acidity of resulting 3-pyridinethiol. The gas-phase acidities of 3-pyridinethiol and its 5- and 6-substituted derivatives were estimated from the proton affinity [PA(S⁻)] values of the respective anions $(X-C_5NH_3-S^-)$. The PA(S⁻) values were computed from enthalpies of neutral and anionic species obtained at the B3LYP/6-311++G(2df,2p)//6-311G(d,p) level of theory. These data are shown in Table 2. As demonstrated for substituted phenols,[26] these PA(S⁻) values should be closely related to the gas-phase acidity of the S−H bond of neutral substituted 3-pyridinethiol. It is observed from Table 2 that the trend of change of the PA values in the substituted 3-pyridinethiols is quite similar to those observed for the corresponding substituted phenols and thiophenols.[14,15] The EDGs at both the 5- and the 6-position of 3-pyridinethiol increase the PA(S⁻) value; however, the effect at the 6-position is much more pronounced for the very strong EDGs such as OCH_3, NH_2, and $N(CH_3)_2$. On the other hand, as expected, EWG enhances the acidity of the S−H bond by reducing the PA value. Once again the effect is found to be more when EWG is at the 6-position of 3-pyridinethiol. Comparisons of these PA values with the corresponding data for thiophenols[15] show that incorporation of nitrogen atom in the phenolic ring (from thiophenol to 3-pyridinethiol) reduces the PA(S⁻) value of $X-C_5NH_3-S^-$ by 20−25 kJ/mol. Thus nitrogen atom incorporation in the phenolic ring is found to increase the acidity of the S−H bond of thiophenol. It should be relevant here to discuss the effect of these substituents on the stabilization of substituted 3-pyridinethiol and its anion. An EWG can stabilize an anion more than an EDG, because it can reduce the amount of charge at the charge

Figure 2. Plot of BDE(S−H) values for 6-substituted 3-pyridinethiol (♦) and para-substituted thiophenols (○) against Hammett's parameter (σ_p^+).

Figure 3. Correlation of BDE(S−H) values for 5-substituted 3-pyridinethiol (♦) and meta-substituted thiophenols (○) with Hammett's parameter (σ_m^+).

center due to inductive effect and as a result an EW substituent increases the acidity of the S−H bond in 3-pyridinethiol.

3.4. Correlation of BDE(S−H) and PA(S⁻) with Hammett's Parameter. It is clear from Table 1 that for substituents at the 6-position of 3-pyridinethiol the BDE(S−H) values vary within a broad range of 26 kJ/mol. This shows that BDE(S−H) depends strongly on the nature of substituent. The substituent effect is found to be mild (vary within a narrow range of 8 kJ/mol) at the 5-position of 3-pyridinethiol. These substituent effects can be seen in terms of correlation with Hammett's substituent parameters (σ). Generally, a modified set of parameters (σ^+) is used for such correlation to take into account the effects of direct resonance interaction of the substituent with the reaction site. This effect is especially important for electron donor groups, such as CH_3, OCH_3, NH_2, etc., at the para position (6-position for 3-pyridinethiol). Figures 2 and 3 show the correlation of BDE(S−H) values of 5- and 6-substituted 3-pyridinethiol with σ_p^+ and σ_m^+ parameters, respectively. The
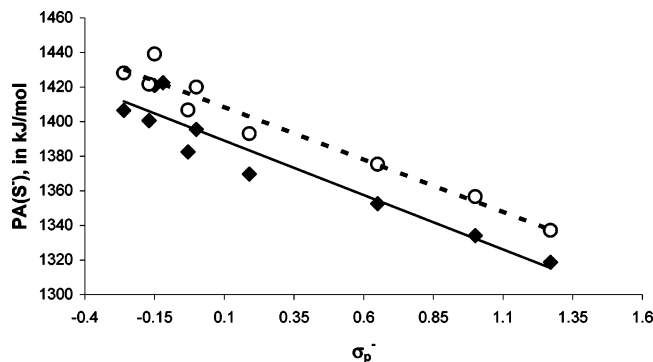
Figure 4. Plot of proton affinity values at the sulfur atom [PA(S$^-$)] for 6-substituted 3-pyridinethiol (♦) compounds and the para-substituted thiophenols (○) against Hammett's parameter (σ_p^-).

BDE(S$-$H) values for substituted thiophenols are also included in the figures for comparison with the pyridinethiol results. The σ_p^+ and σ_m^+ parameters were taken from the compilations of Hammett's parameter by Hansch, Leo, and Taft.[27] The σ_m^+ and σ_m parameters are nearly the same for substituents at the meta position. The substituents with negative σ_p^+ values reduce the BDE(S$-$H), whereas substituents with positive σ_p^+ values tend to increase the BDE(S$-$H). A good linear correlation between the BDE(S$-$H) and σ^+ parameters can be observed from Figures 2 and 3 for both 5- and 6-substituted 3-pyridinethiol. These figures also show that BDE(S$-$H) values for 5- and 6-substituted 3-pyridinethiol are very close to the corresponding thiophenol product. The linear correlation equations obtained from straight line fitting for 5- (eq 4) and 6-substituted (eq 5) 3-pyridinethiol can be expressed as

$$BDE(S-H) = 333.72 + 10.420\sigma_m \quad kJ/mol$$
$$(R^2 = 0.9541) \quad (4)$$

$$BDE(S-H) = 330.94 + 14.767\sigma_p^+ \quad kJ/mol$$
$$(R^2 = 0.9775) \quad (5)$$

We expect to obtain good antioxidant property from 3-pyridinethiol by placing strong EDGs (having negative σ^+ values) at the 6-position of 3-pyridinethiol, because strong EDG will reduce the S$-$H bond strength and as a result bond cleavage will be faster.

Strong correlation between PA(X$^-$) and the modified Hammett's parameters (σ^-) were demonstrated before by Haeberlein and Brinck[26] and in our earlier works for substituted phenol,[14] thiophenol[15] and phenylphosphine[16] systems. The modified substituent parameter (σ_p^-) should be used for systems where a permanent negative charge on the reaction center can be resonance stabilized by the substituents. This is important mainly for electron withdrawing para substituents. On the other hand, the modified σ_m^- and σ_m parameters are found to be almost the same.[27] Figures 4 and 5 demonstrate correlations of Hammett's parameters with PA(S$^-$) values of both 5- and 6-substituted 3-pyridinethiol. The corresponding thiophenol data are also included in Figures 4 and 5 for comparison. Here again, the correlation between PA values of 5- and 6-substituted 3-pyridinethiols and Hammett's substituent constants (σ^-) is found to be impressive. It is interesting to observe that the correlation lines for substituted 3-pyridinethiol and thiophenol are almost parallel. This indicates that the effect of nitrogen atom incorporation on PA is almost independent of the nature of substituent already present in the phenyl ring. This observation is parallel to the similar observation made for BDEs of substituted
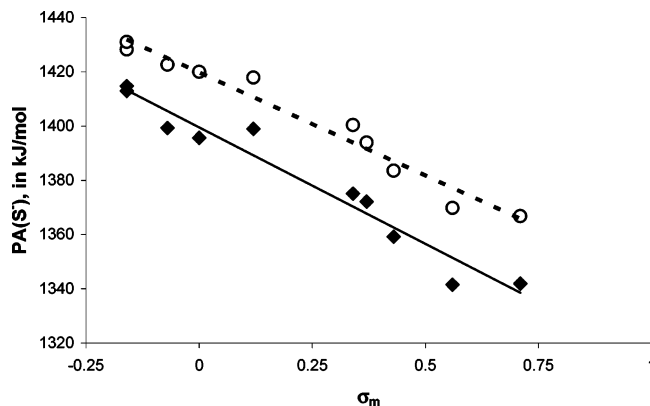

Figure 5. Plot of proton affinity values at the sulfur atom [PA(S$^-$)] for 5-substituted 3-pyridinethiol (♦) compounds and the meta-substituted thiophenols (○) against Hammett's parameter (σ_p^-).

3-pyridinols[10] and for 3-pyridinethiols. The linear equations obtained from the correlation can be expressed as

$$PA(S^-) = 1399.5 - 84.610\sigma_m \quad (R^2 = 0.959) \quad (6)$$

$$PA(S^-) = 1395.4 - 62.956\sigma_p^- \quad (R^2 = 0.903) \quad (7)$$

These correlation equations can be used to estimate easily the gas-phase acidity from Hammett's parameter for any other substituent for which the results are not known.

3.5. Ionization Energies of 6-X-3-Pyridinethiol, X = CH$_3$, OCH$_3$, NH$_2$, and N(CH$_3$)$_2$. As discussed in the Introduction, the IE is also an important property to be considered while studying the antioxidant activity of a compound. The IE determines the stability of an antioxidant compound in an oxygen-rich environment: the lower the IE, the greater the chance to react directly with oxygen. It is clear from our discussions in the previous sections that 3-pyridinethiol can act as a potential antioxidant (better than thiophenol) if suitable electron donating substituent is present at the 6-position of the phenyl ring. Because EDG at the 6-position of 3-pyridinethiol lowers the BDE(S$-$H) value significantly, the resulting compound can therefore transfer its H-atom of the S$-$H bond much faster to a chain-carrying peroxyl radical. Now, we need to compute the IE values for EDG substituted 3-pyridinethiols to determine their stability under oxygen rich conditions. This is crucial for designing a novel class of antioxidant. We first evaluated the accuracy of our DFT procedure for calculating IE. It is known that IE can be predicted within an error margin of 0.1 eV by using expensive ab initio methods, like G2, G3, G3B3, or CCSD(T).[28] However, these ab initio methods are difficult to apply for larger molecules containing more than 10 heavy atoms. We have therefore used the B3LYP/6-311G(d,p) method for calculating the IE value and then calibrated it with the available experimental results for better agreement with the exact IE value. Recently, Dilabio et al.[29] proposed a correction factor of 0.48 eV to be added to the B3LYP/6-31G(d)//AM1 calculated IE at 0 K to get better accuracy. They also studied the additivity of substituent effects on ionization energies for disubstituted benzenes and the correlation of IEs with Hammett's parameters.[30] We have redefined this correction factor for our B3LYP/6-311G(d,p) calculated IE values. For that matter, we first examined the correlation between our calculated and experimental IE values (given in Table S1 as Supporting Information) for a set of substituted benzenes (X$-$C$_6$H$_5$, X = H, F, Cl, CH$_3$, OCH$_3$, NH$_2$, N(CH$_3$)$_2$, OH, SH, CN and CF$_3$), pyridine, pyrimidine and phophabenzene. We observed a very good linear correlation (shown in Figure

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TABLE 3: B3LYP/6-311G(d,p) Calculated and the Available Experimental Ionization Energies (eV) of Some Selected Aromatic Compounds and Substituted 3-Pyridinethiols

compound	calc (estimated)[a]	expt[b]
phenol	8.23 (8.49)	8.49 ± 0.02
thiophenol	8.09 (8.35)	8.30 ± 0.01
aniline	7.44 (7.70)	7.720 ± 0.002
toluene	8.55 (8.81)	8.828 ± 0.001
pyridine	8.97 (9.23)	9.26 ± 0.01
pyrimidine	9.07 (9.32)	9.33 ± 0.07
3-pyridinol	8.66 (8.91), 8.95[c]	9.5 ± 0.1, 9.55 ± 0.05
3-pyridinethiol	8.44 (8.69)	9.41 ± 0.02, 8.89 ± 0.03
2-pyridinethiol	8.44 (8.69)	
4-pyridinethiol	8.74 (8.99)	
6-methyl-3-pyridinethiol	8.33 (8.58)	
6-methoxy-3-pyridinethiol	7.79 (8.05)	
6-amino-3-pyridinethiol	7.38 (7.64)	
6-(dimethylamino)-3-pyridinethiol	6.98 (7.25)	

[a] Data in parentheses are the estimated IE values from the equation $IE_{expt} = IE_{calc}0.9902 + 0.3363$ (in eV) (see Supporting Information); [b] Experimental values are taken from the NIST Chemistry web book, Number 69, Release June, 2005; http://webbook.nist.gov/chemistry/form-ser.html. [c] Data from ref 10.

TABLE 4: B3LYP/6-311++G(2df,2p) Calculated Ionization Energies (IE, eV) of 5- and 6-Substituted 3-Pyridinethiol Anions (X−C$_5$NH$_{3-S}$$^-$)

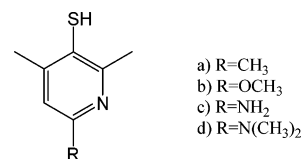| substituent X	X−C$_5$NH$_3$−S$^-$	
	IE$_{5X}$	IE$_{6X}$
H	2.54	2.54
F	2.81	2.66
Cl	2.84	2.76
CH$_3$	2.49	2.41
OCH$_3$	2.52	2.3
NH$_2$	2.35	2.05
N(CH$_3$)$_2$	2.33	1.99
CF$_3$	2.97	3.05
CN	3.13	3.24
NO$_2$	3.18	3.44

S1 in the Supporting Information) between our calculated and experimental IE values. An equation was then derived (see Supporting Information) from the resulting correlation as $IE_{expt} = IE_{calc}0.9902 + 0.3363$ (eV) to scale our calculated IE for better agreement with experimental results.

Table 3 shows the IE values of several substituted benzenes, pyridines and 6-X-3-pyridinethiol. The data in parentheses are computed from the empirical equation proposed above. The experimental IE values are not available for most of the pyridinethiol molecules listed in Table 3. However, the IE values estimated from the correlation equation are expected to be close

CHART 2

a) R=CH$_3$
b) R=OCH$_3$
c) R=NH$_2$
d) R=N(CH$_3$)$_2$

to the exact values for different 3-pyridinethiol products. The IE values of 2-, 3- and 4-pyridinethiol are seen to be much higher than that for thiophenol. Thus incorporation of a nitrogen atom in the phenolic ring enhances the IE value to a great extent. In fact, the behavior of 3-pyridinethiols in this respect is quite similar to that observed for 3-pyridinols.[10] In both the cases, incorporation of a nitrogen atom in the phenyl ring enhances the IE value and weakens the X−H (X = O, S) bond compared to that for the parent molecules. This aspect is important in designing antioxidant compound based on 3-pyridinethiol. The results in Table 3 also exhibit that an EDG lowers the IE value of 3-pyridinethiol. For IE, this can be explained in terms of the increasing electron density on the aromatic ring.[10c] Thus, the effect of the electron donating substituent on ionization energy and BDE(S−H) is in the same direction. In fact, we have observed a strong linear correlation between BDE(S−H) and IE values for 6-X-3-pyridinethiol compounds (shown in Figure S2 of the Supporting Information). The correlation is found to be not very good for the set of 5-X-3-pyridinethiol compounds, but the trend is clear. These correlations have been shown in the Figures S2 and S3 given in the Supporting Information.

Recently, the role of sequential proton loss electron-transfer (SPLET) process has been highlighted to understand the process of scavenging of radicals by antioxidants.[31,32] In the SPLET process, the IE of the anion generated from the loss of a proton of the antioxidant is important to determine the ease of electron transfer.[32] We have therefore calculated the ionization energies of 5- and 6-substituted 3-pyridinethiol anions (X−C$_5$NH$_3$−S$^-$) from the energies of 3-pyridinethiol anion (X−C$_5$NH$_3$−S$^-$) and radical (X−C$_5$NH$_3$−S$^\bullet$). These IE values are reported in Table 4. As expected, the IE values of anions are much lower (∼4−6 eV) than the IEs of substituted 3-pyridinethiol molecules. The electron donating group is seen to reduce the IE value from the parent 3-pyridinethiol anion (C$_5$NH$_4$−S$^-$), whereas the electron withdrawing group increases it.

3.6. New Classes of Antioxidants Based on 3-Pyridinethiol. We have already observed that among the three possible pyridinethiols (cf. Chart 1), the BDE(S−H) of 3-pyridinethiol (333.0 kJ/mol) is almost the same as that for thiophenol (332.6 kJ/mol), whereas its IE value is 0.35 eV greater than that of thiophenol. Thus, 3-pyridinethiol should be a better antioxidant

TABLE 5: (RO)B3LYP-Calculated BDE(S−H) (kJ/mol) and Adiabatic Ionization Energies (IE, eV) of Substituted 3-Pyridinethiols and Thiophenols

Substitution R	BDE(S–H)	IE[a]	BDE(S–H)	IE[a]
CH$_3$	320.6	7.79	325.4	8.07
OCH$_3$	312.5	7.44	315.5	7.75
NH$_2$	303.1	7.06	304.7	7.35
N(CH$_3$)$_2$	299.6	6.78	300.1	7.00

[a] IE values were estimated from the equation $IE_{expt} = IE_{calc}0.9902 + 0.336$ (in eV) and IE_{calc} was calculated from the B3LYP/6-311G(d,p) results.

than thiophenol. In fact, all the EDG substituted 3-pyridinethiol should act as better antioxidant than the corresponding thiophenol. To improve the antioxidant behavior of 3-pyridinethiol further, we have considered multiple EDG substituents in 3-pyridinethiol (as shown in Chart 2). Here, we have introduced a strong electron donating substituent at the 6-position of 3-pyridinethiol along with the presence of two more methyl groups at 2- and 4-positions as in well-known antioxidant compound BHA and BHT. These substituted 3-pyridinethiols are proposed as a new class of antioxidants and are shown in Chart 2.

Table 5 shows the calculated BDE(S−H) and adiabatic IE of some selective 6-substituted 2,4-dimethyl-3-pyridinethiols and also for the corresponding thiophenols. The thiophenol molecules are included to make a direct comparison with the corresponding 3-pyridinethiol products. The multiple EDG substitutions reduce the S−H bond strength to a large extent for both thiophenol and 3-pyridinethiol. But IE values for substituted 3-pyridinethiols are substantially larger than the corresponding thiophenol products. Perhaps the most interesting finding from these data is that both 6-amino-2,4-dimethyl-3- pyridinethiol and 2,4-dimethyl-6-(dimethylamino)-3-pyridinethiol have lower BDE (by 8−10 kJ/mol) and higher IE (by 7−42 kJ/mol) than α-tocopherol (α-TOH). It leads us to believe that 6-amino-2,4-dimethyl-3-pyridinethiol and 2,4-dimethyl-6-(dimethylamino)-3-pyridinethiol can be very good antioxidants. It should be mentioned here that these predictions are based completely on theoretical calculations. Finally, these compounds need to be synthesized in the laboratory to examine its property experimentally. However, our theoretical calculations can be a good guide to design the compound first before going for synthesis, because this procedure can be used to identify potential antioxidant compounds and thus help to streamline the synthesis work.

4. Summary and Conclusions

The effect of nitrogen atom incorporation in the phenyl ring on the strength of the S−H bond is examined and found that insertion at the 3-position does not have any significant effect on BDE(S−H). On the other hand, nitrogen atom incorporation at the 2- and 4-position is seen to enhance the strength of S−H bond. The BDE(S−H) values for a set of 5- and 6-substituted 3-pyridinethiols are then determined theoretically to study the substituent effects on BDE and to design potential antioxidant compounds. A good linear relationship has been observed between BDE(S−H) for substituted 3-pyridinethiols and Hammett's parameters, and this correlation is found to follow the same trend as observed for thiophenols. A strong electron donating group at the 6-position of 3-pyridinethiol makes the S−H bond considerably weaker than the parent molecule and in some cases even brings it lower than those of phenolic antioxidants. The nitrogen atom incorporation in the phenyl ring is seen to increase the acidity of the S−H bond of thiol irrespective of the nature of the substituent present in the ring. The nitrogen atom incorporation in the phenyl ring is found to increase the IE value from the parent molecule. The IE values of substituted 3-pyridinethiols are thus seen to be higher than the corresponding thiophenol molecules. The EDG substituted 3-pyridinethiols are therefore expected to be better antioxidants than the corresponding thiophenols because of their lower BDE and higher IE values. On the basis of these observations on 6-substituted 3-pyridinethiol, some novel antioxidants or precursors of novel antioxidants could be proposed theoretically, namely 2,4-dimethyl-6-nitrodimethyl-3-pyridinethiol, 2,4-dimethyl-6-amino-3-pyridinethiol, 2,4-dimethyl-6-methyl-3-pyridinethiol and 2,4- dimethyl-6-metoxy 3-pyridinethiol.

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