# 5-Pyrimidinols: Novel Chain-Breaking Antioxidants More Effective than Phenols

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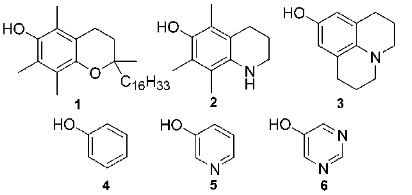
Phenols are the most abundant and widely used natural and synthetic antioxidants. For example, a phenol, α-tocopherol (α-TOH, **1**), is the major lipid-soluble, chain-breaking antioxidant in human blood plasma and low-density lipoprotein.[1] Its mechanism of action as an antioxidant, and that of phenolic compounds in general, relies on its ability to transfer its phenolic H-atom to a chain-carrying peroxyl radical at a rate much faster than that at which the chain-propagating step of lipid peroxidation proceeds.[1]

It is well-known that electron-donating (ED) groups substituted para and ortho to the phenolic hydroxyl lower the O−H bond dissociation enthalpy (BDE) and increase the rate of H-atom transfer to peroxyl radicals.[2] However, efforts to design new phenolic antioxidants with increased rates of H-atom transfer to peroxyl radicals have remained unsuccessful.[3,4] This is because, while the substitution of phenols with increasingly ED groups (e.g., $-NH_2$ and $-NR_2$) decreases their O−H BDEs, it also decreases their ionization potentials (IPs) such that they react directly with oxygen.[3,4]

For example, an aza-analogue of α-TOH (**2**)[3] and 9-hydroxyjulolidine (**3**)[4] were both found to be useless as antioxidants because they reacted directly with oxygen via electron transfer. In an effort to increase the stability of highly reactive, electron-rich phenols under conditions where oxygen is present, we have studied, by both theory and experiment, the effects of incorporating nitrogen into the phenolic ring.



Recently, some of us developed a density functional theory (DFT) model ((RO)B3LYP/6-311+G(2d,2p)//AM1/AM1) which predicts X−H bond energetics (X = C,N,O, and S) for several types of compounds, including phenols, generally to within experimental error.[5] In a separate account, we developed a second model (B3LYP/6-31G(d)//AM1/AM1), which was shown to be capable of accurately evaluating the IPs of polysubstituted aromatics.[6] Using these two DFT models, we have calculated the substituent effects on the O−H BDEs and IPs of 3-pyridinol (**5**) and 5-pyrimidinol (**6**) relative to those we have for phenol (**4**).[5,6]

While substitution of N for C at the 3-position of **4** to give **5** increases the calculated IP from 195.4 to 206.4 kcal/mol, the calculated O−H BDE changes by only 1.1 kcal/mol (87.1 to 88.2 kcal/mol). Introducing a second N at the 5-position to give **6** further raises the IP and O−H BDE to 219.7 and 89.6 kcal/mol, respectively. Thus, despite the increase in IP of 24.3 kcal/mol from **4** to **6**, the O−H BDE increases by only 2.5 kcal/mol. When the effects of para-substituents on the IPs and O−H BDEs in phenols, 6-substituted-3-pyridinols, and 2-substituted-5-pyrimidinols are calculated, it is found that the substituent effects on their O−H BDEs (Figure 1) and IPs (not shown) are conserved (see Supporting Information).

Finally, the O−H BDEs and IPs of further-substituted 5-pyrimidinols were calculated (the 3-pyridinols will be considered separately in a forthcoming publication). The results are presented in Table 1 along with those of their phenolic analogues and α-TOH for comparison. Increasing both the number and strength of ED substituents in the ortho and para positions brings about a steady decrease in the O−H BDE and IP. Consistent with the data in Figure 1, the substituent effects on both the O−H BDE and IP are roughly the same for both compounds.[7]

Our calculations suggest that 5-pyrimidinols should be effective H-atom donors with the advantage of being much more stable to air oxidation than similarly substituted phenols. To confirm this, we prepared four 5-pyrimidinols (**6a**−**6d**) by literature procedures[8] and measured their O−H BDEs by EPR equilibration studies,[2a,c] in the presence of a reference substituted phenol (see Supporting Information). Absolute measured values (±2 SD) were: 85.2 ± 0.5 kcal/mol for **6b**, 84.10 ± 0.25 kcal/mol for **6c**, and 78.16 ± 0.25 kcal/mol for **6d**. As shown in Table 2, these preliminary results support our prediction that substituent effects on the O−H BDE are roughly the same on going from phenols to 5-pyrimidinols.

Although we could not measure the O−H BDE of the unsubstituted 5-pyrimidinol, the results for **6b** and **6c** when compared to their phenolic analogues make it possible to estimate a value of 91.1 kcal/mol for the O−H BDE in **6a** in good agreement with our calculated value of 89.6 kcal/mol. We expect this estimate to be reliable to ±1 kcal/mol.

It is clear from the experimental results that our calculations overestimate the stability of both aryloxyl radicals, and that this overestimation increases with greater substitution and radical stability, bringing about slightly higher calculated ΔBDEs than those determined experimentally.

Perhaps most interesting of this preliminary set of data is that **6d** has a lower O−H BDE than α-TOH by both *theory* (−0.7 kcal/mol) *and experiment* (−0.1 kcal/mol), but a much higher calculated IP (by 7.7 kcal/mol). This suggests that **6d** will transfer its phenolic H-atom to free radicals at least as fast as α-TOH, but be much more stable to air oxidation. Indeed, **6d** could be easily prepared, handled, and purified in an open atmosphere without degradation by air oxidation—a problem encountered when handling α-TOH.

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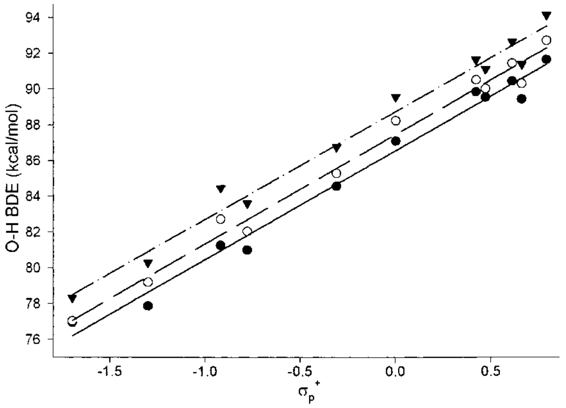

**Figure 1.** Correlations of $\sigma_p^+$ and the calculated gas phase O−H bond dissociation enthalpies (298 K) of 4-substituted phenols[5] (●), 6-substituted-3-pyridinols (○), and 2-substituted-5-pyrimidinols (▼).

**Table 1.** Calculated Substituent Effects on Gas Phase O−H BDEs at 298 K and Adiabatic IPs at 0 K of Symmetrically Substituted Phenols (**4**) and 5-Pyrimidinols (**6**)[a]

| 2 × ortho | para | **6** | **4** |
|---|---|---|---|
| H | H | (89.6)/(219.7) | (87.1)/(195.4) |
| H | $CH_3$ | −2.8/−10.4 | −2.5/−8.5 |
| $CH_3$ | $CH_3$ | −6.4/−22.7 | −6.7/−17.1 |
| H | $OCH_3$ | −6.0/−21.6 | −6.1/−18.9 |
| $CH_3$ | $OCH_3$ | −9.8/−31.4 | −10.1/−26.2 |
| H | $N(CH_3)_2$ | −11.3/−45.1 | −10.1/−37.7 |
| $CH_3$ | $N(CH_3)_2$ | −15.5/−52.7 | −14.8/−43.1 |
| α-TOH (**1**) | | | −12.3/−36.1 |

[a] Data presented BDE/IP in kcal/mol. Absolute values for unsubstituted **6** and **4** are in parentheses.

**Table 2.** Experimental Substituent Effects on Solution-Phase O−H BDEs at 298 K of Substituted 5-Pyrimidinols (**6**) and Phenols (**4**)[a]

| | 2 × ortho | para | **6** | **4**[c] |
|---|---|---|---|---|
| **a** | H | H | (91.1)[b] | (88.3) |
| **b** | $CH_3$ | $CH_3$ | −5.9 | −5.6 |
| **c** | *t*-Bu | $CH_3$ | −7.0 | −7.3 |
| **d** | $CH_3$ | $N(CH_3)_2$ | −12.9 | *d* |
| α-TOH (**1**) | | | | −10.0 |

[a] All values in kcal/mol. Absolute values for unsubstituted **6** and **4** are in parentheses. [b] Estimate (see text). Could not be measured due to the short lifetime of the 5-pyrimidinoxyl radical. [c] From ref 2c. [d] Not an air-stable compound.

Rate constants for the reactions of **6b**−**c** with alkyl radicals were determined by competition kinetics in benzene with one of either the 5-hexenyl cyclization,[10] $k_r = 1.5 \times 10^5\ s^{-1}$ or neophyl radical rearrangement,[11] $k_r = 1.1 \times 10^3$ as radical clock (Table 3, column 2). Despite higher O−H BDEs for **6b** and **6c** with respect to their phenolic counterparts, their rates of reaction with alkyl radicals were substantially faster.[12] Also, **6d**, which has only a marginally lower O−H BDE than α-TOH reacted 5 times faster with alkyl radicals. An explanation of these results may be given in terms of a polar effect in the transition state of the atom-transfer reaction.[13] The pyrimidine ring better supports a partial negative charge on the aryloxyl oxygen than a phenyl ring,[14] providing better charge separation in the transition state for H-atom transfer, and lowering the barrier to reaction for pyrimidinols compared to phenols with the same O−H BDE.

**Table 3.** Reactivities of Substituted Phenols and 5-Pyrimidinols to Alkyl (298 K) and Peroxyl Radicals (323 K) in Benzene[a]

| | alkyl | peroxyl |
|---|---|---|
| **6b** | $4.6 \times 10^5$ (N)[c,d] | $3.3 \pm 0.4 \times 10^4$ |
| **4b** | $8.5 \pm 0.8 \times 10^4$ (N)[e] | $1.1 \pm 0.1 \times 10^5$ |
| **6c** | $3.2 \pm 0.5 \times 10^4$ (N) | $2.2 \pm 0.3 \times 10^4$ |
| **4c** | $4.8 \pm 1.5 \times 10^3$ (N)[e] | $1.8 \pm 0.3 \times 10^4$ |
| **6d** | $2.9 \pm 1.1 \times 10^6$ (H) | $8.6 \pm 0.5 \times 10^6$[f] |
| α-TOH (**1**) | $6.0 \pm 1.5 \times 10^5$ (H)[e] | $4.1 \pm 0.4 \times 10^6$ |

[a] Radical clocks used for the reactions with alkyl radicals are indicated in parentheses.[b] All rate constants are second order with units of $M^{-1}\ s^{-1}$. Errors represent ±2 SD. [b] H = 5-hexenyl, N = neophyl. [c] Estimate based on correlations of *k* and *β* for $CH_3CN$ ($k = 5.8 \times 10^4$), EtOAc ($k = 8.6 \times 10^3$) and *t*-BuOH ($k = 4.9 \times 10^3$).[9] [d] In 1−5% $D_2O$, $CH_3CN$, $k = 1.9 \pm 0.7 \times 10^4$. [e] Measurements made by L.V. and reported in ref 12. [f] In $D_2O$-saturated benzene, $k = 2.8 \pm 0.6 \times 10^6$.

The reactivities of **6b**−**c** with peroxyl radicals were measured by oxygen consumption experiments,[15,16] studying the inhibited autoxidation of styrene in benzene,[3a] and the results were compared to the values measured for **4b**−**c** and α-TOH under the same experimental conditions (Table 3, column 3). Since the rate constants for reactions with peroxyl radicals are within a factor of 3 for **6b**/**4b** and roughly the same for **6c**/**4c**, a polar effect might still be involved to balance the BDE difference of 2.5−3 kcal/mol. It is, however, a smaller effect as the peroxyl oxygen cannot support a partial positive charge in the transition state as effectively as the alkyl carbon.

The reactions of **6b** with alkyl radicals and **6d** with peroxyl radicals were also performed in dry solvents containing $D_2O$ to obtain the deuterium kinetic isotope effect ($k_H/k_D$) for these reactions. In both cases, $k_H/k_D = 3.1$, consistent with a primary isotope effect and suggesting that H-atom transfer is indeed the mechanism of reaction between alkyl or peroxyl radicals and the pyrimidinols.

In conclusion, by incorporating nitrogen into the aromatic ring, it is possible to substantially increase the IPs of phenolic compounds without greatly affecting their O−H BDEs. The substituent effects upon the O−H BDEs and IPs in these compounds are roughly the same as in phenol, making it possible to design novel compounds that undergo fast H-atom-transfer reactions with radicals, but which are stable to air oxidation. Moreover, the apparent presence of a kinetic polar effect in the H-atom-transfer reactions to chain-carrying radicals makes 5-pyrimidinols more effective chain-breaking antioxidants than phenols having the same O−H BDE.

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**Note Added after ASAP:** There were errors in Tables 1 and 2 in the version posted ASAP April 18, 2001; the corrected version was posted April 20, 2001.

**Supporting Information Available:** Computational details, EPR spectral parameters of the 5-pyrimidinoxyl radicals, full details of the kinetic and thermodynamic measurements (PDF). This material is available free of charge via the Internet at http://acs.pubs.org.

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