ORGANIC LETTERS

2005
Vol. 7, No. 13
2735−2738

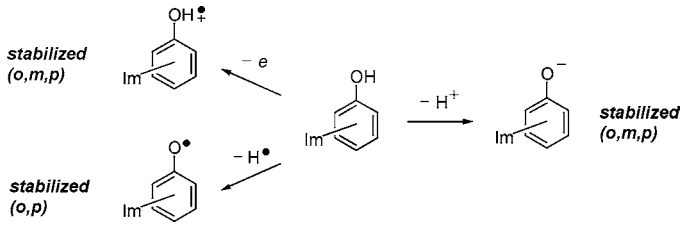
Model Studies of the Histidine-Tyrosine Cross-Link in Cytochrome *c* Oxidase Reveal the Flexible Substituent Effect of the Imidazole Moiety

Derek A. Pratt, Russell P. Pesavento, and Wilfred A. van der Donk*

Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801
vddonk@uiuc.edu

Received April 25, 2005

ABSTRACT



Experimental and theoretical studies were carried out to interrogate the effect of an imidazole substituent in each of the ortho, meta, and para positions on the pK_a, E°, and O–H BDE of phenol. The results reveal that imidazole substitution lowers the pK_a of phenol and increases the E° of phenoxide due to its σ-electron withdrawing ability ($\sigma_p^- = +0.21$, $\sigma_m^- = +0.45$) but decreases the O–H BDE and E° of phenol due to its π-electron-donating ability ($\sigma_p^+ = -0.45$).

Cytochrome *c* oxidase (C*c*O) is the final enzyme complex in the electron-transport chain embedded in the inner membrane of mitochondria in eukaryotes and the cellular membrane of bacteria that respire aerobically. It catalyzes the four-electron reduction of O_2 to H_2O, which ultimately affords the energy required for the biosynthesis of ATP. In the so-called mixed-valence form of the enzyme, three of the four required electrons are proposed to come from the redox-active metals in the heme a_3-Cu_B active site (Fe^{II} and Cu^{I}, Figure 1).[1] It is widely believed that the fourth electron originates from a highly conserved tyrosine (Tyr), which X-ray crystallographic studies have shown is cross-linked to one of the histidine (His) residues coordinated to the active site Cu.[2] Several proposals for a functional redox role of the cross-linked Tyr have been advanced. Yoshikawa and co-workers proposed[2a] a proton transfer from Tyr244 to a ferric peroxide intermediate to generate a hydroperoxo adduct whose O−O bond is reductively cleaved via electron transfer from the tyrosinate. Others have speculated that the cross-linked Tyr might serve as a H-atom donor during the reduction of O_2.[2b,3]

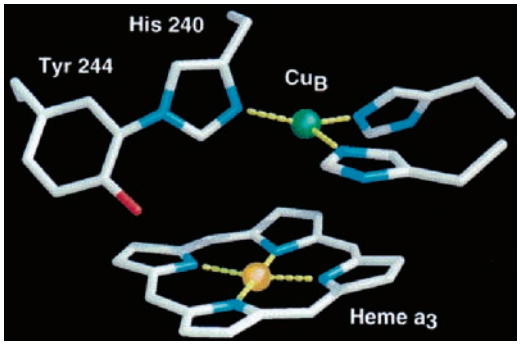


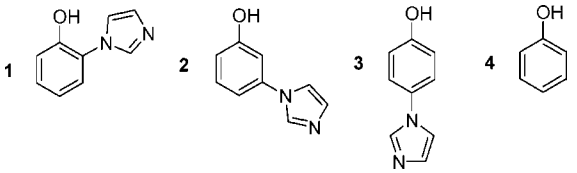
Figure 1. Bimetallic heme a_3-Cu_B active site of C*c*O. Substituents on the porphyrin ring are omitted for clarity.

(1) For a recent review see: Wikstroem, M. *Biochim. Biophys. Acta* **2004**, *1655*, 241.

(2) (a) Yoshikawa et al. *Science* **1998**, *280*, 1723. (b) Ostermeier, C.; Harrenga, A.; Ermler, U.; Michel, H. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 10547. (c) Buse, G.; Soulimane, T.; Dewor, M.; Meyer, H. E.; Bluggel, M. *Protein Sci.* **1999**, *8*, 985.

10.1021/ol050916g CCC: $30.25
Published on Web 05/27/2005

Active-site model studies[4,5] have revealed that imidazole (Im) substitution at the ortho position reduces the phenolic pK_a by 1.1−2.2 units depending on the presence of substituents on the Im ring and/or the ionic strength at which the experiments were carried out.[4] Model studies have also identified an increase in the oxidation potential of the phenoxide by 66 mV.[4a] The factors governing these substituent effects are unclear since they are contrary to the long-known electron-donating effects of Im as a subsitutent on aromatic systems, especially phenyl and substituted phenyl rings.[6] To better understand these substituent effects, we have synthesized the three constitutional isomers of 1-imidazolyl-phenol (hereafter ImPhOH or imidazole-phenol) and explored their acid−base and redox properties by experiment and theory.



The ImPhOHs **1**−**3** were prepared by two routes sharing the corresponding 1-imidazolyl-anisoles as intermediates, which were subsequently demethylated in 48% HBr to yield the phenols. The first route to the 1-imidazolyl-anisoles involved substitution of each of the 2-, 3-, and 4-haloanisoles with imidazole at high temperatures in the presence of base and a copper catalyst.[4b,7] The second involved construction of the imidazole by treatment of each isomer of anisidine with glyoxal, followed by ammonium chloride, formaldehyde and then strong acid.[8] For details, see the Supporting Information.

Spectrophotometric titrations were performed to establish the pK_a of the phenolic moieties of **1**−**3** in aqueous solution relative to that of phenol. Upon deprotonation, each isomer exhibited a red-shift in the UV absorption spectrum from approximately 250 nm to 270−300 nm and the data in Table 1 were collected. The results are fully consistent with an electron-withdrawing (EW) effect of the Im substituent.

Table 1. Some Important Properties of the Three Constitutional Isomers of Imidazole-Phenol[a]

	pK_a [b]	$E°$ [c]	ΔBDE [d]
1	8.69 ± 0.09 (−1.4)	0.941 (+0.069)	−0.3
2	9.01 ± 0.06 (−1.1)	1.028 (+0.156)	+2.1
3	9.61 ± 0.12 (−0.5)	0.869 (−0.003)	−0.8
4	10.09 ± 0.08 (0.0)	0.872 (0.000)	0.0

[a] Differences from phenol in parentheses. [b] Determined for 0.5−1 mM phenol as described in the text at an ionic strength of 0.5 M (KCl). [c] In volts vs NHE and estimated from plots of the anodic peak potentials versus the logarithm of the scan rate for 0.32 mM phenol in 31.25 mM NaOH (pH 12.5) containing 0.12 M $LiClO_4$ using eq 1; see ref 9. [d] Derived from pK_a and $E°$ as in eq 2; see ref 11.

When Im is positioned closer to the phenolic OH, the reduction in pK_a is most prominent, with the ortho isomer being the most acidic (pK_a = 8.69), followed by the meta isomer (pK_a = 9.01) and the para isomer (pK_a = 9.61). The results are somewhat unexpected since, as noted in previous studies,[4] the π-electron-donating (ED) ability of the N-linked Im would be expected to destabilize the conjugate phenoxide.

Cyclic voltammetry was carried out on compounds **1**−**3** and phenol at basic pH to investigate the effects of Im substitution on the oxidation of the phenoxide to the corresponding phenoxyl radical. All of the voltammagrams displayed irreversible behavior. Plots of the anodic peak potentials (E_{pa}) versus the logarithm of the scan rate (logν) between 5 and 1000 mV/s yielded good linear correlations (see the Supporting Information), allowing estimations of $E°$ from eq 1[9] assuming the follow-up chemistry, dimerization of the product phenoxyl radicals, occurs with the same rate constant ($2k = 2.6 \times 10^9$ M^{-1} s^{-1}) for each analyte.[10]

$$E_{pa} = E° + 0.902\frac{RT}{F} - \frac{RT}{3F}\ln\left(\frac{2kC°}{\nu}\frac{2RT}{3F}\right) \qquad (1)$$

The para isomer had the lowest estimated standard potential of the three substituted phenoxides ($E°$ = 0.869 V), very similar to that of the phenoxide/phenoxyl couple, followed by the ortho isomer ($E°$ = 0.941 V) and the meta isomer ($E°$ = 1.028 V). The results appear to be consistent with the EW effect of the Im substituent seen in the pK_a data. However, the trends in the two sets of data are different, with the ortho isomer having the most acidic phenolic proton but the meta isomer having the highest peak potential. Since the stabilization of the phenoxides should be directly related to the pK_a, it is likely that the difference is due to different phenoxyl radical stabilities.

The relative stabilities of the three substituted phenoxyl radicals can be estimated from the corresponding differences in the O−H bond dissociation enthalpies (BDEs), derived using a thermodynamic cycle involving the acidity of the

(3) (a) Proshlyakov, D. A.; Presller, M. A.; Babcock, G. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8020. (b) Gennis, R. B. *Biochim. Biophys. Acta* **1998**, *1365*, 241. (c) Michel, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12189. (d) Proshlyakov, D. A.; Pressler, M. A.; DeMaso, C.; Leykam, J. F.; DeWitt, D. L.; Babcock, G. T. *Science* **2000**, *290*, 1588.

(4) (a) McCauley, K. M.; Vrtis, J. M.; Dupont, J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2000**, *122*, 2403. (b) Collman, J. P.; Wang, Z.; Zhong, M.; Zeng, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1217. (c) Aki, M.; Ogura, T.; Naruta, Y.; Le, T. H.; Sato, T.; Kitagawa, T. *J. Phys. Chem. A* **2002**, *106*, 3436. (d) Cappuccio, J. A.; Ayala, I.; Elliott, G. I.; Szundi, I.; Lewis, J.; Konopelski, J. P.; Barry, B. A.; Einarsdóttir, Ó. *J. Am. Chem. Soc.* **2002**, *124*, 1750.

(5) These results are supported by theoretical calculations. See: Colbran, S. B.; Padden-Row, M. N. *J. Biol. Inorg. Chem.* **2003**, *8*, 855. Himo, F.; Noodleman, L.; Blomberg, M. R. A.; Siegbahn, P. E. M. *J. Phys. Chem. A* **2002**, *106*, 8757.

(6) (a) Pozharskii, A. F.; Simonov, A. M. *Zh. Obshch. Khim.* **1964**, *34*, 224. (b) Pozharskii, A. F. *Zh. Obshch. Khim.* **1964**, *34*, 630. (c) Pozharskii, A. F.; Chegolya, T. N.; Simonov, A. M. *Khim. Getero. Soed.* **1968**, *4*, 503. (d) Pozharskii, A. F.; Sitkina, L. M.; Simonov, A. M.; Chegolya, T. N. *Khim. Getero. Soed.* **1970**, *6*, 209.

(7) Sitlana, L. M.; Simonov, A. M. *Khim. Getero. Soed.* **1966**, *2*, 143.

(8) Liu, J.; Chen, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, *17*, 2661.

(9) (a) Nadjo, L.; Savéant, J. M. *J. Electroanal. Chem. Interfacial Electrochem.* **1973**, *48*, 113.

(10) Alfassi, Z. B.; Shoute, L. C. T. *Int. J. Chem. Kinet.* **1993**, *25*, 79. This assumption appears to be reasonable for monosubstituted phenoxyls; see, e.g.: Li, C.; Hoffman, M. Z. *J. Phys. Chem. B* **1999**, *103*, 6653. For a more detailed discussion, see the Supporting Information.

phenol and the oxidation potential of its conjugate base as in eq 2.[11] Using our measured values,[12] the differences in the O−H BDEs (ΔBDEs) were estimated for **1**−**3** relative to phenol. The values are shown alongside the other relevant data collected in Table 1.

$$\Delta\text{BDE (kcal/mol)} = 23.06\Delta E^\circ + 1.363\Delta \text{p}K_a \qquad (2)$$

The results indicate that the *o*- and *p*-Im-substituted phenoxyl radicals are modestly stabilized relative to phenoxyl, and the meta isomer is more significantly destabilized. This is consistent with what would be expected of a π-ED substituent, which stabilizes phenoxyl radicals when substituted in the ortho or para positions due to both delocalization of the unpaired electron spin and stabilization of the electron-poor phenoxyl ring by π-donation through resonance.[13] Thus, while Im appears to stabilize the electron-rich phenoxides by inductively withdrawing electron density, it also appears to stabilize the electron-poor phenoxyl radicals by donating electron density. The π-ED effect would be expected to be even more dramatic on the direct oxidation of the phenol to the phenolic radical cation. Indeed, when the oxidation of the phenols was examined in organic solution (acetonitrile) by cyclic voltammetry, the anodic peak potentials for the para and meta isomers[14] displayed large shifts to lower potentials relative to phenol (see the Supporting Information).

Given that the O−H BDEs and potentials for the phenoxyl/phenoxide and phenoxyl radical cation/phenol couples are *estimates* based on irreversible *peak* potentials and the results appear somewhat contradictory in the sense that they reveal both significant ED and EW properties of Im as a substituent, we sought to corroborate the foregoing with the results of theoretical calculations.

It has been demonstrated that B3LYP[15] density functional model calculations are generally in excellent agreement with experimental O−H BDEs[13,16] and ionization potentials[17] in substituted phenols, and thus, we performed these and other calculations[18] to help better understand the somewhat puzzling trends observed in our experimental results. The data are presented in Table 2.

It is important to note that the calculated minimum energy conformation of the ortho isomer is in good agreement with the X-ray crystallographic structure of *o*-Im-*p*-cresol,[22] especially the critical angle between the planes of the Im and PhOH rings.[23] The calculated pK_a's are higher than the experimental values by ca. 4 log units. This was not unexpected given the well-documented problems of continuum models in reproducing accurate solvation energies for many anions.[24] Regardless and most importantly, the trend of increasing acidity along the series PhOH < **3** < **2** < **1** is

Table 2. Calculated[a] Solution- and Gas-Phase Properties of the Three Constitutional Isomers of Imidazole-Phenol

Solution Phase[b]

	pK_a [c]	E° [d]	ΔBDE[e]	E° [f]
1	12.9 (−1.8)	0.406 (+0.003)	−2.4	1.82 (−0.10)
2	13.0 (−1.7)	0.578 (+0.175)	+1.7	1.91 (−0.01)
3	13.4 (−1.3)	0.398 (−0.005)	−1.9	1.65 (−0.27)
4	14.7 (0.0)	0.403 (0.000)	0.0	1.92 (0.00)

Gas Phase

	PA[g]	EA[h]	O−H BDE[i]	IP[j]
1	325.8 (−14.9)	63.7 (+10.9)	83.6 (−3.7)	186.8 (−8.4)
2	328.9 (−11.8)	65.8 (+13.0)	89.0 (+1.7)	189.5 (−5.7)
3	328.8 (−11.9)	62.4 (+9.6)	85.3 (−2.0)	184.2 (−11.0)
4[k]	340.7 (0.0)	52.8 (0.0)	87.3 (0.0)	195.2 (0.0)

[a] (U)B3LYP/6-311+G(2d,2p)//(U)B3LYP/6-31G(d) unless otherwise indicated. [b] Solvation energies calculated using the COSMO polarized continuum model[19] for water (ϵ = 78.39) unless otherwise indicated. [c] Calculated from PAs of the phenoxide anions corrected for solvation energies. [d] In volts vs NHE; calculated from EAs of the phenoxyl radicals corrected for solvation energies. [e] In kcal/mol; derived from pK_a and E° as in eq 2. [f] In volts vs NHE in acetonitrile (ϵ = 36.64); calculated from IPs corrected for solvation energies. [g] Proton affinities (ΔG°) of the phenoxide anions. [h] Electron affinities (ΔG°) of the phenoxyl radicals. [i] Absolute bond dissociation enthalpies (ΔH°) of the phenols, calculated using the HLM as in ref 16. [j] Ionization potentials (ΔE_0) of the phenols, calculated as in ref 17. [k] Experimental values: 342.3 ± 2.0 kcal/mol,[20] 52.0 ± 0.1 kcal/mol,[20] 86.7 ± 0.7 kcal/mol,[21] 196.2 ± 0.1 kcal/mol.[20]

(11) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1979.

(12) The calculation of reliable absolute O−H BDEs requires reversible, or quasi-reversible, redox processes. These conditions are not met by the phenoxyl/phenoxide couples studied here.

(13) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334 and references therein.

(14) The ortho isomer has limited solubility in aprotic organic solvents.

(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(16) DiLabio, G. A.; Pratt, D. A.; Lofaro, A. D.; Wright, J. S. *J. Phys. Chem. A* **1999**, *103*, 1653.

(17) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *J. Org. Chem.* **2000**, *65*, 2195.

(18) All calculations were performed with the Gaussian 03 suite of programs. Gaussian 03, Revision B.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(19) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995.

(20) Lias, S. G. *Ionization Energy Evaluation.* In *NIST Chemistry WebBook*; NIST Standard Reference Database Number 69; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, March 2003.

(21) Mulder, P.; Korth, H.-G.; Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Phys. Chem. A* **2005**, *109*, 2647.

(22) Naruta, Y.; Tachi, Y.; Chishiro, T.; Shimazaki, Y.; Tani, F. *Acta Crystallogr. E* **2001** *57*, 500.

(23) The calculated angle between the phenol and imidazole ring planes in *o*-ImPhOH and *o*-Im-*p*-cresol is 42.5°, essentially identical to the crystallographic value of 42.2° for the latter.[22] For comparison, this angle is 44° in bovine heart cytochrome *c* oxidase.[2a] Incidentally, the intramolecularly H-bonded *o*-isomer is the lowest energy conformer (by ca. 1 kcal/mol) in the gas phase. In contrast with previous theoretical studies,[5] we have chosen to present the data for only the non-intramolecularly H-bonded conformer since it should be the only relevant conformer in the condensed phase due to stronger intermolecular H-bonding. This is also the only conformer present in crystal structures of cross-linked models where the hydrogen atoms are resolved; see, e.g., ref 22. The computed angles for *m*-ImPhOH and *p*-ImPhOH were 37.0° and 43.1°, respectively.

captured by the calculations. The underestimation of the calculated standard potentials for the phenoxyl/phenoxide couple can also be ascribed largely to the errors in the solvation energies of the phenoxide anions. Again, the trends are well captured by the calculations, with the exception of the *o*-isomer. Since any conclusions based on the foregoing calculated data could be considered dubious by the solvation energy calculations, we turned to the gas-phase since these quantities are unlikely to be in significant error.[16,17] In good agreement with our experimental data, the trends in both the proton affinities of the phenoxides and electron affinities of the phenoxyl radicals are consistent with a σ-EW effect of Im while the trends in the O−H BDEs and ionization potentials are consistent with a π-ED effect.

Calculations of the interaction energies (ΔE_{int}) between Im and PhOH/PhO$^{\bullet}$/PhO^{-}/PhOH$^{\bullet+}$ in the three isomers allow us to see the substituent effects on each of the species involved in the foregoing acid−base and redox equilibria. This was done using isodesmic reactions[25] as shown below. The results are presented in Table 3, where stabilizing interactions are indicated by positive values.

Table 3. Calculated[a] Interaction Energies in Imidazole-Phenols, Phenoxyls, Phenoxides, and Phenol Radical Cations

	X			
Isomer	OH	O$^{\bullet}$	O^{-}	OH$^{\bullet+}$
ortho[b]	−2.5	1.3	12.4	6.5
meta[b]	0.1	−1.8	11.7	6.1
para[b]	−0.5	1.6	11.2	11.2
para (ϕ=0)[c]	−1.0	4.4	10.2	12.5
para (ϕ=90)[c]	0.1	0.8	12.3	3.1

[a] B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d). All values in kcal/mol. [b] For ϕ values in the optimized geometries of the radicals, anions, and radical cations, see Table S1 in the Supporting Information. [c] Calculated for para isomers of phenol, phenoxyl, phenoxide, and phenol radical cation and 1-phenylimidazole wherein ϕ is fixed at either 0° (maximum conjugation) or 90° (minimum conjugation).

Consistent with what is calculated for other π-ED substituents, such as *p*-NH$_2$,[13] the values of ΔE_{int} indicate that Im stabilizes electron-poor entities such as the phenoxyl radical and the phenolic radical cation. However, unlike the case for most π-ED substituents, a significant σ-EW effect is seen in its ability to stabilize electron rich entities such as the phenoxide anion. This adaptability of Im as a substituent can be understood on the basis of its relatively high acidity for a nitrogen acid (pK_a = 14.2)[26] along with its relatively low lying doubly occupied HOMO (IP = 203.2 ± 0.2 kcal/mol),[20] which ensures good interactions with the phenolic moiety. The latter are sensitive to the angle between the ring planes (ϕ, see Table 3), but are still quite evident in the minimum energy conformations of the ortho and para isomers, where ϕ = 42.5° and 43.1°, respectively.

It is noteworthy that, to the best of our knowledge, Hammett-type substituent constants (e.g., σ^+ and σ^-) for Im attached through nitrogen are absent from the literature.[27] Our pK_a data allow us to derive values for σ_p^- and σ_m^- using the slope of the Hammett correlation used to define the substituent constant ($\sigma^- = \Delta pK_a/2.237$).[28] This yields values of +0.21 and +0.45, respectively. To put this into context, values of σ_p^- for NO$_2$, F, CH$_3$ and OCH$_3$ are +1.25, +0.02, −0.14, and −0.21, respectively. This characterizes Im as a moderate σ-EW group whose full effect in the *o* and *p* positions is somewhat masked due to π-ED effects (since $\sigma_p^- < \sigma_m^-$). We have also estimated a value for the σ_p^+ substituent constant[29] of Im from the excellent linear correlation ($R^2 > 0.995$) of calculated gas-phase ionization potentials of *p*-substituted phenols with σ_p^+ (see the Supporting Information). We obtain a value of −0.45, consistent with a moderate π-ED group (compare to values for NO$_2$, F, CH$_3$, and OCH$_3$ of +0.79, −0.07, −0.31, and −0.78, respectively). In this case, not only is some of the effect masked by the opposing σ-EW effect, but it is also reduced due to the non-optimal overlap of the Im N 2p-type lone pair with the phenolic π-system.[30]

Returning to the role of the His-Tyr cross-link in C*c*O, our studies indicate that the presence of the Im substituent may facilitate the oxidation of the active site Tyr by one of three mechanisms. The σ-EW character of the Im promotes deprotonation of Tyr affording the tyrosinate, which is much more easily oxidized than is Tyr in its protonated form. Alternatively, the π-ED character of Im facilitates both the abstraction of the Tyr phenolic H-atom or its (proton-coupled) one-electron oxidation given the lower homolytic O−H BDE and oxidation potential.

Acknowledgment. This work was supported by the National Institutes of Health (GM44911), the Camille and Henry Dreyfus Foundation (TC-02-055), and the Alfred P. Sloan Foundation. This investigation has been aided by a fellowship to D.A.P. from The Jane Coffin Childs Fund for Medical Research.

Supporting Information Available: Preparation of **1**−**3**, electrochemical data, catesian coordinates and energies for structures in Tables 2 and 3 and the correlation of phenolic IP and σ_p^+. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050916G

(24) See, e.g., Chipman, D. M. *J. Phys. Chem. A* **2002**, *106*, 7413. Baik, M.-H.; Friesner, R. A. *J. Phys. Chem. A* **2002**, *106*, 7407.
(25) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393.
(26) Yagil, G. *Tetrahedron* **1967**, *23*, 2855.
(27) See, for example, the comprehensive collection provided in: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(28) Fischer, A.; Leary, G. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc. B* **1966**, 782.
(29) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(30) This flexible behavior for a substituent group is not unprecedented. The acetamido group is quite similar in its σ-EW ($\sigma^- = 0.47$) and π-ED ($\sigma_p^+ = -0.6$) properties. See: Exner, O. *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978.