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Influence of "Remote" Intramolecular Hydrogen Bonds on the Stabilities of Phenoxyl Radicals and Benzyl Cations

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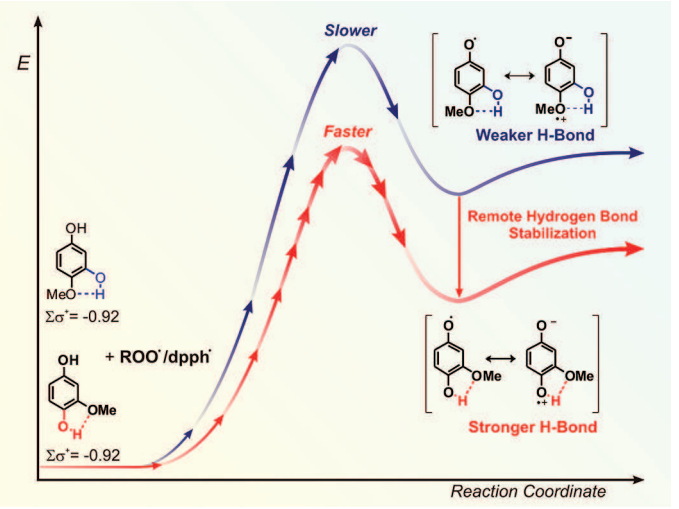

Remote intramolecular hydrogen bonds (HBs) in phenols and benzylammonium cations influence the dissociation enthalpies of their O−H and C−N bonds, respectively. The direction of these intramolecular HBs, para → meta or meta → para, determines the sign of the variation with respect to molecules lacking remote intramolecular HBs. For example, the O−H bond dissociation enthalpy of 3-methoxy-4-hydroxyphenol, **4**, is about 2.5 kcal/mol lower than that of its isomer 3-hydroxy-4-methoxyphenol, **5**, although group additivity rules would predict nearly identical values. In the case of 3-methoxy-4-hydroxybenzylammonium and 3-hydroxy-4-methoxybenzylammonium ions, the CBS-QB3 level calculated C−N eterolytic dissociation enthalpy is about 3.7 kcal/mol lower in the former ion. These effects are caused by the strong electron-withdrawing character of the $-O^{\bullet}$ and $-CH_2^+$ groups in the phenoxyl radical and benzyl cation, respectively, which modulates the strength of the HB. An O−H group in the para position of $ArO^{\bullet}$ or $ArCH_2^+$ becomes more acidic than in the parent molecules and hence forms stronger HBs with hydrogen bond acceptors (HBAs) in the meta position. Conversely, HBAs, such as OCH_3, in the para position become weaker HBAs in phenoxyl radicals and benzyl cations than in the parent molecules. These product thermochemistries are reflected in the transition states for, and hence in the kinetics of, hydrogen atom abstraction from phenols by free radicals (**dpph**$^{\bullet}$ and ROO$^{\bullet}$). For example, the 298 K rate constant for the **4** + **dpph**$^{\bullet}$ reaction is 22 times greater than that for the **5** + **dpph**$^{\bullet}$ reaction. Fragmentation of ring-substituted benzylammonium ions, generated by ESI-MS, to form the benzyl cations reflects similar remote intramolecular HB effects.

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Introduction

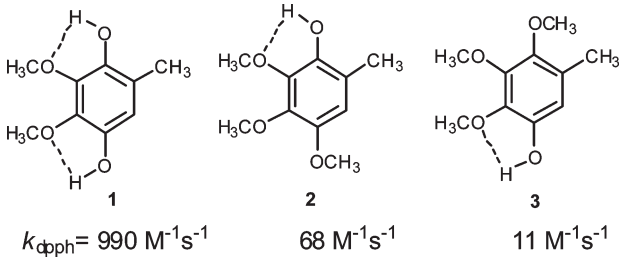
The effects of ring substituents, Y, on YC_6H_4O-H bond dissociation enthalpies (BDEs) are rather well-established.[1] Electron-withdrawing (EW) Y increases and electron-donating (ED) Y decreases YC_6H_4O-H BDEs.[2] These BDEs are very well-correlated by Brown's[3] electrophilic substituent constants, $\sigma^+(Y)$.[1a−c,e] The thermodynamics of YC_6H_4O-H BDEs have kinetic consequences for hydrogen atom abstractions from phenols (ArOH):

$$YC_6H_4O-H + X^\bullet \rightarrow YC_6H_4O^\bullet + X-H \qquad (1)$$

Two of these consequences are that activation energies for reaction 1 decrease and rate constants increase for all $X^\bullet$ radicals as Y becomes a stronger ED group. Further consequences are that $E_{a,1}$ and $\log(k_1)$ correlate with $\sigma^+(Y)$, as has been shown for peroxyl radicals, $X^\bullet = ROO^\bullet$,[4] $X^\bullet$ = 2,2-diphenyl-1-picrylhydrazyl (**dpph**$^\bullet$),[5] and *tert*-butoxyl radicals.[6] These facts become particularly important in situations where phenols are employed (on purpose or by chance) as antioxidants, whether in vitro or in vivo, because the faster reaction 1 ($X^\bullet = ROO^\bullet$) becomes, the more effective (generally) the phenol is as an antioxidant.[7]

Both experiment[8] and theory[9,10] conclude that the electronic effects of *para*-methoxy and *para*-hydroxy[11] on phenolic O−H BDEs are nearly identical.[12] It therefore came as a surprise when two of us[13] discovered that the hydroquinone, ubiquinol-0 (**1**), was more than 10-fold as reactive toward **dpph**$^\bullet$ in alkane solvents[14] as its two monomethyl ethers, **2** and **3** (see Scheme 1). It was later discovered[16] that 2-methoxyhydroquinone, **4**, was much more reactive toward **dpph**$^\bullet$ than 4-methoxyresorcinol, **5**,[17] a result which implies that the "free" O−H BDE in **4** is smaller than in **5**, an implication that contrasts with the prediction that would be made using group additivity rules[10] that these two compounds would have the same free O−H BDEs. The similarly disubstituted phenols, 3,4-dimethoxyphenol, **6**, and sesamol, **7**, both of which lack an intramolecular HB, were of intermediate reactivity (see Scheme 2 and Table 1).

SCHEME 1. Rate Constants for Reactions of Phenols 1−3 with dpph$^\bullet$ in Alkane Solvents at 298 K from Reference 13



The differences in the reactivities of phenols **1**−**3** and **4**−**7** were recognized to arise from the very strong EW character of the incipient O$^\bullet$ atom in the transition state during phenoxyl radical formation (vide infra)[18] and to depend not only on the presence or absence of a "remote" intramolecular hydrogen bond (HB) but also on the *direction* of any such HB. However, this was not specifically commented upon in either report[13,16] because the mechanism of reaction of **dpph**$^\bullet$ with phenols is not straightforward. Computations indicate that the transition state (TS) cannot be described as a "clean" hydrogen atom transfer (HAT, involving primarily 3 electrons and the proton) nor as a "clean" proton-coupled electron transfer (PCET, involving primarily 5 electrons and the proton) but rather as some mixture of these two mechanisms.[16,19] Furthermore, the TSs for these reactions are extremely congested.[16] The possibility that the measured rates for these highly substituted phenols were confounded by interactions of the **dpph**$^\bullet$ with the phenol's substituents (e.g., HB formation, dipole−dipole interactions, etc.) could not be ignored. We therefore withheld comment on the kinetic (and thermodynamic) effects of remote intramolecular HBs until additional kinetic measurements on H-atom abstractions from these phenols could be made using a radical for which the potentially confounding problems in the **dpph**$^\bullet$ reactions would

(1) (a) Mulder, P.; Saastad, O. W.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 4090–4092. (b) Jonsson, M.; Lind, J.; Eriksen, T. E.; Merenyi, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1567–1568. (c) Wayner, D. D. M.; Lusztyk, E.; Ingold, K. U.; Mulder, P. *J. Org. Chem.* **1996**, *61*, 6430–6433. (d) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259–9263. (e) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334–340.

(2) For example,[1b,c,e] $\Delta BDE\{(4\text{-}NO_2C_6H_4O\text{-}H) - (4\text{-}CH_3OC_6H_4O\text{-}H)\}$ = ~10 kcal/mol.

(3) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987.

(4) (a) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744–1751. (b) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2800–2806.

(5) Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 460–477.

(6) Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2816–2825.

(7) See for example: (a) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6475–6477. (b) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194–201. (c) Foti, M. C. *J. Pharm. Pharmacol.* **2007**, *59*, 1673–1685. (d) Foti, M. C.; Amorati, R. *J. Pharm. Pharmacol.* **2009**, *61*, 1435–1448.

(8) Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 928–931.

(9) Pratt, D. A.; de Heer, M. I.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 5518–5526.

(10) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173–1183.

(11) These are two of the strongest ED groups. Although dialkylamino groups are even stronger EDs, they lower the ionization potential of $4\text{-}R_2NC_6H_4OH$ to such an extent that these aminophenols react directly with O_2 and cannot be used as antioxidants. See: (a) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053–7065. (b) Wright, J. S.; Pratt, D. A.; DiLabio, G. A.; Bender, T. P.; Ingold, K. U. *Cancer Detect. Prev.* **1998**, *22*, 204.

(12) It has been concluded that $\sigma_p^+(HO)$ is not −0.92, as originally proposed,[3] but rather that $\sigma_p^+(HO) \approx \sigma_p^+(CH_3O) = -0.78$. (a) See footnote 25 in ref 9. (b) See footnote g to Table 1 and footnote 42 in: Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 11085–11092.

(13) Foti, M. C.; Daquino, C. *Chem. Commun.* **2006**, 3252–3254.

(14) Alkanes are neither HB acceptors nor HB donors, and therefore, kinetic solvent effects due to HB formation between the phenol and solvent do not occur.[5] Furthermore, phenols do not ionize in alkanes, and therefore, the sequential proton-loss, electron-transfer (SPLET) mechanism cannot occur.[15]

(15) (a) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433–3438. (b) Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 5888–5896. (c) Foti, M. C.; Daquino, C.; Geraci, C. *J. Org. Chem.* **2004**, *69*, 2309–2314.

(16) Foti, M. C.; Daquino, C.; Mackie, I. D.; DiLabio, G. A.; Ingold, K. U. *J. Org. Chem.* **2008**, *73*, 9270–9282.

(17) Hydrogen-atom abstractions from **4** and **5** primarily involve the hydroxyl group that is not involved in an intramolecular HB. This is indicated by the k_{dpph} values for phenol, 2-methoxy, 3-methoxy, and 4-methoxyphenol, which are, respectively, 0.1, 0.9, 1.4, and 238 M^{-1} s^{-1} in alkane solvents at 25 °C, and by the *A* factors for these reactions;[16] see also below.

(18) The value of $\sigma_p(O^\bullet) = \sigma_p^+(O^\bullet)$ has been estimated to be as large as 2.0.[12b] This value implies that O$^\bullet$ is a more powerful EW moiety than nitro, $\sigma_p(NO_2) = \sigma_p^+(NO_2) = +0.78$. We are also aware that the possible out-of-plane rotation of the *para*-OMe group in **3** (see Scheme 1) may contribute to making it less reactive than **2**.

(19) For much more detailed descriptions of the HAT and PCET reactions mechanisms see: (a) Mayer, J. M.; Hrovat, D. A.; Thomas, J. L.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 11142–11147. (b) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390. (c) DiLabio, G. A.; Johnson, E. R. *J. Am. Chem. Soc.* **2007**, *129*, 6190–6203.

SCHEME 2. Structures of Phenols 4−15 and Benzylamines 16−28 Used in the Present Study

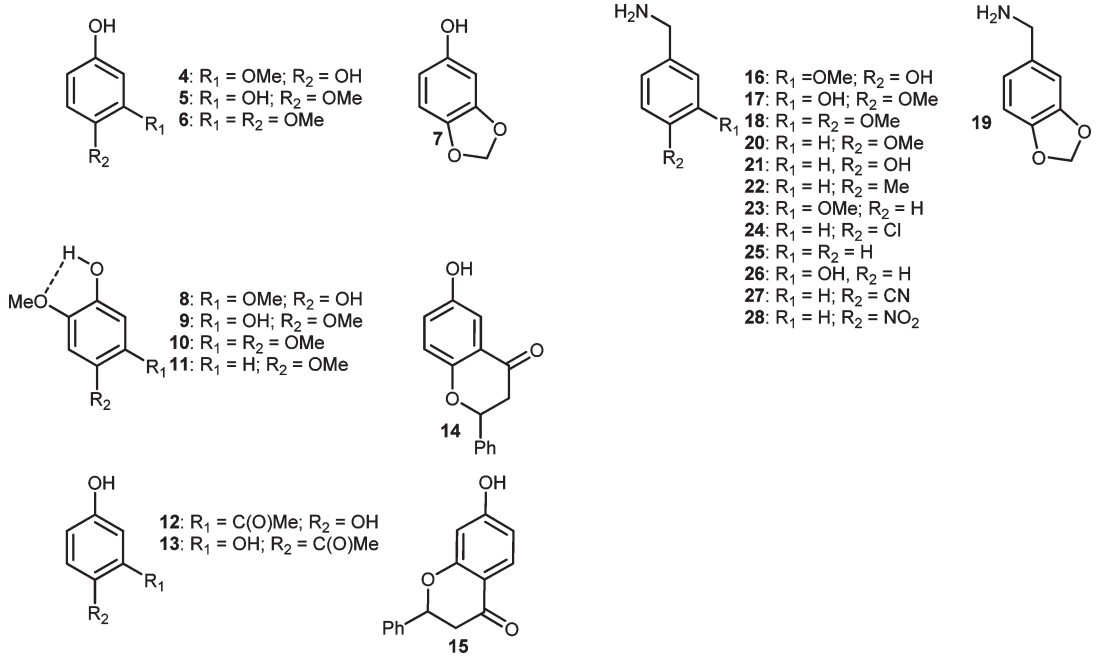


TABLE 1. Arrhenius Parameters (A, M^{-1} s^{-1}, and E_a, kcal/mol) and Rate Constants k_{dpph} (M^{-1} s^{-1}) for the Reaction of Phenols 4−15 with dpph• at 298 K and Rate Constants k_{ROO} (M^{-1} s^{-1}) for the Reaction with ROO• Radicals at 303 K. Experimental (dpph• and EPR Methods, 1 M Standard State) and Calculated (1 atm Standard State) O−H Bond Dissociation Enthalpies (kcal/mol)[a]

					O−H BDE (kcal/mol)			
no. ArOH	$A/10^5$ [b]	E_a [b]	k_{dpph} [c]	$k_{ROO}/10^5$ [d]	dpph[e]	EPR[f]	calcd[g]	additivity[h]
4	11	3.2_5	4400	7.2	80.0	−	80.1	80.9
5	12	5.1	200	2.5	82.1	−	82.6	81.5
6	*12*	*3.8*	1800	4.7	80.4	−	80.3	80.6
7	*12*	*4.2*	935	3.4	80.6	80.8	80.8	−
8	2.3	2.0	*9400*[i]	4.4[i]	≤78.7	78.9	79.7	80.7
9	2.3	3.2	999[i]	1.7[i]	80.0	79.8	80.9	81.3
10	*2.3*	−	1700	3.5	79.3	79.1	−	80.4
11	4.1	4.7	155	0.48	81.5	81.1	82.6	82.3
12	*12*	*5.6*	*97*	1.0	82.6	−	82.5	84.1
13	*12*	*10.8*	*0.015*	−	88.3	−	90.4	86.7
14	*12*	*6.9*	*11*	0.32	84.1	−	85.2	−
15	*12*	*9.7*	*0.09*	−	87.1	−	88.4	−

[a]Some data are from ref 16. To convert from one standard state to the other: O−H BDE (1 atm) = O−H BDE (1 M) + 0.4 kcal/mol; see ref 16. [b]The A factors (in italics) for phenols **6**, **7**, **10**, and **12**−**15** were assumed to be equal to the expected value for free phenolic O−H groups (see ref 16), and the corresponding E_a values (in italics) were calculated from the experimental rate constants. [c]Rate constants determined in cyclohexane and (in italics) rate constants calculated for cyclohexane solvent from measurements made in CH_2Cl_2 (see ref 16); experimental error ±10%. [d]Rate constants determined in chlorobenzene/styrene or cumene; error within ±15%. [e]O−H BDEs obtained from the activation energies of the reaction with **dpph•** (error < ± 1 kcal/mol, ref 16); the O−H BDE of phenol was found to be 86.3 kcal/mol. [f]O−H BDEs obtained by the EPR equilibration technique (error ±0.2 kcal/mol). [g]O−H BDE calculated using the CBS-QB3 approach; the O−H BDE of phenol was calculated to be 87.1 kcal/mol. [h]Calculated using the additive contributions of the individual substituents on the O−H BDE; see the Supporting Information. [i]Not statistically corrected.

be expected to be of much less importance. The peroxyl radical ROO• was chosen for these additional experiments, and the kinetics of its reactions with these same phenols, **4**−**7**, are reported herein. The peroxyl radical was also favored because computations have shown that peroxyl radical + phenol reactions proceed by clean PCET mechanisms, albeit with a cisoid TS being favored over the less congested transoid TS;[19c,20] see also below. In fact, cisoid TSs are surprisingly common in PCET processes.[19c,21]

Because the effects of remote intramolecular HBs on phenoxyl radical stabilities (as reflected by phenol reactivities toward attacking radicals and O−H BDEs) are a consequence of the strong EW character of O• in YC_6H_4O•, it was predicted that similar, or even greater, effects should be observed with benzyl cations, $YC_6H_4CH_2^+$. This prediction has been confirmed in the present work both by mass spectrometric measurements[22] and by theoretical calculations.

Results

Scheme 2 contains the structures of phenols **4**−**7** (with which we are most concerned) and **8**−**15**, and benzylamines **16**−**28** used in the current work. The rate constants k_{dpph} measured in the present work together with some previously reported values[16] and the rate constants k_{ROO} are gathered in Table 1. Also included are values of the free O−H BDEs. These were estimated, as described previously,[16] from the activation energies of the **dpph•** reactions. There is obviously some ambiguity when the molecule in question contains two

(20) Singh, N.; O'Malley, P. J.; Popelier, P. L. A. *Phys. Chem. Chem. Phys.* **2005**, *7*, 614–619.

(21) See for example: (a) DiLabio, G. A.; Ingold, K. U. *J. Am. Chem. Soc.* **2005**, *127*, 6693–6699. (b) Vaidya, V.; Ingold, K. U.; Pratt, D. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 157–160.

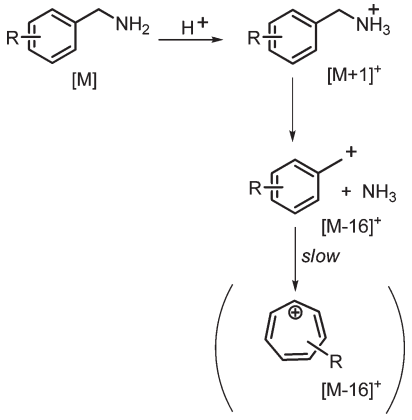
(22) For a recent study on carbocation stabilities by mass spectrometry, see: Ustinov, A. V.; Shmanai, V. V.; Patel, K.; Stepanova, I. A.; Prokhorenko, I. A.; Astakhova, I. V.; Malakhov, A. D.; Skorobogatyi, M. V.; Bernad, P. L., Jr.; Khan, S.; Shahgholi, M.; Southern, E. M.; Korshun, V. A.; Shchepinov, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4593–4608.

(or more) phenolic OH groups in dissimilar environments. When the molecule contains both a free OH group and an OH group involved in an intramolecular HB, it was concluded that the **dpph**• reacted primarily with the free OH.[16,17] It is probably worthwhile exploring this matter again for the phenol structural types relevant to the present paper by comparing the disubstituted phenols, **6**, **7**, and **11**. Compounds **6** and **7** have only a free OH group with alkoxyl groups at the 3 and 4 positions. Compound **11** has only an OH group involved in an intramolecular HB with alkoxyl substitution at the 2 and 4 positions. The ratios of rate constants, $100 \times k_{11}/k_6$, are 8.6 (**dpph**•) and 10.2 (ROO•), while the $100 \times k_{11}/k_7$ ratios are 16.6 (**dpph**•) and 14.1 (ROO•). This indicates that, provided electron donation to the aromatic ring by the substituents is approximately equal, an OH group involved in an intramolecular HB with a methoxyl is only ca. 12% as reactive as a free OH. In phenol **4** that contains both types of OH groups, it certainly would be possible to parse the measured rate constants (and **dpph**• derived O−H BDEs) using this 12% figure. However, such corrections were deemed unnecessary because the changes would probably be less than errors from other sources.

The EPR equilibrium method for measuring O−H BDEs[23] was also employed with phenols **7**−**11**, including the pair of isomeric phenols **8** and **9**, which have the same "remote" substituents as **4** and **5**. Unfortunately, the other phenols yielded phenoxyls that were insufficiently persistent for application of this technique. The EPR-derived O−H BDEs are essentially identical to the values obtained by the **dpph**• method (see Table 1). The O−H BDEs were also calculated for phenols **4**−**9** and **11**−**15** for comparison with the experimental data. The CBS-QB3 methodology, which we have previously shown to accurately predict O−H BDEs, was used for these calculations. The agreement, where comparison is possible, is quite good. The calculated BDEs could be compared directly with those obtained for the additive contributions of each individual substituent, which were derived from separate calculations on the monosubstituted phenols at the same level of theory (see Supporting Information).

Benzyl cations, appropriately substituted for studying the effects of remote intramolecular HBs on their stabilities, were produced in an ESI-MS spectrometer by in-source fragmentation ("in-source collision-induced dissociation")[24] of benzylamines **16**−**28** (see Scheme 2). Extensive studies[25] on benzylpyridinium cations have shown that ion fragmentation depends on several experimental factors, such as pressure, acceleration voltage, nature of the solution, and the gas phase. The initial benzyl cations can isomerize to tropylium ions[25] (see Scheme 3). However, this rearrangement is very unlikely under our conditions because we used the "soft" ESI technique at a low cone voltage.[25,26] In the positive-ion mode with a low cone voltage, the ionization

SCHEME 3. Fragmentation of Substituted Benzylamines in the Electrospray Ion Source



of **16**−**28** provided a pseudomolecular ion, $[M + 1]^+$, and a $[M - 16]^+$ benzyl ion due to NH_3 loss from the $[M + 1]^+$ ion (see Scheme 3 and Figure 1). The relative intensity of these two peaks varies enormously among the differently substituted benzylamines **16**−**28** (see Table 2). The fragmentation ratio (FR) (i.e., the ratio of the peak intensities $[M - 16]^+/[M + 1]^+$) obtained under *identical* experimental conditions increased with increasing ED ability of the substituents (see Table 2 and Figure 2).

The dissociation energies of the benzylammonium ions were also calculated using the same CBS-QB3 approach[27] that was used to compute the O−H BDEs in Table 1. These energies yielded an excellent linear correlation with the log of the intensity ratio $[M - 16]^+/[M + 1]^+$ for all benzylamines, **16**−**28** (see Figure 2). The excellence of this correlation may be due to the fact that there are no potentially confounding media effects since the experiments were conducted in the gas phase. The inset in Figure 2 shows a plot of log(FR) versus $\Sigma\sigma^+$ of the substituents and yields a reasonable straight line. A similar plot of ΔDE versus $\Sigma\sigma^+$ gives a line with $\rho^+ =$ 13.4 kcal/mol (see Supporting Information).

Discussion

Intermolecular HB formation between phenols and HB acceptor (HBA) solvent molecules has long been known to reduce the ability of the phenol to donate a H atom to an attacking radical.[29] These reductions in the rates of H-atom abstraction in HBA solvents have been quantified using Abraham's parameters for HBA activity of the solvent and HB donor (HBD) activity of the phenol.[5] With few exceptions (see below), intermolecular HBs between phenol and solvent reduce the phenol's reactivity.[5] In contrast, "proximate" intramolecular HBs in aryl-1,2-diols and naphthalene-1,8-diols cause these diols to be better H-atom donors than most phenols.[30] This is because the O• atom in a

(23) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259–9263.
(24) Gabelica, V.; De Pauw, E. *Mass Spectrom. Rev.* **2005**, *24*, 566–587.
(25) (a) Katritzky, A. R.; Watson, C. H.; Dega-Szafran, Z.; Eyler, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 2471–2478. (b) Collette, C.; De Pauw, E. *Rapid Commun. Mass Spectrom.* **1998**, *12*, 165–170. (c) Gabelica, V.; De Pauw; Karas, M. *Int. J. Mass Spectrom.* **2004**, *231*, 189–195.
(26) Isomerization of the benzyl cation to the tropylium cation has a computed activation energy of 32.7 kcal/mol. See: Cone, C.; Dewar, M. J. S.; Landman, D. *J. Am. Chem. Soc.* **1977**, *99*, 372–376.
(27) Montgomery, J. A., Jr.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1994**, *101*, 5900.
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(30) (a) Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Barclay, L. R. C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190–5196. (b) Foti, M.; Ruberto, G. *J. Agric. Food Chem.* **2001**, *49*, 342–348. (c) Lucarini, M.; Pedulli, G. F.; Guerra, M. *Chem.—Eur. J.* **2004**, *10*, 933–939.

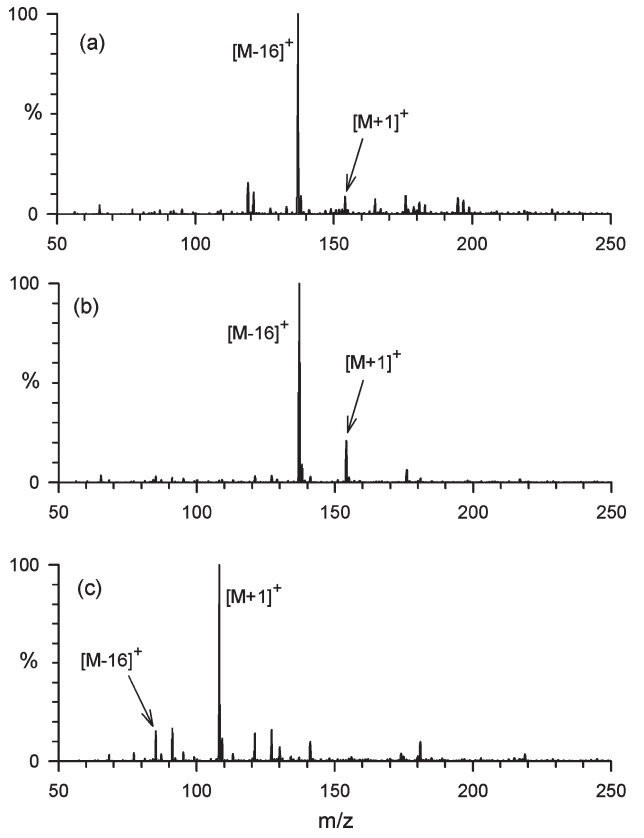


FIGURE 1. Spectra obtained by direct injection of a methanolic solution of benzylamines (2×10^{-5} M) (from the top) **16**, **17**, and **25** in an electrospray mass spectrometer recorded at a 15 V cone voltage.

TABLE 2. Fragmentation Ratio, FR = $[M - 16]^+/[M + 1]^+$, Brown's Electrophilic Substituent Constants, σ^+, and CBS-QB3 Calculated Dissociation Enthalpies (DE) of Benzylammonium Ions

no.	substituent(s)	log FR	$\Sigma\sigma^+$ [a]	DE[b] kcal/mol	ΔDE[c] kcal/mol
16	4-OH, 3-OMe	1.11		26.6	−16.0
17	4-OMe, 3-OH	0.68		30.3	−12.3
18	3,4-di-OMe	1.30	−0.92[d]	24.8 (BA)	−17.8
19	3,4-OCH_2O-	0.67		28.8	−13.8
20	4-OMe	0.93	−0.78	27.7	−14.9
21	4-OH	0.52	−0.78[e]	30.7	−11.9
22	4-Me	−0.18	−0.31	37.3	−5.3
23	3-OMe	−0.50	−0.14[f]	39.5 (*tw*)	−3.1
				42.0 (*aw*)	−0.6
				40.7 (BA)	−1.9
24	4-Cl	−0.51	+0.11	39.3	−3.3
25	H	−0.78	0	42.6	0.0
26	3-OH	−0.76	−0.14[g]	41.3 (*tw*)	−1.3
				43.2 (*aw*)	0.6
				42.9 (BA)	0.3
27	4-CN	−1.08	+0.66	47.2	4.6
28	4-NO_2	−1.32	+0.79	49.5	6.9

[a]From ref 3 unless otherwise noted. [b]Where conformations of different energy were found, they are indicated as follows: *tw* (toward), i.e., with the OMe or OH group pointing toward the $-CH_2^+$; *aw* (away), OMe or OH group pointing away from the $-CH_2^+$; BA, Boltzmann averaged. [c]Calculated with respect to the unsubstituted benzyl cation **25**. [d]By additivity, i.e, −0.78 + (−0.14). [e]Assumed = σ^+ (4-OMe), see ref 12. [f]From ref 28. [g]Assumed = σ^+ (3-OMe).

phenoxyl is a much stronger HBA than the OH group that it replaces in the diol. As a consequence, the intramolecular HB in the diol's semiquinone radical is stronger than in the parent diol, and hence, the O−H BDE of the HBA OH group (i.e., the free OH) is lower than in simple phenols.[8,30]

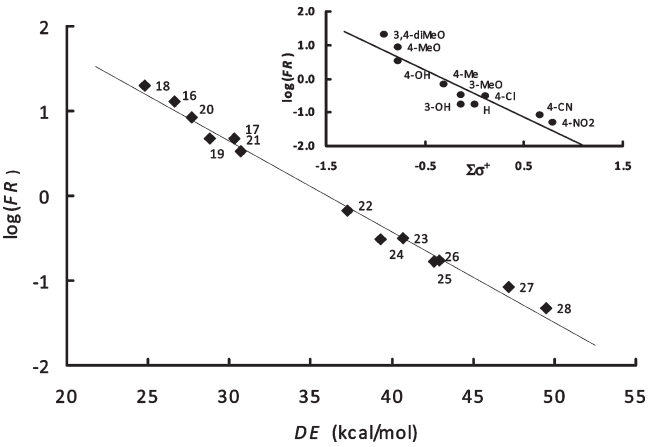


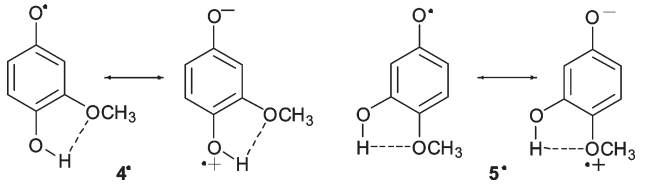
FIGURE 2. Relation between the logarithm of the fragmentation ratio (FR = $[M - 16]^+/[M + 1]^+$) and the calculated dissociation enthalpies of substituted benzylammonium ions. The equation of the best-fit line is log(FR) = −0.11 × DE (kcal/mol) + 3.87 (R^2 = 0.99). Inset: Correlation of log(FR) with the known values of $\Sigma\sigma^+$: log(FR) = $-1.40\Sigma\sigma^+ - 0.45$ (R^2 = 0.87).

Of more relevance in the present context, some of us reported that the addition of small amounts of CH_3CN or DMSO (two strong HBAs) to a CCl_4 solution of 2,5-di-*tert*-butylhydroquinone, *increased* its rate of reaction with **dpph**$^\bullet$ and ROO$^\bullet$ radicals,[31] while larger quantities of either HBA produced the expected rate decrease.[31] These results suggested that the O−H BDE in this hydroquinone is weakened, and its reactivity toward radicals is increased, when the other (remote) OH group forms an intermolecular HB to an added HBA molecule. This decrease in O−H BDE can be assigned to reinforcement, relative to the hydroquinone, of the *intermolecular* HB in the semiquinone radical and, hence, also in the TS leading to hydroquinone formation. This reinforcement arises because the EW O$^\bullet$ atom makes the *para*-OH group more acidic than in the hydroquinone and, hence, a stronger HBD.

The kinetics for the reactions of **dpph**$^\bullet$ with **1** versus **2** and **3** (Scheme 1), **4** versus **6** and **7**, and **8** versus **10** (Scheme 2 and Table 1) are congruent with the effects of low concentrations of HBAs on the kinetics of H-atom abstraction from 2,5-di-*tert*-butylhydroquinone,[31] *except* that it is now the remote *intramolecular* HB in hydroquinones **1**, **4**, and **8** that is strengthened in the TSs of the reactions leading to formation of the semiquinone radicals (see Scheme 4). Conversely, the higher reactivities of **6** and **7** compared with **5** and of **10** compared with **9** (Table 1) indicate that the remote intramolecular HBs in resorcinols **5** and **9** are *weakened* in their phenoxyl radicals. This is because the electron density on the methoxy group in 4-methoxyresorcinol, for example, is reduced in its phenoxyl radical, which makes for a weaker intramolecular HBA in the radical compared with its parent molecule and also in the TS for formation of the radical. This raises the BDE of the free OH (Scheme 4). Thus, the direction of a remote intramolecular HB can either *lower* the free O−H BDE (para → meta intramolecular HB, i.e., hydroquinones with an HBA

(31) Amorati, R.; Franchi, P.; Pedulli, G. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 6336–6338.

SCHEME 4. Resonance Structures with Charge Separation in the Phenoxyl Radicals Derived from 4 and 5



group at the 2 position) or *raise* the free O−H BDE (meta → para intramolecular HB, i.e., resorcinols with an HBA group at the 4 position). Both results are due to the strong EW character of the O• substituent. Similar intramolecular HB effects explain the decreased reactivity of **14** in comparison to **12** and of **13** in comparison to **15**. These compounds can serve as models for studying intramolecular HB effects in many natural polyphenols, such as hesperitin and quercetin (the structures of which are presented in the Supporting Information).

Phenols are considerably more reactive toward peroxyls than toward **dpph**• for both thermodynamic, viz. BDE(ROO−H) ≈ 88 and BDE(**dpph**−H) = 78.9 kcal/mol, and steric reasons.[16] Importantly, the four phenols of primary concern exhibit the same pattern of reactivities toward both of these radicals, that is, **4** > **6** > **7** > **5** (see Table 1). Consistently, phenols **8**−**10**, analogues of **4**−**6**, follow the same pattern of reactivity toward **dpph**• and ROO•, that is, **8** > **10** > **9** (see Table 1). The order of reactivity of these phenols to both **dpph**• and peroxyl radicals are, therefore, unlikely to be due to any "special" effects related to either radical. Instead, they simply reflect the differences in the ArO−H BDEs (and thus in the E_a of the transition states;[16] see Table 1), which we suggest are due to the absence or presence *and* the direction of remote intramolecular HBs.[32] We can see this directly in the calculated structures and activation enthalpies for the reactions of phenols **4** and **5** with methylperoxyl (a model peroxyl), as is shown in Figure 3. While both **4** and **5** have preferred transition state structures for the reaction that features the expected (vide supra) cisoid geometry to facilitate the PCET reaction, the calculated activation enthalpy is lower by 1.7 kcal/mol for **4** relative to **5**.

Thermodynamic effects of remote intramolecular HBs on the O−H BDEs in phenols underlie the more readily measured kinetic effects ($k_{\mathbf{dpph}}$ and k_{ROO}). The O−H BDEs obtained by EPR agreed with the values obtained by the **dpph**• method[16] to within ±0.4 kcal/mol (see Table 1). A similar agreement was also found between calculated and **dpph**• derived O−H BDEs (see Table 1), confirming the reliability, that is, the "authenticity", of O−H BDEs determined by the **dpph**• method. Of course, remote intramolecular HBs produce small, but significant, differences between measured or calculated O−H BDEs and values estimated using group additivity principles,[10] for example, ($BDE_{calculated}$ − $BDE_{additivity}$)/kcal/mol = −0.8 (**4**), +1.1 (**5**), but only −0.3 for **6** which has no remote intramolecular HB (see Table 1).[33]

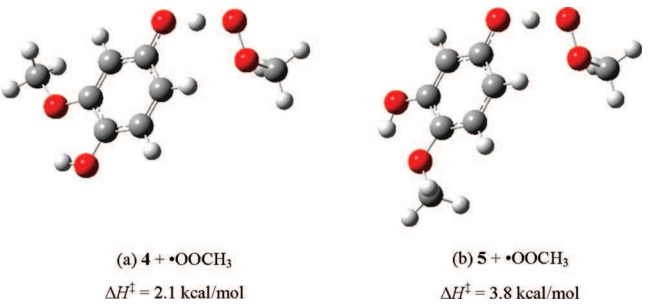


FIGURE 3. Calculated (UB3LYP/CBSB7) minimum energy transition state structures for the reactions of phenols **4** and **5** with methylperoxyl radical. The given calculated enthalpies of activation were determined at the same level and are Boltzmann-averaged (to include the contributions of higher energy conformers) relative to H-bonded pre-reaction complexes.

The origin of the above-described effects on the kinetics and thermodynamics of H-atom abstractions from phenols lies in the strong EW nature of O• in $XC_6H_4O^•$. Similar, but larger, effects were therefore predicted to be present in benzyl cations, $XC_6H_4CH_2^+$. These were generated from benzylamines (see Results and Scheme 3). Formation of the $[M - 16]^+$ benzyl ion by loss of NH_3 from the $[M + 1]^+$ ion (see Scheme 3 and Figure 1) was favored by ED substituents that stabilize the benzyl cation (see inset in Figure 2). The plot of the logarithm of the intensity ratio $[M - 16]^+/[M + 1]^+$ against the calculated dissociation enthalpies (DE) of the benzylammonium ions gave an excellent linear relation (see Figure 2). Remote HB effects are quite apparent. For example, the substituent pattern for the benzylammonium ion pair, **16** and **17**, is the same as the pattern seen for the phenol pair, **4** and **5**. As predicted, the remote HB-induced differences between the DE values for formation of the two benzyl cations is slightly greater than the differences in O−H BDEs between the correspondingly substituted phenols, viz. $\Delta DE_{calculated}$/kcal/mol: (**17** − **16**) = +3.7, versus ΔOH $BDE_{calculated}$/kcal/mol: (**5** − **4**) = +2.5 kcal/mol. Surprisingly, although the appropriate 3,4-disubstituted phenols that lack remote intramolecular HBs, such as **6** and **7**, exhibit reactivities toward radicals that are intermediate between those of **4** and **5** (see Table 1), the analogously substituted benzylammonium ions lacking remote intramolecular HBs, such as **18** and **19**, do not show the same pattern with the **18** ion fragmenting slightly more readily than the **16** ion and fragmentation of the **19** ion occurring as readily as for the **17** ion (see Table 2). We prefer not to speculate on the origin of these differences between the

(32) Though not directly related to the main thrust of the present paper, there is a sometimes an unrecognized factor that plays an important role in determining both the absolute magnitudes and the patterns of reactivity of phenols toward free radicals. Comparison of the disubstituted phenols, **4**, **5**, and **6** (all of which have one "free" OH group that is presumed to be the main site of reaction[16]) with the "comparable" trisubstituted phenols, viz. **8**, **9**, and **10**, respectively, shows that the trisubstituted phenols are as reactive as their disubstituted counterparts despite their lack of a free OH group. In more detail, toward **dpph**•, the pairwise relative reactivities are **8** > **4**; **10** ∼ **6**; **9** > **5**; and toward ROO•, they are reversed, viz. **8** < **4**; **10** < **6**; **9** < **5**; these orders are essentially maintained whether or not a statistical correction is applied to **8** and **9**. Despite the absence of a free OH, the trisubstituted phenols tend to be more active towards **dpph**• than the disubstituted phenols, but this is not the case for ROO• radicals. These patterns suggest that polar effects are important in stabilizing the TSs in these reactions, being more important for the very electron deficient **dpph**• than for ROO• and being more important for the phenols substituted with three electron-donating substituents than for those with only two such substituents, such as charge-separated contributions to the TS of the type:

$$[X^•ArOH \leftrightarrow X^- ArOH^{•+}]^‡$$

are more important when X• = **dpph**• than when X• = ROO•.

(33) Relevant isodesmic reactions are given in the Supporting Information.

properties of phenols, **4**, **5**, **6**, and **7**, and the properties of the corresponding benzylammonim ions, **16**, **17**, **18**, and **19**.[33]

In summary, *remote* intramolecular HBs, O−H → OCH_3, have appreciable thermodynamic effects on the O−H BDEs of phenols and the DE values of with benzylammonium ions and hence on the kinetics of many of their reactions. These effects are due to the strong EW ability of $O^{\bullet}$ and CH_2^+ groups. Intramolecular *para*-OH → *meta*-OCH_3 HBs weaken, while intramolecular *meta*-OH → *para*-OCH_3 HBs strengthen both the O−H BDEs and the benzylammonium ion DEs compared with similarly substituted (e.g., 3,4-dimethoxy) molecules lacking an intramolecular HB.

Experimental Section

General. The procedures (and some kinetic results) for the **dpph**$^{\bullet}$ reactions in saturated hydrocarbon solvents (cyclohexane or *n*-hexane) at 298 K have been presented previously.[16] The rate constants for the $ROO^{\bullet}$ + ArOH reactions were determined from rates of azo-initiated, phenol-inhibited autoxidation of styrene (in chlorobenzene) or of cumene at 30 °C.[4a,b,11a,34] The O−H BDEs of phenols were experimentally determined from the activation energies[16] of ArOH + **dpph**$^{\bullet}$ reactions and, in the case of persistent phenoxyl radicals, by the EPR radical equilibration technique.[23] All solvents and compounds (except for **8**,[16] **9**,[16] and **10**) were purchased at high purity from commercial suppliers.

ESI-MS Measurements. Mass spectra of the benzylamines (2×10^{-5} M in MeOH) were obtained by direct infusion with a microsyringe pump (15 μL/min) into a Micromass ZMD ESI-MS spectrometer using the following instrumental settings: positive ions; desolvation gas (N_2), 250 L/h; cone gas (skimmer), 22 L/h; desolvation temperature, 100 °C; capillary voltage, 3.0 kV; cone voltage, 10−40 V; hexapole extractor, 3 V; RF lens, 0.3 V.

Theoretical Calculations. All calculations were carried out using the CBS-QB3 method of Petersson and co-workers[27] as it is implemented in the Gaussian 03[35] suite of programs, compiled to run on Sun Microsystems SunFire 25000 or Enterprise M9000 servers with UltraSPARC-IV+ or Sparc64 VII CPUs, respectively.

Synthesis of 10. Hydroquinone, **8**[16] (100 mg, 0.59 mmol), was dissolved in 2 mL of DMSO, and the solution was degassed with argon, followed by the addition of 23.6 mg of 60% pure NaH (0.59 mmol). This solution was left under stirring until effervescence ceased (ca. 15 min), after which about 6 mmol of CH_3I was added and left to react under argon for about 1 h at room temperature. After this, the solution was acidified with 2 N HCl and extracted with ethyl acetate (3×60 mL). The organic phase was washed in succession with $NaHCO_3$ solution, water, and brine and then dried over Na_2SO_4, filtered, and the solvent removed. The residue was purified by chromatography on silica gel. The initial eluent was a mixture of hexane, CH_2Cl_2, and CH_3OH in a volume ratio of 50:50:0.5, respectively. This was gradually changed to 100% CH_2Cl_2. The final yield of **10** was 45%: ^{1}H NMR (400.13 MHz in acetone-d_6) three resolved singlets at δ 3.74, 3.75, and 3.79 (3H each, three nonequivalent OCH_3), two singlets at δ 6.56 (1H) and 6.71 (1H), and a singlet at δ 7.18 (1H, OH, which disappeared upon addition of D_2O); ^{13}C NMR (100.62 MHz in acetone-d_6) δ 55.9, 56.5, and 56.7 ppm (OCH_3); 101.7 and 102.3 ppm (CH); 140.6, 140.7, 142.3, 144.3 ppm (quaternary Cs); ESI-MS in the negative ion-mode gave a base peak at m/z 183 $[M - H]^-$.

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Supporting Information Available: Computational data, plot of ΔDE vs $\Sigma\sigma^+$; calculated enthalpies of isodesmic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

(34) (a) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 1851–1864. (b) Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1975; Vol. 2, Chapter 12. The oxidations were followed by monitoring the oxygen uptake using the automatic recording gas absorption apparatus previously described. See: (c) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142–2146.

(35) All calculations were performed using Gaussian 03: 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.; 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.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Pittsburgh PA, 2003.