Preparation, Structural Characterization, and Thermochemistry of an Isolable 4-Arylphenoxy Radical

Thomas R. Porter,† Werner Kaminsky,† and James M. Mayer*‡§

†Department of Chemistry, University of Washington, Box 351700, Seattle, Washington 98195-1700, United States
‡Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520, United States
§Supporting Information

ABSTRACT: The preparation and full characterization of the 4-(nitrophenyl)-phenoxy radical, 2,6-di- tert-buty1-4-(4′-nitrophenyl) phenoxy radical (Bu3NPArO⁻) is described. This is a rare example of an isolable and crystallographically characterized phenoxy radical and is the only example in which the parent phenol is also crystallographically well-defined. Analysis of EPR spectra indicates some spin delocalization onto the secondary aromatic ring and nitro group. Equilibrium studies show that the corresponding phenol has an O–H bond dissociation free energy (BDFE) of 77.8 ± 0.5 kcal mol⁻¹ in MeCN (77.5 ± 0.3 kcal mol⁻¹ in toluene). This value is higher than related isolated phenoxy radicals, making this a useful reagent for hydrogen atom transfer (HAT) studies. Additional thermochemical and spectroscopic parameters are also discussed.

INTRODUCTION

Stable and transient phenoxy radical species are important in chemical processes spanning a large range of applications. Examples include tyrosine/tyrosyl radical mediated enzymatic electron transfers and hydrogen atom transfers,¹ food preservation (such as butylated hydroxytoluene or BHT),² and fundamental studies of proton-coupled electron transfer (PCET)/hydrogen atom transfer (HAT) reactions.³ While most phenoxy radicals are transient, sufficiently sterically encumbered phenoxy radicals can be stable in solution under anaerobic conditions.⁴ The 2,6-di- tert-butyl-4-phenylphenoxyl radical (Bu2NPArO•), for instance, was prepared by Müller and co-workers in 1959, and isolated in 78–88% purity.⁵ Our laboratory has reported the clean isolation and structural characterization of the 2,6-di- tert-butyl-4-methoxyphenoxy radical (Bu2MeOArO•).⁶ The latter has a very weak C–C bond and is primarily dissociated in solution. The O–H bond dissociation free energies (BDFEs) of the 2,6-di- tert-butyl-6-R-phenols are significantly modulated by the R substituent. The H atom affinities of the corresponding phenoxy radicals (described by phenolic O–H BDFEs) range from 73.8 kcal mol⁻¹ for the isolable ² R = OMe species to 80.4 kcal mol⁻¹ for the transiently lived ⁸ R = NO₂ species (BDFEs in toluene), with the R = Bu and Ph derivatives being the same within error.⁹ The isolable R = Bu and OMe derivatives have proved to be useful hydrogen atom accepting reagents,¹⁰ complementary due to their different hydrogen atom affinities.¹⁰a,b With the goal of preparing an isolable phenoxy radical with a higher H atom affinity, we report here the preparation, full characterization, and thermochemistry of 2,6-di- tert-butyl-4-(4′-nitrophenyl)phenoxy radical, or Bu3NPArO•.

RESULTS AND DISCUSSION

Bu3NPArO• was prepared by treating a benzene solution of 2,6-di- tert-butyl-4-(4′-nitrophenyl)phenol, Bu3NPArO-H,¹¹ with aqueous 1 M sodium hydroxide and potassium ferricyanide under anaerobic conditions. After 30 min, removal of the solvent under vacuum, extraction of the dark green material with pentane, and crystallization at −30 °C over 24 h yielded black crystals. These were found to be of high purity from elemental analysis and the ¹H NMR spectra showed only minor diamagnetic impurities (<5%; see the Supporting Information).

High-quality X-ray crystal structures of Bu3NPArO• and its parent phenol were collected for structural comparison (Figure 1, Table 1). This type of direct structural comparison of a phenoxy radical/phenol has previously not been possible. The parent phenol of the only previously structurally characterized phenoxy radical, Bu3ArO-H, was found to be disordered over three positions in its crystals.⁶

Figure 1. ORTEP drawing of Bu3NPArO• showing 50% probability thermal ellipsoids and labels for select atoms. Hydrogen atoms are omitted for clarity.

Received: July 10, 2014
Published: September 3, 2014
The largest difference between the phenoxy and phenol structures is in the O1–C1 bond distance, 1.251 vs 1.379 Å. This bond shortening of 0.128 Å is consistent with previous angle measured for C5 vs 31.9°.

Table 1. Select Bond Lengths (Å) and Aryl–Aryl Torsion Angles (deg) of 'Bu$_2$NPArO$^*$ and 'Bu$_2$NPArO-H

|            | 'Bu$_2$NPArO$^*$ | 'Bu$_2$NPArO-H | difference |
|------------|------------------|----------------|------------|
| O1–C1      | 1.2509(14)       | 1.3794(12)     | −0.1285(18)|
| C1–C2      | 1.4699(17)       | 1.4100(14)     | 0.0599(22) |
| C2–C3      | 1.3696(16)       | 1.3944(13)     | −0.0248(21)|
| C3–C4      | 1.4194(16)       | 1.3928(13)     | 0.0266(21) |
| C4–C5      | 1.4228(17)       | 1.3964(13)     | 0.0264(21) |
| C5–C6      | 1.3711(16)       | 1.3941(14)     | −0.0230(21)|
| C6–C1      | 1.4751(16)       | 1.4120(14)     | 0.0631(21) |
| C4–C7      | 1.4754(16)       | 1.4829(13)     | −0.0075(21)|
| C7–C8      | 1.4069(17)       | 1.4008(14)     | 0.0061(22) |
| C8–C9      | 1.3833(17)       | 1.3861(14)     | −0.0028(22)|
| C9–C10     | 1.3873(18)       | 1.3839(15)     | 0.0034(23) |
| C10–C11    | 1.3828(19)       | 1.3842(15)     | −0.0014(24)|
| C11–C12    | 1.3842(17)       | 1.3853(14)     | −0.0011(22)|
| C12–C7     | 1.4114(16)       | 1.4023(14)     | 0.0099(21) |
| C10–N1     | 1.4272(16)       | 1.4672(13)     | −0.0400(21)|
| N1–N2      | 1.2262(16)       | 1.2312(13)     | −0.0050(21)|
| N1–N3      | 1.2289(16)       | 1.2286(13)     | −0.0003(21)|
| avg Ar–Ar torsion angle$^*$ | 17.5(1) | 31.9(1) | −14.4(1) |

$^*$Average aryl–aryl torsion angle (deg) refers to the average dihedral angle measured for C5–C4–C7–C12 and C3–C4–C7–C8.

The Journal of Organic Chemistry

The X-band CW EPR spectrum of 'Bu$_2$NPArO$^*$ in toluene displays a multiline pattern centered at $g = 2.007(2)$ that is well modeled by simulation (Figure 2). Hyperfine coupling constants were assigned by comparison to previously reported phenoxyl radical data$^9$ and from the structural changes observed in the crystal structure: $a_{3,3}(2H) = 1.80$ G, $a_{8,12}(2H) = 1.61$ G, $a_{3,3}(2H) = 0.74$ G and $a_{NO3(1N)} = 0.50$ G.$^{14}$ The $^{14}$N hyperfine coupling indicates spin density on the nitro group, as depicted in the bottom of Scheme 1. The observed spin density onto the nitro group suggests that the thermochemistry of 'Bu$_2$NPArO$^*$ should be perturbed from that of the unsubstituted 'Bu$_2$PhArO$^*$.

The O–H BDFE of 'Bu$_2$NPArO-H, was determined by equilibration with the thermochemically well-established$^{5a}$ 'Bu$_2$ArO$^*$ radical. In either acetonitrile-$d_3$ or toluene-$d_8$, a known concentration of 'Bu$_2$NPArO-H was combined with several different concentrations of 'Bu$_2$ArO$^*$ (eq 1).

\[ \text{Bu}_2\text{NPArO-H} + \text{Bu}_2\text{ArO}^* \rightarrow \text{Bu}_2\text{NPArO}^* + \text{Bu}_2\text{ArO-H} \]

Integration of the $^1$H NMR signals of these solutions gave equilibrium concentrations from which equilibrium constants were determined: $K_{eq}(\text{acetonitrile}) = 0.25 \pm 0.03$, $K_{eq}(\text{toluene}) = 0.26 \pm 0.03$. Thus, the O–H bond in 'Bu$_2$NPArO-H is 0.8 ± 0.1 kcal mol$^{-1}$ stronger than that in 'Bu$_2$Ar-O-H in both acetonitrile and toluene. Using the known BDFE values of 'Bu$_2$Ar-O$^*$ and eq 2 gives BDFE('Bu$_2$NPArO-H$_{MeCN}$) = 77.8 ± 0.5 kcal mol$^{-1}$ and BDFE('Bu$_2$NPArO-H$_{tol}$) = 77.5 ± 0.5 kcal mol$^{-1}$. While this is a small increase, 'Bu$_2$NPArO$^*$ is to our knowledge the thermodynamically strongest isoleptic, reagent quality organic hydrogen atom abstractor available.

\[ \text{BDFE('Bu}_2\text{NPArO-H)} = \text{BDFE('Bu}_2\text{ArO-H)} - RT \ln(K_{eq}) \]

(2)

Pedulli and co-workers have previously reported an empirical correlation between the O–H bond strengths of 2,6-tert-butyl-substituted phenols with the EPR hyperfine coupling constants, $a_{3,3}$, of the corresponding phenoxyl radicals.$^{26}$ Figure 3 shows a slightly modified version of this correlation using revised BDFE values.$^{15}$ The values for 'Bu$_2$NPArO$^*$ follow this correlation very closely.

Cyclic voltammetry of 'Bu$_2$NPArO$^*$ in acetonitrile with 0.1 M [$^3$Bu$_2$N]PF$_6$ as a supporting electrolyte displayed a reversible couple with $E_{1/2} = −0.436 \pm 0.010$ V vs FC$^{+/−}$. This value is 0.26

Scheme 1. Radical Resonance Forms of 'Bu$_2$NPArO$^*$

![Scheme 1. Radical Resonance Forms of 'Bu$_2$NPArO$^*$](image)
This is much larger than the reported potential, $E_a$ is presumably irreversible due to loss of the proton from the potential, $E_a^\dagger$ (Scheme 2). We have included the irreversible anodic peak significance of the (nitrophenyl)phenol has a 9 units lower than that of the phenol.

The reduction potential of $Bu_2NPArO-H$ is due to the shifts in $pK_a$ and $E^\circ$ not exactly in free energy terms. These values can be assembled into a square scheme that describes the PCET thermochemistry of $Bu_2NPArO-H$ (Scheme 2). We have included the irreversible anodic peak potential, $E_{a,p}$ even though it is not a thermochemical value. Using this value to crudely estimate the PCET thermochemistry of $Bu_2NPArO-H$ is due to the shifts in $pK_a$ and $E^\circ$ not exactly in free energy terms.

In conclusion, the $4$-(nitrophenyl)phenoxyl radical $Bu_2NPArO^+$ is a previously unreported phenoxyl radical that is easily prepared in high purity and reasonable yield. Equilibrium studies show that the $Bu_2NPArO-H$ BDFE is modestly stronger than that of its unsubstituted isoal relative, $Bu_3PhArO^+$ ($\Delta BDFE_{toluene} = 0.8$ kcal mol$^{-1}$).

$Bu_2NPArO-H$ has the highest reported BDFE of any isoal organic hydrogen atom acceptor: $77.8 \pm 0.5$ kcal mol$^{-1}$ in acetonitrile and $77.5 \pm 0.5$ kcal mol$^{-1}$ in toluene. The combination of easy isolation of the phenoxyl radical in pure form and its relatively high hydrogen atom affinity should make this a useful reagent for studying hydrogen atom transfer reactions.

### EXPERIMENTAL SECTION

**Materials.** Unless otherwise noted, all chemicals were purchased from commercial sources and used without purification. Toluene was dried using a “Grubb’s type” Seca Solvent System. Acetonitrile was purchased from Burdick & Jackson (low-water brand) and stored in an argon-pressurized glovebox plumbed directly into the glovebox. Toluene-$d_8$ and acetonitrile-$d_3$ were dried over NaK and CaH$_2$, respectively, and vacuum distilled. $Bu_2ArO$ and $Bu_2NPArOH$ were prepared following literature methods.

**Synthesis of $Bu_2NPArO$.** A 100 mL two neck round-bottom flask was charged with 467 mg (1.43 mmol) of $Bu_2NPArOH$ dissolved in ~15 mL of benzene, 5 mL of 1 M NaOH and a stir bar. The flask was fitted with a 180° Schlenk adapter on one neck and a solid addition funnel containing 1.20 g (3.64 mmol) of solid K$_3$Fe(CN)$_6$, on the other neck. The biphasic mixture was degassed by 3 sequential freeze–pump–thaw cycles. After degassed, the mixture was frozen and the K$_3$Fe(CN)$_6$ was added. The frozen mixture was allowed to thaw at room temperature and left to stir. After 1 h of stirring, the solvents were removed in vacuo and extracted with pentane. Crystals were grown from a saturated pentane solution at $30^\circ$C. Yield: 279 mg, 52%. Anal. Calcd for C$_{20}$H$_{24}$NO$_3$: C, 73.59; H, 7.41; N, 4.29. Found: C, 73.88; H, 7.60; N, 4.34.

### ASSOCIATED CONTENT

**Supporting information**

NMR and optical spectra, BDFE calculations, electrochemical data, crystallographic information, and an ORTEP of $Bu_2NPArOH$. This material is available free of charge via the Internet at http://pubs.acs.org.

### AUTHOR INFORMATION

**Corresponding Author**

*E-mail: james.mayer@yale.edu.*

**Present Address**

Department of Chemistry, Yale University, 225 Prospect St, New Haven, CT 06520.

**Notes**

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the US National Institute of Health (2R01GM054422). We thank Professor Stefan Stoll for useful discussions about EPR simulation.
REFERENCES

(1) (a) Styring, S.; Sjöholm, J.; Mamedov, F. Biochim. Biophys. Acta 2012, 1817, 76. (b) Reece, S. Y.; Nocera, D. G. Annu. Rev. Biochem. 2009, 78, 673. (c) McEvoy, J. P.; Brudvig, G. W. Chem. Rev. 2006, 106, 4455. (d) Whittaker, J. W. Chem. Rev. 2003, 103, 2347.

(2) Babich, H. Environ. Res. 1982, 29, 1.

(3) (a) Warren, J. J.; Tronic, T. T.; Mayer, J. M. Chem. Rev. 2010, 110, 6961. (b) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. Chem. Rev. 2012, 112, 4016.

(4) Altwicker, E. R. Chem. Rev. 1967, 67, 475.

(5) (a) Müller, E.; Schick, A.; Scheffler, K. Chem. Ber. 1959, 92, 474. (b) Related 4-tolyl- and 4-anisyl-phenoxyl radicals have been reported but not isolated; see ref 4.

(6) Manner, V. W.; Markle, T. F.; Freudenthal, J. H.; Roth, J. P.; Mayer, J. M. Chem. Commun. 2008, 256.

(7) Wittman, J. M.; Hayoun, R.; Kaminsky, W.; Coggins, M. K.; Mayer, J. M. J. Am. Chem. Soc. 2013, 135, 12956.

(8) Cook, C. D.; Gilmour, N. D. J. Org. Chem. 1960, 25, 1429.

(9) (a) Brigati, G.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. J. Org. Chem. 2002, 67, 4828. (b) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. J. Org. Chem. 1996, 61, 9259. (c) Lucarini, M.; Pedulli, G. F. Chem. Soc. Rev. 2010, 39, 2106. (d) Reiker, A.; Scheffler, K. Justus Liebigs Ann. Chem. 1965, 689, 78.

(10) (a) Waidmann, C. R.; Zhou, X.; Tsai, E. A.; Kaminsky, W.; Hrovat, D. A.; Borden, W. T.; Mayer, J. M. Am. Chem. Soc. 2009, 131, 4729. (b) Warren, J. J.; Mayer, J. M. Proc. Natl. Acad. Sci. U. S. A. 2010, 107, 5282. (c) Valdez, C. N.; Braten, M. B.; Soria, A.; Gamelin, D. R.; Mayer, J. M. J. Am. Chem. Soc. 2013, 135, 8492. (d) Schrauben, J. N.; Hayoun, R.; Valdez, C. N.; Braten, M. M.; Fridley, L.; Mayer, J. M. Science 2012, 338, 1298. (e) Manner, V. W.; Lindsey, A. D.; Mader, E. A.; Altwicker, J. E.; Mayer, J. M. Chem. Sci. 2012, 3, 230. (f) Warren, J. J.; Mayer, J. M. J. Am. Chem. Soc. 2011, 133, 8544. (g) Mader, E. A.; Manner, V. W.; Markle, T. F.; Wu, A.; Franz, J. A.; Mayer, J. M. J. Am. Chem. Soc. 2009, 131, 4335.

(11) Chern, Y. T.; Ju, M. H. Macromolecules 2009, 42, 169.

(12) (a) O’Malley, P. J. J. Phys. Chem. B 2002, 106, 12331. (b) Xie, C.; Lahti, P. M.; George, C. Org. Lett. 2000, 2, 3417.

(13) Average torsion angle refers to the average dihedral angle measured for atoms C3–C4–C7–C8 and C5–C4–C7–C12.

(14) EPR hyperfine coupling constants reported have an assumed error margin of ~±0.05 G.

(15) The correlation in ref 9a used bond dissociation enthalpies (BDEs), which were determined from equilibration experiments. ΔBDE values were obtained from these equilibrium constants and then converted to BDEs using a gas-phase BDE of 'Bu3ArO-H. Here, we take their equilibrium constants to be ΔBDFEs and scale them to the reported BDFE of 'Bu3ArO-H in benzene.3

(16) (a) Steuber, F. W.; Dimroth, K. Chem. Ber. 1966, 99, 258. (b) Values reported in (a): $E_{1/2}( Bu_3PhArO^{+} ) = -0.014 V$; $E_{1/2}( Bu_3ArO^{+} ) = -0.059 V$ (both vs Ag/AgCl; in 9:1 MeCN/H$_2$O). $0.01m$ [Me$_4$N$^+$][OH$^-$], $0.01m$ [Me$_4$N$^+$][Cl$^-$]).

(17) The pK$_a$ of 'Bu$_3$PhArO-H is taken to be roughly equal to the pK$_a$ of 'Bu$_3$ArO-H (~28 in MeCN; ref 3) since their BDFEs and E° are roughly equivalent.

(18) C$_S$ is a constant that contains the free energy of formation of H*, free energy of solvation of H*, as well as the nature of the electrode. In MeCN, C$_S$ = 4.9 kcal mol$^{-1}$. A more detailed description can be found in ref 3.

(19) Chern, Y. T.; Ju, M. H. Macromolecules 2009, 42, 169.