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Remote aromatic stabilization in radical reactions

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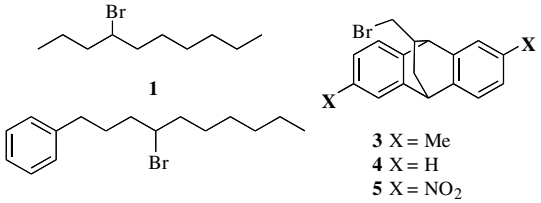
Abstract

The rates of free radical reduction of a series of anthracene derivatives and 1-phenyl-4-bromodecane with tributyltin hydride are mediated by the remote aromatic substituent in an apparent through-space interaction. Density functional calculations suggest that this enhancement is not due to direct stabilization of the free radical intermediate, and is likely to be achieved through the interaction of the aromatic moiety with the polarized transition state leading to the intermediate.

Cation-π and, to a lesser extent, anion-π interactions have been clearly established as having important influences on the structural stability of biological and designed macromolecular systems. The influence of these interactions on the reactivity of cation intermediates was dramatically shown in the 1960s with the pioneering experiments of Cram.[1] Since this time, much literature on cation–aromatic stabilization,[2,3] and growing literature on possible anion–aromatic interactions[4–7] have appeared. The potential influence of aromatic moieties on radical reactions has been established for radical chlorination reactions, where an aromatic solvent effect for free radical chlorination reactions was first described by Russell in the late 1950s.[8–11] Additionally, it has been reported that aromatic solvents may play a role in mediating the radical polymerization of methyl methacrylate.[12] It has been established that radical cations can be directly stabilized by electron-rich π-systems.[13,14]

Anchimeric assistance in radical reactions is quite rare and reports have mostly been restricted to 1,3 neighbouring group effects. Recently, it has been reported that the rate of radical reactions can be influenced through electron donation by neighbouring groups located 1,4-, 1,5- and 1,6- to the site of radical formation.[15,16] In particular, amido groups are able to stabilize the transition state of a hydrogen abstraction reaction from a benzylic position better than the corresponding ester. In the case of phenylalanine derivatives, the corresponding halogen-abstraction reaction with tri-butyltin hydride, where an electron-rich centre forms during the transition state, showed no rate difference between esters and amides. This is consistent with the neighbouring group interaction preferentially donating electron density to the positively polarized transition state of the hydrogen abstraction.[17,18]

Here, we report preliminary evidence for remote involvement of an aromatic ring in halogen-abstraction reactions. We have examined the relative rates of halogen abstraction by tri-butyltin hydride in standard competitive experiments for three classes of model systems: a non-aromatic control **1**, non-rigid 1-phenyl-4-bromodecane **2** and rigid anthracene derivatives **3**–**5**. DFT calculations have been carried out on molecules **3**–**5** and their corresponding radicals.



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The anthracene derivatives **3**–**5** were selected because of their relative ease of synthesis and rigid geometries, which hold the putative radical above the aromatic cloud. Related models have also been successfully used to examine cation–π interactions.[19]

Model systems **1**–**5** were prepared from commercially available reagents as supplied, without further purification unless otherwise stated. All reactions that required an inert atmosphere were carried out under Schlenk conditions using either dry nitrogen or dry argon as the inert gas through a standard nitrogen line. The solvents were distilled and dried by standard methods unless otherwise stated. 4-Bromodecane **1** was synthesized in 96% yield from the corresponding commercially-available alcohol, 4-decanol. The synthesis of 1-phenyl-4-bromodecane **2** was via a two-step process involving initial conversion of 3-bromopropyl benzene to the corresponding Grignard reagent with magnesium turnings in dry ether with iodine catalysis, followed by treatment with one equivalent of heptanal to produce 1-phenyl-4-decanol in 77% yield. Following purification by column chromatography in 50:50 petrol ether/dimethyl ether, this alcohol was treated with two equivalents of triphenylphosphine and two equivalents of carbon tetrabromide to afford derivative **2** in 95% yield.

The unsubstituted derivative **4** was prepared in three steps through a modification of literature methodology.[20] Firstly, Diels-Alder reaction of anthracene with an equivalent each of ethyl acrylate and $AlCl_3$ afforded the 9,10-bridged ester after 24 h in 88% yield, which was reduced with 2.5 equiv of $LiAlH_4$ to yield the corresponding alcohol in 80% yield. This alcohol was transformed with two equivalents each of triphenylphosphine and carbon tetrabromide to give compound **4** in 89% yield. Nitro-derivative **5** was synthesized as a separable mixture of regioisomers in 92% yield overall of dinitrated material from **4** by treatment with 8.5 equiv of trifluoroacetic anhydride and 2.5 equiv of ammonium nitrate. Chromatography afforded the required 2,6-derivative **5** in 39% yield and the corresponding 2,7-derivative in 54% yield. The dimethyl analogue **3** was prepared from 2,6-dimethylanthraquinone, which was reduced to the corresponding anthracene in alkaline solution with zinc dust under reflux. The subsequent preparation of the brominated anthracene derivative **3** then followed the same general procedure outlined for **4**, in 34% overall yield. Detailed descriptions of the synthetic procedures are available in the Supplementary data.

Relative rates of reaction of bromides **1**–**5** were obtained through standard competitive reduction with tributyltin hydride (see Supplementary data), by measuring the relative rates of consumption of the starting materials using either ^{1}H NMR spectroscopy or GC/MS. In the case of the rates calculated from ^{1}H NMR, the disappearance of the CHBr signals at δ 4.06 ppm for compounds **1** and **2**, and at ca. δ 2.80 and 3.10 for compounds **3**–**5** were measured relative to 0.2 equiv of mesitylene, which was utilized as an internal standard. The formation of products was not monitored, as the ^{1}H NMR signals relating to the reduced centre overlapped those of the starting material making it difficult to monitor accurately the rate of their appearance in the spectra. Reactions were carried out at least in triplicate with less than 5% variation between replicates. Values for the relative rates of reaction are reported relative to standard **1**, and are presented in Table 1.

The relative rates of reaction of derivatives **1**–**5** reflect the relative rates of formation of the corresponding radicals, as bromine abstraction by the tributyltin radical is the first committing step in the reduction. The large differences in the relative rates of reaction for compounds **3**–**5** are not, however, reflected by the stabilities of the corresponding radicals **6**–**8**. This was confirmed through the calculation of the radical stabilization energies (RSEs) for radicals **6**–**8** using density functional theory (DFT) and ab initio methods. Geometries were optimized for each molecule **3**–**8** at the B3LYP/6-31G(d) level, with single point energies at the RMP2/6-31G(d) level. The use of restricted MP2 with DFT geometries has been shown to provide reliable energies for large radical systems.[22–24] The corresponding RSEs are presented in Table 2.

Whilst there is a very slight variation in the RSE values consistent with the electronic nature of the substituent relative to an electron deficient radical, the direct stabilization afforded by the aromatic ring is virtually zero. This is confirmed by both theoretical methods. Therefore, the relative reactivity cannot be accounted for by direct stabilization of the intermediate radical. The relative rates appear, however, to be determined by the electron-withdrawing and electron-donating abilities of the aryl substituents, indicating a through-space interaction. Furthermore, for compounds **3**–**5**, the relative rates follow a Hammett relationship with a correlation coefficient (R^2) of 0.9953 and a positive ρ value of 0.92. This is consistent with the reaction proceeding through a transition state with a weak negative charge (Fig. 1), as has been previously proposed for tributyltin hydride reactions.[25]

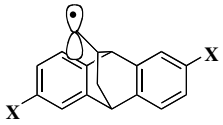
The anthracene models possess a restricted geometry, ensuring that interaction takes place. It is interesting to note, however, that the unrestricted aromatic derivative **2**, did show a slightly larger rate relative to **1**. As the competitive reactions ensure that each compound experiences

Table 1
Rates of reaction of compounds **2**–**5**, relative to that of alkyl bromide **1**

Compound	X	k_{rel} (Bu_3SnH)	RSD[a] (%)
1	n/a	1[b]	—
2	H	1.24 ± 0.05[c]	4.9
3	CH_3	1.12 ± 0.05[d]	3.7
4	H	1.39 ± 0.04[d]	4.0
5	NO_2	7.98 ± 0.28[d]	4.0

[a] Relative standard deviation.
[b] Assigned as unity.
[c] Data obtained via GC/MS. All other relative rates obtained by ^{1}H NMR.
[d] It is worth noting that these are rates of reaction at a 1° centre, whereas rates for **1** and **2** are at 2° centers. The estimated rate increase for Bu_3Sn for a 2° centre over a 1° centre is 2.9 fold.[21]

Table 2
Radical stabilization energies (RSEs) of the radicals **6**–**8** in kJ mol^{-1}, relative to radical **7**



6 X = Me
7 X = H
8 X = NO_2

Radical	X	B3LYP/6-31G(d)	RMP2/6-31G(d)
6	CH_3	0.16	0.16
7	H	0.00	0.00
8	NO_2	−0.41	−0.32

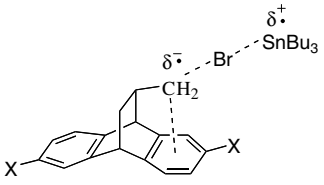


Fig. 1. Proposed electron-rich transition state during bromine abstraction by tributyltin radical.

the same intermolecular environment, this suggests that an increased local concentration of the aromatic within the vicinity of the putative radical centre plays a role in mediating the reactivity. The effect of constraining the system appears modest, but supports an intramolecular effect. It is expected that more significant rate differences will be observed in either improved model systems, such as [9]-paracyclophanes, or with more highly polarized systems, that might better mimic a charge transfer effect in the transition state.

In conclusion, relative rate measurements of tributyltin hydride reduction of compounds **1**–**5** indicate that a proximal aromatic moiety mediates the kinetic profile of bromine abstraction. These effects appear to be active in the process of forming the radical, but a remote electronic effect does not alter the stability of the radical itself. This process is analogous to neighbouring group participation previously observed in free radical brominations,[15,16] and either judiciously placed aromatics or specific manipulation of the polarization characteristics of the transition state may provide a supramolecular mechanism for directing free radical reactions on this basis.

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Supplementary data

Full synthetic details, methodology for the competitive experiments, and calculated geometries for molecules **3**–**8** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.009.

References and notes

1. Cram, D. J.; Goldstein, M. *J. Am. Chem. Soc.* **1963**, *85*, 1063–1074.
2. Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.
3. Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.
4. Casellas, H.; Massera, C.; Buda, F.; Gamez, P.; Reedijk, J. *New J. Chem.* **2006**, *30*, 1561–1566.
5. de Hoog, P.; Gamez, P.; Mutikainen, H.; Turpeinen, U.; Reedijk, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5815–5817.
6. Quinonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389–3392.
7. Rosokha, Y. S.; Lindeman, S. V.; Rosokha, S. V.; Kochi, J. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 4650–4652.
8. Russell, G. A. *J. Am. Chem. Soc.* **1957**, *79*, 2977–2978.
9. Russell, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 4987–4996.
10. Russell, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 4997–5001.
11. Russell, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 5002–5003.
12. Wunderlich, W.; Benfaremo, N.; Klapper, M.; Mullen, K. *Macromol. Rapid Commun.* **1996**, *17*, 433–438.
13. Werst, D. W. *J. Am. Chem. Soc.* **1991**, *113*, 4345–4346.
14. Werst, D. W. *J. Phys. Chem.* **1992**, *96*, 3640–3646.
15. Croft, A. K.; Easton, C. J. *Aust. J. Chem.* **2004**, *57*, 651–654.
16. Easton, C. J.; Merrett, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 3035–3036.
17. Friedrich, S. S.; Friedrich, E. C.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1969**, *34*, 900–905.
18. Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129–3134.
19. Wilt, J. W.; Chenier, P. J. *J. Org. Chem.* **1970**, *35*, 1571–1576.
20. De Meijere, A.; Faber, D.; Heinecke, U.; Walsh, R. D.; Muller, T.; Apeloig, Y. *Eur. J. Org. Chem.* **2001**, *2001*, 663–680.
21. Menapace, L. W.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047–3051.
22. Parkinson, C. J.; Mayer, P. M.; Radom, L. *Theor. Chem. Acc.* **1999**, *102*, 92–96.
23. Croft, A. K.; Easton, C. J.; Radom, L. *J. Am. Chem. Soc.* **2003**, *125*, 4119–4124.
24. Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2305–2313.
25. Kuivila, H. G.; Walsh, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 571–576.