RADICAL CYCLIZATIONS OF DIOSPHENOL ω-HALOALKYL ETHERS TO OXABICYCLOALKANONES

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Abstract: Radical cyclization of diosphenol ω-haloalkyl ethers gives spiro- and fused oxabicycloalkanones.

The intramolecular addition of a radical to an unsaturated bond is an important synthetic strategy for the formation of rings.[1] It is notable that the 5-hexenyl radical cyclizes preferentially to the cyclopentyl-methyl radical and not to the (more stable) cyclohexyl radical.[2] Beckwith[3] rationalized this regiochemical preference twenty-five years ago by postulating a polarized transition state with acceptor character to the double bond and with a •C---C=C angle greater than 90°. This transition-state geometry is less constraining in (1, n)-*exo* ring closures than it is in (1, n+1)-*endo* ring closures, a fact later elaborated on by Baldwin.[4] In recent years theoretical calculations have supported the Beckwith transition state model.[5]

It occurred to us that the regiochemical outcome of a radical cyclization might be altered by attachment of radical-stabilizing groups to the acceptor double bond.[6] In particular, we speculated that *endo* cyclization might be favored in radicals derived from diosphenol ω-haloalkyl ethers (of type 1) since the resulting radical **4** and presumably the polarized[5] transition state **3** leading to it would be stabilized:[9, 11]
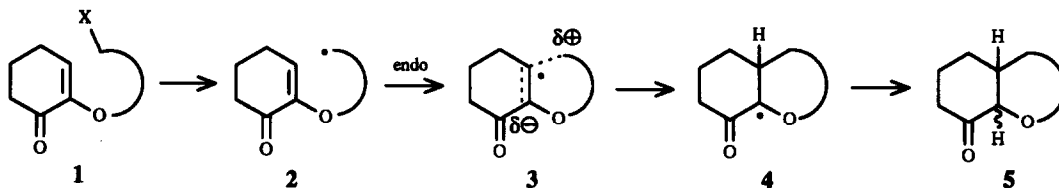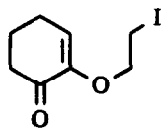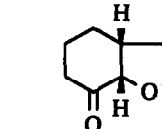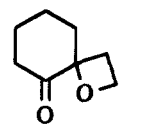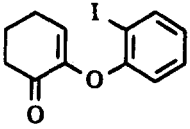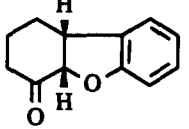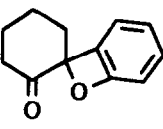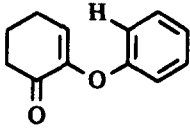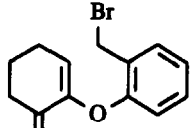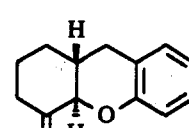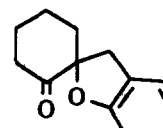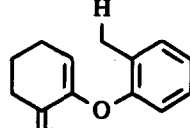

To test this hypothesis we prepared **6**[16] and treated its 0.2 M solution in benzene with two equivalents of tributyltin hydride at 80 °C. Cyclization is the major reaction:
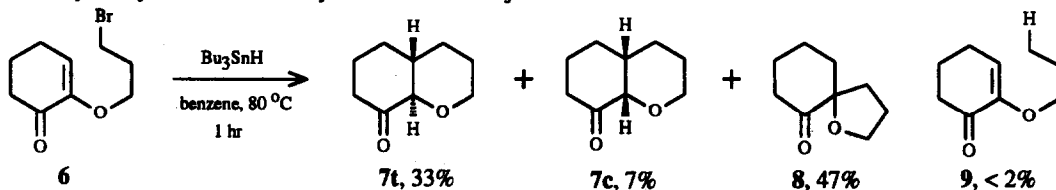
These results can be compared with those of Beckwith ([**10**]$_{init}$ = 0.21 M; [Bu$_3$SnH]$_{init}$ = 0.1 M):[17]
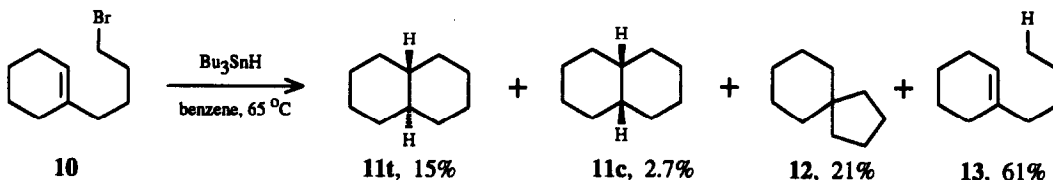
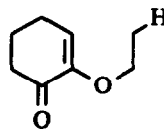The functional groups present in **6** promote cyclization since, even with a two-fold excess of Bu₃SnH and relatively high initial substrate concentration (0.2 *M*), little or no simple reduction to **9** is observed.[18] On the other hand, it is not clear if any significant stabilization occurs in the *endo*-cyclization transition state since the ratio of *endo/exo* cyclization in **6** is the same as that found in the unfunctionalzed system **10** (0.85 and 0.84, resp). Because of the possible utility of such fused and spiro oxabicycloalkanones in natural products synthesis, we undertook a systematic study of this reaction using a variety of diosphenol ω-haloalkyl ethers, all as 0.2 *M* solutions in benzene. The results are presented in the table below.[19]

substrate	endo product	exo product	redn product
14	**15** 18% cis	**16** < 2%	**17** 72%
18	**19** 57% cis	**20** < 2%	**21** 22%
22	**23** 3% trans	**24** < 2%	**25** 55%
26	**27** 6% c; 32% t	**28** 24%	**29** 15%

The small amount of 5-*endo* cyclization in **14** is noteworthy since 4-penten-1-yl radicals, in general, do not cyclize.[20, 21a] We suggest that this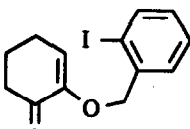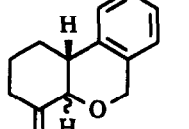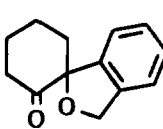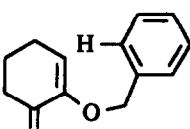 effect is due, at least in part, to a change in the required approach trajectory for radical additions when substituents are attached to the acceptor double bond. A radical approaches an unfunctionalized double bond above and directly behind the p orbitals[5] (see arrow in **30**), causing great angle strain in the 5-*endo* transition state **31**. Attachment of a carbonyl group may change this required trajectory (see arrow in **32**) in accordance with Baldwin's approach vector analysis,[22] so that the radical now approaches the double bond above and behind the p orbitals, *but also away from the carbonyl group*. The consequence of this new trajectory is a less strained transition state **33**. The substantial cyclization of the 4-phenyl-4-penten-1-yl radical[21b] can be explained along similar lines.

30   →   **31**   **32**   →   **33**

It is notable that **18** cyclizes to a greater extent than **14**. The propensity of aryl radicals to add to alkenes is recognized,[20, 23] and may be due to their low stability compared with primary alkyl radicals.[24] This increased energy produces but a small increase in rate of reaction with tributyltin hydride ($\Delta\Delta H^\dagger = 2$ kcal/mole),[25] but may cause a substantial rate increase in the (more difficult) addition reaction; thus cyclization is promoted to a greater extent than simple reduction. Analogously, the small amount of cyclization of **22** can be rationalized in terms of the high stability of the intermediate benzylic radical.

References and Notes

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6   There is sparse data in the literature related to this matter. Synthetically-oriented (non-kinetic) studies show that vinyl and aryl radicals tethered (via an ether linkage) to the α-carbon of α,β-unsaturated carbonyl systems cyclize by the 6-*endo* (and not the 5-*exo*) pathway.[7] On the other hand, a kinetic study[8] revealed that the large increase in *endo/exo* cyclization regioselectivity attending attachment of methyl to C-5 in the 5-hexenyl radical is due mainly to the 50-fold *decrease* in the rate of *exo* cyclization (steric hindrance) and not to the 2-fold increase in the rate of *endo* cyclization.

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8   Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett.* **1974**, 2251.

9   In this system carbonyl is regarded as strongly activating towards cyclization;[10] alkoxyl is probably[10a] slightly deactivating. See also ref. 7 above.

10   a. Cyclohexyl radical adds to 3-buten-2-one 3000 x faster than to 1-hexene, and to 2-methoxyacrylate 5 x slower than to 2-methylacrylate: Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.
      b. A particular 5-*exo* radical cyclization, crucial to the synthesis of gelsemine, occurs only if the acceptor alkene is activated by carboethoxy: Choi, J. K.; Ha, D. C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279.

11   The effect of alkene substituents on radical addition rates correlates more with their effect on the energy of the alkene LUMO than with their effect on the stability of the addend radical.[5, 10a] Nevertheless, it is noteworthy that an α-methoxy substituent stabilizes the acetophenonyl radical by 13 kcal/mole, the same amount that methoxy stabilizes the methyl radical.[12] Although there is no "strict" captodative[13-15] (greater than additive) effect between carbonyl and alkoxy, Bordwell and Lynch (ref. 12) point out that substituent effects are usually less than additive and finally conclude that a small synergistic interaction (4 to 5 kcal/mole) occurs between these substituents.

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16   Ponaras, A. A.; Meah, Md. Y. *Tetrahedron Lett.* **1986**, *27*, 4953.

17   Beckwith, A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, *25*, 1081.

18   3-(3-Chloropropoxy)-2-cyclohexen-1-one is reduced (without cyclization) when treated with Bu₃SnH: Moriya, O.; Urata, Y.; Ikeda, Y.; Ueno, Y.; Endo, T. *J. Org. Chem.* **1986**, *51*, 4708.

19   The reaction mixture was diluted with ether and shaken with aq. KF soln. Yields were determined by internal standard GC. The products were isolated by chrom on silica gel and characterized by PMR, IR and HRMS. Compounds **9, 17, 21, 25** and **29** are known substances. **7c** was made from 2-methoxyphenol; equilibration with base provided **7t**. **8** was made from 2-hydroxycyclohexanone. **15** was made from 1-benzofuran-8-ol. **19** was made from 3-phenoxy-1-cyclohexene. **23** was made from 3-(2-hydroxybenzyl)-1-cyclohexene. **27** was made from 2-(3-cyclohexenyl)-benzyl alcohol. **28** was made from 2-bromobenzyl alcohol and 2-methoxy-2-cyclohexen-1-one.

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23   Similarly, vinyl radicals: Stork, G.; Baine, N. *Tetrahedron Lett.* **1985**, *26*, 5927.

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