Remarkable Cyclization Reactivities of Partially-Fluorinated 6-Heptenyl Radicals†

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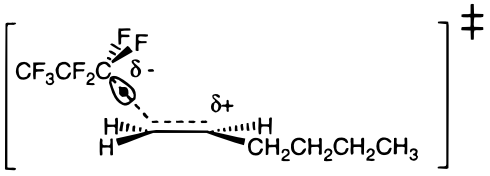
In a recent, systematic study of the impact of fluorine substitution on the cyclization reactivities of 5-hexenyl radicals,[3] we found that the rates of the 5-exo cyclization could be substantially enhanced if a perfluoroalkyl radical segment is combined with a hydrocarbon alkenyl segment as exemplified in Scheme 1. The 166-fold rate enhancement (relative to the hydrocarbon 5-hexenyl radical) was attributed largely to the high electrophilicity of the radical site in **1**, which when combined with the nucleophilicity of the alkene segment leads to highly advantageous transition state charge-transfer interactions. Such charge-transfer interactions were also invoked to explain the 30 000-fold rate ratio which we observed for n-$C_3F_7^{\bullet}$ versus $RCH_2CH_2^{\bullet}$ addition to 1-hexene as depicted in **2**.[4]

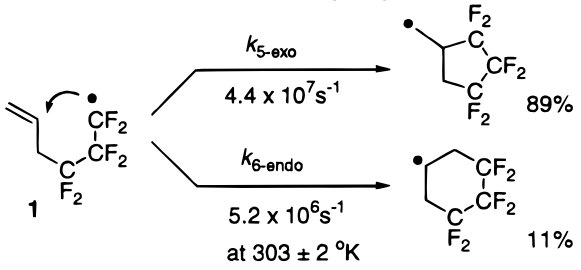


2

Another interesting aspect of the 5-hexenyl cyclization study was the fact that, for many of these systems, 6-*endo* cyclization became quite competitive with the 5-*exo* mode of cyclization, as shown in Scheme 1.[3]

Because of the significant rate enhancement observed in the 5-hexenyl radical system, it was of interest to determine the impact of fluorine substituents on the cyclization rate constants of the much slower 6-heptenyl radical system. The rate constant for 6-*exo* cyclization of the hydrocarbon 6-heptenyl radical ($k_{6-exo} = 5.4 \times 10^3$ s^{-1})[5] is 40 times smaller than that for of the 5-*exo* cyclization of the 5-hexenyl radical,[6] and as a result, such cyclizations are much less attractive for use in synthetic applications.

Scheme 1. 5-Hexenyl Cyclization



Measurement of the rate constant for cyclization of the 1,1,2,2,3,3,4,4,-octafluoro-6-heptenyl radical, **4**, should provide an excellent probe of the effect of fluorine-induced electrophilicity on 6-heptenyl radical cyclization reactivity. The rate constant for cyclization of radical **4** was obtained via the smooth, photoinitiated, free radical chain competition process depicted in Scheme 2,[7] with the rate constant for cyclization (k_{6-exo}) being obtained by means of a plot of experimental concentration data using eq 1.

Using the reported value for k_H of $(TMS)_3SiH$ in H-transfer reactions with perfluoro-*n*-alkyl radicals,[8] one obtains a value of $k_{6-exo} = 1.99\ (\pm 0.20) \times 10^7\ s^{-1}$ for the cyclization of **4** at 298 K. This remarkably large rate constant for 6-*exo* cyclization is 3700 times larger than that for the hydrocarbon system, and it actually approaches the value for 5-*exo* cyclization of its fluorinated 5-hexenyl analogue, **1**!

The particularly large enhancement in k_{6-exo} exhibited by **4** is probably simply the result of a slow reaction (such as a 6-*exo* cyclization) being able to be affected more by favorable structure change than a fast reaction (such as a 5-*exo* cyclization). As it is, the value of k_{6-exo} of **4** comprises by far the fastest 6-heptenyl radical cyclization yet measured. Even the cyclization of 7,7-diphenyl-6-heptenyl radical, which forms a highly stabilized radical upon cyclization, has a rate constant of only $5 \times 10^5\ s^{-1}$, 40 times slower![9]

Beckwith earlier demonstrated that replacement of one of the methylenes with an oxygen atom in the skeleton of the 5-hexenyl radical led to a radical system which exhibited a substantially greater 5-*exo* cyclization rate constant, $8.5 \times 10^6\ s^{-1}$, 37 times greater than that of the parent system.[5] Since we were interested in trying to attain the largest possible rates for cyclization of a 6-heptenyl system, it seemed appropriate to see if a similar rate increase would be obtained by replacement of one of the methylene groups of **4** with an oxygen atom.

However, when radical **8** was generated in a competition experiment analogous to that used for **4**, in Scheme 2,[10] a plot of the data which were obtained, combined with

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(5) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941.

(6) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

(7) Iodide precursor **3** was prepared by a (n-$Bu_3Sn)_2$ catalyzed, photoinduced reaction of $I(CF_2)_4I$ with allyl bromide, and **3**, **5**, and **6** were fully characterized by ^1H and ^{19}F NMR and by HRMS. Competition experiments were carried out in a manner which has been described previously.[3,8]

(8) Dolbier, W. R., Jr.; Rong, X. X. *J. Fluorine Chem.* **1995**, *72*, 235−240.

(9) Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674−3684.

(10) Iodide precursor **7** was prepared by the autoclave reaction of ICF_2CF_2COF, CsF, and allyl iodide in diglyme at 100 °C, and it along with its reduction and cyclization products were fully characterized by ^1H and ^{19}F NMR and by HRMS.

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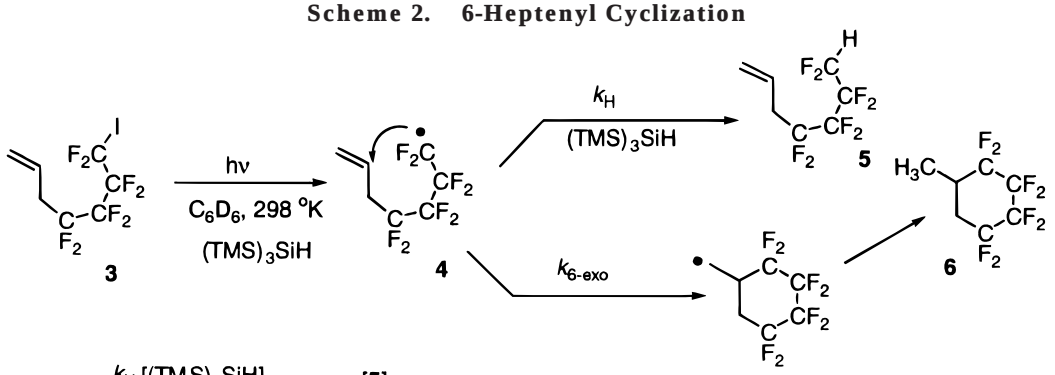
Scheme 2. 6-Heptenyl Cyclization

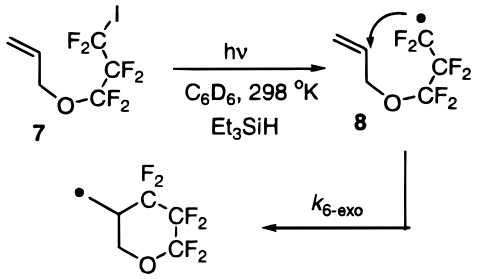


$$\frac{k_H[(TMS)_3SiH]}{k_{6\text{-exo}}} = \frac{[5]}{[6]} \qquad \text{eq (1)}$$

$$k_{6\text{-exo}} = k_H/2.56\ (\pm 0.08) \qquad k_H = 5.1\ (\pm 0.5) \times 10^7 M^{-1}s^{-1} \text{ at } 298\ ^\circ K$$

$$k_{6\text{-exo}} = 1.99\ (\pm 0.20) \times 10^7 s^{-1} \text{ at } 298\ ^\circ K$$

the value for k_H of Et_3SiH,[8,11] gave a rate constant which was ~16 times *smaller* than that for cyclization of **4**.



$$k_{6\text{-exo}} = \frac{k_H}{0.412 \pm 0.023}$$

$$k_H = 5.0\ (\pm 0.4) \times 10^5 M^{-1}s^{-1} \text{ at } 298\ ^\circ K$$

$$k_{6\text{-exo}} = 1.21\ (\pm 0.12) \times 10^6 s^{-1} \text{ at } 298\ ^\circ K$$

Why should insertion of an ether linkage be beneficial to cyclization of a hydrocarbon radical, but detrimental to cyclization of our hydrofluorocarbon radical system? The site of the oxygen is too distant to have any significant effect on the reactivity of the *radical site* in either of the two systems. The answer probably lies in the fact that the oxygen in each case is *allylic* with respect to the double bond. If the transition state for cyclization maintains the C−O bond in a geometry which will allow interactive overlap of the C−O σ^* orbital with the π and π^* orbitals of the double bond, such perturbation would be expected to lower the energies of both the HOMO and the LUMO of the alkenyl segment.

In the case of the hydrocarbon system, such lowering of the LUMO would be beneficial to the transition-state dipolar interaction of the electron-rich radical SOMO with the now more electron-deficient alkenyl LUMO, thus giving rise to the observed rate enhancement for cyclization of the hydrocarbon ether radical. However, in fluorinated system **8**, the allylic oxygen should have quite a different kinetic effect. First, the fluorine substituents in **8** make the allylic OR_F group a much better leaving group, that is, a weaker base, with a significantly lower energy σ^* orbital being associated with the allylic C−O bond. Thus, the perturbation of the π orbital should be much greater for **8** than for the hydrocarbon system. This substantial lowering of energy of the alkenyl HOMO of **8** will diminish the transition state SOMO−HOMO interaction which is most important in determining the reactivity of a perfluoro-*n*-alkyl radical with an alkene. Thus the rate constant of cyclization of **8** should be diminished relative to that of **4**.

Therefore, the dramatically different effect of a skeletal allylic oxygen atom on the rate constants for cyclization of a hydrocarbon versus a fluorohydrocarbon radical system can be readily understood in terms of the difference in the dipolar nature of their respective transition states.

It is also interesting to note that, unlike the situation in the 5-hexenyl radical system (i.e., **1**), where 6-*endo* cyclization was enhanced even more than the 5-*exo* cyclization such that the two were competitive, the presence of fluorine substituents in the 7-heptenyl radical system apparently did *not* give rise to a similar regiochemical effect, with the result that there were *no* observed products from 7-*endo* cyclization in either of the two systems studied.

It is expected that, as was the case for the fluorinated 5-hexenyl system **1**,[3,12,13] such large rate enhancements as observed for the cyclizations of 7-heptenyl radical systems **4** and **8** should allow the design of appropriate diene monomers which should undergo efficient cyclopolymerization to form novel polymers containing six-membered rings. Such studies are currently underway.

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Supporting Information Available: Synthetic procedures and product characterization; tables and plots of kinetic data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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