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The Influence of Geminal Disubstitution on Efficiencies of 4-Exo-Trig Radical Cyclizations.

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Abstract: The competition between tributyltin hydride-induced cyclization and reduction of a series of 6-bromo-2-hexenoates was explored computationally. Different methods show that modification of the gem -substituents is not as crucial for cyclization as once thought.

Generation of radicals by bromine abstraction from 5,5-disubstituted 6-bromo-2-hexenoates, **1**, leads to radical cyclizations to give 3,3-disubstituted cyclobutanecarboxylates, **3**.[1,2] Table 1 summarizes these results. Some substituents – R = ethoxy, propylenedioxy, and bis(carboethoxy) – are very effective in promoting cyclization to the cyclobutanes under normal (slight excess) of hydride present, while others – R = methyl, ethylenedioxy – produced largely the products of simple reduction **2**,[3] under normal conditions, with a marked increase on the amount of cyclized product under low hydride concentration. Finally, the unsubstituted compound, **1a**, failed to yield any cyclic product under either set of conditions.

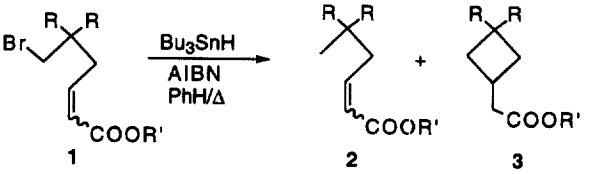

Table 1. Ratios of Cyclized:Reduced Products

Compound	R	Ratio **2/3**
1a	H	100/0
1b	Me	75/25[a] (12/88)[b]
1c	OEt	0/100
1d	$O(CH_2)_2O$	75/25 (25/75)[b]
1e	$O(CH_2)_3O$	3/97
1f	CO_2Et	30/70

a) **2b** is a 2:1 mixture of the enoate and the saturated analogue. b) Ratio obtained upon slow addition of Bu_3SnH over 8h.

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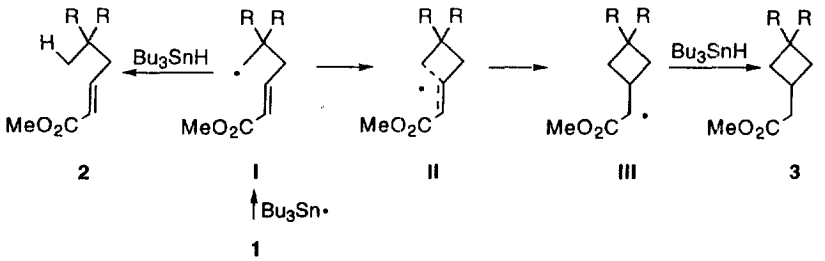
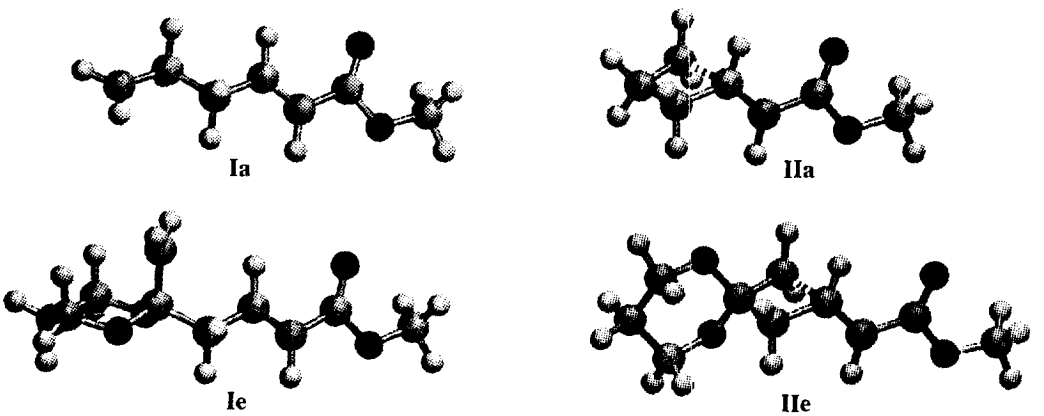
With excess hydride present, some effects are subtle: the acyclic and 6-membered ketals, **1c** and **1e**, cyclize well to give the cyclobutane products, **3c**, and **3e**, while the 5-membered ketal, **1d**, gives only about 25% of the desired cyclobutane, **3d**, and 75% of the reduced product, **2d**. Under low hydride concentration however, the ratios of reduction to cyclization are remarkably close for reactions of **1b** - **1f**. In an attempt to better understand this reaction and to eventually be able to predict the outcome of a cyclization yet to be performed experimentally, we have investigated this system computationally to match the observed experimental results.

Scheme 1 shows the steps in the reaction of **1** with tributyltin hydride. Radical **I** cyclizes via the transition state **II** to give the product radical **III** which is finally reduced by the tin hydride to the observed product **3**. Alternatively, the initially formed radical **I** can be reduced with tin hydride to give **2**. Optimization

Scheme 1



of the structures of the bromides **1**, the products **3**, the acyclic and cyclic radicals **I** and **III**, and the transition structure **II** - were carried initially using the semi-empirical PM3 method.[4] Radical cyclizations have also been investigated with force-field methods,[5] and a combination of semi-empirical and force-field methods.[6b] Figure 1 shows two radicals (**I**) and transition structures (**II**), for the cyclizations of **1a** and **1e**.



The radical structures **I** and **III** and the transition state **II** for the cyclization were also optimized using an ab initio methods (UHF/3-21G) and (UHF/6-31G*). The energies of the UHF-3-21G optimized structures

were further determined via single point energy calculations using the 6-31G* basis set with UHF, DFT, and UMP2 methods. The relative activation energies for all these results are provided along with the absolute PM3 values in Table 2. The $\Delta\Delta G^{\ddagger}$ values provided for comparison were calculated from the relative amounts of cyclic product present in each substrate at 80 °C.

All methods predict that the dihydrido compound **1a**, which gave none of the cyclic product **3a**, has the highest activation energy for cyclization by all methods, compared with the other substituted substrates. All methods agree that the activation energies for cyclization of **1b** - **1f** are with 2 kcal/mol, and 1a is 2-4 kcal/mol more difficult. The simple 4-pentenyl bromide **4**, a compound known not to undergo radical cyclization,[6] also has a large activation energy for cyclization (14.7 kcal/mol by PM3). *Gem*-disubstitution causes a 2-5 kcal/mol drop in the activation

Table 2: Experimental activation energy differences between reduction and cyclization, and calculated activation energies for the 4-exo cyclizations[a]

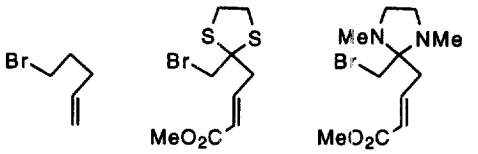
Compound	$\Delta\Delta G^{\ddagger}_{exptl.}$[a]	PM3 (abs)	PM3 (rel)	UHF/6-31G*[b] (rel)	MP2/6-31G*[b] (rel)	B3LYP/6-31G*[b] (rel)	UHF/6-31G* (rel)
1a	> 3.2	14.2	5.6	1.7	1.7	2.0	1.8
1b	0.8 (-1.4)[c]	10.6	2.0	-1.8	-0.8	-1.5	-1.7
1c	-3.2	8.6	0.0	0.0	0.0	0.0	0.0
1d	0.8 (-0.8)[c]	9.1	0.5	-1.7	-0.4	-1.3	-1.6
1e	-2.5	9.2	0.6	-0.9	-0.1	-1.0	-0.9
1f	-0.6	9.8	1.2	-1.6	0.1	-1.2	-1.6
5		11.1					
6		9.9					

a) at 353 K; b) single point energies; c) with low Bu_3SnH concentration.

energy in all cases; the energy required to convert an anti to syn conformer for cyclization is overcome by the geminal substituents, which create a syn conformer as the global minimum. The activation energies of *gem*-disubstituted compounds are sufficiently close in energy to allow an increase in the amount of cyclization by a decrease in Bu_3SnH concentration. This corroborates the low hydride experiments in which the percentages of cyclic product became nearly identical for all disubstituted systems.

We used this system to estimate whether cyclization of certain other unprepared substrates might be feasible or not, e.g., to predict beforehand whether certain *gem*-disubstituent effects might be effective. The activation energies calculated for cyclizations of the *gem*-dithioalkoxy and the *gem*-bis(dialkylamino) systems **5** and **6** predict that the dithioalkoxy analogue **5** will not cyclize well while the bis(dialkylamino) substrate **6** should undergo cyclization in reasonable yield under excess hydride conditions. There is good evidence that the

gem-dithioalkoxy effect is not as large as the *gem*-dialkoxy effect,[7] most likely a result of the long C-S bond length. We also have some preliminary evidence that bis(dialkylamino) systems undergo cyclization easily.[8]



4 **5** **6**

The origins of these variations in related cyclization efficiencies have been discussed previously.[9] All substituents promote cyclization, but the magnitude of the gem-disubstituent effect varies: methyl and ethylenedioxy are less effective compared to dialkoxy or propylenedioxy, dithioalkoxy is predicted to be mediocre as a cyclization promoters and bis(alkylamino) groups should work reasonably well.

In conclusion, while the semi-empirical PM3 results are comparable to those obtained at higher levels of theory for this particular system, the activation energy differences for each case are too close at all levels to allow us at present to quantitatively predict the amount of cyclized product for a particular case. Further extensions of this process, both computationally and experimentally, are underway.

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