Rate Constants for the Additions of Cyclohexyl Radicals to Acrylamides, Imides and Sulfonimides

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Summary: Competition experiments are used to provide estimated rate constants for the addition of cyclohexyl radical to a series of acrylamides, imides and sulfonimides.

Asymmetric radical addition reactions to alkenes bearing chiral auxiliaries are emerging as valuable synthetic methods.[1] Many of the best auxiliaries for such additions are based on an amide, imide or sulfonimide motif.[2] Figure 1 shows a variety of auxiliaries (1-3) that give high, predictable levels of selectivity when attached to alkenes at the site of radical attack (α-stereochemistry). So far, the "Rebek-imide" 4 is unique in its ability to control β-stereochemistry. These auxiliaries often provide comparable levels of selectivity when attached to radicals as well.[3]

Figure 1. Amide-, Imide-, and Sulfonimide-Based Chiral Auxiliaries
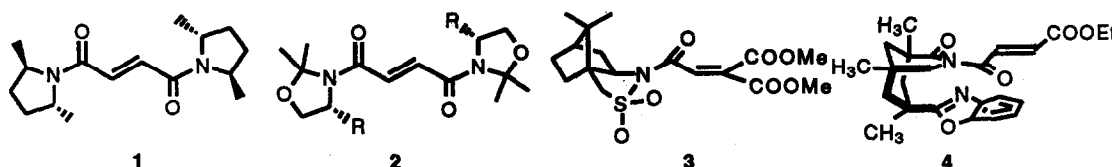
A knowledge of the relative reactivities of such alkenes towards alkyl radicals is essential for the development of a detailed understanding of both the regio- and stereoselectivities in reactions of alkenes 1-4.[4] One of the most important factors controlling the rates of nucleophilic radical additions is the β-polar effect, and the magnitude of this effect is usually assessed by comparing relative reactivities of various alkenes to a standard like methyl acrylate or styrene.[5] Among the many classes of alkenes whose relative rates have been measured, there are only a few amides,[4] and no imides or sulfonimides. We have independently undertaken a series of competition experiments (see eq 1) to measure the relative reactivity of important acrylamides, imides, and sulfonimides, and we now jointly report the results of these experiments. Figure 2 shows the alkenes selected for competition.
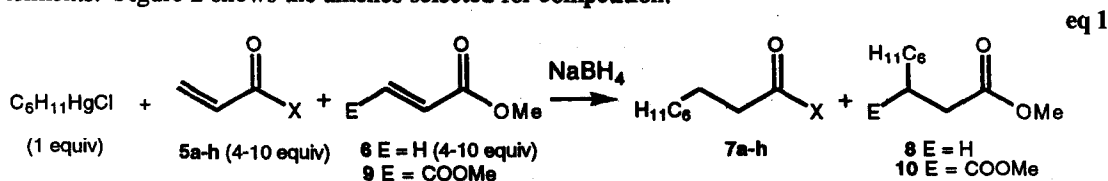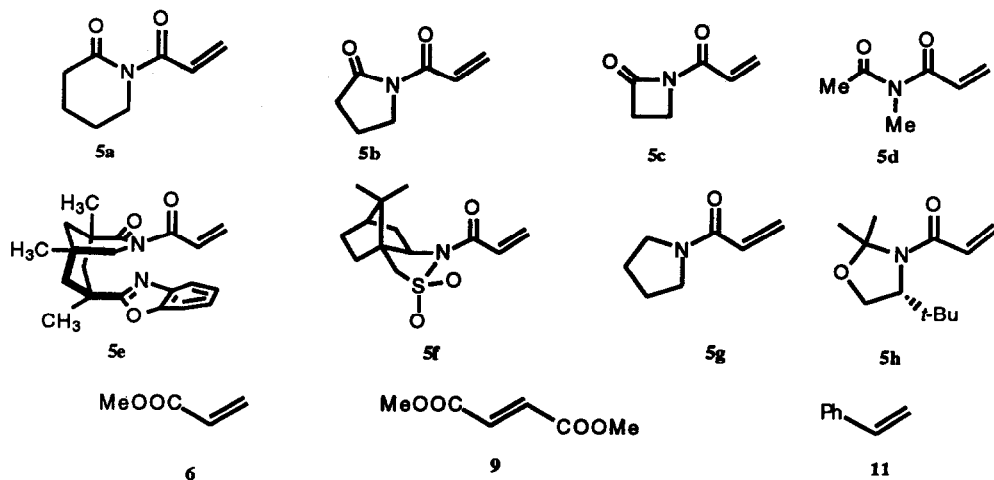
eq 1

$C_6H_{11}HgCl$ + (1 equiv) 5a-h (4-10 equiv) 6 E = H (4-10 equiv) 9 E = COOMe → 7a-h 8 E = H 10 E = COOMe

Figure 2. Substrates (5a-h) and Standards (6,9,11) for Competition Experiments

We prepared acrylamides (**5g,h**), acrylimides (**5a-e**) and sulfonimide (**5f**) by standard acylation procedures,[6] and conducted a series of competition experiments by the mercury method (eq 1). Analysis of the crude product mixture by ^{1}H NMR or gas chromatography integration provided competition rate constants[7] for alkene pairs.[5] In the standard procedure for competitions versus methyl acrylate, a few drops of water were added to a mixture of cyclohexyl mercuric chloride (1 equiv), methyl acrylate (4 equiv), substrate **5** (4 equiv) and excess sodium borohydride in CH_2Cl_2 at 0°C. After one hour, the reactions were worked up and the product ratios (**7/8**) were determined by integration of appropriate resonances in the crude ^{1}H NMR spectrum. To assign resonances, authentic samples of all products were prepared. Table 1 summarizes the calculated competition constants[8] and the recommended k_{rel} versus styrene (NMR method).

We also conducted a series of cross-checks by competing several substrates against each other and against dimethyl fumarate (**9**). Giese reports that dimethyl fumarate is 10 times more reactive than methyl acrylate (at 25°C),[5] and under our conditions we measured the relative reactivity of these substrates to be 8.4 (at both 0°C and 25°C). This then predicts a relative reactivity of **5b/9** of 0.26, and the observed product ratio **5b/9** in a competition experiment was 0.25. In contrast to this well-behaved system, cross-checks with camphor sultam **5f** identified a problem. A cross-check of **5f** with **5b** by using methyl acrylate as a reference is consistent: k_{rel} **5f/5b** predicted = 2.5, **5f/5b** observed = 2.6. However, a cross check directly with dimethyl fumarate (**9**) gave an observed product ratio that was about two times higher than that predicted: k_{rel} **5f/9** predicted = 0.7; **5f/9** observed = 1.3.

Competition experiments for several of the alkenes were also monitored by gas chromatography. In these experiments, an aqueous solution (minimum amount of water) of excess sodium borohydride (2-10 equiv) was added to a CH_2Cl_2 solution of cyclohexyl mercuric acetate or chloride (1 equiv) and the alkene pair (10 equiv) at 22 °C. The mixture was filtered through magnesium sulfate, and the drying agent was washed with dichloromethane several times. The combined dried solution was concentrated and analyzed on a 30 m SPB-5 or a 15 m SPB-1 capillary column. The detector response factors of all addition products were determined by analysis of authentic mixtures.[4] The data for these experiments are also summarized in Table 1 (GC method). While Giese reported that methyl acrylate is nearly 7 times more reactive than styrene, k_{rel} **6/11** = 6.7, in our hands this relative rate is 13. Our number is also internally consistent with the other relative rates that we determined. Thus, k_{rel} **6/11** = 13.2 is calculated from k_{rel} **5g/11** = 4.5, k_{rel} **9/5g**

= 29.4, and Giese's k_{rel} 9/6 = 10; (4.5 • 29.4)/10 = 13.2. The measured relative rate of 9 to 5h is k_{rel} 9/5h = 15 which is close to the predicted k_{rel} 9/5h = 15.5 from (k_{rel} 9/5g.)/(k_{rel} 5h/5g). The relative rate constants k_{rel} 5e/9 and k_{rel} 5e/5h are also internally self-consistent.

A complete tabulation of competition constants and recommended relative rate constants (in decreasing order) is presented in Table 1. The one inconsistency in the data is in the relative rates for the sulfonimide 5f; the GC method provides a considerably higher relative reactivity than the NMR method. We suggest that the k_{rel} preferred is 160 for 5f versus 11 since the NMR analysis does not give internally consistent results. The GC analytical method is generally preferred to NMR analysis because pseudo-first order conditions are more rigorously maintained throughout the reaction and because there is inherently less error associated with this analytical method.

Table 1. Competition Constants for Addition of Cyclohexyl Radical to Alkenes.

Alkene	Competition Constant	Method of Analysis	k_{rel} vs. styrene	recommended k_{rel}
5c	15.6 vs. 6	NMR	200	200
5f	1.3 vs. 9	NMR and GC	166	160
	5.6 vs. 6	NMR	72	
	2.6 vs. 5b	NMR	70	
	18.7 vs. 5h	GC	160	
9	10 vs. 6	ref 5	130	130
	15.2 vs. 5h	GC	128	
	29.4 vs. 5g	GC, ref 4	132	
5b	2.2 vs. 6	NMR	28	28
5d	2.0 vs. 6	NMR	26	26
5e	1.6 vs. 6	NMR	21	21
5a	1.3 vs. 6	NMR	17	17
6	13 vs. 11	GC	13	13
5h	1.9 vs. 5g	GC	8.5	8.5
5g	4.5 vs. 11	GC	4.5	4.5
11	≡ 1.0			≡ 1.0

The relative rates for addition of cyclohexyl radical to alkenes can be understood based upon polar effects that operate with this nucleophilic radical.[5] Substituents that lower the LUMO of the alkene promote addition. Thus, of the compounds we examined, simple amide substituents (5g,h) are more reactive than styrene but less reactive than methyl acrylate while the more electron-deficient imides (5a-e) and sulfonimide (5f) are more reactive than methyl acrylate. The reactivity pattern within the imide/sulfonimide class is of some interest. Reactivity increases dramatically as the ring size of the lactam substituent is decreased to four (compare 5a,b,d with 5c). Indeed, the sulfonimide 5f and the imide 5c are among the most reactive alkenes reported in the addition of cyclohexyl radicals. The relative reactivity of the "Rebek" acrylimide 5e is almost identical to that of the simple model 5a, which in turn is only marginally more reactive than methyl acrylate (6). This suggests that the unusual regioselectivity profile of mixed fumarimide 4[2g] (Figure 1) is *not* due to a difference in β-polar effects between imide and ester substituents.

These relative rate constants can be translated to an absolute scale by multiplying the recommended k_{rel} by the accepted absolute rate constant for the addition of the cyclohexyl radical to styrene (k = 4.0 x 10^4 M^{-1} s^{-1} at 25°C).[5] These values help extend our fundamental understanding of how substituents effect the rates or additions of nucleophilic radicals, and they also can serve as a basis for rationalizing

regio- and stereoselective reactions of related substrates. Finally, imides derived from β-lactams and sulfonimides show good promise as radical acceptors with improved reactivity profiles compared to the more commonly used esters, ketones, and nitriles.

References and Notes

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6. The synthesis of acrylamides is straightforward. Pyrrolidine or oxazolidines, prepared *in situ* are acylated with acryloyl chloride/triethylamine.[3c] The preparation of sulfonimide **5f** and imide **5e** has been described[3a] and the synthesis of imides **5a-d** is carried out by deprotonation of the corresponding amide with MeMgBr (THF), followed by addition of acryolyl chloride. All yields were good (≥76%), except for **5c** (17%).

7. Review: Newcomb, M. *Tetrahedron* **1993**, *49*, 1151-78.

8. In these reactions, competition constants were obtained from raw product ratios by using the second order rate equations in reference 7.