

Cram's Rule for Radicals: Stereoselective Hydrogen Abstraction Reactions of N-H Substituted Radicals

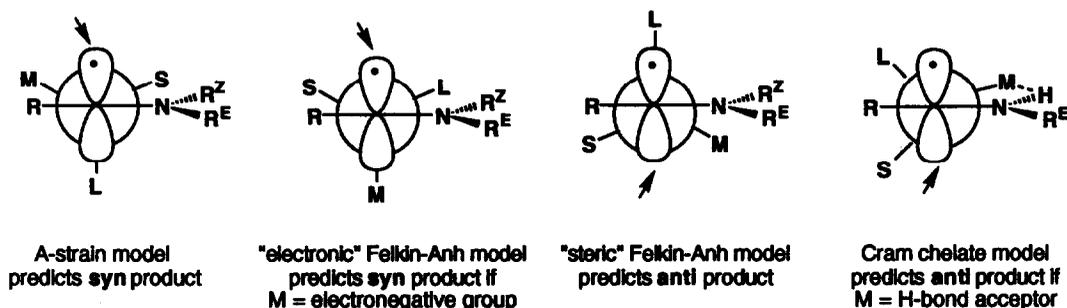
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Summary: Radical reductions of chiral thiazolidines with $(TMS)_3SiH$ reveal stereochemical parallels between ionic reactions of ketones/imines and radical reactions of aminoalkyl radicals bearing NHR substituents.

Related classes of ionic and radical reactions often show sustained stereochemical parallels.¹ In substrate controlled 1,2-asymmetric induction, parallels are observed between carbonyl-substituted radicals and enolates² and between oxygen-substituted radicals and ketones/aldehydes.³ Stereoselective reactions of carbonyl-substituted radicals and enolates both follow A-strain models, while reactions of oxygen-substituted radicals and ketones both follow Felkin-Anh models. These two models (which usually predict opposite products) are often pitted against each other in the case of nitrogen substituted radicals (Figure 1). We^{4a} and Renaud^{4b} have recently shown that reactions of nitrogen-substituted radicals with large R^E and R^Z groups follow the A-strain model. This makes sense because transition states with "Felkin-Anh" conformations will be destabilized by interactions between R^Z and the medium or large sized group.⁵

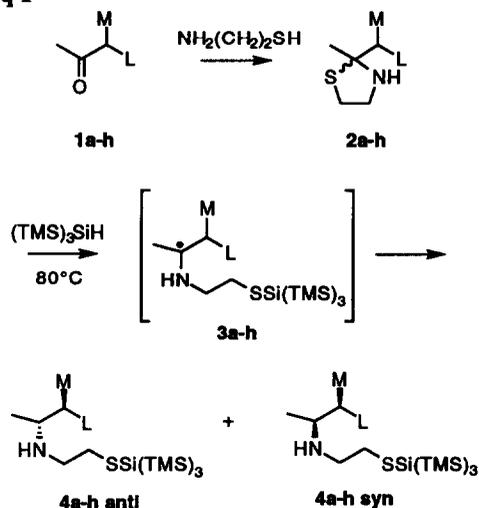
Figure 1. Stereochemical Models for Reactions of Nitrogen Substituted Radicals



In this Letter, we report experiments to determine the direction and level of selectivity of radical reactions of N-H substituted radicals ($R^Z = H$). These reactions have potential preparative utility, and they address two new points in the context of stereoselective reactions of acyclic radicals. First, the ionic/radical parallel predicts a decrease in syn selectivity of N-H substituted radicals relative to their N-R counterparts, and we now show that this prediction is observed as a selectivity reversal. Second, once established, this parallel between N-H radicals and carbonyl/imine groups allows us to ask what will happen when a "chelating" substituent is introduced ($M = \text{heteroatom}$). Will such radicals follow an "electronic" Felkin-Anh model, a "steric" Felkin-Anh model, or a Cram chelate model?

Eq 1 summarizes our general approach to survey this class of radical reactions, which follows from the work of Arya and coworkers.⁶ Readily available ketones **1a-h** were converted to thiazolidines **2a-h** by reaction with 2-aminoethane thiol. These thiazolidines, (~1/1 mixtures of diastereoisomers) were then reduced with tris(trimethylsilyl)silicon hydride⁷ (80°C, benzene, AIBN). These reductions generally produced good yields of mixtures of 2°-amines **4-syn** and **4-anti**. Product ratios were readily determined by intergrations of GC chromatograms, and isolated yields were determined after flash chromatography. We assume that standard radical chains operate, and that the product ratios are determined when radical **3** abstracts a hydrogen from (TMS)₃SiH.

eq 1

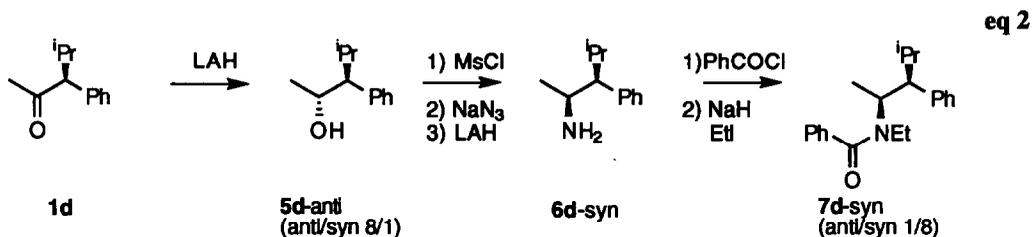
Table 1. Reductions of **2a-h**

Entry	M	L	anti/syn ratio	Yield
a	Me	Et	52/48	50%
b	Me	Ph	60/40	82%
c	Et	Ph	67/33	75%
d	iPr	Ph	84/16	92%
e	MeO	Ph	74/26	70%
f	C ₆ H ₁₃ O	Me	57/43	72%
g	MeO	Et	73/27	74%
h	MeO	iPr	86/14	64%

Table 1 summarizes the results of the reductions of **2a-h** under the standard conditions. With groups of similar size and electronic requirements (entry a), little selectivity is observed. In a series of substrates bearing an alkyl group (M) and a phenyl group (L, entries b-d), anti selectivity increases as the size of the alkyl group increases. With an M = isopropyl, a reasonable anti selectivity (84/16) is attained at 80°C. Substrates bearing alkoxy groups exhibit anti selectivity that again increases with the size of the alkyl group (L, entries f-h). With L = isopropyl, the anti selectivity reaches 86/14. The alkoxy-bearing substrate with L = Ph exhibits about the same level of selectivity as that with L = Et (compare entries e and g).

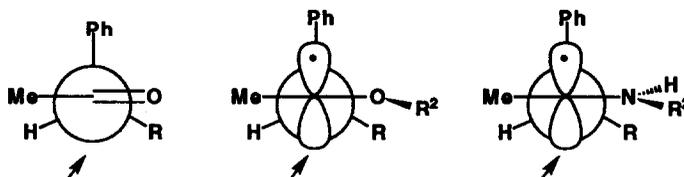
In five cases (entries b-e and h), the configurations of the products were assigned by a synthetic correlation. The configurations of the remaining products were then assigned by analogy. A typical correlation is shown in eq 2. Reduction of ketone **1d** with LAH follows Cram's rule to provide an 8:1 mixture of alcohols **5d**. This mixture was mesylated, and the crude mesylate was displaced with azide.⁸ Reduction of the azide with LAH provided amine **6d**, which was then benzoylated and ethylated to give **7d**. Pure **4d-anti** was then correlated with **7d** by reductive desulfurization (Bu_3SnH) and benzoylation. According to analysis by capillary GC, the major isomer from the radical reduction was identical to the minor isomer from the correlation. Since an inversion occurred during the preparation

of **7** from **5**, this means that reduction of **1d** by LAH and reduction of **2d** by $(\text{TMS})_3\text{SiH}$ proceed with the same facial selectivity.



Results of reductions of substrates **2a-d** provide a preliminary validation of the predicted selectivity reversal. Unlike their $\bullet\text{C-NR}^E\text{R}^Z$ counterparts, selectivities with these $\bullet\text{C-NHR}^2$ radicals are not predicted by the A-strain model. As the size of R^Z decreases to hydrogen, A-strain no longer dominates the conformations of these radicals (see A-strain model in Figure 1). Now, selectivities of $\bullet\text{C-NHR}$ -radicals parallel the reductions of oxygen-substituted radicals with silicon hydride, which in turn roughly parallel the reductions of ketones with LAH. ESR spectra and AM1 calculations suggest that oxygen substituted radicals react through a transition state analogous to the Felkin-Anh model, and we suggest that these $\bullet\text{C-NHR}$ -radicals behave similarly. The three analogous models are shown in Figure 2. For simplicity, we draw these three models planar, but calculations suggest that pyramidalization of the radical in the transition state may be significant.^{3e,f}

Figure 2. Felkin-Anh Analogies



The directions and trends in selectivity for reductions of the alkoxy radicals (**2e-h**) are inconsistent with either the A-strain model or an “electronic” Felkin-Anh model. This makes sense because A-strain should again not dominate the conformations of these radicals and because the stereoelectronic effects⁹ that operate in the electronic Felkin-Anh model as applied to reductions of (electrophilic) ketones probably should not be at work in the hydrogen abstraction reactions of (nucleophilic) radicals. The results are consistent with either a “steric” Felkin-Anh model or a Cram chelate model. Hydrogen bonding^{2b,f,g} and Lewis acid complexation¹⁰ have been proposed as features that can effect stereoselectivity in radical reactions; however, these aminoalkyl radicals are fundamentally different from previous examples. In structures like β -hydroxy carbonyl radicals^{2b,f,g} (Figure 3), the radical is conjugated with the H-bond acceptor and the H-bonding should be weaker in the radical than in a closed-shell analog. In contrast, for aminoalkyl radicals, the radical is conjugated with the H-bond donor and thus H-bonding should be stronger in the radical than in a closed shell analog. Despite this suggestive argument, the conformations of the steric Felkin-Anh model and the Cram chelate model are quite closely related, and it is not possible to differentiate them with the limited information that is currently available.

Figure 3. Closed Shell/Radical Analogies for H-Bonding



In summary, we have verified the prediction based on ionic reactions that the hydrogen abstraction reactions of “NHR”-substituted radicals should show opposite facial selectivity to their “NR¹R²”-substituted counterparts. We interpret this trend by suggesting that, as the size of R¹ decreases to H, transition states resembling the A-strain model yield to transition states resembling the “steric” Felkin-Anh model. We have not uncovered any evidence in such radical reactions for stereoelectronic effects like those proposed in the “electronic” Felkin-Anh model for ionic reactions. With “NHR” substituted radicals bearing H-bond acceptors, transition states resembling Cram’s chelate model may be important, but more information is needed before the “steric” Felkin-Anh and Cram chelate models can be differentiated.

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only product not formed
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