Role of σ-Donation in the Stereocontrol of Hydrogen-Transfer Reactions Involving Acyclic Radicals

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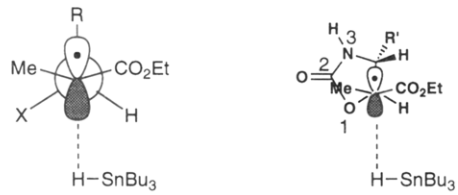
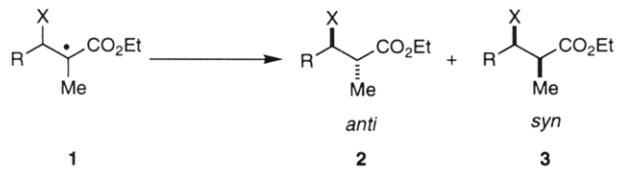
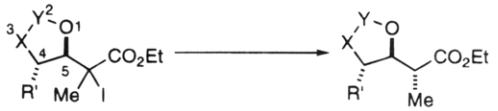
1,2-Stereoinduction has been demonstrated in the hydrogen-transfer reactions or allylation of acyclic radicals.[1−4] Although different mechanistic proposals[1b,2−4] rationalize the stereochemical outcome of reactions involving an acyclic radical **1** flanked by a carbonyl and a stereogenic center, the pool of experimental data is most consistent with the transition state model depicted as **A**.





This transition state model, predictive of the predominant (*anti*) product, takes into consideration both steric and electronic factors. In this model, destabilizing allylic 1,3-interactions are alleviated and there are two ways in which electronic factors could additionally stabilize the transition state. Firstly, the opposition of the ester and electronegative X groups should reduce intramolecular electrostatic repulsions; the most compelling evidence for this concept is the impressive stereoselectivity (20:1) of the hydrogen-transfer reaction of a substrate in which X is a small group such as fluorine.[3] The second electronic effect involves the stabilization of an electron-poor radical by hyperconjugation[5,6] with the best σ-donor[7] (electron-donating) substituent (which is R rather than X)[3] and is manifested in the alignment of the σ_{C-R} bond with the singly occupied p orbital. In this paper we provide experimental substantiation of the role of σ-donation through hyperconjugation in controlling the stereoselectivity of reductions involving acyclic radicals adjacent to an ester.

Table 1. Radical-Mediated Reduction of Conformationally-Rigidified Substrates[a]



entry	substrate[b]	X	Y	R′	product[c]	ratio[d] *anti*:*syn*	yield (%)
1	**4**	NH	CO	H	**5**	3:1	73
2	**6**	NH	CO	Me	**7**	9:1	77
3	**8**	NH	CO	Et	**9**	9:1	85
4	**10**	NH	CO	*i*-Pr	**11**	9:1	76
5	**12**	NH	CO	*c*-C_6H_{11}	**13**	8:1	87
6	**14**	NH	CO	*t*-Bu	**15**	12:1	82
7	**16**	NH	CO	Ph	**17**	11:1	76
8	**18**	O	CO	H	**19**	1:1[e]	91
9	**20**	O	CO	Me	**21**	2:1[f]	95
10	**22**	CH_2	CO	H	**23**	7:1	>95
11	**24**	CH_2	CO	Me	**25**	20:1	>95
12	**26**	CH_2	CH_2	H	**27**	11:1	90
13	**28**	CH_2	CH_2	Me	**29**	52:1	93
14	**30**	CH_2	CH_2	F	**31**	6:1	86

[a] Reactions were conducted at −30 °C in toluene with 0.1 M concentration of substrate, 2.0 equiv of Bu_3SnH, and AIBN/GE 275 W sunlamp or Et_3B for initiation. Mode of initiation did not significantly affect *anti*/*syn* ratios. [b] Mixture is enriched with *R* isomer at the stereogenic center adjacent to ester group. No effort was made to separate these two epimers since reduction of each gives the same product ratio. [c] Only the major product (*anti*) is shown. [d] Ratios were determined on crude reaction isolates by capillary GLC or 400 MHz NMR. [e] Ratio was unchanged when reaction was conducted in CH_2Cl_2. [f] Reaction was performed in CH_2Cl_2.

Substrates resembling **1** have considerable rotational freedom and are unsuitable to probe electronic influences since modifications to R are likely to produce both electronic *and* steric perturbations at the reactive center. Thus, we were faced with the selection of a substrate template based on **1** that would permit differentiation between steric and electronic effects in the hydrogen-transfer reaction. Ideally, modifications intended to differ electronically would have to be either sufficiently remote from the radical center or approximately isosteric in nature on substrates of limited conformational mobility. A template that meets this criterion is one in which the X and R substituents in **1** are linked to afford a conformationally-rigidified series, such as the oxazolidinones shown in entries 1−7 of Table 1. In these oxazo-

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(1) For recent reviews see: (a) Smadja, W. *Synlett* **1994**, 1−26. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296−303.

(2) Hart, D.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457−4470 and references cited therein.

(3) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Slassi, A.; Lavallée, J.-F.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166−1178 and references cited therein.

(4) (a) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G.; *Tetrahedron Lett.* **1992**, *33*, 1863−1866 and references cited therein. (b) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841−4858 and references cited therein.

(5) Another interpretation involves the hypothesis that the energy of the activated complex in a reaction can be lowered by the delocalization of electrons comprising an antiperiplanar vicinal s bond into the σ* orbital of the bond being formed. Therefore, it is possible to imagine that when the radical reacts with Bu_3SnH (see **A**), the $\sigma^{*‡}$ orbital will be stabilized by the adjacent σ_{C-R} bond: (a) Bodepudi, V. R.; Le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001−2006. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552. (c) The conclusions of Le Noble have been challenged recently by the attribution of experimental observations to electrostatic effects: Adcock, W., Clark, C. I., Trout, N. A. *Tetrahedron Lett.* **1994**, *35*, 297−300.

(6) One argument against the role of hyperconjugation in this reaction is based on the premise that tributyltin hydride is a nucleophilic reagent.[4b] An extension of this assumption suggests that the most reactive radical exists in a conformation that enhances its electrophilicity; i.e., the X group is eclipsed with the radical p-orbital and *anti* to the incoming hydride. However, this rationale is *not* predictive of the observed (*anti*) product. Nevertheless, there is clearly a need for kinetic studies involving such radicals.

(7) March, J. *Advanced Organic Chemistry,* 3rd ed.; Wiley: New York, 1985; p 247.

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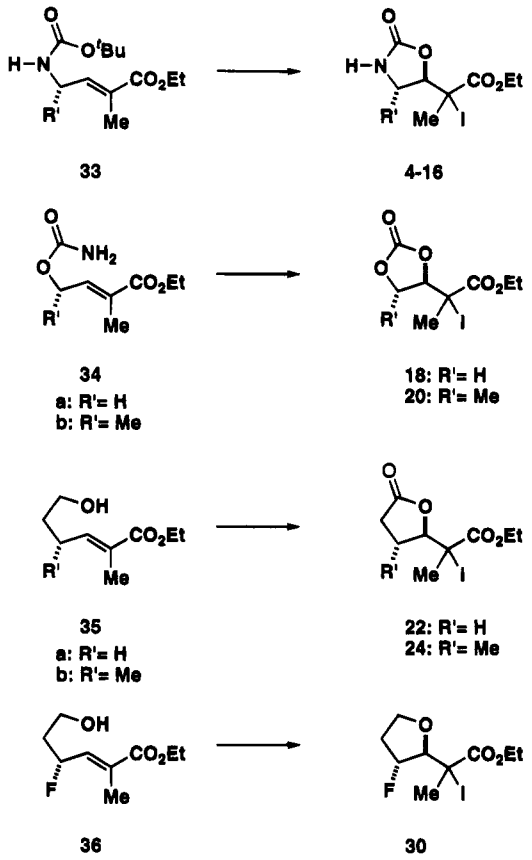
lidinones, the *trans* relationship of R′ and the radical-bearing appendage with respect to the ring (see **B**) would allow modification of R′ with minimal steric impact.



Using an improved iodocyclization protocol[8] recently developed in our laboratories, we prepared several oxazolidinone substrates with varying steric bulk at R′ and subjected them to radical-mediated hydrogen-transfer reactions (Table 1, entries 1–7). These reductions proceeded with the expected *anti*-stereoselection, and as foreseen, the size of the distant alkyl R′ group had little impact (entries 2–7) on the stereochemical outcome. Interestingly, despite the remoteness of R′ from the reactive radical center, there is, however, a significant difference in stereoselectivity when R′ = alkyl (8:1 to 12:1) *versus* R′ = H (3:1). Assuming that the hydrogen is a poorer σ-donor than an alkyl group,[9] the hydrogen at R′ is not as effective at promoting hyperconjugation and, thus, alignment of the C_4-C_5 bond with the radical p-orbital. Another surprising but noteworthy observation is the good diastereoselectivity displayed by an oxazolidinone in which R^1 = Ph (11:1). From an electronic standpoint, phenyl is generally accepted as an electron-withdrawing group, for which one would have expected poorer *anti*-selectivity in comparison to isosteric cases R^1 = *i*-Pr (9:1) or R^1 = *c*-C_6H_{11} (8:1).[10]

In seeking further testimony to the role of σ-donation in these hydrogen-transfer reactions, we considered alteration of the electronic character of the C_4-C_5 bond by endocyclic substitution or removal of the oxazolidinone heteroatoms; such modifications within the plane of the ring are more likely to influence the reaction in an electronic rather than a steric nature. Thus, the hyperconjugative ability of the C_4-C_5 bond would be attenuated by substitution of the oxazolidinone nitrogen by the more electronegative oxygen; this would account for the lack of stereoselectivity in the reduction of the resultant 1,3-dioxolan-2-one (cf. entries 1 and 8, Table 1). Alternatively, enhancement of the hyperconjugation between the C_4-C_5 bond and the SOMO p-orbital, by replacement of the oxazolidinone nitrogen with the more electropositive methylene group to afford a γ-lactone (entry 10, Table 1), leads to better stereoselectivity relative to the oxazolidinone analogue (entry 1, Table 1). This effect is amplified further by removal of the γ-lactone carbonyl to give a tetrahydrofuran (entry 12, Table 1).

The increase in the stereoselectivity of hydrogen-transfer reactions by alkyl substitution at the carbon vicinal to the radical-bearing appendage is a general phenomenon for the cyclic substrates described herein. As shown in the oxazolidinone series (cf. entries 1 and 2, Table 1), replacement of H (R′) by a methyl group enhances *anti*-preference in the radical reduction of the 1,3-dioxolan-2-one (cf. entries 8 and 9, Table 1), γ-lactone (cf. entries 10 and 11, Table 1), and tetrahydrofuran series (cf. entries 12 and 13, Table 1). On the other hand, substitution of R′ with an electron-withdrawing group, such as fluorine, has a deleterious effect (cf. entries 12 and 14, Table 1) on the stereoselectivity of the hydrogen-transfer reaction. Presumably, the fluorine substitution weakens the SOMO–(C_4-C_5) interaction to produce a deterioration in *anti*-selectivity.

Taken together, these results demonstrate the role of σ-donation in governing the facial selectivity of radical-mediated reductions of α-halo esters. More specifically, hyperconjugation of a σ bond with the radical p-orbital, conferred by good σ-donating substituents, may contribute significantly to the enhancement of *anti*-selectivity in hydrogen-transfer reactions for a number of α-halo esters bearing heterocycles.

Although this electronic effect could be rationalized,[5] the mechanism by which it enhances *anti*-selectivity requires better characterization of the transition states for *both anti*- and *syn*-products. We recently proposed several models[2] that could account for *syn*-product formation. Among these was a model in which the reacting radicals in both *anti* and *syn* transition states have essentially the same conformation. That is, the products would simply arise from reagent attack on both faces of the radical. Facial discrimination would be affected by the alignment of the C_4-C_5 bond with the radical p-orbital (see **B**), which in turn is influenced by hyperconjugation. Thus, a slight angular offset of this alignment would diminish the ability of the ring residue at C_4 to shield the radical's top face from attack by tributyltin hydride and consequently give way to more *syn* product formation.

Supplementary Material Available: Experimental procedures and spectral data for compounds **4**–**31** (16 pages). The author has deposited atomic coordinates for **32** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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(8) Guindon, Y.; Slassi, A.; Ghiro, É.; Bantle, G.; Jung, G. *Tetrahedron Lett.* **1992**, *33*, 4257–4260.

(9) (a) There is controversy in the literature over whether a hydrogen or methyl is a better σ-donating group and over their role in hyperconjugation; see: (a) Reference 5a. (b) Reference 5c. (c) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867–1876.

(10) Conformational analysis and calculation have been initiated to assess whether **16** or its radical intermediate has the same conformation as the other members in the oxazolidinone series.