The Effect of Polar Substituents on the Conformation and Stereochemistry of Enolate Radicals

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Abstract: ESR measurements and AM1 calculations show that ester substituted radicals 2 and 6 prefer conformation A as a result of allylic strain effects. But dipolar repulsion between substituents X and CO_2Et in 2 and 6 has a pronounced effect on the conformation and the stereoselectivity of radicals 2 and 6.

Recently, Hart et al.[1] and Giese et al.[2] have shown that enolate radicals substituted by a tertiary alkyl group adopt preferred conformation **A**. In this conformer the hydrogen atom at the tertiary carbon atom points towards an oxygen of the ester group, thus minimizing A-strain effects. According to this model, the different shielding by the substituents R and X at the prochiral radical center induces stereoselectivity of the radical hydrogen abstraction reaction.[1-4]
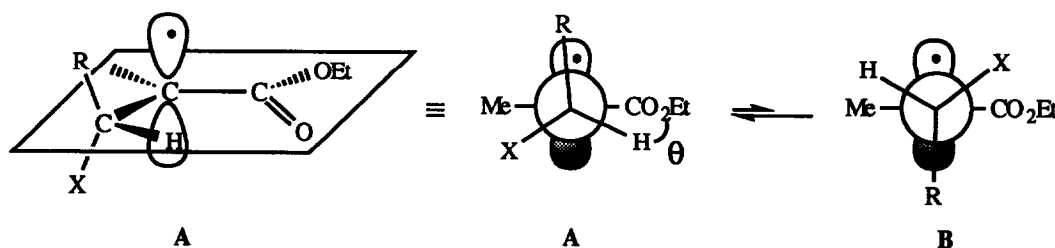
Guindon et al.[5] pointed out that dipole dipole interactions can play a role if substituent X at the stereogenic center is a powerful electronegative group. Thus, conformer **B** should be disfavoured not only because of the steric (A-strain model) but also because of dipolar effects (Cornforth model). Furthermore, the dipolar repulsion between the ester group and substituent X should distort the ideal A-strain conformation by increasing the dihedral angle θ.

In order to study the importance of polar effects on the conformation and stereoselectivity of enolate radicals, we generated radicals **2a-c** from bromides **1a-c**.[6] The energy difference between the conformers **2A** and **2B**, the dihedral angle θ and the ESR coupling constant $a(H_\beta)$ were calculated,[7] compared with the experimental coupling constant,[8] and the stereoselectivity of the hydrogen atom abstraction from Bu_3SnH was measured.
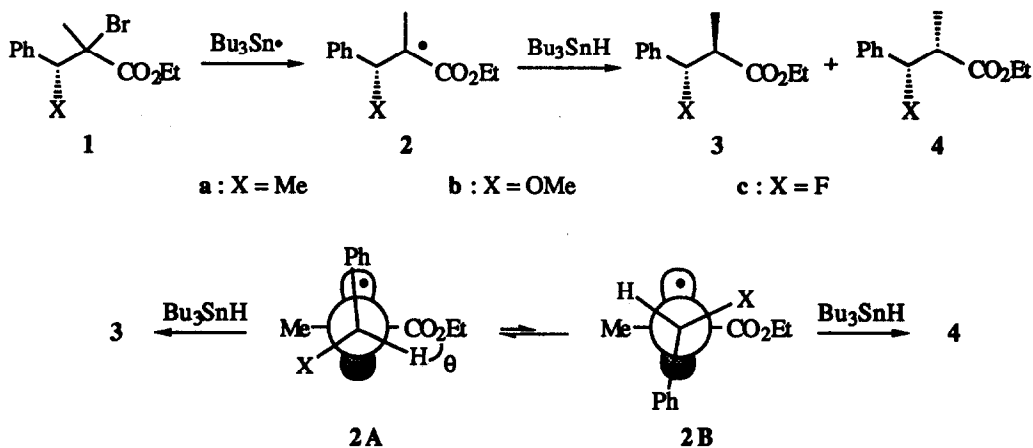
a : X = Me   b : X = OMe   c : X = F

Table 1. Influence of substituent X on the energy difference ΔE_{2B}-ΔE_{2A}, dihedral angle θ, the β-coupling a(H$_\beta$), and the stereoselectivity of hydrogen atom abstraction.

X	θ	ΔE_{2B}-ΔE_{2A}	a(H$_\beta$)$_{calc.}$	a(H$_\beta$)$_{exp.}$	3 : 4	Yield
	AM1 Calculation		ESR		H-Abstraction	
		kcal/mol	Gauss	Gauss	(-78°C)	(%)
Me	4°	0.5	7.0	6.0	66 : 34	85
OMe	34°	2.4	9.0	8.0	97 : 3	90
F	31°	2.3	11.0	9.0	95 : 5	88

According to AM1 calculations radicals without (X=Me) as well as with (X=OMe, F) powerful electronegative substituents preferentially adopt conformation **2A**. But the energy differences ΔE_{2B}-ΔE_{2A} increases from 0.5 to 2.3-2.4 kcal/mol if X=Me is exchanged by the polar OMe or F groups (Table 1). In the same order the dihedral angle θ of the minimum conformation **2A** is increased from nearly 0° to larger than 30°. This increase of the energy difference and of the dihedral angle leads to an increase of the β-coupling constant in the ESR spectrum. A complete conformational analysis for the rotation around the bond between the radical and the stereogenic center is shown in Fig. 1.
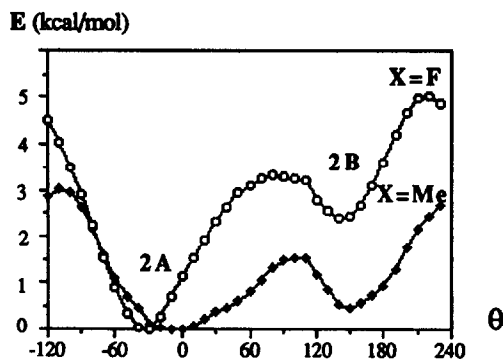
Fig. 1. Conformational analysis of radicals **2** (X = Me, F)

The influence of the substituent on the energy and conformation of the radical leads to a remarkable increase in stereoselectivity. Polar substituents OMe and F clearly disfavour conformer **2B** and increase the dihedral angle θ in conformation **2A**. Both effects lead to an increase of the selectivity from 66:33 (X=Me) to 97:3 (X=OMe), and 95:5 (X=F).

A reverse effect is expected if in radical **6** polar substituents X are attached to the radical center. Radical **6** was generated *via* addition of *t*-butyl radicals to substituted fumarates **5**. Subsequent trapping reactions with Bu$_3$SnH leads to products **7** and **8**.[9]
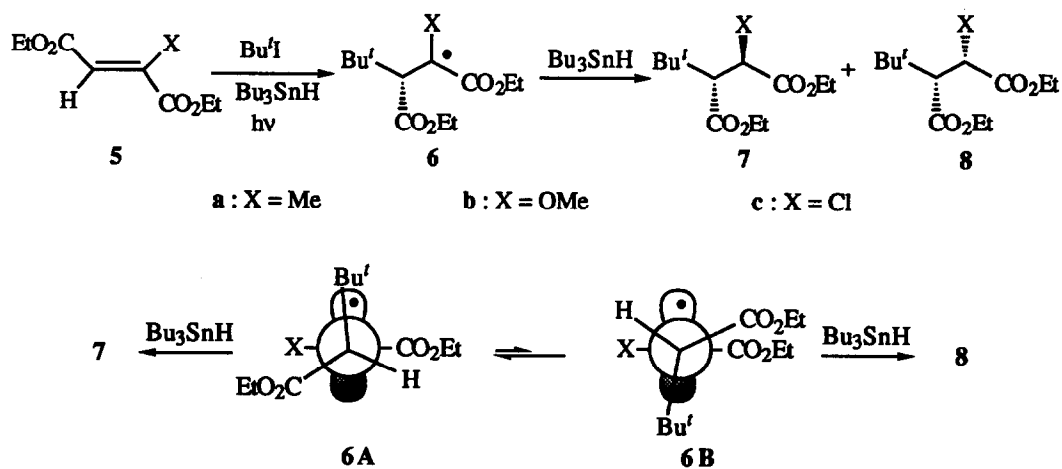
X	7 : 8 (20°C)	Yield (%)	$\Delta E_{6B} - \Delta E_{6A}$
Me	96 : 4	80	3.6
OMe	84 : 16	77	2.0
Cl	88 : 12	45	1.7

Again the A-strain conformers **6A** are favoured for X=Me, OMe, and Cl. But the energy difference ΔE_{6B}-ΔE_{6A} now decreases from 3.6 kcal/mol to 1.7-2.0 kcal/mol if X=Me is exchanged by the more electronegative substituent OMe and Cl, respectively. This decrease in the energy difference leads to a decrease in stereoselectivity.[10] Now radical **6** with an unpolar substituent (X=Me) is most selective (96:4), whereas polar groups decrease the selectivity to 84:16 (X=OMe) and 88:12 (X=Cl), respectively.

Conclusion: The influence of the polarity of substituents X in radicals **2** and **6** clearly demonstrates that in addition to steric A-strain effects dipole dipole interactions influence the conformation and the stereoselectivity of radicals.

References and Notes

1. D.J. Hart, R. Krishnamurthy, *Synlett* **1991**, 412.
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3. For reviews that contain further discussions of this model, see: N.A. Porter, B. Giese, D.P. Curran, *Acc.Chem.Res.*, **1991**, *24*, 296; D.P. Curran, P.S. Ramamoorthy, *Tetrahedron* **1993**, *49*, 4841.
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6. Bromides **1a,b** were prepared by a Mukaiyama reaction of the trimethylsilyl ketene acetal derived from ethyl 2-bromopropionate with 1-chloro-1-phenylethane and benzaldehyde dimethyl acetal, respectively.
   Fluoride **1c** was prepared by treating the corresponding alcohol (obtained by the aldol condensation of ethyl 2-bromopropionate and benzaldehyde) with DAST.
7. Calculations were done using the AM1-AUHF method as implemented in the VAMP4.4 or the SCAMP4.1 versions of Dr. T. Clark (University Erlangen). This method calculates a spin annihilation between the SCF-cycles and therefore eliminates quartet contamination from the density matrix that is passed on to the next cycle. The radicals under consideration here show, due to the phenyl substituent, a large spin contamination (S^2>1)using the normal UHF wave function. The AUHF method can eliminate completely such spin contamination. In analogy to the method developed ¦ by Nelsen (S.F. Nelsen, *J. Chem. Soc., Perkin Trans. II* **1988**, 1005) a factor of 1208 Gauss was obtained from the proportionality between the AM1-AUHF calculated spin populations and the coupling constants. Using the same radicals as already employed by Nelsen, the same quality of correlation was obtained as observed by Nelsen, when only β-couplings were used for the fit.
   Radicals without a phenyl substituent were calculated with the normal AM1-UHF method.
8. The ESR measurements were carried out at -40° in C_6H_5F with $Bu_3SnSnBu_3$ by UV irradiation, see: A. Koch, C. Lamberth, F. Wetterich, B. Giese, *J. Org. Chem.* **1993**, *58*, 1083.
9. The reactions were carried out using *t*-Bul and Bu_3SnH at 20° under photolytic conditions. The configurations of the products were determined as described earlier: B. Giese, M. Zehnder, M. Roth, H.-G. Zeitz, *J. Am. Chem. Soc.* **1990**, *112*, 6741.
10. Variation of substituent X also influences the SOMO energy of radical **6**. But this should have only a minor effect on the stereoselectivity.