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The Curtin-Hammett Principle: Stereoselective Radical Additions to Alkenes

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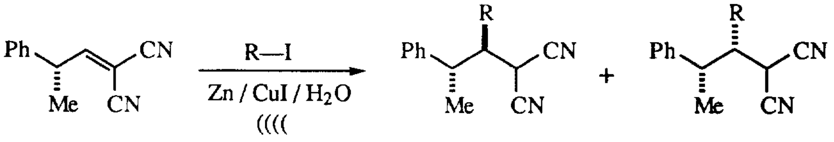
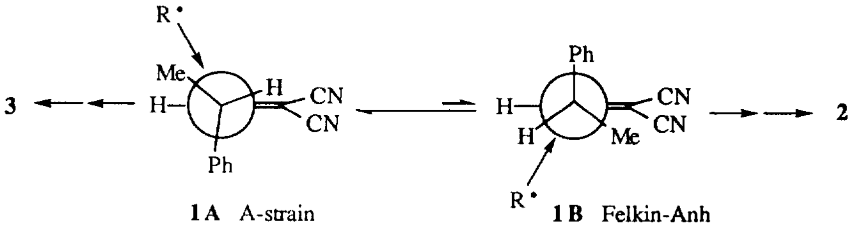
Abstract: *The more stable "A-strain" conformer 4A of alkene 4 (L = Bu^t) reacts much slower with alkyl radicals than the less stable "Felkin-Anh" conformer 4B. This leads to* anti*-isomer 6 as the main product if the attacking radical is bulky.*

Recently, we have demonstrated that alkyl radicals attack alkene **1** predominantly at the less stable conformer **1B**, leading to *anti* isomer **2** as the major product.[1] We explained this result by the steric repulsion between the methyl substituent of the "A-strain" conformer 1A and the attacking radical R•. This shielding effect is absent in the reaction of the "Felkin-Anh" conformer 1B which is therefore much more reactive. As a result of these steric effects, the major product is formed from the less stable but more reactive conformer.



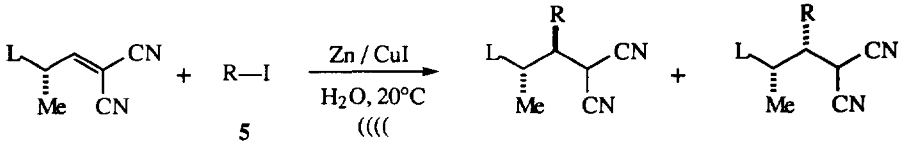
1 **2** *anti* **3** *syn*

R = Bu^t 85 : 15
R = Bu^n 79 : 21



1A A-strain **1B** Felkin-Anh

In order to see how general this "Curtin-Hammett"[2] situation is in radical chemistry, we have varied the large substituent L of alkene **4**[3] and the bulk of radical R•, generated from alkyl iodide **5** by sonication[4] in the presence of Zn/CuI. The structure determination of the products **6** and **7** is based on the X-ray analysis of isomers **6a** (R = Bu^t) and **7a** (R = Me)[5] and on NMR spectroscopy[6]. The selectivities of the radical addition reactions are collected in Table 1.



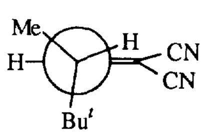
4 5 6 *anti* 7 *syn*

Table 1. Selectivity (**6** : **7**) of the addition of alkyl radicals R• to alkenes **4a–c**.

entry	alkene	alkene substituent L	R•	**6 : 7** *anti* : *syn*	yield (**6**+**7**) (%)
1	**4a**	Bu^t	Bu^t•	>99 : 1	32
2	**4a**	Bu^t	Pr^i•	80 : 20	50
3	**4a**	Bu^t	Et•	50 : 50	20
4	**4a**	Bu^t	Me•	39 : 61	50
5	**4b**	Pr^i	Bu^t•	84 : 16	45
6	**4c**	Et	Bu^t•	72 : 28	61

The data of Table 1 show that with *tert*-butyl as large substituent L at the alkene **4a** and as the radical R•, only the *anti* product **6a** (R = Bu^t) is formed (Table 1, entry 1). By decreasing the bulk of group L, the *anti* : *syn* ratio (**6** : **7**) decreases to 84 : 16 (L = Pr^i, entry 5) and 72 : 28 (L = Et, entry 6). In a similar way the *anti* : *syn* ratio (**6** : **7**) becomes smaller if the bulk of the attacking radical is reduced (Table 1, entries 1–4). With R = Me the formation of the *syn* isomer **7a** is already favored (**6** : **7** = 39 : 61, entry 4).

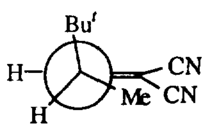
From X-ray analyses[5] and AM1 calculations[7], the A-strain conformers of alkenes **4a–c** turned out to be the most stable conformers. With L = Bu^t (alkene **4a**) the A-strain conformer **4A** is 3.0 kcal/mol lower in energy than **4B** (AM1 calculations). However, only the small methyl radical reacts predominantly with the preferred conformer **4A**. By ab initio calculations[8] this attack leads to transition state **8A** which is slightly lower in energy than attack at the conformer **4B** (transition state **8B**).



4A A-strain

≡ 0 kcal/mol

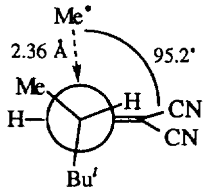
$\rightleftharpoons$



4B Felkin-Anh

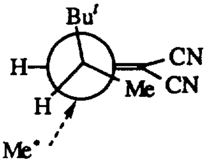
3.0 kcal/mol

8A



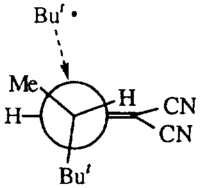
≡ 0.0 kcal/mol

8B



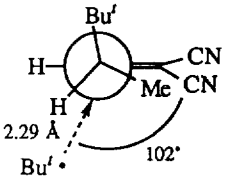
0.3 kcal/mol

9A



8.6 kcal/mol

9B



≡ 0.0 kcal/mol

Although the energy difference between the alkene conformers **4A** and **4B** is 3.0 kcal/mol, the energies of the transition states for the methyl radical addition (**8A** and **8B**) are very similar. This demonstrates the steric effect between the methyl substituent at the alkene and the methyl radical in transition state **8A**. As expected the repulsion increases if the bulkier *tert*-butyl radical attacks alkene **4A**. In this case the attack at the more stable conformer **4A** leads to transition state **9A** which is 8.6 kcal/mol higher in energy than transition state **9B** (ab initio calculations[8]). The calculated reaction profiles of the addition of alkyl radicals R• to alkene **4** are shown in Figure 1.

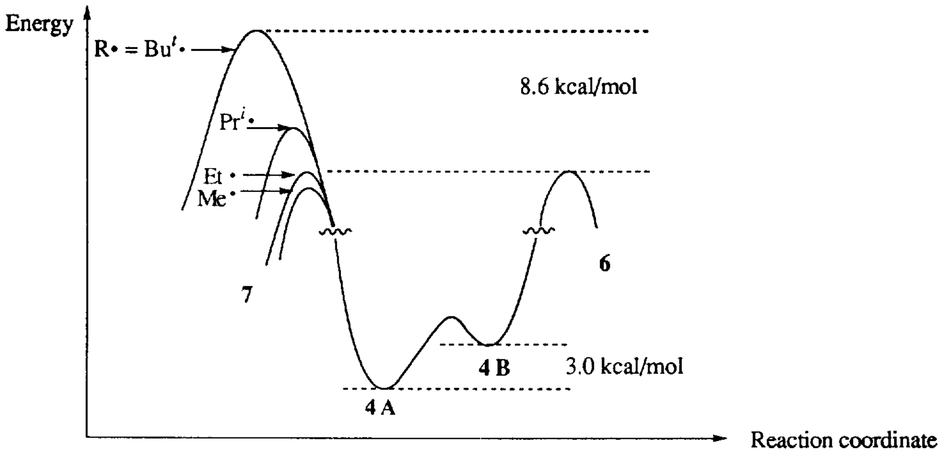


Fig. 1. Energy profiles for the reactions of radicals R• with alkene **4**.

Figure 1 shows that all alkyl radicals attack the less stable "Felkin-Anh" conformer **4B** faster than the "A-strain" conformer **4A**. With the bulky *tert*-butyl and isopropyl radicals the difference in activation energies is larger than the energy difference between the alkene conformers **4A** and **4B**. Therefore *anti* products **6** (R = Bu^t, Pr^i) are formed as major isomers. With the ethyl radical the energy difference between the ground states and transition states just compensates and the reaction is unselective. Only the methyl radical leads to the *syn* isomer **7** (R = Me) as major product because the reactivity difference with the small methyl radical is less important than the ground state difference of the alkene conformers.

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References and Notes

1. B. Giese, W. Damm, M. Roth, M. Zehnder, *Synlett* **1992**, 441. See also: Y. Yamamoto, S. Nishii, T. Ibuka, *J. Am. Chem. Soc.* **1988**, *110*, 617.
2. J. I. Seemann, *Chem. Rev.* **1983**, *83*, 83.
3. The alkenes were synthesized by Knoevenagel condensation of malonodinitrile with suitably substituted aldehydes.
4. The formation of radicals by the sonication method is described in: C. Petrier, C. Dupuy, J. L. Luche, *Tetrahedron Lett.* **1986**, *27*, 3149; P. Erdmann, J. Schäfer, R. Springer, H.-G. Zeitz, B. Giese, *Helv. Chim. Acta* **1992**, *75*, 638.
5. The X-ray structures will be published in *Acta Cryst.C.*
6. Reaction products **6** and **7** (L = Bu^t) exhibit significant trends in the NMR spectra: H_α (δ: 3.75–4.00), C_α (δ: 11.3–14.0), and C_β (δ: 40.9–55.3) appear at lower field in the *anti* isomer **7** (C_α is the C-atom which is substituted by the two nitrile groups). In addition, the coupling $J_{H\beta,H\gamma}$ (0.5–1.6 Hz) is slightly smaller in compound **6** than in compound **7**.
7. The AM1 calculations of **4A** and **4B** were carried out using the MOPAC6 program QCPE 455. AM1 calculations: M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. Stewart, *J. Am. Chem. Soc.* **1985**, *121*, 2063.
8. The calculations were carried out with Gaussian 92/DFT, Revision F.2, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Foresman, J. B.; Robb, M. A.; Head-Gordon, M.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1993. The transition state structures **8** and **9** were calculated at the MP2/6-31G*//UHF/3-21G level of theory.

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