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Reprint

Isoselective Relationship for the Stereoselectivity of the Transfer of Hydrogen Atoms to Cyclic Alkyl Radicals**

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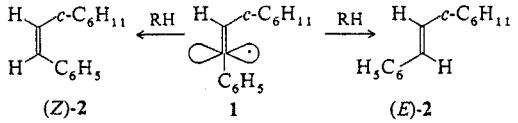
With the increasing use of radical reactions in organic synthesis a more detailed understanding of the reactivities and selectivities is of decisive importance.[1] Especially important is an exact knowledge of the stereoselectivity of hydrogen transfer and the possibility of controlling it, since this reaction is frequently the decisive product-forming step in radical reactions.[2]

Using the π-alkenyl radical **1** as example we have shown that the stereoselectivity of hydrogen transfer to give (*Z*)-**2** and (*E*)-**2** can be steered by both variation of the H donor RH as well as by the temperature, and that it obeys the

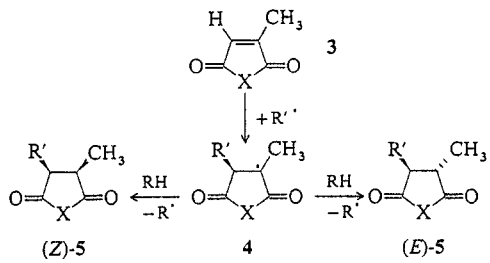


(*Z*)-**2** **1** (*E*)-**2**

isoselective relationship (a) with an isoselective temperature T_{iso} of 60–80 °C.[3] At this isoselective temperature, variation of the H donor has no influence on the selectivity.[4a]

$$T_{iso} = \frac{\delta(\Delta H_E^{\ddagger} - \Delta H_Z^{\ddagger})}{\delta(\Delta S_E^{\ddagger} - \Delta S_Z^{\ddagger})} \qquad (a)$$

Such isoselective realtionships are of practical importance, but also enable us to assess the selectivity of a series of reactions over a large temperature range and possibly to anticipate reversal of selectivity as a function of the temperature.[4] In addition, the occurrence of an isoselective relationship points to a common reaction mechanism. Hitherto a series of reactions in which isoselectivity occur, were experimentally measured with variation of only one reaction partner.[4a] We have now for the first time, by H trapping with the radical **4**, measured a series of reactions, which upon variation of both reaction partners—radical **4** and H donor RH—leads to a single isoselective relationship (Scheme 1).



(*Z*)-**5** **4** (*E*)-**5**

Scheme 1. X = O, PhN; RH = Bu_3SnH, PhMe, PhEt, $c\text{-}C_6H_{12}$; R′:Me (a), $n\text{-}C_6H_{13}$ (b), $PhCH_2$ (c), $c\text{-}C_6H_{11}$ (d), PhCH(Me) (e).

The radicals **4** were obtained by addition of a radical R′· to methylmaleic anhydride or *N*-phenyl(methyl)maleimide **3**. Transfer of H from H donors RH to the planar π-alkyl radical **4** leads to formation of (*Z*)-**5** and (*E*)-**5**, whose ratio was determined in the temperature range 0–400 °C. The stereoselectivity of the H transfer is significantly greater with the alkyl radical **4** than with the alkenyl radical **1** as acceptor. It is strongly influenced by the β-substituent R′, by the H donor and by the temperature, but is largely independent of whether **3** is employed as the *N*-phenylimide or the anhydride (Table 1).

Since the approach of the H donor RH upon **4** from the *anti*-side with respect to R′ is less hindered than from the *syn*-side, the activation enthalpy for the formation of (*Z*)-**5** is 3.5–10.9 $kmol^{-1}$ lower than for the formation of (*E*)-**5**.

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Table 1. Activation parameters for the stereoselectivity of the transfer of H to the alkyl radicals **4** and ratio of the products [(*Z*)-**5**]:[(*E*)-**5**].

No.	4	RH	$\Delta\Delta H^{\neq}$ [e] [kJ mol^{-1}]	$\Delta\Delta S^{\neq}$ [e] [J mol^{-1}K^{-1}]	[(*Z*)-**5**]:[(*E*)-**5**)]	*T* [°C]
1	**a**[a]	Bu_3SnH	5.1 ± 0.3	8.6 ± 0.8	3.0:1[c]	0–140[7]
2	**b**[a]	Bu_3SnH	5.4 ± 0.3	9.0 ± 1.2	3.0:1[c]	0–110[7]
3	**c**[a]	Bu_3SnH	5.7 ± 0.7	11.3 ± 2.1	3.5:1[c]	0–80 [7]
4	**d**[a]	Bu_3SnH	8.2 ± 0.5	14.3 ± 1.5	5.6:1[c]	0–140[7]
5	**d**[b]	Bu_3SnH	9.4 ± 1.2	16.6 ± 3.7	6.7:1[c]	0–110[7]
6	**d**[b]	*c*-C_6H_{12}	9.7 ± 0.3	15.2 ± 0.7	1.91:1[d]	180–400[8]
7	**d**[b]	*c*-C_6H_{12}	10.9 ± 0.6	17.6 ± 1.2	1.96:1[d]	200–260[8]
8	**c**[a]	PhMe	3.5 ± 0.2	7.0 ± 0.5	1.04:1[d]	180–260[8]
9	**e**[a]	PhEt	4.8 ± 0.4	8.7 ± 0.8	1.18:1[d]	180–260[8]

[a] X = PhN. [b] X = O. [c] 20 °C. [d] 200 °C. [e] In each case the value for (*E*)-**5** − the value for (*Z*)-**5**.

Thereby, the energy difference $\Delta H^{\neq}((E)\text{-}5) - \Delta H^{\neq}((Z)\text{-}5)$ with the same H donor tributyltin hydride increases with increasing size of the β-substituent R′ from 5-6 (methyl, *n*-hexyl,benzyl) to 8.2 kJ mol^{-1} (cyclohexyl), and accordingly the stereoselectivity increases. Since also the differences in the activation entropies increase in the same direction from 9 (methyl, *n*-hexyl) through 11.3 (benzyl) to 14.3 J mol^{-1} K^{-1} (cyclohexyl), the compensation of the activation enthalpies and activation entropies leads to an isoselective temperature[4a] of 750 K with $[(Z)\text{-}5]/[(E)\text{-}5] = 0.72 + 0.07$ (Fig. 1). At this temperature, which lies outside the measurement range, the radicals **4a**–**4d** (X = PhN) react with the H donor tributyltin hydride (Experiments 1–4) with the same stereoselectivity.

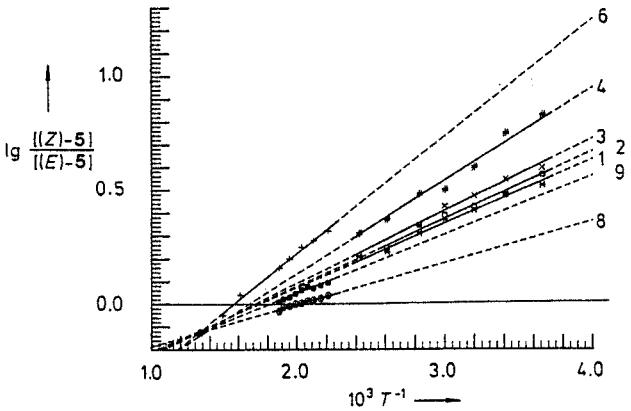

Fig. 1. Temperature dependence of the stereoselectivity of the H transfer to the alkyl radicals **4** by Bu_3SnH, *c*-C_6H_{12}, PhMe and PhEt. The numbers on the Arrhenius curves correspond to the experiment numbers in Table 1. The unbroken portions of the curves demarcate the ranges of measurement (cf. Table 1).

The H transfer from toluene to **4c** (X = PhN), from ethylbenzene to **4e** (X = PhN), and from cyclohexane to **4d** (X = O) (Experiments 8, 9, and 6) obey the same isoselective relationship as the H transfer from tributyltin hydride to the radical **4** (Fig. 1). This is a remarkable result, since it shows that the reactions of five sterically differently shielded radicals **4** with four differently reactive H donors RH[5] obey a common isoselective relationship. It can therefore be concluded that the stereoselectivity of the H transfer is determined by the steric interaction between H donor and β-substituent in radical **4**. The finding that **4c** (X = PhN) reacts more selectively with the H donor tributyltin hydride (Experiment 3) than with the much less reactive toluene, is surprising, since the difference in the steric shielding by R′ should have all the more stronger effect on the activation energies the less reactive the H donor is.[3a] Our result—a further deviation from the reactivity–selectivity principle[6]—shows that the steric effect of tributyltin hydride on **4c** (X = PhN) is greater than that of toluene in the transition state of the H transfer, so that the above effect is overcompensated. In contrast, in the case of the radical **4d** (Experimental pairs 4 and 7 as well as 5 and 6), the expected behavior is observed even when the differences are smaller than in the case of the alkenyl radical **1**.[3]

The temperature dependence of the stereoselectivity with incorporation of the isoselective point is shown in Figure 1. The selectivity $\lg\{[(Z)\text{-}5]/[(E)\text{-}5]\}$ decreases as expected with increasing temperature, and between 475 K (Experiment 8) and 638 K (Experiment 6) is equal to zero. Above these temperatures the selectivity increases again, and entropically favored preferentially (*E*)-**5** is formed. This reversal of selectivity lies within the range of measurement in the case of Experiments 6–9, and could therefore be measured directly.

Our investigations on the alkyl radicals **4** show that the stereoselectivity of radical hydrogen transfer reactions can be controlled by variation of the β-substituent, the H donor, and the reaction temperature. These results are important for the planning of syntheses in which the subsequent H transfer takes place at a prochiral center.

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3 (X = O), 616-02-4; **3** (X = PhN), 3120-04-5; **4a** (X = PhN), 132750-69-7; **4b** (X = PhN), 132750-70-0; **4c** (X = PhN), 132750-71-1; **4d** (X = PhN), 132750-72-2; **4d** [b] (X = O), 65149-70-4; **4e** (X = PhN), 132750-73-3; (*E*)-**5a** (X = PhN), 35393-95-4; (*Z*)-**5a** (X = PhN), 6144-74-7; (*E*)-**5b** (X = PhN), 132750-74-4; (*Z*)-**5b** (X = PhN), 132750-78-8; (*E*)-**5c** (X = PhN), 132750-75-5; (*Z*)-**5c** (X = PhN), 132750-79-9; (*E*)-**5d** (X = PhN), 132750-76-6; (*Z*)-**5d** (X = PhN), 132750-80-2; (*E*)-**5d** (X = O), 65424-96-6; (*Z*)-**5d** (X = O), 65424-93-3; **5e** (X = PhN), 132750-77-7.

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[5] The rate constants for the transfer of H to primary alkyl radicals were determined for tributyltin hydride, ethylbenzene, toluene, and cyclohexane at 100 °C to be 8.3×10^6, 1.3×10^3, 4.2×10^2, and 16×10^2 M^{-1}s^{-1}, respectively: C. Chatgilialoglu, K. U. Ingold, J. C. Scaiano, *J. Am. Chem. Soc. 103* (1981) 219; V. E. Agabekov, N. L. Budeiko, E. T. Denisov, N. I. Mitskovich, *React. Kinet. Catal. Lett. 7* (1972) 437; P. J. Boddy, E. W. R. Steacie, *Can. J. Chem. 39* (1961) 13.

[6] B. Giese, *Angew. Chem. 89* (1977) 162; *Angew. Chem. Int. Ed. Engl. 16* (1977) 125.

[7] A mixture of one equivalent of alkyl iodide or alkyl bromide R′Y, two equivalents of tributyltin hydride, two equivalents of alkene **3**, and 0.1 equivalent of azobisisobutyronitrile in toluene was irradiated for 5–30 min or heated, and the ratio of the products [(*Z*)-**5**]:[(*E*)-**5**] determined gas chromatographically.

[8] 3 and the H-donor, which concomitantly supplies R′, (molar ratio 1:1000) contained in pyrex ampoules below the critical temperature of the H donor[9], in a high-pressure/high-temperature flow reactor above the critical temperature[9] were allowed to react in the absence of air. The reaction time was so chosen that the conversion sufficed for determination of the sterisomeric ratio even though no isomerization was detectable. The ratio [(*Z*)-**5**]:[(*E*)-**5**] was determined by capillary gas chromatography with on-column injection.

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