Tetrahedron Letters,Vol.27,No.23,pp 2645-2648,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ELECTRONIC CONTROL OF STEREOSELECTIVITY IN THE METAL HYDRIDE REDUCTIONS OF 7-BENZONORBORNENONES

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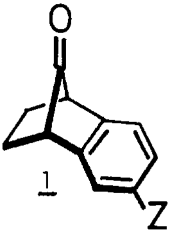
Summary: Electronic control of the *anti/syn* stereoselectivity in metal hydride reductions of 7-benzonorbornenones 2a-d is proposed.

Stereoselectivity in nucleophilic additions toward 7-norbornenone has received considerable attention. Experimental data so far available confirm that the nucleophiles stereoselectively attack the carbonyl group from the *syn*-side of the double bond. For example, the reactions with sodium borohydride,[1] Grignard reagents,[2a,b] alkyl lithium reagents,[3] diazomethane,[4] and with sulfonium[5] or sulfoxonium[2b] ylides gave the products of *syn* attack in a stereoselective or stereospecific manner. Exceptions can be seen in the reaction with vinyl lithium[6] and phenyl lithium.[7] Mechanistic problems as to whether the observed stereoselectivity is due to steric or electronic effects are controversial. Attack from the *anti* side of the double bond seems to be slightly more hindered owing to the steric repulsion of the $H_{5,6}$-exo protons with incoming nucleophiles. An empirical calculation evaluating congestion or tortional-corrected congestion, however, suggested that attack from the side of the double bond is slightly more hindered,[8] leading to a consideration that the stereoselectivity may be due to a chelating effect of the double bond rather than a steric or tortional effect.[8] A similar electronic interpretation was also proposed by Bly and Bly.[2b] An insight into this selectivity can be drawn by the experiments reported by Tanida who investigated the metal hydride reductions of mono-substituted 7-benzonorbornenones 1 as references for the solvolysis experiments of the corresponding *anti*-brosylates.[9] A maximum variation for the selectivity of *anti/syn*-alcohols was obtained in the disiamylborane reductions (52/48 for Z=Cl, 45/55 for Z=H, 36/64 for Z=OMe). However, the auther argued the selectivity in terms of the subtle change of steric environment, and did not refer to the electronic effect. For demonstration of the electronic effect, much wide variations in the selectivity are desirable. We wish to report the metal hydride reductions of the carbonyl group of 7-benzonorbornenones, 2a-d.

Lithium aluminum hydride reductions of 2a-d in ether at 0°C gave *anti*-(3a-d) and *syn*-alcohols (4a-d) in high yields with the ratios of 100:0, 95:5, 81:19, 79:21, respectively. The same reductions in THF gave *anti*- and *syn*-alcohols with much widely variable stereochemical responce, 100:0, 92:8, 62:38, and 45:55.

The stereochemistries of the *anti*- and *syn*-alcohols were determined by use of NMR shift reagents, $Eu(fod)_3$.[10] Furthermore, the NMR signals of the H_7-protons in *anti*-alcohols appear at higher field (δ_{ppm} in $CDCl_3$ 3.90, 3.81, and 3.72 for 3b, c, and d) than that in *syn*-alcohols (δ 4.20, 4.09, and 4.06 for 4b, c, and d, respectively) owing to the anisotropic effect of the benzene ring.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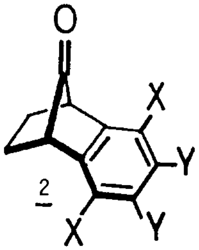
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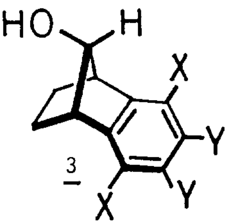
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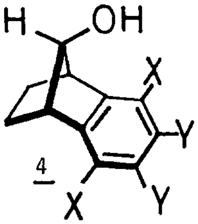
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a; X=Y=F, b; X=Y=Cl, c; X=Y=H, d; X=OMe, Y=H

Table 1 summarizes the results of reductions with various typical reagents along with the reaction conditions. In spite of the different sizes and reactivities of the reagents, the same stereoselectivity-sequence (2d → c → b → a) is observed. Obviously steric effect of the substituents on the benzene ring or the $H_{5,6}$-exo protons do not provide a rationalization for the observed stereoselectivity-sequence. In addition, the following features are notable from Table 1; (1) 2a and 2b show high selectivity toward all the reagents giving *anti* alcohols exclusively or overwhelmingly, (2) the main product is switched to the *syn* alcohol when 2d is reduced by DIBAL-H, $BH(Sia)_2$, and $LiAlH_4$ in THF. Apparently the electron withdrawing groups on the benzene ring favor *syn* attack, whereas the electron donating groups are inclined to increase the portion of *anti* attack, indicating importance of electronic effects.[11]

The observed variability in the *anti/syn* ratios suggests the operation of several electronic mechanisms. The predominant *syn* addition is explicable by either or both of the following electronic factors.[12] 1) The LUMO of 7-benzonorbornenones is distorted to *syn*-side through the σ^*-orbital (carbonyl σ^*) mixing[13] caused by the through-space interaction[14] of the carbonyl π^* and the benzene π-orbitals. This explanation is essentially the same with the presentation that incorporates some aspects of earlier proposals.[15a,b,16,17] 2) Electrostatic potential fields[15b,18,19] developed on the electron-deficient benzene ring can provide an opportunity to stabilize the negative charge of the nucleophiles in the transition state.

However, when the electron-donating groups are positioned on the benzene ring the contribution of the nonclassical carbonium ion character, which favors *anti* attack, seems to gain importance in the transition state. This factor may be particularly important for the reagents having a Lewis acid-character such as DIBAL-H, B_2H_6, and $BH(Sia)_2$ or having a strong coordination character to the carbonyl group prior to the hydride transfer as convincingly suggested by Ashby et al.[20] for $LiAlH_4$ in THF.

More rigorous choice of one or more from the above explanations cannot be allowed at present. In any events, this study clearly demonstrates that the *syn/anti* stereoselectivity is in fact controlled by electronic effect and strongly suggests that the origin of stereoselectivity of 7-norbornenone is also due to the same electronic factors.

Table 1. Stereoselective reductions of 7-benzonorbornenones 2a-d[a]

Metal hydride	Ketone	Isomer percentage[b]		Solvent
		anti-Alcohol[c]	*syn*-Alcohol[c]	
$LiAlH_4$	2a	3a 100 (mp 124°C)	4a 0	ether
	2b	3b 95 (mp 135°C)	4b 5 (mp 165°C)	
	2c	3c 81 (mp 115°C)	4c 19 (mp 105°C[d])	
	2d	3d 79 (mp 108°C)	4d 21 (mp 70°C)	
$LiAlH_4$	2a	3a 100	4a 0	THF
	2b	3b 92	4b 8	
	2c	3c 62[e]	4c 38[e]	
	2d	3d 45	4d 55	
$NaBH_4$	2a	3a 100	4a 0	EtOH
	2b	3b 95	4b 5	
	2c	3c 81[e]	4c 19[e]	
	2d	3d 79	4d 21	
B_2H_6	2a	3a 100	4a 0	THF
	2b	3b 93	4b 7	
	2c	3c 75[e]	4c 25[e]	
	2d	3d 70	4d 30	
$BH(Sia)_2$	2a	3a 100	4a 0	diglyme
	2b	3b -[f]	4b -[f]	
	2c	3c 57[e]	4c 43[e]	
	2d	3d 46	4d 54	
$LiAlH(O^tBu)_3$	2a	3a 100	4a 0	ether
	2b	3b 100	4b 0	
	2c	3c 93	4c 7	
	2d	3d 93	4d 7	
DIBAL-H	2a	3a 100	4a 0	ether
	2b	3b 86	4b 14	
	2c	3c 43	4c 57	
	2d	3d 37	4d 63	

a; At 0°C for all reactions. b; Determined by GLC analysis and/or chromatographic isolation. c; The *anti/syn* stereoselectivity in the text is based on the product ratio of *anti/syn* alcohol. d; Lit, mp 104.1-105.7°C, P. D. Bartlett and W. P. Giddings, J. Am. Chem. Soc., 1960, 82, 1240. e; Similar but slightly different ratios were obtained by H. Tanida, T. Tsuji, and H. Ishitobi in J. Am. Chem. Soc., 1964, 86, 4904, and ref. 9). f; Solubility of 2b in this solvent is too low for the reaction.

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10. The relative shifts, induced by $Eu(fod)_3$, of $H_{1,4}$, $H_{5,6}$-exo, $H_{5,6}$-endo, and H_7-protons are following; 3a: 1.00, 1.23, 0.76, and 2.02; 3b: 1.00, 1.20, 0.66, and 2.16; 4b: 1.00, 0.36, 0.35, and 1.71; 3c: 1.00, 1.20, 0.65, and 2.09; 4c: 1.00, 0.39, 0.35, and 1.82; 3d: 1.00, 1.18, 0.62, and 1.97; 4d: 1.00, 0.42, 0.37, and 1.81, respectively. The values of $H_{5,6}$-exo protons in the *anti* alcohols are considerably larger than those in the *syn* alcohols.
11. A geometrical change associated with $\angle C_1C_7C_4$ would not be important for 2a-e. See the discussion in reference 1 and references cited therein.
12. The aforementioned chelating effect[8,2b] of the π-bond predicts the reverse order.
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(Received in Japan 27 February 1986)