Communications to the Editor

Electrostatic Control of the Stereochemistry of Nucleophilic Additions to Substituted 7-Norbornanones

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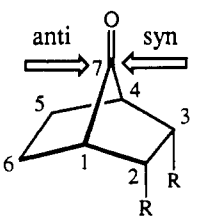
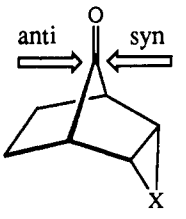
Remote polar substituents can control the stereoselectivity of nucleophilic additions to cyclic ketones even without inducing significant geometrical distortion.[1-4] This has been interpreted in terms of hyperconjugative effects proposed by Cieplak.[5] This theory emphasizes the effect of remote substituents on the electron-donating abilities of allylic bonds. However, calculations on model systems,[6,7] as well as experiments and calculations using 4-substituted decalones and cyclohexanones,[7] indicate that direct electrostatic interactions between remote polar groups and the nucleophile can influence the stereoselectivities of hydride reductions. We have located transition structures of lithium hydride additions to a series of 2,3-disubstituted 7-norbornanones, and we show that electrostatic effects, not hyperconjugative effects, control the stereoselectivities observed in these systems.

Transition structures were located with the 3-21G basis set, and all but reactions of **1b** were reoptimized with the larger 6-31G* basis set. The energies were also evaluated with MP2/6-31G* calculations.[8] The calculated energy differences between syn and anti attack of LiH on **1a-g** and **2a-c** are shown in Table I. These calculated stereoselectivities are in agreement with the experimental observations, which are also given in the table.

A notable feature is the dependence of the calculated stereoselectivity upon the conformation of the substituents for **1a**, **1b**, and **2c**, as found earlier for 4-substituted cyclohexanones.[7] Figure 1 shows four transition structures for the reaction of LiH with **1a**. The syn addition is more stable than the anti by 4 kcal/mol when the two C=O bonds eclipse the C—C bonds (**4** vs **3**). The anti addition becomes 0.6 kcal/mol more favorable when the two C=O bonds eclipse the C—H bonds (**5** and **6**). In the case of



1a



2b

1b, the syn addition is always preferred, but the preference is larger when the C=O group eclipses the C—C bonds. In reality, the most stable conformation has the two carbonyl groups anti to reduce dipole-dipole interactions. The observed stereoselectivity is expected to be a weighted average of the two conformations.[9]

There is essentially no geometrical distortion about the carbonyl group in the ground states of **1**, and the orientation of the remote substituents has little effect on the geometrical distortion. Therefore, torsional effects are not important factors for the stereoselectivity in these systems. This is in contrast to cyclohexanone and related systems, where torsional effects are dramatic control elements.[7,10-12] The calculated orientational dependence of stereoselectivity also cannot be explained by the hyperconjugative effects, because the orientations of the substituents do not influence significantly the electron-donating ability of the allylic bonds.

According to a natural bond orbital analysis,[13] the hydrides in the various transition structures bear about 0.5 unit of negative charge. To evaluate electrostatic interactions between substituents and nucleophile, we calculated the relative stabilities of the four distorted carbonyls by removal of the LiH from the four transition structures, **3-6**, with or without an added 0.5 unit of negative charge placed at the location of the hydride in the transition structures. With the negative charge, the calculated relative energies of the four species are quite similar to those of the transition structures. On the other hand, without the negative charge, the calculated relative energies resemble those of ground states. This clearly indicates that the relative stabilities of the syn and anti additions of LiH are largely determined by electrostatic interactions. As shown in **3-6**, the favorable transition structures (**4** and **6**) have the hydride nearer the charged atoms. The two anti transition structures (**3** and **5**) have much weaker stabilizing interactions with the positive carbon centers, and structure **3** suffers somewhat from destabilizing interactions with the carbonyl oxygens.

This qualitative argument can be applied to the rest of the systems. Electron-withdrawing substituents induce positive charges

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(12) Torsional effects that we emphasize are related to orbital distortion arguments (Klein, J. *Tetrahedron Lett.* **1983**, 4307), because orbital distortion originates from geometrical distortion.[6c]
(13) NBO 3.0 program: Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. University of Wisconsin, Madison, WI 53706.

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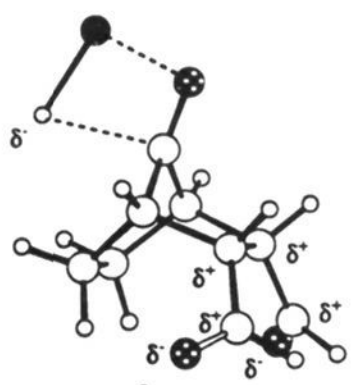
Table I. Calculated Relative Energies (kcal/mol) of Transition Structures for the Reactions of Lithium Hydride with **1a–g** and **2a–c**, Along with Available Experimental Data for $NaBH_4$ Reductions

	$E_{(anti)} - E_{(syn)}$		
compd, R (**1**) or X (**2**)	6-31G*	MP2/6-31G*	experimental[a]
1a, CHO (CC)[b]	3.0	4.0	
CHO (CH)[c]	−0.2	−0.6	
1b, CO_2Me (CC)[b]	2.8		0.9
CO_2Me (CH)[c]	1.0		
1c, CH_2F	0.5	0.7	
1d, CH_2OH	−0.1	−0.1	−0.2[d]
1e, $CH{=}CH_2$	−0.3	−0.4	−0.3
1f, CH_3	−0.5	−0.6	−0.8[e]
1g, SiH_3	−0.8	−0.3	
2a, CH2	−1.8	−3.1	−1.6[h]
2b, O	1.1	0.3	
2c, NH (anti)[f]	0.8	0.2	>2.5[h]
NH (syn)[g]	−2.0	−4.0	

[a] Data for **1** from ref 1, and data for **2** from ref 2. [b] C=O bonds eclipse the ring C_1—C_2 and C_3—C_4 bonds. [c] C=O bonds eclipse C—H bonds. [d] R = CH_2OCH_3. [e] R = CH_2CH_3. [f] NH anti to C_1—C_2. [g] NH syn. [h] MeLi addition; NPh in the experiment (ref 2b) is apparently anti.



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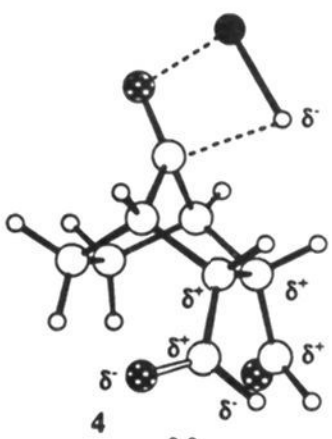
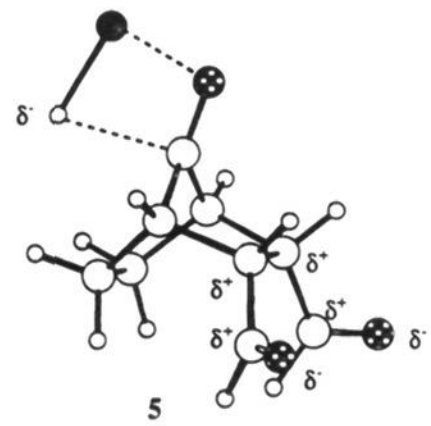


4

TS	4.0	0.0
TS, no LiH	0.0	0.8
TS, no LiH, 0.5 e at H	4.6	0.0



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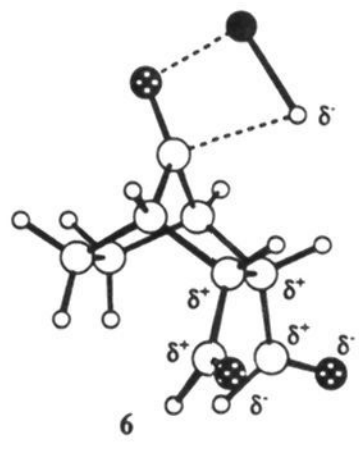


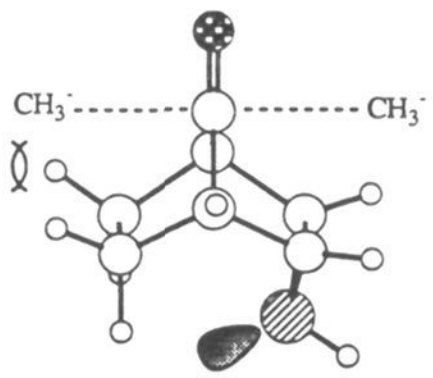
6

TS	5.6	6.0
TS, no LiH	2.4	2.6
TS, no LiH, 0.5 e⁻ at H	3.9	4.4

Figure 1. Transition structures of lithium hydride addition to 2,3-diformyl-7-norbornanone. Relative energies (kcal/mol, MP2/6-31G*) of the transition structures (TS), TS without LiH (TS, no LiH), and TS without LiH but with 0.5 unit of negative charge placed at the hydride position.

at C_2 and C_3 (**1a–c**, **2b**, and **2c**), and syn addition is favorable. On the other hand, electron-donating substituents (**1f**,**1g**,**2a**) induce negative charges at C_2 and C_3, and anti addition becomes favorable. Hydroxymethyl (**1d**) and vinyl (**1e**) substituents are weakly electron-withdrawing, and the anti preference for them is caused by electrostatic repulsions in the syn transition structure between the hydride and the electronegative OH or vinyl group, similar to that in structure **6**.

The low calculated stereoselectivity of **2c** deserves special comment. The structure with the NH anti to the norbornyl ring (see **7**) is about 1 kcal/mol more stable than the syn structure, for steric reasons. Syn addition of LiH is calculated to be favorable, but the magnitude of the calculated stereoselectivity is much smaller than that observed for the MeLi addition.[2b] Anti addition by MeLi is significantly destabilized by steric interactions between the methyl group and C_4-H and C_5-H, as shown in **7**. This steric effect will also operate in **2a** and **2b**.[2]



7

In summary, we have shown that electrostatic effects of remote substituents can have a significant influence on the stereoselectivities of nucleophilic additions, while hyperconjugative effects have little influence. The combination of torsional[7,10,11] and electrostatic effects[6,7] rationalizes the large body of observed stereoselectivities.

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Carbon-Linked Galactosphingolipid Analogs Bind Specifically to HIV-1 gp120

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The principal mode of infection by the human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) involves the interaction of the HIV envelope protein gp120 with CD4, a molecule on host lymphoid cells.[1] The susceptibility of many CD4-negative cell lines to HIV infection, however, strongly suggests the presence of an alternative entry pathway.[2] Recently, Harouse et al. have

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