Electrostatic and Steric Control of π-Facial Stereoselectivity in Nucleophilic Additions of LiH and MeLi to *endo*-5,6-Disubstituted Norbornen-7-ones: an *ab initio* MO Study

Lisa Williams and Michael N. Paddon-Row*

School of Chemistry, University of New South Wales, PO Box 1, Kensington, NSW 2033, Australia

Fully optimized transition structures for the addition of LiH and MeLi to several *endo*-5,6-disubstituted norbornen-7-ones have been located at the HF/6-31G(d) level of theory; single point MP2/6-31G(d) energies, together with point charge calculations suggest that a combination of electrostatic and steric effects, and not hyperconjugative effects, control the π-facial stereoselectivity of LiH and MeLi additions.

The problem of delineating the factors which are responsible for controlling π-facial stereoselectivity in nucleophilic additions to the carbonyl group, and estimating their relative importance remains a hotly debated topic[1] that continues to attract intense activity, both experimental[2,3] and theoretical.[4–7] The main point of contention is the relative importance of torsional[4,8] and electrostatic effects,[5] compared to hyperconjugative interactions.[9]

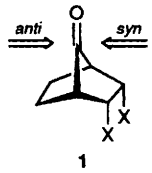
The results of recent *ab initio* MO calculations on a series of *endo*-2,3-disubstituted norbornan-7-ones, **1** demonstrated that π-facial stereoselectivity in these systems could be adequately explained in terms of electrostatic effects, and that hyperconjugative interactions need not be invoked.[5c] In contrast, a semiempirical MNDO study on nucleophilic addition to a series of *endo*-5,6-disubstituted-7-norbornenones **2**, using artificially constructed transition structures, implied that Cieplak type hyperconjugative interactions[9b] were mainly responsible for the observed facial stereoselectivity in these molecules.[7] That hyperconjugative interactions should control facial stereoselectivity in **2** but not in **1** is surprising and warranted a more detailed investigation of the former system using *ab initio* MO theory and properly located transition structures. Herein, we report our preliminary results for the addition of LiH and MeLi to **2a–e**.

Transition structures were located at the Hartree-Fock (HF) level using the 3-21G and 6-31G(d) basis sets, and were fully characterized at the HF/3-21G level by analytical frequency calculations.[10] The energies were further evaluated at the MP2/6-31G(d) level of theory, using the HF/6-31G(d) optimized geometries. The calculated energy differences between the *anti* and *syn* modes of attack by LiH and MeLi on the norbornenones are given in Table 1. (A positive value for this quantity indicates that the *anti* transition structure is less stable than the *syn* transition structure.)

The results reveal a preference for *syn* attack by LiH for all substituents considered, ranging from strongly electron donating (SiH_3) to strongly electron withdrawing (CN). This uniform preference for *syn* attack cannot be explained using either Cieplak[9b] or Anh-Eisenstein[9a] hyperconjugative models, since the former predicts preferred *anti* attack for electron donating substituents, such as **2a**, and the latter *anti* attack for electron withdrawing substituents, such as **2e**.

Electrostatic effects between the hydride component of LiH and the C=C double bond and the substituents, X, of **2** explain the calculated *syn* facial stereoselectivity. Sterically, the nucleophile would prefer the *anti* approach since the cyclopentenyl ring presents a more open face than the cyclopentyl ring. Opposing this is the electrostatic repulsion between the π electrons of the double bond and the electron density associated with the nucleophile. For a small nucleophile, such as hydride, the electrostatic effect predominates and *syn* attack is preferred for unsubstituted norbornen-7-one, **2c**. This preference is modulated by the nature of the substituent X. For electron donating groups (SiH_3, CH_3), or groups with lone pairs (CH_2OH), the preference for *syn* attack is weaker, compared to **2c**, because of electrostatic repulsion between the nucleophile and the CHX groups. For the strongly electron withdrawing group, X = CN, this electrostatic interaction becomes stabilizing and the preference for *syn* attack for **2e** becomes stronger than for **2c**.

The electrostatic argument was verified by carrying out point charge calculations in which the LiH moiety in each transition structure is replaced by a point negative charge,



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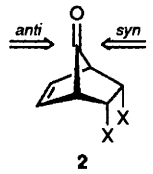

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a; X = SiH_3
b; X = Me
c; X = H
d; X = CH_2OH
e; X = CN

Table 1 Calculated relative energies (kJ mol^{-1}) of transition structures for the reactions of lithium hydride and methyl lithium with **2a–e** in the gas phase (ε = 1)

	E(*anti*)–*E*(*syn*)						
	Lithium hydride additions				Methyl lithium additions		
Molecule **2** X	LiH 3-21G[b]	LiH 6-31G(d)[c]	LiH MP2/6-31G(d)[c]	Point charge[a] 6-31G(d)	MeLi 3-21G[b]	MeLi 6-31G(d)[c]	MeLi MP2/6-31G(d)[c]
a SiH_3	2.19	3.79 (4.77[d])	10.14	1.06	−20.49	−19.33	−14.56
b CH_3	5.56	4.68 (4.23[d])	8.32	1.17	−16.47	−17.26	−14.06
c H	6.92	7.84 (7.24[d])	12.38	4.46	−12.32	−11.59	−7.88
d CH_2OH	8.74	6.52 (4.39[d])	7.83	3.18	−12.35	−15.20	−11.28
e CN	28.37	26.80 (37.53[d])	34.78	24.59	1.30	−2.51	7.19

[a] See text for explanation. [b] At the HF/3-21G optimized geometry. [c] At the HF/6-31G(d) optimized geometry. [d] SCRF results obtained using ε = 32.7.

located at the position vacated by the hydride, and bearing a charge equal to the Mulliken charge of the replaced hydride. The HF/6-31G(d) *anti-syn* energy differences for these modified transition structures for **2a–e**, parallel those for the corresponding genuine transition structures (Table 1),† thereby confirming that electrostatic effects are largely responsible for the calculated preferred *syn* addition of LiH to **2a–e** in the gas phase.

Solvent effects on the *anti-syn* π-facial stereoselectivity in LiH addition to **2a–e** were investigated using self consistent reaction field (SCRF) theory.[11] Fully optimized transition structures at the HF/6-31G(d) level for these additions were determined for a dielectric constant of ε = 32.7, corresponding to a polar solvent, such as methanol (but lacking specific solvent effects such as H-bonding). The SCRF results (shown in Table 1 in parentheses) indicate that the SCRF *anti-syn* energetic preference along the series **2a–e** closely parallels the gas phase results. We conclude that, within the context of the SCRF model, (nonspecific) solvation effects are unlikely to change significantly the trends in the calculated gas phase *anti-syn* preferences for additions to **2** by LiH, and probably by other similar nucleophiles, such as MeLi (*vide infra*).

The predicted preference for *syn* addition of LiH additions to **2c** and **2d** is at odds with experimentally observed preference for *anti* attack on these molecules‡ by alkyl lithium reagents, Grignard reagents, and $NaBH_4$[3c,7,12] although *syn* attack is observed to be favoured when X is an electron withdrawing group, such as ester or cyano.[3c,7]

This discrepancy was resolved by calculating the transition structures for addition of MeLi monomer to **2a–e**. It was found that, for all levels of theory, the *anti* mode of attack is now preferred for **2a–d**, and only **2e** is still predicted to favour *syn* attack (at the MP2 level). These predictions agree with the available experimental data.[3c,7,12]

Steric factors are probably responsible for the different facial preferences expressed by LiH and MeLi in their addition to **2a–d**. Thus, the steric demand of the methyl group is sufficiently large for it to override the electrostatically favoured *syn* attack, although the electrostatic influence increases along the series **2a** → **e**, as evidenced by the steadily diminishing *anti* preference. The steric effect may be seen from the transition structures for addition of LiH and MeLi to **2c**, shown in Fig. 1.§ For *syn* attack by MeLi, two of the methyl hydrogens lie only *ca.* 2.1 Å from the respective *exo* C(5)–H and C(6)–H hydrogens. This steric congestion is much less evident in the case of *syn* attack by LiH. The steric argument is not vitiated by the observed preference for *syn* attack by vinyl lithium and phenyl lithium on **2c**;[12d] the planarity of the vinyl and phenyl moieties enables these groups to adopt a conformation in which the molecular planes of the vinyl and phenyl groups face the *exo* C-5 and C-6 hydrogens in the *syn* transition structures, thereby reducing steric congestion.

The *anti-syn* energy differences obtained for MeLi additions to the members of the series **2a–e** are uniformly shifted to smaller values, relative to those for the respective LiH additions, by *ca.* 19–25 kJ mol^{-1} (at the MP2 level). The steric effect for the methyl group is therefore worth about 22 kJ mol^{-1} for these MeLi additions. The observed *anti* facial stereoselectivity for borohydride reductions of **2c**[3c,12a] and the bismethyl ether derivative of **2d**[3c] can likewise be attributed to steric effects since the solvated BH_4^- moiety is bulky.

In summary, we find that π-facial stereoselectivity in nucleophilic additions to *endo*-5,6-disubstituted norbornen-7-ones is governed by a combination of electrostatic effects and steric demands of the attacking nucleophile. For small nucleophiles (*e.g.* LiH, vinyl lithium) electrostatic effects dominate, whereas for larger nucleophiles (*e.g.* alkyl lithium reagents), steric demands of the nucleophile override electrostatic effects, except for those cases in which the norbornenone substituents are strongly electron withdrawing. There is no compelling need to invoke hyperconjugative interactions, as was recently done on the basis of an apparently flawed MNDO model.[7] The combination of torsional,[4,8] electrostatic,[4b,5] and steric effects satisfactorily explain an impressive bulk of experimental results on π-facial stereoselectivity.

Finally, we note that recent calculations indicate that electrostatic effects also play an important role in controlling the π-facial stereoselectivity in electrophilic additions to 7-alkylidenenorbornanes (*i.e.* **1** in which C=O is replaced by $C{=}CR_2$).[13]

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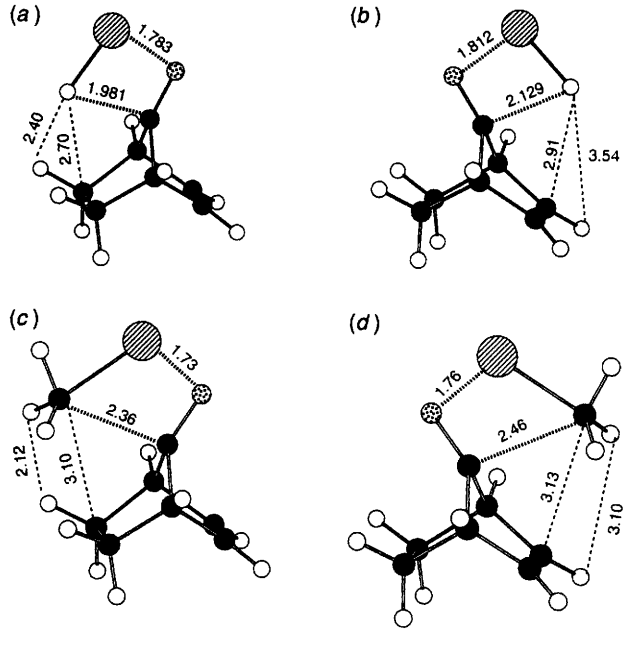

Fig. 1 HF/6-31G(d) optimized transition structures for the addition of LiH [(*a*) and (*b*)] and MeLi [*c*) and (*d*)] to **2c**. Distances are given in Å.

Footnotes

† In contrast to our calculations, and those on benzobicylo[2.2.2]-octanone,[5d] MNDO point charge calculations (probably erroneously) predict that electrostatic effects favour *anti* attack by hydride on **2c** and various substituted norobornen-7-ones.[7]

‡ Experimental studies were actually carried out on the bismethyl ether of **2d** (X = CH_2OMe).[3c]

§ Two stationary points of C_s symmetry were located for each mode of addition of MeLi to **2**, which differ by the methyl group adopting either a staggered or an eclipsed conformation (Fig. 1) with respect to the C-7 bonds. For all cases, the staggered geometries have two imaginary frequencies and these structures are about 5 kJ mol^{-1} higher in energy (MP2) than the respective eclipsed structures; consequently, only results for the eclipsed structures are given here. The eclipsed structures for *anti* attack are genuine transition structures, having only one imaginary frequency, whereas those for *syn* attack possess two imaginary frequencies, the lower of the two (*ca.* 70 cm^{-1}) corresponding to methyl group rotation. The true transition structures for *syn* attack would appear, therefore, to have C_1 symmetry, the location of which is presently beyond our resources. However, the fact that nearly identical *anti-syn* energy differences were obtained using either staggered or eclipsed C_s 'transition structures' for **2a–e**, suggests that these values should be no different from those obtained if one were to use genuine C_1 transition structures for *syn* attack.

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