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Manifestation of stereoelectronic effects on the calculated carbon–nucleophile bond lengths in nucleophilic addition to sterically unbiased ketones

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Abstract—Calculations at the B3LYP/6-311G(d,p) level of the structures of diastereoisomeric pairs of alcohols **1*E***–**12*E*** and **1*Z***–**12*Z***, resulting from either reduction or methylation of sterically unbiased ketones show that the newly formed C–Nu bond lengths of the major isomers are larger than those of the minor isomers.

Electronic effects of substituents on the stereoselectivity of nucleophilic additions to ketones is a topic of major importance.[1] Many studies have been devoted to reactions where the carbonyl group is placed in an isosteric environment.[1i] For instance, le Noble and co-workers added various nucleophilic reagents to a series of 5-substituted adamantan-2-ones with a skeleton involving little or no intrinsic facial bias.[1g] For these model systems, ambiguities associated with conformational mobility and steric bias are precluded.

It was observed that the preferred direction of attack by the nucleophile was *anti* to the best electron-donor bond. The origin of this diastereofacial selectivity has been interpreted by two models. The most widely known is the so-called 'Felkin–Anh model' in which the incipient bond is stabilized by the presence of an antiperiplanar withdrawing group, able to stabilize the transition state by delocalization of electron density from the nucleophile to the antibonding orbital of the antivicinal bond $(\sigma_{\text{incipient bond}} \rightarrow \sigma^*_{\text{antiperiplanar bond}})$ (electron-rich transition state).[2] Inspired by the kinetic anomeric effect, Cieplak proposed that the two-electron stabilizing interaction of the vicinal-occupied orbital with the antibonding orbital of the incipient bond should stabilize the transition state $(\sigma_{\text{antiperiplanar bond}} \rightarrow \sigma^*_{\text{incipient bond}})$ (electron-deficient transition state).[1d,3] In most cases, reaction results, such as le Noble experiments, were interpreted in terms of Cieplak models.[4] The following figure resumes both hypothesis (Fig. 1).[5]

According to Cieplak's hypothesis, the most important interaction is the electron delocalization from the σ (hyperconjugation) or π (homoconjugation) orbitals of

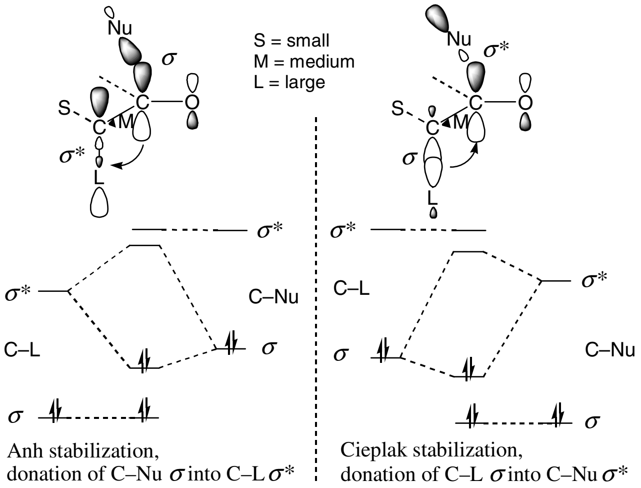

Figure 1. Molecular orbital illustration of Anh versus Cieplak stabilization.

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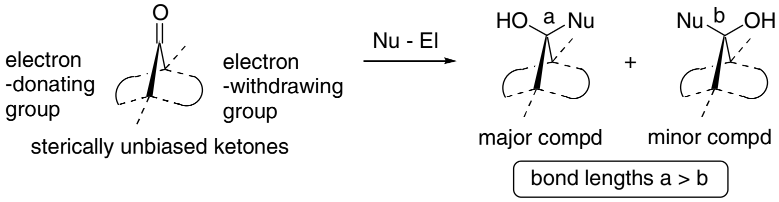
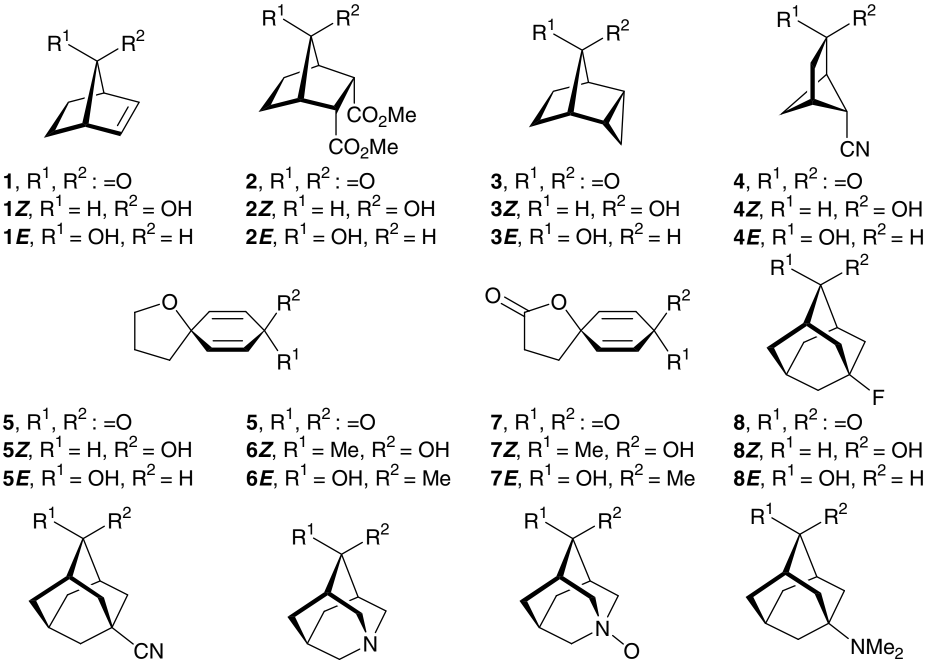


Scheme 1.



1, R^1, R^2 : =O
1*Z*, R^1 = H, R^2 = OH
1*E*, R^1 = OH, R^2 = H

2, R^1, R^2 : =O
2*Z*, R^1 = H, R^2 = OH
2*E*, R^1 = OH, R^2 = H

3, R^1, R^2 : =O
3*Z*, R^1 = H, R^2 = OH
3*E*, R^1 = OH, R^2 = H

4, R^1, R^2 : =O
4*Z*, R^1 = H, R^2 = OH
4*E*, R^1 = OH, R^2 = H

5, R^1, R^2 : =O
5*Z*, R^1 = H, R^2 = OH
5*E*, R^1 = OH, R^2 = H

5, R^1, R^2 : =O
6*Z*, R^1 = Me, R^2 = OH
6*E*, R^1 = OH, R^2 = Me

7, R^1, R^2 : =O
7*Z*, R^1 = Me, R^2 = OH
7*E*, R^1 = OH, R^2 = Me

8, R^1, R^2 : =O
8*Z*, R^1 = H, R^2 = OH
8*E*, R^1 = OH, R^2 = H

9, R^1, R^2 : =O
9*Z*, R^1 = Me, R^2 = OH
9*E*, R^1 = OH, R^2 = Me

10, R^1, R^2 : =O
10*Z*, R^1 = H, R^2 = OH
10*E*, R^1 = OH, R^2 = H

11, R^1, R^2 : =O
11*Z*, R^1 = H, R^2 = OH
11*E*, R^1 = OH, R^2 = H

12, R^1, R^2 : =O
12*Z*, R^1 = H, R^2 = OH
12*E*, R^1 = OH, R^2 = H

Scheme 2.

the stereogenic centre into the σ^* orbital of the incipient bond (σ^* orbital of the transition state). By consequence, a similar electron donating effect should persist in the major diastereoisomer, by weaking the Nu–C bond and increasing its bond length (Scheme 1).[6] This delocalization into the σ^* orbital of the new bond should be less important than in the σ^* orbital of the incipient bond, because the energy level of the latter is lower than that of the σ^* orbital of the newly formed bond.[7]

We have calculated at the B3LYP/6-311G(d,p) level, the structure of each diastereoisomeric pairs of alcohols **1*E***–**12*E*** and **1*Z***–**12*Z*** resulting from reduction or methylation of the sterically unbiased ketones **1**–**5** and **7**–**12** (Scheme 2). Table 1 collects the energies and the C–Nu bond lengths of these alcohols.

For each diastereoisomeric pair of *Z* and *E* alcohols, comparison of the H–C(OH) or Me–C(OH) bond length values shows that bond lengths are larger for the major compound than for the minor one. The calculated differences are weak but always in the same way as a 'fossil testimony' of the transition state structure. So, the H–C(OH) or Me–C(OH) bond *anti* to the electron donating group is weaker than the same bond *anti* to the electron withdrawing group (Scheme 1). By virtue of Onsager's principle of microscopic reversibility,[16] the easiest bond to cleave is also the easiest bond to form.[17] In particular, this is the case of the kinetic anomeric effect[18] where the α-anomer is the kinetic product and, for example, in glucose, the (C(1)–OH) α-anomeric bond is slightly longer than the corresponding β-anomeric bond (Fig. 2).[19]

Calculations at the B3LYP/6-311G(d,p) level of the structure of 2-hydroxytetrahydropyran confirm that the axial C–OH or C–H bonds are slightly longer than the corresponding equatorial bonds (Fig. 3).[20]

Table 1. Product distribution in the nucleophilic addition to ketones **1**–**5** and **7**–**12**, total energies and optimized bond lengths of the alcohols **1*Z***–**12*Z*** and **1*E***–**12*E*** calculated at the Becke3LYP/6-311G(d,p) level

Ketone	Reaction product distribution (Ref.)	Energy[a] (hartrees)	H–C(OH) or Me–C(OH) bond length (Å)	Percent. (‰)	C–OH bond length (Å)
1	$NaBH_4$/MeOH	**1*Z***, −348.043844	**1*Z***, 1.09234	2.45	**1*Z***, 1.41091
	1*E*:**1*Z*** = 85:15 (8)	**1*E***, −348.044533	**1*E***, 1.09503		**1*E***, 1.42119
2	MeLi/Et_2O	**2*Z***, −844.488156	**2*Z***, 1.52730	1.56	**2*Z***, 1.43632
	2*E*:**2*Z*** = 90:10 (9)	**2*E***, −844.485259	**2*E***, 1.52954		**2*E***, 1.43231
3	$LiAlH_4$/Et_2O	**3*Z***, −387.349334	**3*Z***, 1.09315	2.0	**3*Z***, 1.41515
	3*Z*:**3*E*** = 2:1 (10)	**3*E***, −387.349342	**3*E***, 1.09100		**3*E***, 1.41763
4	$NaBH_4$/MeOH	**4*Z***, −402.190495	**4*Z***, 1.09565	0.47	**4*Z***, 1.42544
	4*E*:**4*Z*** = 75:25 (11)	**4*E***, −402.189524	**4*E***, 1.09617		**4*E***, 1.42417
5	$NaBH_4$/MeOH	**5*Z***, −500.714532	**5*Z***, 1.10336	6.06	**5*Z***, 1.44033
	5*Z*:**5*E*** (Not determined)	**5*E***, −500.718202	**5*E***, 1.09667		**5*E***, 1.44305
6	MeMgBr/THF	**6*Z***, −540.042580	**6*Z***, 1.54110	5.0	**6*Z***, 1.44725
	6*Z*:**6*E*** = 8.6:1 (12)	**6*E***, −540.046914	**6*E***, 1.53340		**6*E***, 1.45195
7	MeMgBr/THF	**7*Z***, −614.108431	**7*Z***, 1.54072	4.7	**7*Z***, 1.44441
	7*Z*:**7*E*** = 32:1 (12)	**7*E***, −614.110990	**7*E***, 1.53347		**7*E***, 1.44914
8	$NaBH_4$/MeOH	**8*Z***, −565.344318	**8*Z***, 1.09380	0.29	**8*Z***, 1.42906
	8*E*:**8*Z*** = 62:38 (13)	**8*E***, −565.343684	**8*E***, 1.09412		**8*E***, 1.42825
9	MeLi/Et_2O	**9*Z***, −597.655362	**9*Z***, 1.52953	0.1	**9*Z***, 1.44027
	9*E*:**9*Z*** = 68:32 (14)	**9*E***, −597.655571	**9*E***, 1.52969		**9*E***, 1.43935
10	$NaBH_4$/MeOH	**10*Z***, −482.089753	**10*Z***, 1.09427	0.55	**10*Z***, 1.42987
	10*E*:**10*Z*** = 62:38 (15)	**10*E***, −482.090285	**10*E***, 1.09488		**10*E***, 1.42993
11	$NaBH_4$/MeOH	**11*Z***, −557.271175	**11*Z***, 1.09308	0.68	**11*Z***, 1.42545
	11*E*:**11*Z*** = 96:4 (15)	**11*E***, −557.270157	**11*E***, 1.09382		**11*E***, 1.42476
12	$NaBH_4$/MeOH–H_2O	**12*Z***, −600.056989	**12*Z***, 1.09410	0.16	**12*Z***, 1.43086
	12*E*:**12*Z*** = 63:37 (14)	**12*E***, −600.056728	**12*E***, 1.09428		**12*E***, 1.43037

[a] Without zero point energy (ZPE) correction.

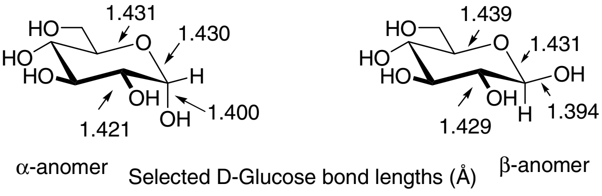


Figure 2. Crystal structure determination of α-D- and β-D-glucose.

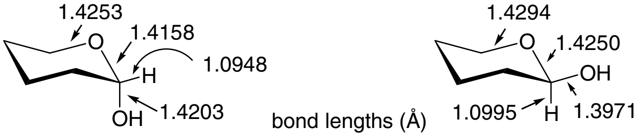


Figure 3. Bond length calculations of 2-hydroxytetrahydropyran at the B3LYP/6-311G(d,p) level.

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