Pergamon

Tetrahedron 57 (2001) 3987–3995

TETRAHEDRON

A detailed ab initio MO investigation of the diastereoselectivities of five- and six-membered ring ketones bearing O and S, C and S, and C and O substituents at the α-carbon

Veejendra K. Yadav* and V. Sriramurthy

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Received 29 November 2000; revised 6 February 2001; accepted 22 February 2001

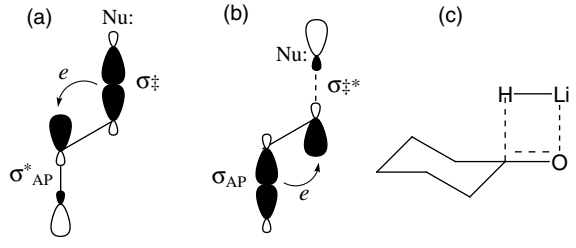
Abstract—The steric effects in the geometry on cation-chelation predict the experimental π-selectivity of 1-oxa-4-thiaspiro[4.5]decan-6-one, 1-oxa-4-thiaspiro[4.4]nonan-6-one, 1-thiaspiro[4.4] nonan-6-one, and 1-oxaspiro[4.4]nonan-6-one. The reversal in the selectivity of 1-oxa-4-thiaspiro[4.4]nonan-6-one on reduction with $(i\text{-Bu})_2$AlH appears to be a direct consequence of the steric interactions arising from the large *i*-Bu substituents. The antiperiplanar effects are not as significant as the steric effects.

1. Introduction

The diastereofacial selection of substituted cycloalkanones is an area of considerable interest.[1] The popular amongst the several models proposed to explain the observed facial preferences are the torsional model of Anh and Felkin,[2] the hyperconjugation model of Cieplak,[3] and the TS model of Houk.[4] The pictorial representations of these models are given in Fig. 1. The orbital distortion model by Frenking,[5] exterior frontier orbital extension (EFOE) model by Tomoda,[6] polarized π-frontier molecular orbital (PPFMO) model by Dannenberg[7] and electrostatic control models by Chandrasekhar and Mehta,[8a] Houk,[8b] and Hehre[8c] have also contributed significantly to the understanding of π-selection.

The Anh–Felkin model assumes the TS to be electron-donating and it requires a nucleophile to attack antiperiplanar to an electron-attracting σ bond at the α carbon. In contrast, the Cieplak model assumes the TS to be electron-attracting and it requires a nucleophile to attack antiperiplanar to an electron-donating σ bond. These two models, therefore, predict opposite selectivities for the same substituent type. Houk's model is not general either because, for instance, the extrapolation of the true ax selection of 2-ax-Cl-cyclohexanone to 2-ax-OR-cyclohexanone contradicts the experiment; 2-ax-OR-cyclohexanone exhibits eq-selectivity.[9] Further, Houk's model cannot explain the changes in selectivity with the changes in the cation component of the nucleophile. The ax:eq selectivity, for instance, has been known to vary from 7.7:1 to 16:1 to 25:1 in reactions of a 3,5-dioxacyclohexanone derivative with $LiAlH_4$, $(i\text{-Bu})_2$AlH and Grignard reagents (RMgX), respectively.[10] The selectivity, however, remained almost constant at 25:1 when the nucleophile was varied from Me^- to $n\text{-Bu}^-$ to Ph^- derived from the respective Grignard species. We have reasoned[11] that this failure is due to the ignorance of the experimentally well-documented cation-complexation and/or chelation effects[12,13] and, hence, the consequent geometrical changes in the substrate. In this manuscript, we describe an application of our cation-complexation model to account for the observed selectivities of 1-oxa-4-thiaspiro[4.5]decan-6-one, **1**, 1-oxa-4-thiaspiro[4.4]nonan-6-one, **2**, 1-thiaspiro[4.4]nonan-6-one, **3**, and 1-oxaspiro[4.4]nonan-6-one, **4** (Fig. 2).

Dimitroff and Fallis[14] have recently reported the experimental selectivities of substrates **1**–**4** from reactions with a diverse range of nucleophiles. With the exception of the reaction of **2** with $(i\text{-Bu})_2$AlH, both **1** and **2** were found to be



(a) Anh-Felkin model (b) Cieplak model (c) Houk model

Figure 1. Pictorial representations of: (a) the Anh–Felkin model; (b) the Cieplak model; and (c) the Houk model for axial attack on cyclohexanone with LiH as the nucleophile. Nu:=nucleophile.

Keywords: facial selection; cation-complexation; antiperiplanar interactions; steric effects.

* Corresponding author. Tel.: +91-512-597439; fax: +91-512-597436; e-mail: vijendra@iitk.ac.in

Abbreviations: TS, transition state; ax, axial; eq, equatorial.

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00276-9

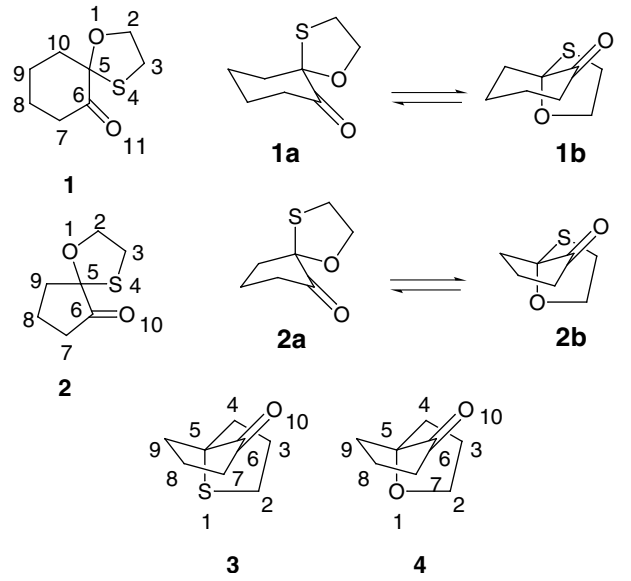


Figure 2. Structures of the substrates **1**–**4** and their numberings.

highly selective as they reacted predominantly *anti* to the sulfur. The species **3** and **4** were even more interesting as they showed diastereoselection *anti* to the heteroatom substituent. The selection of **4** *anti* to the oxygen is in clear violation of the Cieplak model. The authors explained the results as "a consequence of the interplay of the reagent, the preferred angle of attack, the tendency for chelation, torsion angle and steric effects as well as the electronegativity of the atoms and the polarity of the adjacent bonds." The authors stated further, "In general, the nucleophile seeks to avoid interaction with the lone pair of the heteroatom and reduce the torsional strain when the alternative face contains carbon. With sulfur present, the steric effect is increased and generally *anti* attack is enhanced."

It is true that all the above parameters must contribute to the observed selectivities, some amongst these, however, must be more significant than others. Further, while the effect of the electronegativity of the substituent atom and the polarity of the adjacent bond are manifest in the ground state geometry of the reactant species, the preferred angle of attack and steric effects are concerned more with a transition state than with ground state geometry. *The two features, therefore, cannot be mixed together particularly in view of the recent theory of π-facial selection; the selection is understood to depend on the ground state distribution of conformers.*[6,15] In this paper, we demonstrate that the steric effects in the geometry after cation-chelation are largely responsible for the observed selectivities.

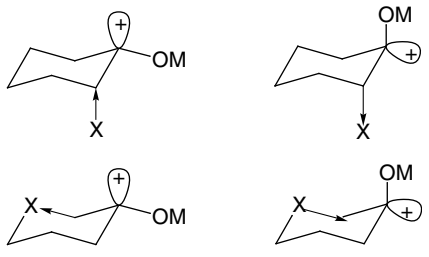


Figure 3. ax/eq-orientations of $p_{C=O}$ in substituted cyclohexanones.

2. Background

Cation-complexation activates the carbonyl carbon for reaction with nucleophiles by increasing the p orbital coefficient on the carbonyl carbon ($p_{C=O}$) and, thus, lowering the energy of activation. This complexation generally precedes the actual nucleophilic attack[12] and it occurs in the $\sigma_{C=O}$ plane.[13] The cation-complexation causes significant geometrical changes around the carbonyl carbon due to its enhanced pyramidalization;[16] the changes are such that the resultant structure achieves maximum possible conformational stability. The electron-poor $p_{C=O}$ orients antiperiplanar to an electron-donating substituent at the adjacent carbon to allow for stereoelectronic stabilization.[17] In 2-ax-substituted cyclohexanones, this translates into an axial $p_{C=O}$ orientation when the substituent is electron-donating and an equatorial orientation when the substituent is electron-attracting. These notions are depicted in Fig. 3. Since a nucleophilic reaction is essentially a consequence of the interactions of an electron-deficient $p_{C=O}$ with a filled orbital of the nucleophile, the axial and equatorial $p_{C=O}$ orientations translate, respectively, into ax- and eq-preferences in the absence of other control elements.

In substituted cyclohexanones, the geometrical consequence of an axial orientation of $p_{C=O}$ is ring-flattening. This results in increase of the absolute torsion angles of the carbonyl oxygen with the ring positions 3 and 5 across the intervening bonds on the axial face. Likewise, an equatorial orientation of $p_{C=O}$ results in ring-puckering and the above torsion angles are reduced. Thus, an increase or decrease in these torsion angles predicts ax- or eq-selectivity, respectively. The ring-flattening and ring-puckering are also reflected in the decrease and increase of the torsion angles C6–C1–C2–C3 and C5–C6–C1–C2, respectively.

The above simple premise has led us to study the facial selectivities of substituted cycloalkanones in reactions with nucleophiles. The ab initio MO calculations of the geometrical changes on complexation with cations such as H^+ and Li^+ have correctly predicted the selectivities of 2-ax- and 2-eq-substituted cyclohexanone,[11a] 3-oxa-, 3-thia- and 3,5-dioxacyclohexanones,[11b] 3-ax- and 3-eq-Cl/F-cyclohexanones,[11c] 4-substituted cyclohexanones with external substituents such as F, Cl, OR and SR (both axial and equatorial),[11d] several 5-substituted 2-adamantanones,[11e] and some 2,3-disubstituted 7-norbornanones.[11f]

Some caution, however, must be exercised in the selection of the cation. As long there are no heteroatom substituents in the vicinity of the carbonyl function, particularly on the α carbon, a cation as simple as H^+ would suffice. However, in the presence of such heteroatoms, a cation with chelation ability must be used to predict reactions with nucleophiles possessing chelating cations. We preferred to use Li^+ for two reasons: (a) the C═O…Li^+ bond is long enough to allow its chelation with a heteroatom on the adjacent carbon, and (b) the C═O…Li^+ bond is only a little shorter than a C═O…$[MgCl]^+$ bond[18] and, thus, it mimics the reactions of Grignard reagents just as well.

One may be tempted to think that free ions like Li^+ and $[MgCl]^+$ are not at all present in reactions with nucleophiles

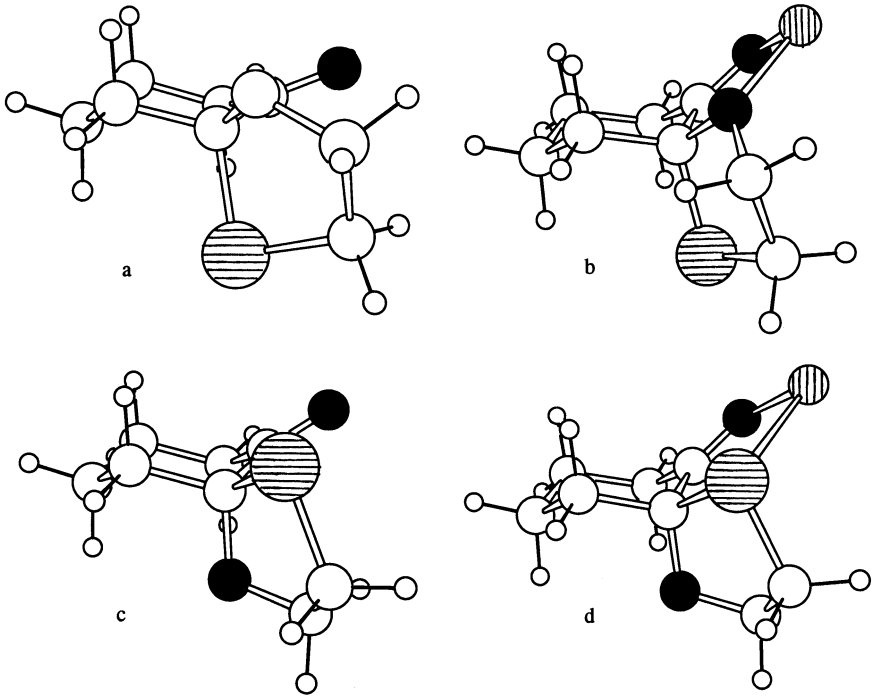


Figure 4. 3D structure of: a. **1a**, b. **1a**-Li^+, c. **1b**, d. **1b**-Li^+. Circles in black=O, circles with horizontal lines=S, circles with vertical lines=Li^+.

containing these and, thus, question the suitability of the cation-complexation approach. A cation, after all, is a Lewis acid with its strength dependent on the associated anionic partner(s). With the complexation in place, this must enable the same direction of geometrical changes irrespective of whether one has used a free cation or a cation with its associated anionic partner(s) like those in MeLi, MeMgCl, and Me_2Mg. To substantiate this argument, we have studied complexes with MeMgCl and Me_2Mg in selected cases and compared the results with those obtained from the use of a free cation.

3. Computational methods

All calculations were performed with Gaussian 94.[19] Stationary points (energy minima, all positive eigenvalues of the Hessian Matrix) on the potential energy surface were fully optimized using the Hartree Fock (HF) and Becke3LYP methods. The 6-31G* basis set was used throughout. The HF geometry was used as the initial guess for Becke3LYP calculations. The antiperiplanar effects were calculated from Second Order Perturbation Theory Analysis of Fock Matrix in NBO Basis.[20]

Table 1. Selected B3LYP /6-31G* geometrical parameters for **1a** and **1b** and their complexes with Li^+ and BH_3. D1=O11–C6–C5–C10, D2=O11–C6–C7–C8, D3=C7–C6–C5–C10; D4=C8c7–C6–C5; D5=S4–C5–C6–O11; D6=O1–C5–C6–O11

Substrate	D1	D2	D3	D4	D5	D6
1a	141.17	−138.37	−40.66	43.49	−95.80	18.21
1a-Li^+	123.63	−123.95	−52.25	51.78	−112.89	1.05
1b	127.75	−127.01	−52.73	53.47	2.31	−114.67
1b-Li^+	120.20	−121.41	−56.81	55.61	−4.03	−120.78

4. Results and discussion

4.1. 1-Oxa-4-thiaspiro[4.5]decan-6-one (1)

The species **1** may be expected to exist as an equilibrium mixture of **1a** and **1b** (**1a**–**1b**=−1.81 kcal mol^{-1}). This energy difference is raised when the isomers are allowed to complex with Li^+. **1a**-Li^+, Fig. 4b, is 5.66 kcal mol^{-1} more stable than **1b**-Li^+, Fig. 4d. The enhanced stability of **1a**-Li^+ over **1b**-Li^+ is due apparently to the better complexation ability of Li^+ with the acetal oxygen in **1a** than that with sulfur in **1b**.[21] This large energy difference indicates very clearly that species like **1a**-Li^+ are the abundant species available for reaction with nucleophiles. It should be noted that at low temperatures, −78 to 0°C, when reactions of **1** are carried out, the relative concentration of **1a**-Li^+ will be even larger than that of **1b**-Li^+ in accordance with the Boltzmann law of distribution.[22]

A nucleophile will approach the carbonyl group *anti* to S as the same from *syn* to S will suffer from large steric interactions with the large S atom. Additionally, the *syn* to S attack is *endo* to the bicyclo[3.3.0] unit present in **1a**-Li^+ which is sterically prohibitive. Li^+ is almost equidistant (1.85–1.90 Å) from both the oxygen atoms in **1a**-Li^+.

The torsion angles D1 (=O11–C6–C5–C10) and D2 (=O11–C6–C7–C8) have reduced in magnitude from 141.17° and 138.37° to, respectively, 123.63° and 123.95° on chelation of **1a** with Li^+ (Table 1). A corresponding increase in the torsion angles D3 (=C7–C6–C5–C10) and D4 (=C8c7–C6–C5) must also be noted. If the steric effects arising from the above *endo* attack to the bicyclo[3.3.0] system present in **1a**-Li^+ are ignored, the electronic effects alone predict *syn* to S attack.

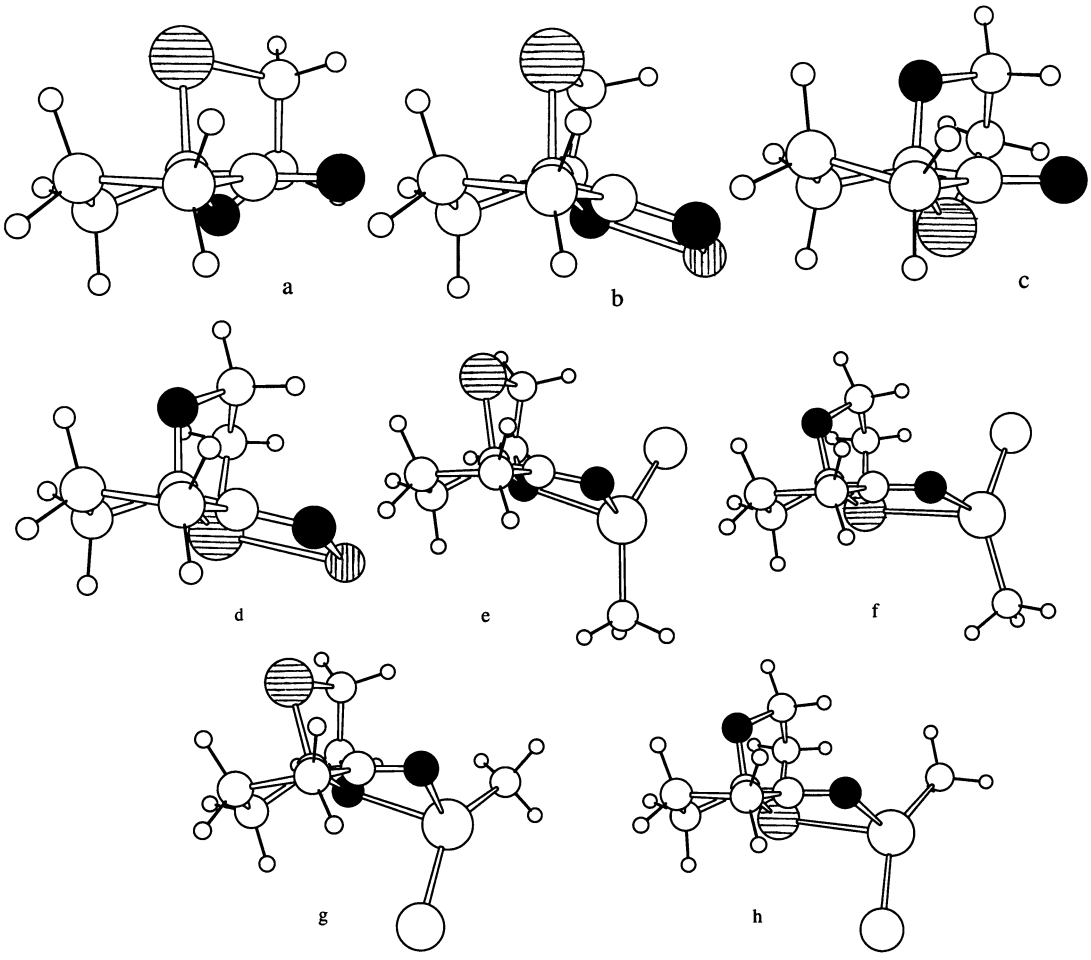


Figure 5. 3D structure of: a. **2a**, b. **2a**-Li+, c. **2b**, d. **2b**-Li^+, e. **2a**-MeMgCl (Me *anti* to S), f. **2b**-MeMgCl (Me *anti* to O), g. **2a**-MeMgCl (Me *syn* to S), h. **2b**-MeMgCl (Me *syn* to O). Circles in black=O, circles with horizontal lines=S, circles with vertical lines=Li^+.

The predicted facial selection is in compliance with the experiments. The experimental selectivity varied in between 83:17 and 91:9 in favor of an attack *anti* to the sulfur atom. The observed erosion in selectivity is due probably to the reactions of less abundant species like **1b**-Li^+ that may be present in equilibrium with species like **1a**-Li^+. Some erosion in selectivity due to the direct participation of **1a** and **1b** may also be envisaged.

4.2. 1-Oxa-4-thiaspiro[4.4]nonan-6-one (2)

Like 1-oxa-4-thiaspiro[4.5]decan-6-one, **1**, 1-oxa-4-thiaspiro[4.4]nonan-6-one, **2**, can also exist as an equilibrium mixture of **2a**, Fig. 5a, and **2b**, Fig. 5c, that are only 0.38 kcal mol^{-1} apart. In the more stable conformer **2a** the sulfur atom occupies an ax-like orientation. Chelation with Li^+ enlarges the energy difference; **2a**-Li^+, Fig. 5b, is 4.47 kcal mol^{-1} more stable than **2b**-Li^+, Fig. 5d. The species **2a**-Li^+, therefore, is the abundant species present for reaction with nucleophiles. In **2a**-Li^+, Li^+ is chelated to both the oxygen atoms with the interatomic distances being 1.87 Å from the carbonyl oxygen and 1.94 Å from the acetal oxygen. In **2b**-Li^+ that possesses the acetal sulfur in eq-like orientation, Li^+ is 1.86 Å and 2.49 Å away from the carbonyl oxygen and the acetal sulfur, respectively.

Taking into account the steric effects arising from the large sulfur atom in **2**a-Li^+, an attack *anti* to the sulfur will be predicted. It is important to note that this attack is *endo* to one bicyclo[3.3.0] unit and *exo* to the other present in **2a**-Li^+. This diastereoprediction is in agreement with the experimental observations. The selectivity varied from 59:41 to 91:9 in favor of *anti* to S in reactions with diverse nucleophiles. Once again, an erosion in the experimental selectivity may be due to the reaction of **2b**-Li^+ that will be present as a minor constituent in equilibrium with **2a**-Li^+; **2b**-Li^+ will capture the nucleophile largely *anti* to the acetal oxygen to avoid steric interactions arising from it. However, oxygen-assisted delivery of nucleophiles *syn* to the acetal oxygen in **2b**-Li^+ may as well be expected to raise the overall diastereoselection in favor of *anti* to the sulfur.

We have also studied the complexes of **2a** and **2b** with MeMgCl. The complex **2a**-MeMgCl, Fig. 5e, is 4.78 kcal mol^{-1} more stable than the complex **2b**-MeMgCl, Fig. 5f (*cf.* 4.47 kcal mol^{-1} difference of **2a**-Li^+ and **2b**-Li^+). These complexes contain the Me group on the carbonyl face that is *anti* to the ax-like heteroatom. In both, the Mg atom is 2.15 Å away from the carbonyl oxygen; further bound to the eq-oxygen in **2a**-MeMgCl (Mg…O1= 2.30 Å) and the eq-S in **2b**-MeMgCl (Mg…S4=2.82 Å). Furthermore, the Mg atom is located on the side of the

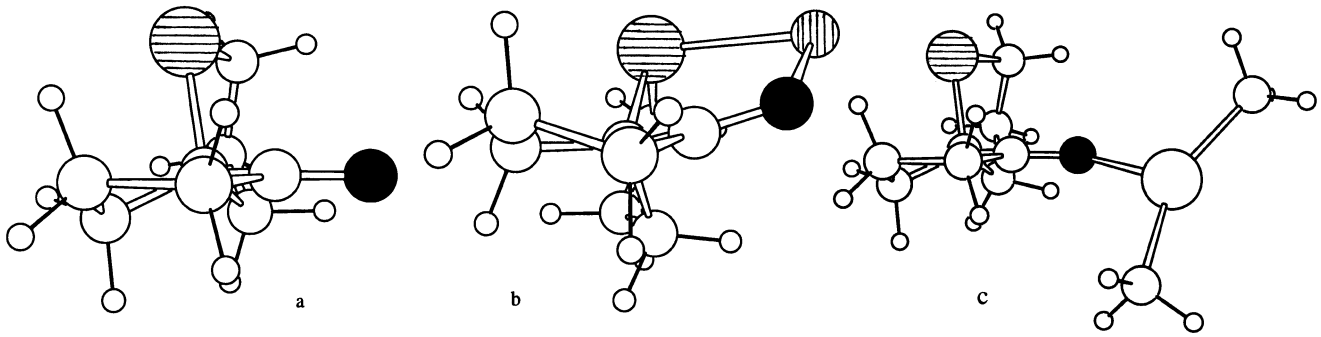


Figure 6. 3D structure of: a. **3**, b. **3**-Li^+, c. **3**-$MgMe_2$. Circles in black=O, circles with horizontal lines=S, circles with vertical lines=Li^+.

$\sigma_{C=O}$ plane that is opposite to that occupied by the ax-heteroatom (**2a**-MeMgCl, Mg–O10–C6–C5=− 20.60°; **2b**-MeMgCl, Mg–O10–C6–C5=− 35.67°).

It is interesting to note that the complex **2a**-MeMgCl, Fig. 5g, that has the locations of the methyl group and the chlorine atom on Mg exchanged as compared to those in **2a**-MeMgCl, Fig. 5e, is 1.26 kcal mol^{-1} less stable. In contrast, the complex **2b**-MeMgCl, Fig. 5h, that has the methyl group and the chlorine atom exchanged their locations as compared to those in **2b**-MeMgCl, Fig. 5f, is 1.77 kcal mol^{-1} more stable. In both 5g and 5h, the Mg atom is located on the side of $\pi_{C=O}$ plane that is *anti* to the ax-heteroatom (5i, Mg–O10–C6–C5=− 34.24°; 5j, Mg–O10–C6–C5=− 24.95°). Fortunately, **2a**-MeMgCl, Fig. 5e, is still 3.00 kcal mol^{-1} more stable than **2b**-MeMgCl, Fig. 5h. The structure 5e, therefore, turns out to be the dominant species present for reaction with nucleophiles. The methyl group in 5e may conceivably migrate to the carbonyl carbon through a four-centered transition state to bring about the desired reaction *anti* to the S. Nakamura and Morokuma[23] have considered such a methyl migration to explain the selectivities of Me_2Mg additions to α- and β-alkoxy aldehydes and ketones.

4.3. 1-Thiaspiro[4.4]nonan-6-one (3)

Only that conformer of **3** was studied that possessed the heteroatom of the *spiro* ring ax-like. This is in keeping with the known dominance of the ax-isomer in spirotetrahydrofurans.[24] The stereostructures of **3** and **3**-Li^+ are shown in Figs. 6a and 6b, respectively. The geometrical changes caused on complexation with Li^+ are indeed very large. The torsion angles S1–C5–C6–O10 and C4–C5–C6–O10 changed from −88.86 and 26.90° in **3** to −39.54 and 73.76° in **3a**-Li^+, respectively. The *spiro*C–C and C–S bonds have, thus, almost exchanged their relative dispositions with respect to the carbonyl function. Such a geometrical change is required to allow Li^+ to chelate with the neighboring S atom (Li^+…O10=1.86 Å, Li^+…S1=2.47 Å).

The parent cyclopentane ring and the five-ring comprising Li^+ and S have taken a deep boat shape in which the ax-like hydrogen on C8 appears to block effectively the entry of a nucleophile *syn* to it. This will be expected to force a nucleophile to attack *syn* to C4. Fortunately, an attack *syn* to C4 in **3**-Li^+ will generate a triquinane-like species that will have the newly generated alkoxide ion and the S atom bound to Li^+ throughout the progress of the reaction. This will lower the energy of the process and facilitate the reaction. An *anti* to S attack is thus predicted which is in full agreement with the experiments.

The study of the complex **3**-Me_2Mg turned out to be somewhat interesting. The Mg atom was placed *syn* to the *spiro*-carbon, C5, in the initial guess. This ended up being *anti* in the fully optimized structure as shown in Fig. 6c. Consequently, there is no chelation of Mg with the sulfur atom. However, the overall situation is similar to that in **3**-BH_3. The atoms S and C4 have retained their respective ax- and eq-orientations (S–C5–C6–O10=− 90.54°, C4–C5–C6–O10=24.91°) which will allow a nucleophile to attack from opposite to the S. The migration of Me_2Mg from *syn*

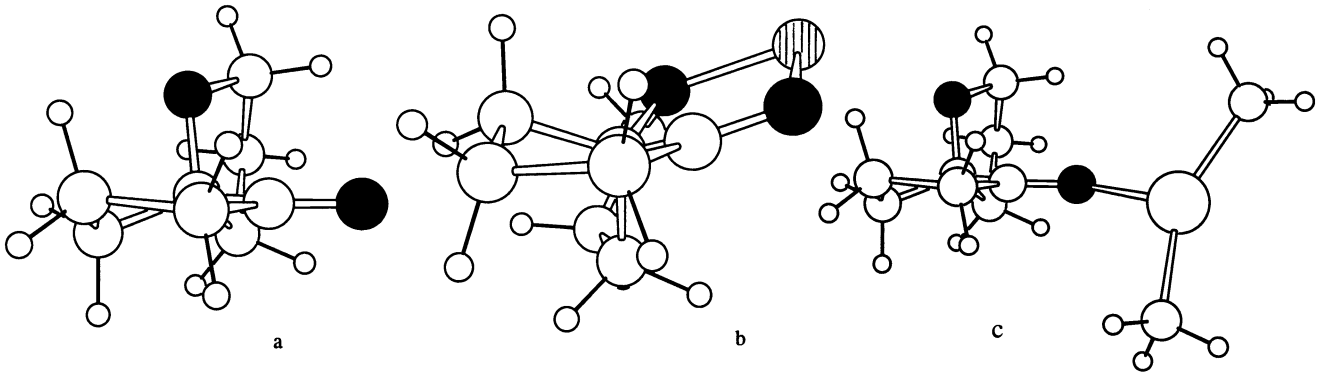


Figure 7. 3D structure of: a. **4**, b. **4**-Li^+, c. **4**-$MgMe_2$. Circles in black=O, circles with vertical lines=Li^+.

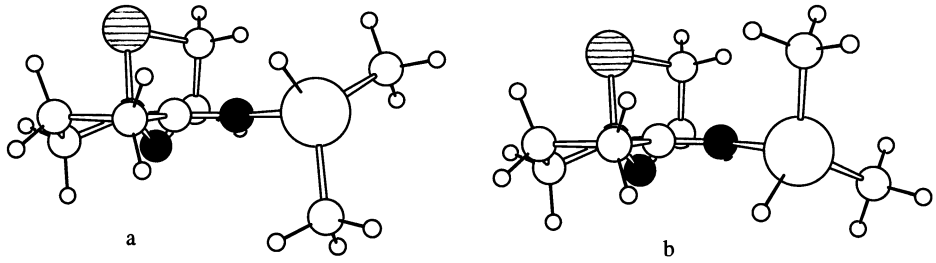


Figure 8. 3D structures of: a. **2**-Me_2AlH with Al-H *syn*to S, b. **2**-Me_2AlH with Al-H *anti* to S. Circles in black=O, circles with horizontal lines=S.

to C5 to *anti* to C5 is possibly due to the steric interactions between a methyl group on Mg and the methylene groups of the S-containing five-membered ring.

The above predictions that favor a nucleophilic attack *anti* to the S are in good compliance with the experimental results. The observed selectivities ranged from 84:16 to 100:0. The highest selectivity was observed from reactions with MeLi, MeMgBr and $LiAlH_4$ in ether at 0°C.

4.4. 1-Oxaspiro[4.4]nonan-6-one (4)

As for **3**, only that conformer of **4** was studied that possessed the heteroatom of the *spiro* ring ax-like. The 3D structures of **4** and **4**-Li^+ are shown in Figs. 7a and 7b, respectively. Like **3** and **3**-Li^+ above, the geometry changed from the one having the C–O bond ax-like (O1–C5–C6–O10= −86.52°) to the one with the C–O bond eq-like (O1–C5–C6–O10=−19.91°). The carbon substituent on the *spiro*-carbon, in turn, changed its disposition from eq-like (C4–C5–C6–O10=29.26°) in **4** to ax-like in **4**-Li^+ (C4–C5–C6–O10=94.23°). Furthermore, Li^+ in **4**-Li^+ is almost equidistant from both the oxygen atoms (1.88–1.90 Å).

Table 2. The antiperiplanar effects in the substrates **1**–**4** (threshold value=0.50 kcal mol^{-1}). 'Hup' and 'Hdn' show the H atoms that are pointing upward and downward, respectively, on C7 in the 3D structures given in Figs. 4–7.

		Donor bond	Acceptor bond	kcal mol^{-1}
1a	*anti* to S	σ_{C5-S}	$\pi^*_{C=O}$	5.96
		σ_{C7-Hax}	$\pi^*_{C=O}$	6.85
	anti to O	σ_{C5-C10}	$\pi^*_{C=O}$	0.72
		σ_{C7-C8}	$\pi^*_{C=O}$	1.20
1b	*anti* to S	σ_{C5-C10}	$\pi^*_{C=O}$	1.39
		σ_{C7-C8}	$\pi^*_{C=O}$	2.24
	anti to O	σ_{C5-O}	$\pi^*_{C=O}$	1.41
		σ_{C7-Hax}	$\pi^*_{C=O}$	5.67
2a	*anti* to S	σ_{C5-S}	$\pi^*_{C=O}$	5.45
		σ_{C7-Hup}	$\pi^*_{C=O}$	3.37
	anti to O	σ_{C5-O}	$\pi^*_{C=O}$	<0.50
		σ_{C7-Hdn}	$\pi^*_{C=O}$	5.47
2b	*anti*to S	σ_{C5-S}	$\pi^*_{C=O}$	1.10
		σ_{C7-Hdn}	$\pi^*_{C=O}$	6.57
	*anti*to O	σ_{C5-O}	$\pi^*_{C=O}$	1.96
		σ_{C7-Hup}	$\pi^*_{C=O}$	2.38
3	*anti* to S	σ_{C5-S}	$\pi^*_{C=O}$	6.06
		σ_{C7-Hup}	$\pi^*_{C=O}$	3.59
	*anti*to C	σ_{C7-Hdn}	$\pi^*_{C=O}$	5.33
		σ_{C4-C5}	$\pi^*_{C=O}$	0.68
4	*anti* to O	σ_{C5-O}	$\pi^*_{C=O}$	2.78
		σ_{C7-Hup}	$\pi^*_{C=O}$	3.18
	anti to C	σ_{C7-Hdn}	$\pi^*_{C=O}$	5.97
		σ_{C4-C5}	$\pi^*_{C=O}$	<0.50

If the attack of a nucleophile *syn* to the oxygen is *endo* to one bicyclo[3.3.0] unit, the attack *syn* to the carbon is *endo* to the other bicyclo[3.3.0] unit. However, only the attack *syn* to the carbon will preserve the chelation of Li^+ with the oxygen atoms throughout the progress of the reaction. Additionally, the approach of a nucleophile *syn* to the oxygen is hindered by an ax-like hydrogen on C9 for its proximity to the carbonyl carbon (H–C9–C5–C6= 78.32°). The observed selectivity varied from 80:20 to 100:0 in favor of *syn* to the carbon with a range of nucleophiles; the reactions were fully selective with MeLi and MeMgBr in ether at 0°C.

The chemistry of complexation of **4** with Me_2Mg is similar to that of **3** discussed above. Me_2Mg migrated from *syn* to C5 in the initial guess geometry to *anti* to C5 in the fully optimized structure and the oxygen and carbon substituents retained their ax- and eq-like dispositions (O1–C5–C6–O10=− 87.45°, C4–C5–C6–O10=28.13°). As is evident from Fig. 7c for **4**-Me2Mg, the approach of a nucleophile from *syn* to the oxygen is sterically prohibited from both the ax-like *spiro*-oxygen and the ax-like hydrogen on C8.

4.5. The reduction of 2 with (*i*-Bu)$_2$AlH

The reversal in the selectivity of **2** on reduction with (*i*-Bu)$_2$AlH is an interesting observation of Dimitroff and Fallis and it deserves special attention. We wished to investigate this using the complexation model. The immediate difficulty from computation point of view, however, was the large size of (*i*-Bu)$_2$AlH in addition to that of the substrate **2** itself. We compromised somewhat and used Me_2AlH instead for the complexation. For the non-chelating nature of the reagent and also the large steric interactions between the oxathiolane ring and the substituents on Al, the complexation *anti* to the *spiro*-carbon was favored over the complexation *syn* to it. In one instance when a complexation *syn* to the *spiro*-carbon was attempted, Me_2AlH had moved eventually to the side *anti* to it. This proves the large steric interactions involved in the *syn* complexation.

We have studied only the conformer **2a** for two reasons; (a) the conformer **2a** is more stable than the conformer **2b**, and (b) just as **2a**-BH_3 is more stable (1.8 kcal mol^{-1}) than **2b**-BH_3, **2a**–Me_2AlH will also be expected to be more stable than **2b**–Me_2AlH. While the arrangement shown in Fig. 8a has the Al–H bond *syn* to the S, the arrangement in Fig. 8b has it *syn* to the oxygen; the former being 0.04 kcal mol^{-1} more stable than the latter. This energy difference translates into a 8a:8b=1.08:1.0 distribution at 0°C. This energy difference, however, will be larger for the complexes

Table 3. Comparison of the experimental selectivities with those predicted from the Anh–Felkin model, Cieplak model, and cation-complexation model

Substrates	**1**	**2**	**3**	**4**
Experimental selectivity	*anti* to S	*anti*to S	*anti* to S	*anti* to O
Anh–Felkin selectivity	*syn* to S	*syn* to S	*syn* to S	*anti* to O
Cieplak selectivity	*anti* to S	*anti* to S	*anti* to S	*syn* to O
Present selectivity	*anti* to S	*anti* to S	*anti* to S	*anti* to O

with $(i\text{-Bu})_2$AlH. The larger size of *i*-Bu over that of Me will cause greater steric interactions with the axial S in the complex corresponding to 8b. The migration of H from Al to the carbonyl carbon in the favored structure 8a constitutes an attack *syn* to the S. The observed reversal in selectivity with $(i\text{-Bu})_2$AlH as the reducing species, therefore, is likely to be a direct consequence of the large bulk of its *i*-Bu substituents.

5. Antiperiplanar effects

The electronic interaction of an electron-rich and an electron-poor bond/orbital that are held (almost) antiperiplanar to each other through a third bond connecting them is called the antiperiplanar effect. This effect, when applied to the π^* of a carbonyl group, is of great value as it determines the direction and extent of its polarization. The larger is the effect, the greater is the polarization, and, thus, the faster is the reaction of a nucleophile at the carbonyl carbon. The values of the *app*effects ($\sigma-\pi^*$ interactions) in substrates **1**-**4** are collected in Table 2. Whereas the interactions of σ_{C5-C10} and σ_{C7-C8} with $\pi^*_{C=O}$ constitute *app* effects in eq-direction in **1**, the interactions of σ_{C5-S} and σ_{C7-Hax} in **1a** (Fig. 4a) and σ_{C5-O} and σ_{C7-Hax} in **1b** (Fig. 4c) with $\pi^*_{C=O}$ constitute *app* effects in ax-direction. The sum of the two ax-*app* effects, 12.81 kcal mol^{-1}, is six times as large as the sum of the two eq-*app* effects, 1.92 kcal mol^{-1}, in **1a**. The ax-face (anti to S), therefore, must react in preference to the eq-face (anti to O). Likewise, the total ax-*app* effect, 7.08 kcal mol^{-1}, is almost two times as large as the total eq-*app* effect, 3.63 kcal mol^{-1}, in **1b**. The ax-face (anti to O) of **1b** must therefore react in preference to the eq-face (anti to S). Since **1a** is the predominant isomer at equilibrium (**1a**:**1b**=>28:1 at 0°C), reaction through conformer **1a** involving an *anti* to S attack must predominate. This is indeed observed.

In the conformer **2a** (Fig. 5a), the total *app* effect, 8.82 kcal mol^{-1}, that favors *anti* to S attack is 1.6 times as large as the total *app* effect, 5.47 kcal mol^{-1}, that favors *anti* to O attack. Likewise, in **2b** (Fig. 5c), the *app* effect, 7.67 kcal mol^{-1}, that favors *anti* to S attack is about 1.8 times as large as the *app* effect, 4.34 kcal mol^{-1}, which favors *anti* to O attack. *While it is pleasing to note an overall* anti *to S preference supported by* app *effects to comply with experiments, the anti to S attack in* **2b** *is disturbing for its contra-steric approach.* A selectivity as high as 9:1 in favor of *anti* to S was achieved from a reaction of **2** with MeMgBr in ether at 0°C.

Disregarding the steric approach control, the *app* effect appears to apply to **1** and **2**. This approach, however, fails for **3** and **4**. In 3, the total *app* effect, 9.65 kcal mol^{-1}, that favors attack *anti* to S is >1.5 times as large as the total *app* effect, 6.01 kcal mol^{-1}, that favors attack *anti* to the carbon. Predominantly *anti* to S attack will, therefore, be predicted. In practice, however, the predominant product stemmed from attack *anti* to the carbon with the single exception of a reaction with $Zn(BH_4)_2$ in Et_2O at 22°C. This selectivity was, in fact, 100:0 from reaction with MeLi, MeMgBr and $LiAlH_4$ in Et_2O at 0°C. In **4**, the *app* effect that favors attack *anti* to C, if at all, is only slightly superior to that which favors *anti* to O attack. An equal distribution of the two possible products will, therefore, be predicted. This, again, contrasts experiments as the observed selectivities, 80–100:20–0, are predominantly *anti* to the carbon. A reaction with $Zn(BH_4)_2$ was again an exception as both the products were formed in equal amounts.

6. Comments

The predominant *anti* to S attack in **1**–**3** may be construed to follow the Cieplak model, the results from **4** are against it. The Cieplak model predicts attack *syn* to oxygen in **4** but the observed preference is for the opposite. The Anh–Felkin model[2] will prefer **1b** and **2b** as the preferred conformers for reaction as they possess the electron-attracting C–O bond axial and, thus, well suited to receive electrons from the forming Nu–C σ bond through an *app* arrangement. The attack is though axial but *syn* to S. The Anh–Felkin model, therefore, predicts an altogether unobserved diastereoselectivity for both **1** and **2**. This model, however, succeeds in predicting the observed *anti* to oxygen attack in **4** but fails, once again, for **3** wherein the attack must be *syn* to the electron-donating[25] sulfur in contrast with the experimental observation.

7. Conclusions

The results of the present study are collected along with the results from the experiments and the results expected from other models in Table 3. The steric effects alone in the cation-chelated species predict the experimental π-selection of the substrates **1**–**4**. The nucleophile attacks *anti* to the sulfur when the choice is between a sulfur and an oxygen atom and *anti* to both sulfur and oxygen when the choice is between a carbon atom and one of sulfur and oxygen atoms. The antiperiplanar effects do not always support the experimental selectivity. The present study demonstrates very well the significant role that a cation complexation/chelation with the substrate plays in π-facial determination.[23,26]

8. Supplementary material

The coordinates of the substrates **1**–**4** and their complexes optimized at Becke3LYP/6-31G* level (8 pages).

Acknowledgements

The authors thank CSIR and DST, Government of India, for funding, Dr. S. Manogaran for helpful discussions, and the staff of Computer Center, IIT, Kanpur for generous

allocation of computer time on the Silicon Graphics series of minisupercomputers.

References

1. (a) For a series of articles on diastereoselection, see: Thematic Issue on Diastereoselection *Chem. Rev.* **1999**, *99(5)*. (b) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263.
2. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
3. (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
4. (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.
5. Frenking, G.; Kohler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.
6. (a) Ref. 1(a), pp 1243-1263. (b) Senju, T.; Tomoda, S. *Chem. Lett.* **1997**, 431. (c) Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057. (d) Tomoda, S.; Senju, T. *Chem. Commun.* **1999**, 423. (e) Tomoda, S.; Senju, T. *Chem. Commun.* **1999**, 621. (f) Tomoda, S.; Senju, T. *Chem. Lett.* **1999**, 353. (g) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 3871. (h) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 5303. (i) Tomoda, S.; Senju, T.; Kawamura, M.; Ikeda, T. *J. Org. Chem.* **1999**, *64*, 5396.
7. (a) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertran *J. Am. Chem. Soc.* **1993**, *115*, 4024. (b) Huang, X. L.; Dannenberg *J. Am. Chem. Soc.* **1993**, *115*, 6017. (c) Franck, R. W.; Kaila, N.; Blumenstein, M.; Geer, A.; Huang, X. L.; Dannenberg *J. Org. Chem.* **1993**, *58*, 5335.
8. (a) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734. (b) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (c) Kahn, S. D.; Hehre *J. Am. Chem. Soc.* **1987**, *109*, 663.
9. (a) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. (b) Loben, P. C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 6990.
10. (a) Harada, T.; Nakajima, H.; Ohnishi, T.; Takeuchi, M.; Oku, A. *J. Org. Chem.* **1992**, *57*, 720. (b) Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890. (c) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
11. (a) Yadav, V. K.; Jeyaraj, D. A.; Balamurugan, R. *Tetrahedron* **2000**, *56*, 7581. (b) Jeyaraj, D. A.; Yadav, A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 4483. (c) Jeyaraj, D. A.; Yadav, V. K. *Tetrahedron Lett.* **1997**, *38*, 6095. (d) Yadav, V. K.; Jeyaraj, D. A. *J. Org. Chem.* **1998**, *63*, 3474. (e) Yadav, V. K.; Senthil, G.; Jeyaraj, D. A. *Tetrahedron* **1999**, *55*, 14211. (f) Yadav, V. K.; Balamurugan, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 01.
12. (a) Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3821. (b) Marouka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588. (c) Laemmle, J. T.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526. (d) Evans, D. A. *Science* **1988**, *240*, 420. (e) Pierre, J. L.; Handel, H. *Tetrahedron Lett.* **1975**, 2317. (f) Dubois, J. E.; Fellmann, P. *Tetrahedron Lett.* **1975**, 1225. (g) Lefour, J. M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597. (h) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (i) Warnhoff, E. W.; Warnhoff, P. R.; Wong, M. Y. H. *J. Am. Chem. Soc.* **1980**, *102*, 5956. (j) Mackey, M. D.; Goodman, J. M. *Chem. Commun.* **1997**, 2383. (k) Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041. (l) Lecea, B.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **1997**, *62*, 6485.
13. The cation complexed to the carbonyl oxygen is expected to lie in the nodal plane of the $\pi_{C=O}$ bond as established by the X-ray structure of a methylaluminum diaryloxide complex of benzophenone. See; Power, M. B., Bott, S. G., Atwood, J. L., Barron, A. R. J. Am. Chem. Soc. 1990, 112, 3446; Fraser, R. R., Faibish, N. C., Kong, F., Bednarski, K. J. Org. Chem. 1997, 62, 6164. The plane that is orthogonal to the carbonyl π plane is defined, herein, as the carbonyl σ plane.
14. (a) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1998**, *39*, 2527. (b) Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1998**, *39*, 2531.
15. (a) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177. (b) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1993**, *58*, 7038.
16. (a) Laube, T.; Hollenstein, S. *J. Am. Chem. Soc.* **1992**, *114*, 8812. (b) Laube, T. *J. Org. Chem.* **1999**, *64*, 8177. (c) For electronic similarities with 1-methyl-1-cyclohexyl cation, see: Hogeveen, H.; Gasabeck, C. J. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1305. (d) Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1978**, *100*, 1487. (e) Kirchen, R. P.; Ranganayakulu, K.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811. (f) Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7816. (g) Rauk, A.; Sorensen, T. S.; Maerker, C.; Carneiro, J. W.; de, M.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1996**, *118*, 3761.
17. (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983. (b) Newitt, L. A.; Steel, P. G. *J. Chem. Soc., Perkin Trans 1* **1997**, 2033. (c) Adcock, W.; Head, N. J.; Lokan, N. R.; Trout, N. A. *J. Org. Chem.* **1997**, *62*, 6177. (d) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867.
18. We have computed the complex of CH_2O with $[MgCl]^+$ and Li^+ and found the C═O…$[MgCl]^+$ and C═O…Li^+ distances at 1.9380 and 1.8052 Å (Becke3LYP/6-31G*), respectively. These are to be compared, again, with the C═O…Li^+ distances (1.85-1.88 Å) in the complexes of species **1**-**4**.
19. Frish, M. J., Trucks, G. W., Schlegel, H. B., Gill, P. M. W., Johnson, B. G., Robb, M. A., Cheeseman, J. R., Keith, T., Peterson, G. A., Montgomery, J. A., Raghavachari, K., Al-Laham, M. A., Zakrzewski, V. G., Ortiz, J. V., Foresman, J. B., Cioslowski, J., Stefanov, B. B., Nanayakkara, A., Challacombe, M., Peng, C. Y., Ayala, P. Y., Chen, W., Wong, M. W., Andres, J. L., Replogle, E. S., Gomperts, R., Martin, R. L., Fox, D. J., Binkley, J. S., Defrees, D. J., Baker, J., Stewart, J. P., Head-Gordon, M., Gonzalez, C., Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1995.
20. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 8899.
21. Without BSSE (Basis Set Superimposition Error) correction, the lowering in energy on complexation of Li^+ with the oxygen and sulfur in Me_2O and Me_2S was computed to be 43.17 and 30.67 kcal mol^{-}1 at Becke3LYP/6-31G* level.
22. *Physical Chemistry*; Atkins, P. W., Ed.; W. H. Freeman and Company: New York, 1990; Chapter 24, p 726.
23. For computational studies on the complexation of Me_2Mg with a range of simple acyclic α-alkoxycarbonyls, see: Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055.

24. (a) Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmondson, S. C.; Rogers, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 506. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947. (c) Basso, A.; Kaiser, C.; Rittner, R.; Lambert, J. B. *J. Org. Chem.* **1993**, *58*, 7865.
25. The σ-donor abilities of common atom combinations increase in the order: σCO<σCN<σCCl<σCC<σCH<σCS. See: Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernard, F. *Top. Curr. Chem.* **1977**, *70*, 1 Thus, a σCC bond is electron attracting in comparison to a σCS bond.
26. α-Chelates have been established experimentally as the true intermediates in the addition of Me_2Mg in THF. See: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778 and references cited therein.