Theoretical Studies on Chelation-Controlled Carbonyl Addition. Me_2Mg Addition to α- and β-Alkoxy Ketones and Aldehydes

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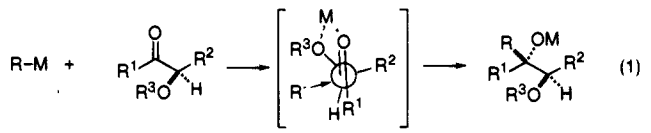
Abstract: The ab initio theoretical calculations on the C–C bond forming stage of the addition of Me_2Mg to α- and β-alkoxy carbonyl compounds (methoxyacetone, methoxyacetaldehyde, 3-methoxy-2-butanone, 2-methoxypropanal, 4-methoxy-2-butanone, 3-methoxypropanal, and 3-methoxybutanal) were carried out to investigate the reaction mechanism of chelation-controlled carbonyl addition reactions, for which experimental information is scarce. The carbonyl substrate and Me_2Mg first form a stable chelate complex with >20 kcal/mol exothermicity, which undergoes C–C bond formation via 1,3-migration of the nucleophilic methyl group to the carbonyl carbon with a 6–9 kcal/mol activation energy and then gives rise to a product chelate. Chelate structure was retained throughout the reaction process. The experimental stereoselectivity of the α- and β-chelation-controlled addition has been adequately reproduced. It was found for the first time that the β-chelation-controlled reaction may proceed via either a stereoselective chair or nonselective boat transition state, the latter being energetically more favored than the former in the present system. The calculations suggested that the C–C bond forming stage is a stereochemistry determining stage as has previously been assumed.

Since the first discovery by Cram,[1] 1,2-asymmetric induction in the addition of an organometallic reagent to an α-alkoxy carbonyl compound has been widely employed in organic chemistry.[2,3] Despite its historical and practical significance, the mechanistic understanding of this reaction is surprisingly poor, yet Cram's original model **A** for the "chelation-controlled

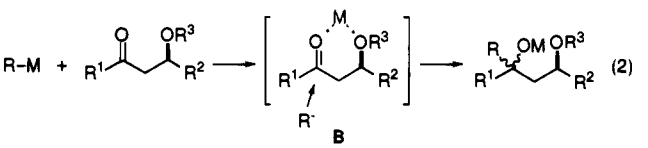


(1)

A

addition" has long been accepted as a useful operational model. In this model, the metal countercation conformationally fixes the carbonyl substrate by the coordination to the two Lewis basic oxygen atoms and the nucleophilic R group attacks the carbonyl carbon from the less hindered side opposite to the R^2 group.

β-Chelation represents another case of "chelation-controlled addition".[4] However, the sense and level of the selectivity are highly dependent on conditions and reagents, and there has been proposed no generalized model of β-chelation controlled reaction.[5]



(2)

B

While the "chelation models" have been applied to the analysis of a variety of experimental results, there have also been many cases which do not conform to these models. Such anomalies have routinely been referred as "non-chelation" reactions (Schemes 1 and 2).[6] There often remains ambiguity in the mechanistic discussions because the data are always based only on the product analysis. Fundamental questions such as the following still remained unanswered. (1) Is the chelate complex a true intermediate of the reaction or just a dead-end stable species? (2) What is the rate-determining step of the chelation-controlled reaction? It appears that the C–C bond forming stage has been silently assumed to be rate determining without proof. (3) What is the molecular background of the selectivity? It is worthy of note that there is no proof even for the long-standing assumption that the stereochemistry-determining stage is the C–C bond forming reaction. (4) How is the R group connected to the metal atom in the transition state (cf. **A**), and what is the nucleophilic trajectory in such a chelate?

Studies on dynamic properties of the chelation-controlled reaction (in a coordinating solvent normally employed) are very

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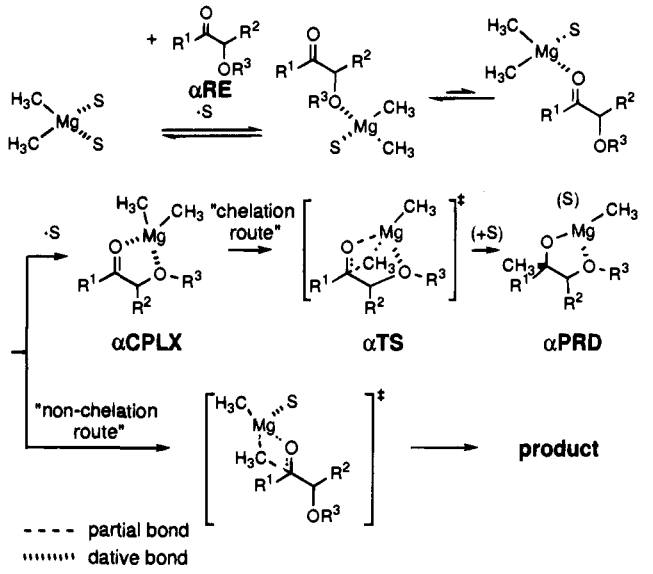
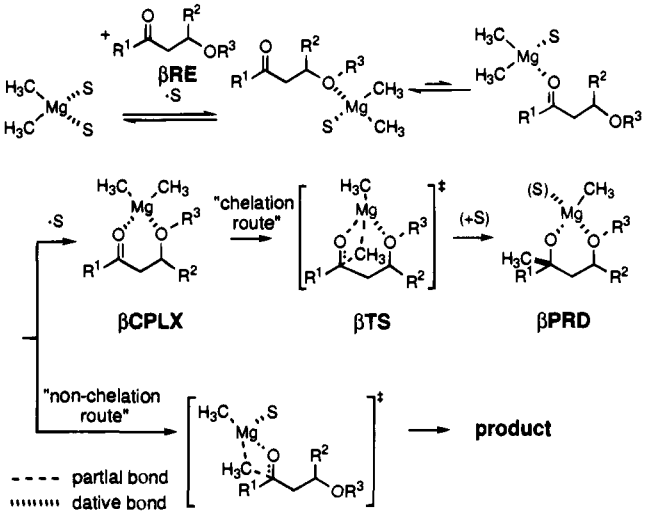
Scheme 1. Chelation and Non-Chelation Addition of Me_2Mg to an α-Alkoxy Carbonyl Compound (S = solvent)



Scheme 2. Chelation and Non-Chelation Addition of Me_2Mg to a β-Alkoxy Carbonyl Compound (S = solvent)



difficult to carry out in part because of solvent participation, as illustrated by simplified pictures shown in Schemes 1 and 2. It is only very recently that Eliel and Frye have shown experimentally that the α-chelate is a true reaction intermediate in the chelation-controlled addition of Me_2Mg in THF (an answer to the first question) through systematic comparison of product selectivity and reaction rate over a range of structurally related substrates.[7,8] They have found that the α-chelation reaction is much faster than the β-chelation reaction, which, in turn, is only slightly faster than the non-chelation reaction. The stability of α-chelation was positively correlated both with the level of diastereoselectivity and with the reaction rate. However, no conclusive interpretation of these rate effects has been obtained yet and the remaining three basic questions above await investigation.

Experimental studies having thus far provided only limited mechanistic information, we turned to the molecular orbital calculations at a high level of theory, since in the theoretical analysis, one can focus on a single important process among a series of other complicated events (cf. Schemes 1 and 2). We have singled out the crucial C−C bond forming stage (i.e., the 1,3-migration of a nucleophilic R group from the complex (CPLX) via the transition structure (TS) to product (PRD)) and evaluated the stability of the chelate, the activation energy of the migration reaction, and the diastereoselectivity for both α- and β-chelation systems. In this first systematic theoretical study on a chelation-controlled organometallic addition,[9] it will be suggested that the C−C bond formation stage is not a rate-limiting stage in the overall reaction pathway of the addition reaction in a coordinating solvent, while it is the stereochemistry-determining stage as has long been assumed. The studies also provided new insights into the factors that influence the level of stereoselectivity in the α- and β-chelation reaction.[10,11]

Selection of Models and Computational Method. Experimental studies of Eliel and Frye[7,8] on chelation-controlled additions of Me_2Mg to α- and β-alkoxy ketones as pictured in Schemes 1 and 2 are currently the single source of kinetic data for chelation-controlled reactions. We have studied the conversion of the complex (CPLX) to the product (PRD) via the transition structure (TS). For the α-chelation studies (Scheme 1), methoxyacetone, methoxyacetaldehyde, 2-methoxypropanal, and 3-methoxy-2-butanone were employed, and for the β-chelation studies (Scheme 2), 4-methoxy-2-butanone, 3-methoxypropanal, and 3-methoxybutanal were employed. These model compounds are somewhat simpler than the compounds used experimentally but likely embody the important features for this discussion. The assumption of 1:1 stoichiometry for the carbonyl substrate and Me_2Mg as in Scheme 1 and 2 is a reasonable one, since the Me_2Mg additions to alkoxy ketones have been shown to be first order in both reactants.[12]

Although there have been frequent allusions to single-electron-transfer mechanisms in Grignard additions, experimental verification of this mechanism has been exclusively for carbonyl substrates that are highly susceptible to one-electron reduction.[13] The vast majority of experimental data for the addition of reactive aliphatic carbanion to unbiased aliphatic carbonyl compound are consistent with a two-electron nucleophilic mechanism.

Calculations were performed with a GAUSSIAN 92 program,[14] and the structures of the stationary points were optimized without any geometrical assumptions at the HF/6-31G* [15] level. Most of the stationary points were also optimized at the HF/

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(9) For a recent study on a chelation-controlled reaction using LiH as a model, see: Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3983.

(10) A part of the content of this article was orally communicated: Nakamura, M.; Mori, S.; Nakamura, E.; Koga, N.; Morokuma, K. The 65th Annual Meeting of the Chemical Society of Japan, Tokyo, 1993; Abstract II, p 326. Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. The 67th Annual Meeting of the Chemical Society of Japan, Tokyo, 1994; Abstract II, p 1192. Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. The 41st Symposium on Organometallic Chemistry, Japan, Sakai, 1994; Abstracts, p 367.

(11) Although there are cases of "chelation-controlled" carbonyl additions in the Lewis acid mediated addition of a neutral nucleophilic reagent (cf. Mukaiyama aldol reaction), we have excluded these reactions from our present considerations, since the mechanistic information on such reactions is limited. See ref 6a and the following: Reetz, M. T.; Raguse, B.; Marth, C. F.; Hügel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1993**, *48*, 5731.

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3-21G(*) [16] level to reach qualitatively the same structures and energies. The accuracy of the organomagnesium structures obtained by the HF calculations was confirmed at the 3-21G(*) level against the X-ray crystallographic structure of EtMgBr-$(Et_2O)_2$.[17] In addition, it may be noted that the reliability of the HF/6-31G* level calculations for the evaluation of tortional and steric energies in carbonyl compounds has previously been demonstrated,[18] and hence, the discussion on the diastereoselectivity described below can be considered to be quite reliable. In addition, it may be noted that we have noted that the energetics obtained at the MP2(FC)/6-31+G*//HF/6-31G* [19] can be qualitatively reproduced at the HF/6-31G*//HF/6-31G* level (see energies in figures in the text for comparison). Normal coordinate analysis was performed at the HF/6-31G* level for all stationary points to confirm their nature and to obtain the zero point energy (ZPE) (scaled with a factor of 0.91[20]).

In addition to obtaining data for stationary points, we performed the intrinsic reaction coordinate (IRC) analysis[21] of some reactions, since we previously noted that this information is imperative for deeper understanding of organic reaction mechanisms.[22] The IRC analysis was carried out at the HF/3-21G(*) level.

The energies were recalculated with electron correlation at the MP2(FC)/6-31+G* level for the HF/6-31G* geometry, i.e., at the MP2(FC)/6-31+G*//HF/6-31G* level. For discussion of energetics, the enthalpy at 0 K (*H*) was employed, which is the sum of the potential energy and the ZPE. All the energies in the text are at the MP2(FC)/6-31+G*//HF/6-31G*+ZPE level unless noted otherwise. The difference between CPLX and TS was also evaluated for the Gibbs free energy (*G*) and the entropy (*S*) at 203.15 K (−70 °C) and 1 atm, unless noted otherwise.

Treatment of solvent effects is problematic in the theoretical studies, especially in those dealing with Lewis acidic metals in solution, which may change coordination state during a reaction. Fortunately, the Me_2Mg chelates (CPLXs) and the transition structures (TSs) studied in the present work are coordinatively saturated[23] and ligand effects during conversion from CPLX to TS are expected to be small. Therefore, reasonable estimation of the solvent effects may be possible simply by taking the bulk polarity effects into accounts. Estimation of these effects were done with the self-consistent reaction field (SCRF)[24] method, as applied for the molecular geometry optimized at the HF/3-21G(*) level, and indicated, as shown later, that polarity effects on the structures and energies of the reactions are rather small.

Results

Addition of Solvated Me_2Mg to Acetone: A Reference Reaction. Before analysis of the chelation-controlled additions, we needed to examine a non-chelation reference. For this purpose, we took the reaction of monosolvated $Me_2Mg(H_2O)$, REw, with acetone and optimized, at the HF/6-31G* level, the structure of the initially formed complex (CPLX0) and the TS (TS0), as shown in Figure 1. Except for the C_1 symmetry of the TS, the structures and energetics are similar to those previously obtained in the lower level calculations for unsolvated MeLi[25] and MgH_2[26] under the assumption of C_s symmetry of TSs and reactants. As in the chelation reactions (vide infra), the metal atom is tetracoordinated both in CPLX0 and in TS0. In CPLX0, the magnesium atom is coordinated to the nonbonding orbital of the carbonyl oxygen, and the Mg−O−C angle is 137.8°. The transition structure is four-centered and early with C−Mg bond of 2.246Å, which is only 4.2% longer than in the complex. The Bürgi-Dunitz attack angle[27] (<CH_3−C−O) is a reasonable value of 106.8°. In Figure 1 and Table 1 are also shown the calculated activation parameters ($\Delta E^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$) as well as energies and enthalpies (0 K) of intermediates relative to the reactants. The stabilization energy (ΔE_C) and enthalpy (ΔH_C) in the complexation between $Me_2Mg(H_2O)$ and acetone are 14.3 and 13.3 kcal/mol, respectively. As shown in Figure 1, the activation enthalpy at 0 K ($\Delta H^{\ddagger}$) from the complex to the TS is 10.5 kcal/mol, which is in reasonable agreement with the value of 13.7 kcal/mol obtained for the MeMgBr addition to benzophenone in ether at 20−40 °C.[28] The calculated activation entropy ($\Delta S^{\ddagger}$) was −15.1 e.u.

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(17) By starting with the X-ray crystal structure, the structure of EtMgBr-$(Et_2O)_2$ (ref 23b) was optimized both at the HF/3-21G(*) level and with the PM3 hamiltonian (MOPAC ver. 5.0) and the structures and some important parameters are shown below. The high performance of the HF/3-21G(*) calculations stands in contrast to the very poor performance of the much cheaper PM3 calculations.

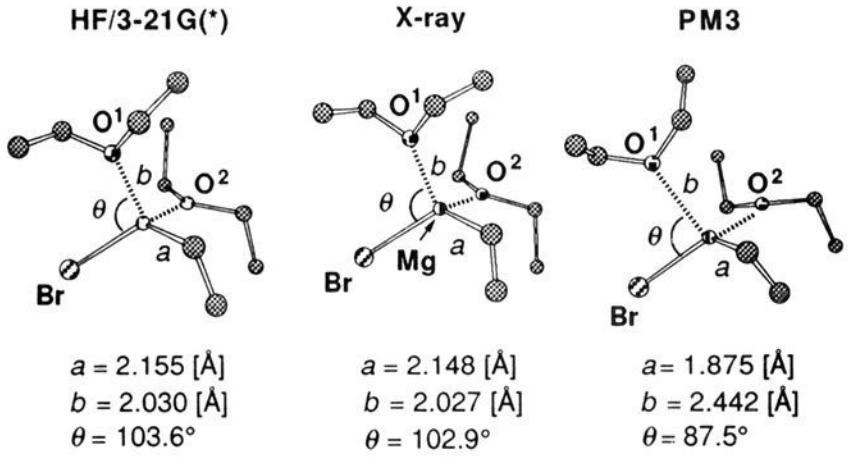

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Table 1. Energies and Enthalpies of Intermediates in the $Me_2Mg(H_2O)$ Addition to Acetone, Me_2Mg Addition to Methoxyacetone and Methoxyacetaldehyde[a]

	acetone/H_2O	methoxyacetone	methoxyacetaldehyde
reactants[b]	−547.867327	−585.810696	−546.631899
$(ZPE)_R$[c]	107.50	113.78	139.32
ΔE_C[d]	−14.3	−25.9	−23.1
ΔH_C[e]	−13.3	−25.0	−22.2
ΔE_T[f]	−5.1	−17.8	−15.7
ΔH_T[g]	−2.8	−16.1	−14.1
ΔE_P[h]	−52.3	−68.1	−80.9
ΔH_P[i]	−47.1	−63.3	−75.8

[a] Total energies of REw, RE, RE0, αRE1, and αRE2 in hartrees are −355.333 374, −279.098 435, −192.533 953, −306.712 261, and −267.533 464, respectively. [b] Total energies of reactants in hartrees. [c] $(ZPE)_R$ is the total ZPE of reactants in kcal/mol calculated at the HF/6-31G* level and scaled by a factor of 0.91. [d] Energy of CPLX in kcal/mol relative to reactants. [e] Enthalpy of CPLX at 0 K in kcal/mol relative to reactants. [f] Energy of TS in kcal/mol relative to reactants. [g] Enthalpy of TS at 0 K in kcal/mol relative to reactants. [h] Energy of PRD in kcal/mol relative to reactants. [i] Enthalpy of PRD at 0 K in kcal/mol relative to reactants.

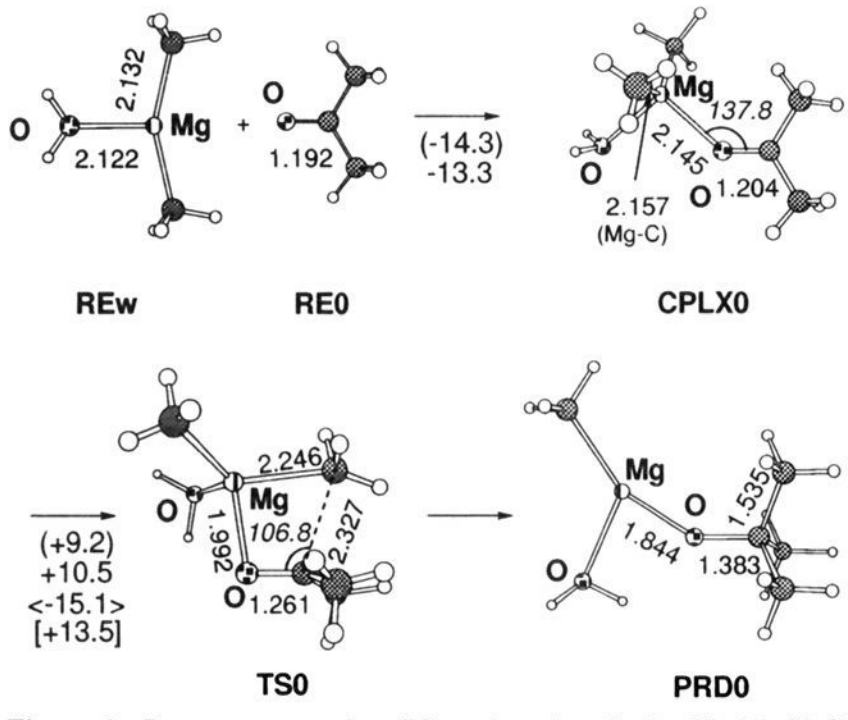


Figure 1. Reactants, complex, TS, and product in the $Me_2Mg(H_2O)$ addition to acetone. Bond lengths are in angstroms, and angles in italic are in degrees at the HF/6-31G* level. Numbers under the arrows are the differences between the two species in the energy (in parentheses), the 0 K enthalpy in kcal/mol at the MP2(FC)/6-31+G*//HF/6-31G* level (without parentheses), the entropy in e.u. at 203.15 K (in brackets), and the Gibbs-free energy at 203.15 K in kcal/mol derived from these (in square brackets). Vibrational frequencies used for ZPE and entropy are calculated at the HF/6-31G* level and scaled.

at −70 °C, which is also in good agreement with the above experimental value of −12.2 e.u. As shown in Table 1. The energy (ΔE_T) and the enthalpy (ΔH_T) of TS0 relative to the reactants are −5.1 and −2.8 kcal/mol, respectively, and thus the TS is more stable than the reactants. The exothermicity in the reaction (ΔH_P) is 47.1 kcal/mol.

Though no detail will be shown for brevity, similar results were obtained for the reaction of monosolvated $Me_2Mg(H_2O)$ with acetaldehyde. We just note that the activation enthalpy (0 K) here was calculated to be 9.6 kcal/mol.

Addition to α-Methoxy Carbonyl Compounds. 1. Methoxyacetone. α-Chiral α-methoxy ketones are a typical substrate for the α-chelation-controlled addition of organometallics and have been studied kinetically by Eliel and Frye et al. We have studied the Me_2Mg addition to methoxyacetone (αRE1). In Figure 2a are shown the optimized geometries and energies of the starting materials, the complex, the TS, and the product. The five-membered chelate structure of αCPLX1 is puckered, the metal is coordinated to the lone pair of the carbonyl oxygen, and the methoxy oxygen is not pyramidalized. These are the features observed in the X-ray crystal structure of the $SnCl_4$ complex of an α-benzyloxy ketone,[29] as well as the theoretical structure of the CH_3TiCl_3 complex of methoxyacetaldehyde.[30] Both in the complex and in the TS, the nucleophilic methyl group is located above the five-membered ring as dictated by the compact chelation structure.

In αCPLX1, the distance between the magnesium atom and the carbonyl oxygen (O^1) is 2.193 Å and is shorter than that between the metal and the methoxy oxygen (O^2) which is 2.264 Å. The TS of the reaction is slightly earlier than that of the non-chelation reference (vide supra) as judged by the shorter C^1-O^1 bond length (1.244 vs 1.261 Å) and the longer forming C−C bond (2.347 vs 2.327 Å). In the product αPRD1, the $Mg-O^1$ bond (1.860 Å) is now much shorter than the $Mg-O^2$ bond (2.096 Å).

In Figure 2 and Table 1 are also shown the calculated activation parameters, ($\Delta E^‡$, $\Delta H^‡$, $\Delta S^‡$, and $\Delta G^‡$) as well as energies and enthalpies of intermediates relative to the reactants. Me_2Mg (RE) and the ketone αRE1 first form a stable complex αCPLX1 with 25.0 kcal/mol exothermicity (Table 1), and then an intramolecular methyl group transfer from the metal to the carbonyl carbon takes place through αTS1 with the activation enthalpy (0 K) of 8.9 kcal/mol, which is significantly smaller than that of the (nonchelation) addition to acetone (10.5 kcal/mol, vide supra). This is due to the fact that, as shown in Table 1, the chelation reaction is more exothermic and thus its TS is earlier than the acetone reaction. Indeed, the comparison of the deformation of the carbonyl fragment in the TS indicated that the deformation energy[31] with acetone was larger than with the methoxyacetone by as much as 4.5 kcal/mol (MP2(FC)/6-31+G*//HF/6-31G*). As is seen from Table 1, the effect of the ZPE on the activation energy ($\Delta H^‡$) is very small (0.8 kcal/mol, HF/6-31G*). The activation entropy ($\Delta S^‡$) at 203.15 K is −10.8 e.u., and the Gibbs free energy of activation ($\Delta G^‡$) is 11.1 kcal/mol at 203.15 K.

2. Methoxyacetaldehyde. The Me_2Mg addition to methoxyacetaldehyde was studied next. As in the methoxyacetone case, a set of stationary points were obtained at the HF/6-31G* level and are shown in Figure 2b. The structure of αCPLX2 also agrees well with the crystal and theoretical structures of related compounds.[29,30] The position of the transition state is earlier than that for the methoxyacetone as indicated by the longer forming C−C bond length in αTS2 (2.380 Å) than in αTS1 (2.347 Å).

(29) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881.
(30) Jonas, V.; Frenking, G.; Reetz, M. T. *Organometallics* **1993**, *12*, 2111.
(31) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325. Morokuma, K. *Acc. Chem. Res.* **1977**, *10*, 294. Morokuma, K.; Kitaura, K. *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum: New York, 1981; p 215.

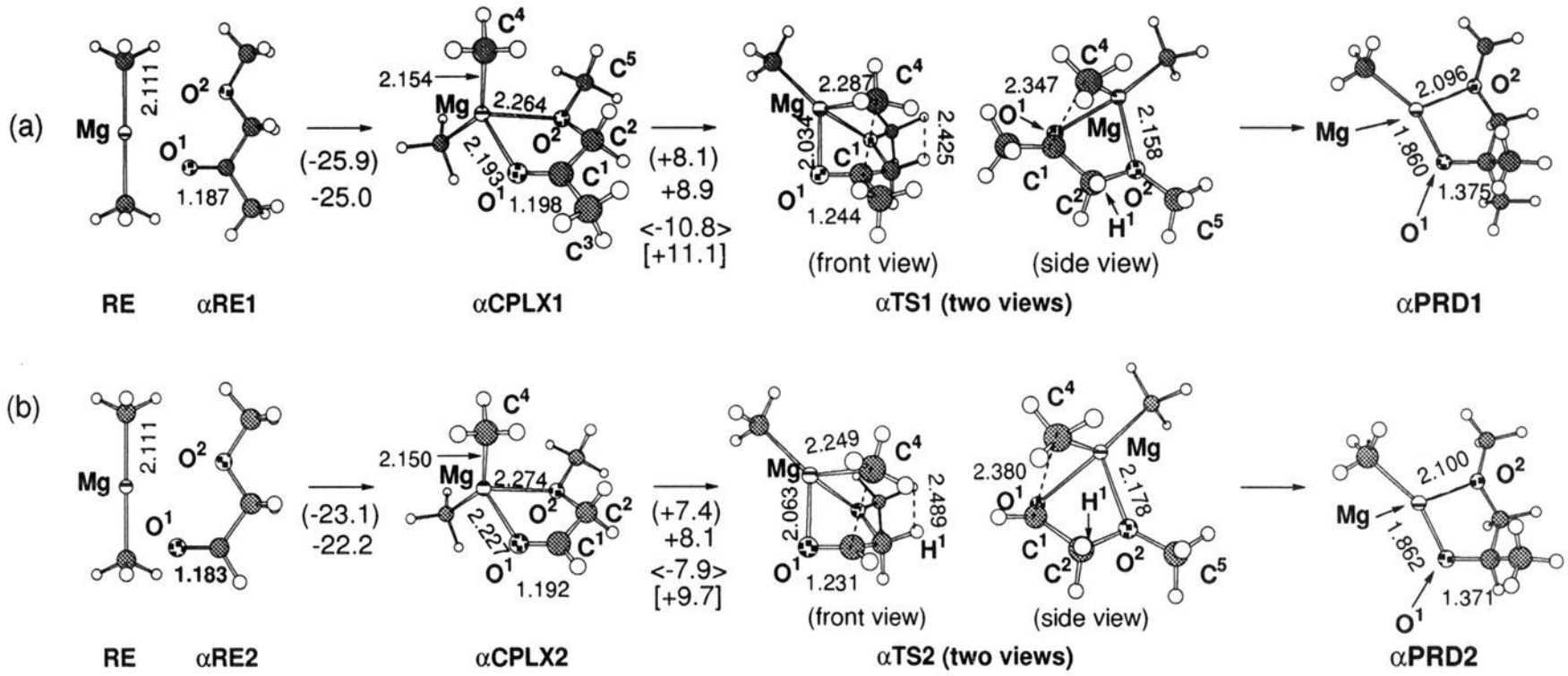


Figure 2. Reactants, chelate complexes, TSs, and products in the Me_2Mg addition to methoxyacetone and methoxyacetaldehyde. See Figure 1 for details.

It is seen in comparison of the side views of αTS1 and αTS2 in Figure 2 that the attacking methyl group (C^2) in methoxyacetaldehyde lies further away (the $C^2-C^1-C^4-O^1$ dihedral angle of 110.0° as compared with the 108.5° value for the ketone) from the chelate structure, avoiding steric interactions with the α-methylene group (C^5). In addition, for the methoxyacetaldehyde reaction (αTS2), the distance between the H^1 hydrogen of the α-methylene group and the proximal hydrogen in the attacking methyl group is 2.489 Å, which is longer than that for the methoxyacetone reaction (αTS1, 2.425 Å). These structural parameters suggest the occurrence of smaller steric interactions[32] between the α-methylene group and the incoming nucleophile and hence lower stereoselectivity in an α-substituted (i.e., α-chiral) α-alkoxy aldehyde than in an α-alkoxy ketone. This is supported not only by the calculations of appropriate substituted models (vide infra) but also by experimental observations.[2a]

In Figure 2 and Table 1 are also shown the calculated energetics of the system. The stability of the chelate complex αCPLX2, 22.2 kcal/mol, is 2.8 kcal/mol smaller than that of αCPLX1, likely reflecting the lower Lewis basicity of aldehyde than ketone. In line with this analysis, the metal/carbonyl oxygen ($Mg-O^1$) distance is longer for the aldehyde complex, αCPLX2 (2.227 Å), than for the ketone complex, αCPLX1 (2.193 Å).

The activation enthalpy for the aldehyde (8.1 kcal/mol) is smaller than that for the ketone (8.9 kcal/mol), and once a chelate is formed, an aldehyde reacts faster than a ketone. This activation enthalpy is also smaller than that (9.6 kcal/mol) obtained for the non-chelate reference reaction ($Me_2Mg(H_2O)$ addition to acetaldehyde, vide supra). The reason of lower relative activation enthalpy (by 0.8 kcal/mol) for aldehyde than for ketone is the result of much lower relative stability at the chelate complex (by 2.8 kcal/mol; cf. Table 1) than at the transition state (by 2.0 kcal/mol). The aldehyde is more reactive because its lower basicity makes the complex less stable than the ketone.

The Gibbs free energy of activation, 9.7 kcal/mol (Figure 2b, as well as the energy and the 0 K enthalpy of activation), for methoxyacetaldehyde is smaller than that obtained for methoxyacetone, 11.1 kcal/mol (Figure 2a). The calculated energetics indicate that α-chelate complexes are highly reactive species and that the aldehyde is more reactive than the ketone. This is in good agreement with the experimental results.

3. Reaction Path of α-Chelation-Controlled Addition. The reaction path for the conversion of the chelate complex to the product was examined for methoxyacetaldehyde, and a few representative intermediates on the IRC are shown in Figure 3. The *s* value refers to a reaction coordinate based on mass-weighted coordinate,[33] with its zero taken at the transition state. It has become clear for the first time that the α-chelate complex goes smoothly to the product through a low-energy transition state *with retention of the chelate structure*. These snapshots confirm the observations made for the TS, i.e., αTS2; namely, as the reaction proceeds, the nucleophilic methyl group located over the chelate ring in the chelate complex moves toward the outside of the ring, thereby avoiding steric interactions with the α-methylene group. In addition, the cleavage of the C^4-Mg bond takes place mostly after the TS, which suggests that the coordination state of the magnesium metal at the TS would not be very different whether it is in gas phase or in solution. The present theoretical model is hence expected to be a reasonable approximation of the actual transformation from the chelate complex to the TS.

Addition to β-Methoxy Carbonyl Compounds. 1. 4-Methoxy-2-butanone. β-Chiral β-methoxy ketones are generally non-diastereoselective substrates for the nucleophilic additions of organomagnesium reagents.[4] Unlike an α-alkoxy group which accelerates the Me_2Mg addition reaction, a β-alkoxy substituent has be shown to have very minor effects on the rate of the Me_2Mg addition reaction. We have studied 4-methoxy-2-butanone as a substrate and found chelated reaction pathways (Figure 4). Most notably, there exist two isomeric TSs, a chair TS (βTS1a) and a boat TS (βTS1b), of which the latter is more stable than the former by 2.7 kcal/mol for both the 0 K enthalpy and the Gibbs free energy. While the energy decomposition analysis[31] was not possible due to the strong interactions between the two reactants, the deformation energy of the carbonyl substrate fragment in the TSs was higher for the chair than the boat by as much as 4.7 kcal/mol, while the interaction energy between the deformed carbonyl fragment and the deformed Me_2-

(32) Cf.: Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. Lodge, E. R.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819.

(33) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

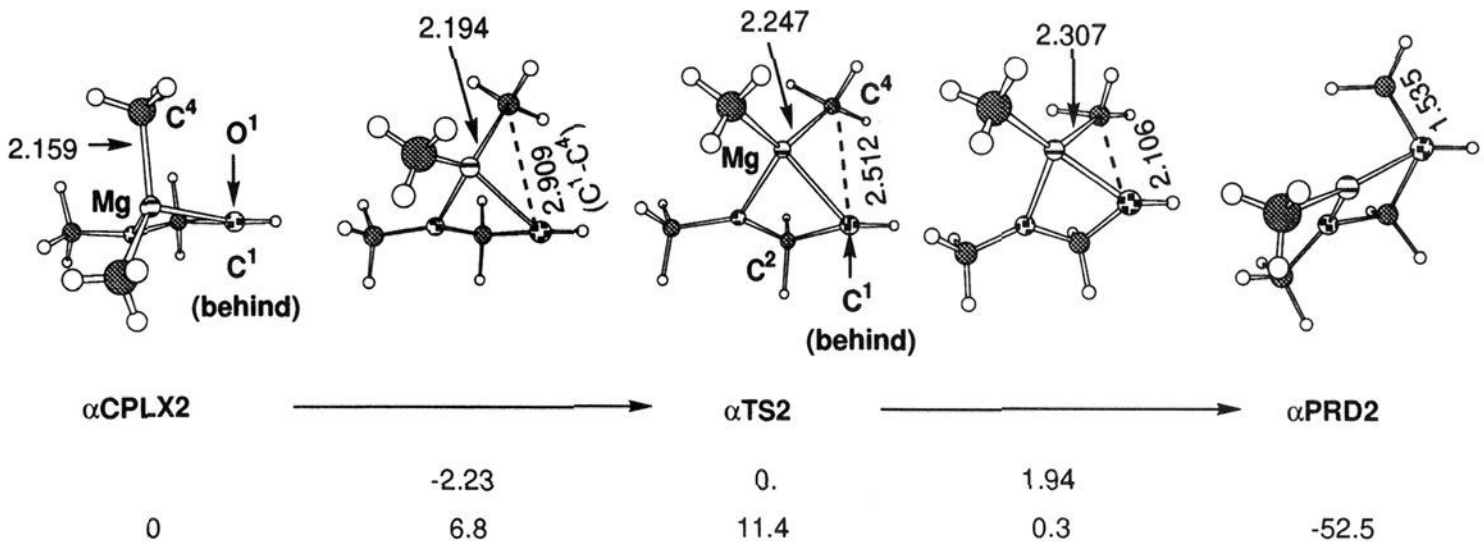


Figure 3. Representative intermediates on the IRC of the Me_2Mg addition to methoxyacetaldehyde (HF/3-21G(*)). *s* is the reaction coordinate. Bond lengths between C^1 and C^4, and between C^4 and Mg are in angstroms. The carbonyl carbon (C^1) is hidden behind the carbonyl oxygen (O^1).

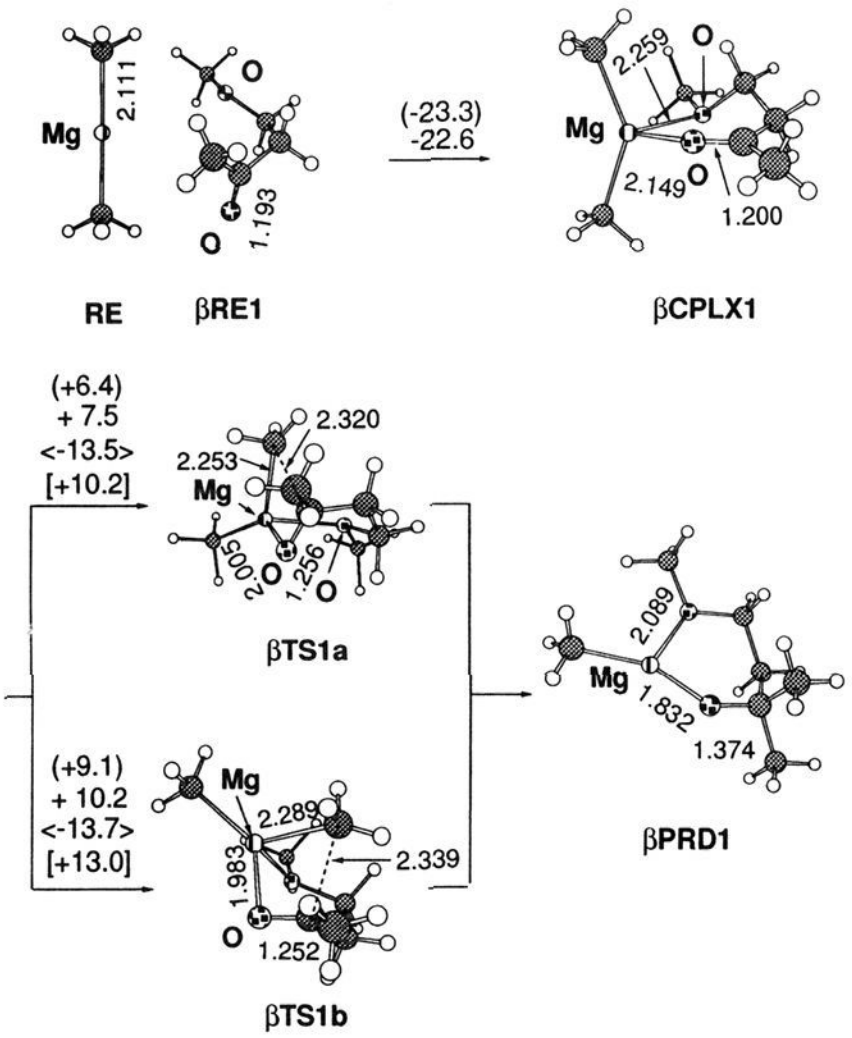


Figure 4. Reactants, chelate complexes, TSs, and product in the Me_2Mg addition to 4-methoxy-2-butanone. See Figure 1 for details.

Mg fragment was 0.6 kcal/mol more favorable for the chair TS. This energy difference arises in part from the staggered conformation for the H—C(=O)—C—H arrangement in the substrate fragment of the chair TS.

As shown in Figure 4 and Table 2, stabilization by chelate formation is 22.6 kcal/mol, which is larger than in that for α-chelation by 2.4 kcal/mol. The exothermicity of the β-chelation reaction (58.1 kcal/mol, Table 2) is lower than that of α-chelation reaction (63.3 kcal/mol, Table 1). More importantly, the activation enthalpy and Gibbs free energy of the β-chelation boat TS pathway of 4-methoxybutan-2-one are 7.5 and 10.1 kcal/mol, respectively, which are smaller than 8.9 and 11.1 kcal/mol, respectively, in the α-chelation reaction of methoxyacetone. Thus, the theoretical data for the C—C bond forming stage predict that the β-chelate pathway is faster than the α-chelate reaction. This is against what was found experimentally[7,8] for the *net* reaction rate of the β-chelation-controlled reaction. This point will be discussed again in detail.

2. 3-Methoxypropanal. 3-Methoxypropanal was also studied to obtain qualitatively the same results, as shown in Figure 5 and Table 2. Chair (βTS2a) and boat (βTS2b) TSs were also found for this aldehyde, and the former was less stable than the latter by 2.8 and 1.9 kcal/mol in the 0 K enthalpy and the Gibbs free energy, respectively. The reaction path from the two TSs led to two different conformers βPRD2a and βPRD2b of the product with a small energy difference. As previously noted for α-chelates, the stability of the aldehyde chelate βCPLX2 as compared with the starting materials is slightly smaller (by 0.9 kcal/mol) than the ketone case possibly due to lower Lewis basicity of the aldehyde. The activation energy and Gibbs free energy of activation from the chelate complex to the boat TS, 6.0 and 8.4 kcal/mol, respectively, are slightly lower than 7.5 and 10.2 kcal/mol obtained for the ketone.

Table 2. Energies and Enthalpies of Intermediates in the Me_2Mg Addition to 4-Methoxy-2-butanone and 3-Methoxypropanal[a]

	4-methoxy-2-butanone	3-methoxypropanal
reactants[b]	−624.988708	−585.807399
$(ZPE)_R$[c]	113.78	139.32
ΔE_C[d]	−23.3	−22.8
ΔH_C[e]	−22.6	−21.7
ΔE_T[f]	−16.9 (−14.2)	−17.7 (−15.0)
ΔH_T[g]	−15.1 (−12.4)	−15.7 (−12.9)
ΔE_P[h]	−62.7	−67.1 (−62.0)
ΔH_P[i]	−58.1	−66.2 (−61.0)

[a] Total energies of RE, βRE1, and βRE2 in hartrees are −279.098 435, −345.890 273, and −306.708 964, respectively. [b,c,d,e] See the footnotes in Table 1 for the definitions of the abbreviations. [f,g] Energy or enthalpy at 0 K of βTS1a and βTS2a and, in parentheses, βTS1b and βTS2b, in kcal/mol relative to reactants. [h,i] Energy or enthalpy at 0 K of βPRD1 and βPRD2a and, in parentheses, βPRD2b, in kcal/mol relative to reactants.

3. Reaction Path of β-Chelation-Controlled Addition. The reaction path for the conversion of the chelate complex to the product was examined for 3-methoxypropanal, and representative intermediates on the IRC are shown in Figure 6. Chelation is maintained throughout the reaction. As found for the α-chelate, the nucleophilic methyl group initially located over the chelate ring moves outside of the ring, thereby avoiding steric interaction with the α-CH_2 group, and this tendency is more pronounced here than in the α-chelate pathway (Figure 3). Nucleophilic attack of the asterisked methyl group leads to the boat TS, and that of the double-asterisked one leads to the chair TS.

Cursory analysis of the TSs for the position of the metal relative to the carbonyl group (Figure 6, βTS2b) may appear to suggest that the metal activates the carbonyl group by π-complexation.[34] However, close examination of the intermediates on the IRC indicates that there exists no local minimum on the potential energy surface corresponding to a carbonyl/metal

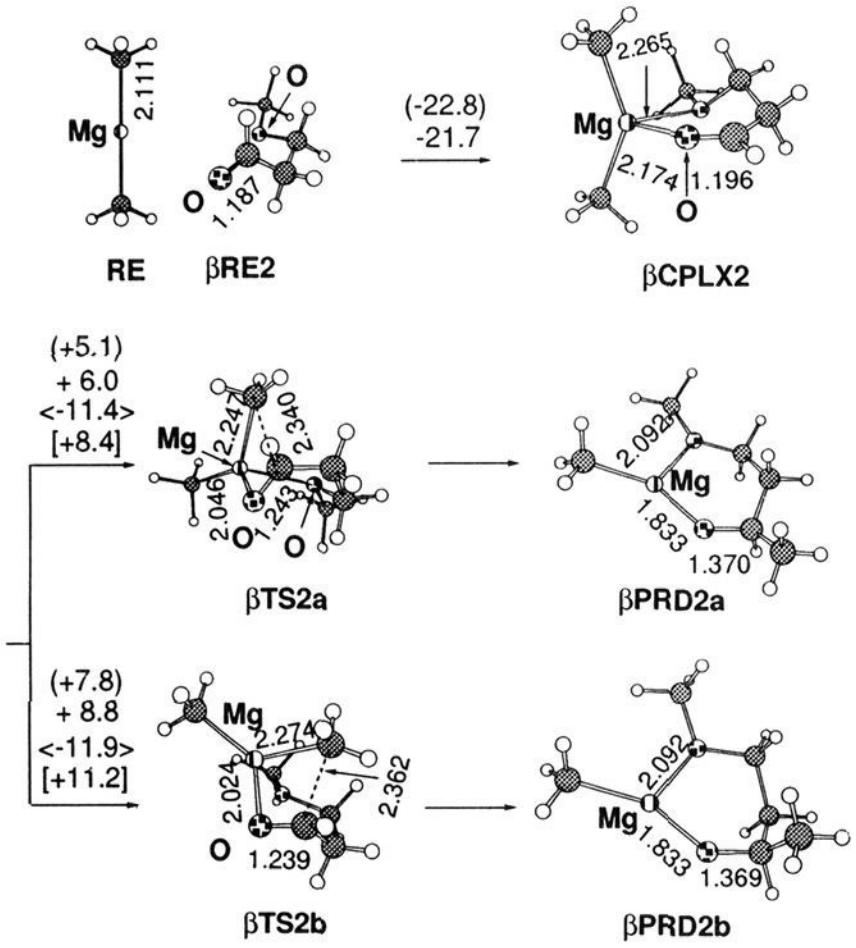


Figure 5. Reactants, chelate complexes, TSs, and product in the Me_2Mg addition to 3-methoxypropanal. See Figure 1 for details.

π-complex and, hence, little possibility for the kinetic importance of metal π-complexation.

Nucleophilic Addition to Chiral Chelating Substrates. 1. α-Chiral α-Alkoxy Aldehydes and Ketones. In order to probe the selectivity of α-chelation-controlled 1,2-asymmetric induction, we examined the TS of the Me_2Mg addition to 3-methoxy-2-butanone by generating two diastereomeric initial structures by the replacement of one of the α-hydrogen atoms with a methyl group in αTS1. Full geometry optimization led to two diastereomeric TSs, *syn*-αTS1 and *anti*-αTS1. Both their 0 K enthalpy and −70 °C Gibbs free energy differences are 1.8 kcal/mol at the HF/6-31G*//HF/6-31G* level as shown in Figure 7. The sense and the level of the *anti*-selectivity are in agreement with the high experimental selectivity. One reason for this energy difference is undoubtedly the very close proximity (2.316 Å) of a hydrogen atom in the nucleophilic methyl group and that in the α-methyl substituent in *syn*-αTS1. This is due to the Bürgi−Dunitz trajectory[27] which places these two methyl group close to each other.

In contrast to the alkoxy *ketones*, α-alkoxy *aldehydes* are known to be much less stereoselective.[35] It has been speculated that the aldehydes react via a non-chelation pathway owing to its lower Lewis basicity.[2a] As described above for the ketone, we generated two TSs for the addition to 2-methoxypropanal and obtained the optimized TSs, *syn*-αTS2 and *anti*-αTS2. The latter is favored only by 0.9 and 0.4 kcal/mol in the 0 K enthalpy and the −70 °C Gibbs free energy, respectively, at the HF/6-31G*//HF/6-31G*, about one-half the difference of the above 3-methoxy-2-butanone. The longer forming C−C bond (cf. Figure 7) and longer distance between the α-methyl and the nucleophilic methyl group in *syn*-αTS2 than in *syn*-αTS1 are likely the reasons for the lower selectivity. The latter is also due to the flexibility of the nucleophilic trajectory in the aldehyde reaction, compared with the ketone reaction, as already mentioned in the trajectory analysis (cf. Figures 3 and 6); that is, the nucleophile avoid interactions with the chiral center by moving closer to the aldehyde hydrogen.

In summary, the lower experimental selectivity for α-alkoxy aldehydes than for ketones can be ascribed to the nature of the

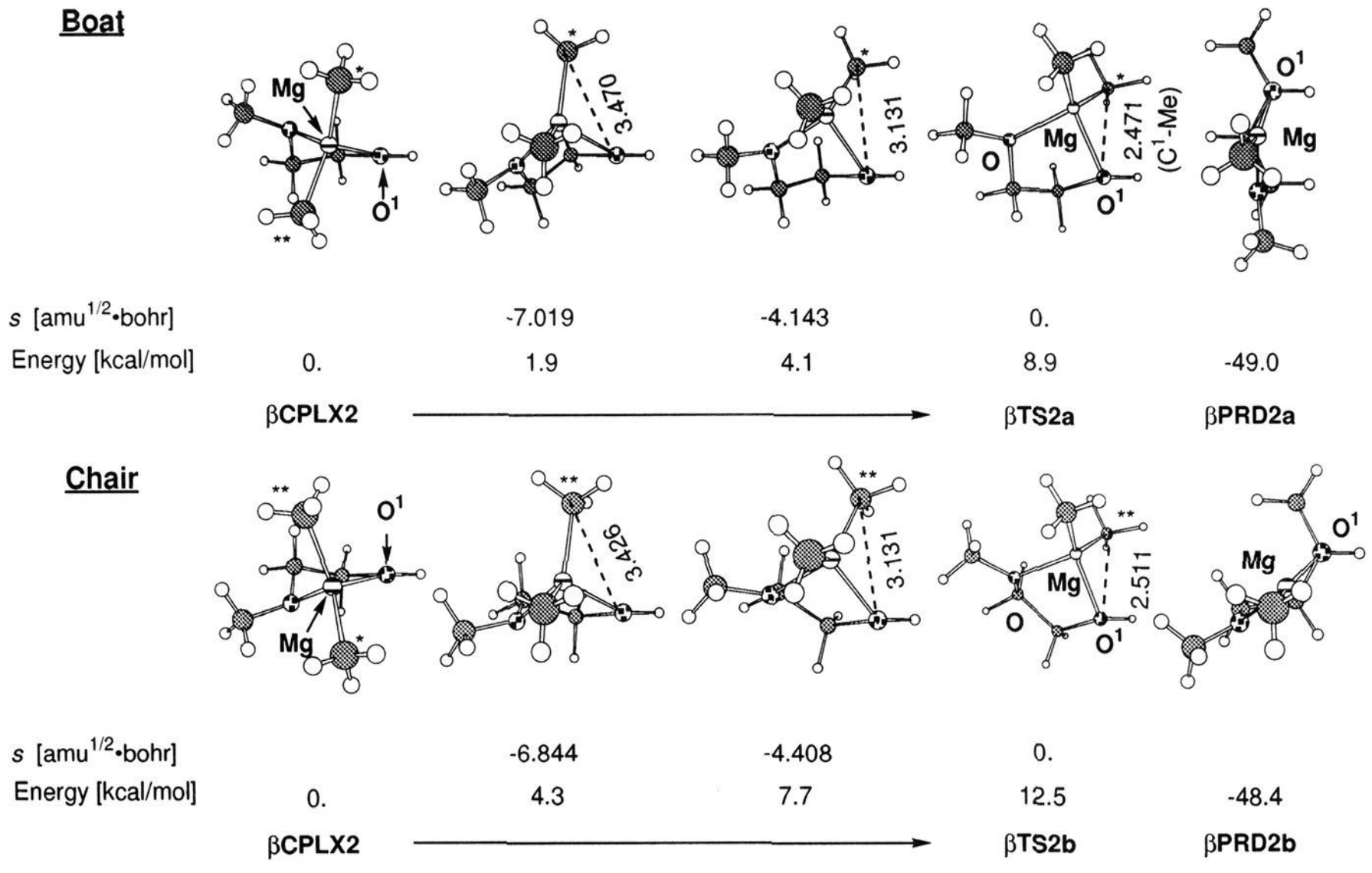


Figure 6. Representative intermediates on the IRC of the Me_2Mg addition to 3-methoxypropanal (HF/3-21G(*)) as viewed along the $O^1{=}C^1$ axis from the O^1 side. *s* is the reaction coordinate. Bond lengths between the attacking Me group and the carbonyl carbon are in angstroms.

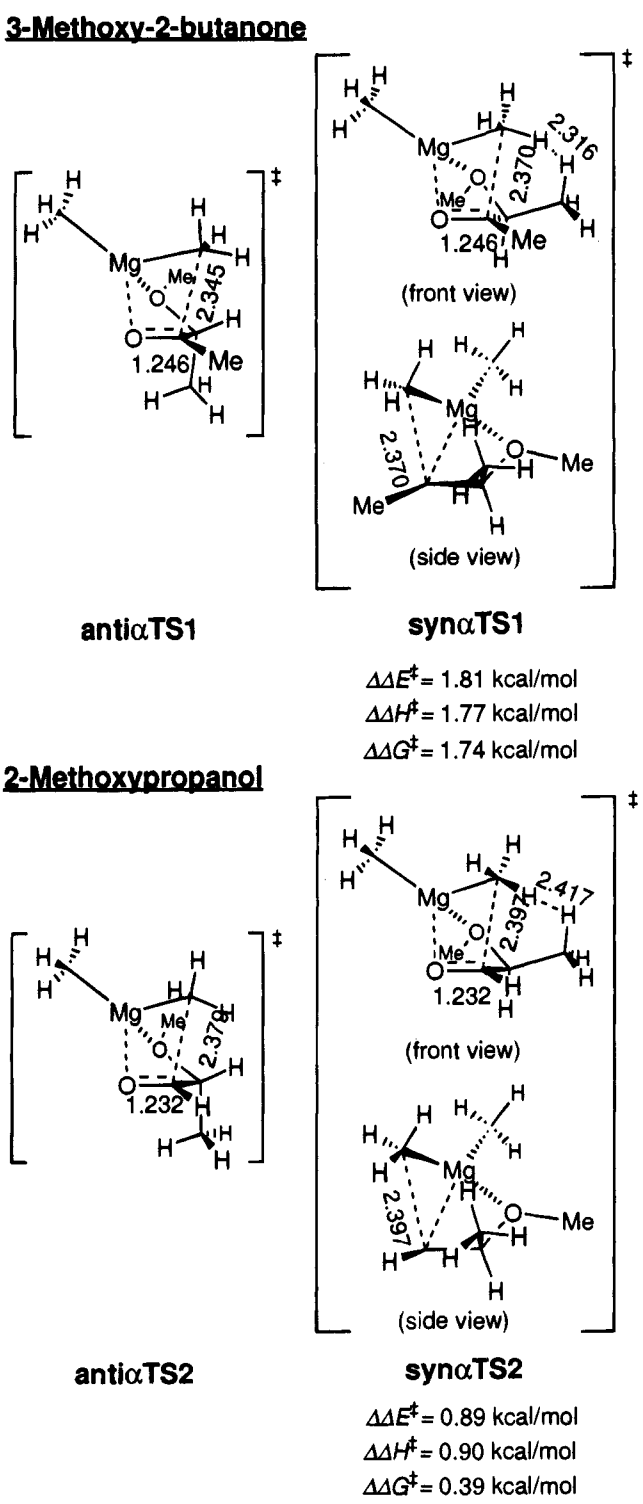


Figure 7. Diastereomeric TSs of the Me_2Mg addition to 3-methoxy-2-butanone and 2-methoxypropanal. Bond lengths are in angstroms. $\Delta\Delta E^{\ddagger}$, $\Delta\Delta H^{\ddagger}$, and $\Delta\Delta G^{\ddagger}$ are the energy, enthalpy at 0 K, and Gibbs free energy at −70 °C, relative to those of *anti*-αTS1 and *anti*-αTS2.

chelated TSs. It is important to recognize that the chelate structure is maintained throughout the reaction for aldehydes as well as for ketones.

2. β-Chiral β-Alkoxy Aldehydes. We next examined 1,3-asymmetric induction, which is known to be a rather unreliable

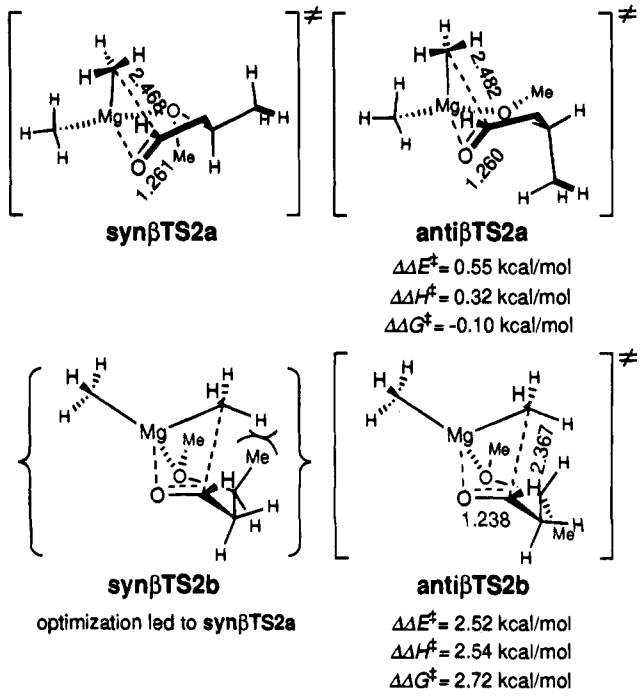


Figure 8. Diastereomeric TSs of the Me_2Mg addition to 3-methoxybutanal (HF/6-31G*). For the sake of clarity, the absolute configuration of the four-centered TS is kept constant. Bond lengths are in angstroms. $\Delta\Delta E^{\ddagger}$, $\Delta\Delta H^{\ddagger}$, and $\Delta\Delta G^{\ddagger}$ are the energy, enthalpy at 0 K, and Gibbs free energy at −70 °C, relative to those of *syn*-βTS2a.

synthetic protocol. Since there exist two TSs in the addition to β-methoxy carbonyl compounds, there are four diastereomeric TSs possible for β-chiral β-alkoxy carbonyl compounds.

For the boat TS, we started with βTS2a and have generated two initial structures by replacing one of the two β-hydrogens of 3-methoxypropanal with a methyl group. Optimization of the structures led to *syn*-βTS2a and *anti*-βTS2a of nearly equal potential energy, as shown in Figure 8. The energy difference totally disappears for the Gibbs free energy. In both structures, the β-methyl group is far from the nucleophilic methyl group and apparently causes little steric effects.

In a similar manner, we generated two structures from the chair TS, βTS2b. While the *syn* TS, *syn*-βTS2b, was smoothly optimized, the *anti* TS had a very high energy and flipped to *anti*-βTS2a due to severe steric interaction between two methyl groups. *anti*-βTS2b was 2.6−2.7 kcal/mol less stable than *syn*-βTS2a. Thus, while the chair TS which would be *anti*-selective is of high energy, the reaction is expected to proceed via a nonselective boat pathway.

Estimation of Solvent Effects by the Reaction Field Model. The effects of solvent polarity on the conversion of the chelated complex to the TS were examined for methoxyacetaldehyde and 3-methoxypropanal with the aid of the SCRF method. The dielectric constant of THF (ϵ_0 = 7.58 at 25 °C) was chosen, since THF is a solvent used in the experimental counterpart of the present studies. The structures and energies of the complex and the TS were essentially the same as those obtained in the gas phase except for the higher activation energies in the solution phase. For instance, for methoxyacetaldehyde shown in Figure 9, the forming C^1-C^4 bond is 2.475 Å as compared with 2.512 Å in the gas phase. For other parameters such as C^1-O^1, C^4-Mg, and O^1-Mg, bond distances were within 1.6% of the gas phase results.[36] The 0 K activation enthalpy of 11.4 kcal/mol

(34) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536.
(35) Arco, M. J.; Tramnell, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075. Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021. Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem. Suppl.* **1983**, 1511. Cf.: Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969.

(36) The cavity size (a_o) remained essentially the same in the gas phase and in THF. For instance, the a_o of αCPLX2 was 4.42 Å and that of αCPLX2 (THF) was 4.40 Å.

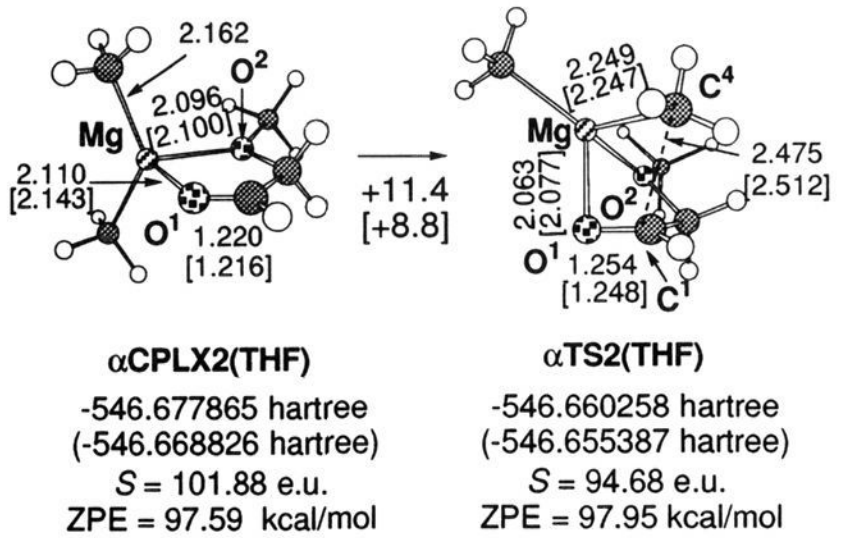


Figure 9. Complex and TS on the addition of Me_2Mg to methoxyacetaldehyde under a dielectronic constant of $\epsilon_0 = 7.58$ (THF). Bond lengths in angstroms and angles in italic in degrees at the HF(SCRF)/3-21G(*) level, the relative 0 K enthalpy in kcal/mol below the arrow, and the total energy in hartrees at the MP2(FC, SCRF)/6-31+G*//HF-(SCRF)/3-21G(*) level are compared with those in the gas phase in square brackets. Entropy (S) in e.u. and ZPE were obtained from the vibrational frequencies scaled by 0.91 at the HF(SCRF)/3-21G(*) level.

in solution is 2.5 kcal/mol higher than 8.8 kcal/mol (MP2(FC)/6-31+G*//HF/3-21G(*)) in the gas phase. Other data are summarized in the supplementary material.

Discussion

The overall picture of the chelation-controlled nucleophilic addition is complicated, and experimental kinetic data are still insufficient. The present theoretical calculations provided some new pieces of information which are complementary to the existing experimental data.

The present study has shown for the first time that a chelate complex between a monomeric organometallic and an alkoxy carbonyl compound undergoes smooth intramolecular 1,3-methyl group transfer with retention of the chelate structure. For both α- and β-chelates, the complex formation is favored by >20 kcal/mol, and the methyl group transfer takes place with an activation energy of ca. 6−8 kcal/mol. Except that the activation energy was increased by a few kcal/mol, there were found rather small effects of solvent polarity on the structures and energetics.

The formation of stable complexes for both α- and β-alkoxy carbonyl compounds agrees well with the chelate-forming properties of $MgBr_2$ in CD_2Cl_2,[37] and the energy profile is consistent with the rate-limiting C−C bond formation in the chelation-controlled addition of $MeTiCl_3$ in a noncoordinating solvent, CD_2Cl_2.[7b] The calculated kinetic parameters for the C−C bond formation are in reasonable agreement with the parameters obtained for the Me_2Mg addition to benzophenone.[12] As summarized in Table 3 for both aldehyde and ketone series in the gas and solution phases, the activation energies of the C−C bond formation decreases in the following order: non-chelation > α-chelation > β-chelation. Considering that the ab initio energetics of the present theoretical level are expected to be quite reliable[18] for comparison between the structurally similar α- and β-chelates (see Selection of Models and Computational Method), this reactivity order appears to be rather curious, since experimentally α-chelate-forming substrates in THF are far more reactive toward Me_2Mg than β-chelate and non-chelation substrates.[7,8] This contradiction may be resolved by considering that the factors determining the net reaction rate are quite complicated; namely, the rate may depend on the solvation/desolvation and chelate formation processes as well as the C−C bond forming stage.

(37) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

Table 3. Comparison of Activation Energies (from the Complex) of the Me_2Mg Addition to Acetone, Acetaldehyde, Methoxyacetone, Methoxyacetaldehyde, 4-Methoxy-2-butanone and 3-Methoxypropanal

reactions	$\Delta H^{\ddagger a}$	$\Delta G^{\ddagger b}$
acetone + $Me_2Mg(H_2O)$	10.5	13.5
methoxyacetone + Me_2Mg	8.9	11.0
4-methoxy-2-butanone + Me_2Mg	7.5	10.2
acetaldehyde + $Me_2Mg(H_2O)$	9.6	11.1
methoxyacetaldehyde + Me_2Mg (in solution)[c]	8.1 (11.5)	9.7 (13.5)
3-methoxypropanal + Me_2Mg (in solution)[c]	6.0 (10.9)	8.4 (12.9)

[a] Activation enthalpy at 0 K. [b] Gibbs energy of activation at −70 °C, both obtained at the MP2(FC)/6-31+G*//HF/6-31G* level. [c] The solution values in parentheses are at the MP2(FC, SCRF)/6-31+G*//HF(SCRF)/3-21G(*) level ($\epsilon_0 = 7.58$).

There were recently obtained experimental data which may address some of the complications. Chen et al.[38] examined the *p*-substituent effects for the Me_2Mg addition to *p*-substituted acetophenone and *p*-substituted α-methoxy acetophenone in CH_2Cl_2 and found that the latter was hardly subject to *p*-substituent effects ($\varrho^+ = 0.022$), whereas the former substrate conformed to a Hammett correlation consistent with the standard nucleophilic reaction ($\varrho^+ = 1.0$).[39] While existing data, both experimental and theoretical, are not sufficient to fully account for this interesting observation, it might well be reconciled by the slightly earlier nature of the TS of the α-chelation reaction relative to the non-chelation counterpart (vide supra)[40] or by the assumption that the C−C bond formation is not rate limiting. It may be important in this respect to note that, in THF, a solvent normally used for such reactions, the equilibrium concentration of both α- and β-chelate complexes is extremely small and, hence, the chelation stage is expected to influence the overall rate.[41,42]

While neither the present calculations nor previous experiments offer a conclusive solution to the reaction rate problems, they support the long-standing assumption that the C−C bond forming stage is the stage that determines the stereochemistry in the α-chelation reaction, since the calculated activation energies of the C−C bond formation provide a reasonable account for the sense of the diastereoselectivity. More interestingly, they also offered new explanations for the factors that determine the level of the selectivity both in the α- and β-chelation. Being a compact bicyclo[2.1.1]hexane-like structure, the TSs of α-chelation-controlled addition are fundamentally more sensitive to the steric effects of substituents than those in the β-chelation reaction. Changing metal atoms and ligand environment are expected to alter the TS and the nucleophilic trajectory, and thus to change the level of diastereoselectivity, as have been amply demonstrated by experiments.[5] It is heuristic to note that subtle structural differences are important in determining the relative energies of the diastereomeric transition states (cf. Figure 7), suggesting that simple empirical

(38) Chen, X.; Harris, R.; Eliel, E. L.; Frye, S. V. Submitted for publication.

(39) A single-electron-transfer mechanism is also consistent with the lack of substituent effects, but it seems rather unlikely that Me_2Mg acts as a reducing agent and that acetophenone and α-methoxyacetophenone react via different mechanisms.

(40) We thank Dr. Frye for pointing out this possibility. The logical correlation between the location of the TS and the *p*-substituent effects, however, is not obvious at this time.

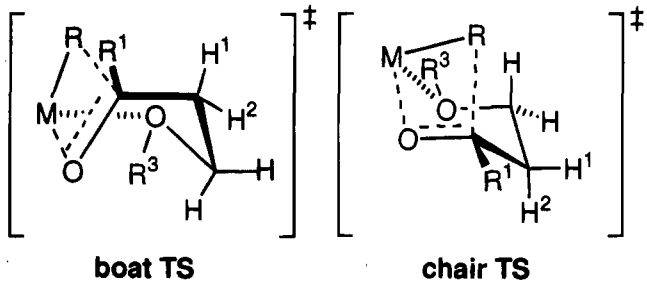
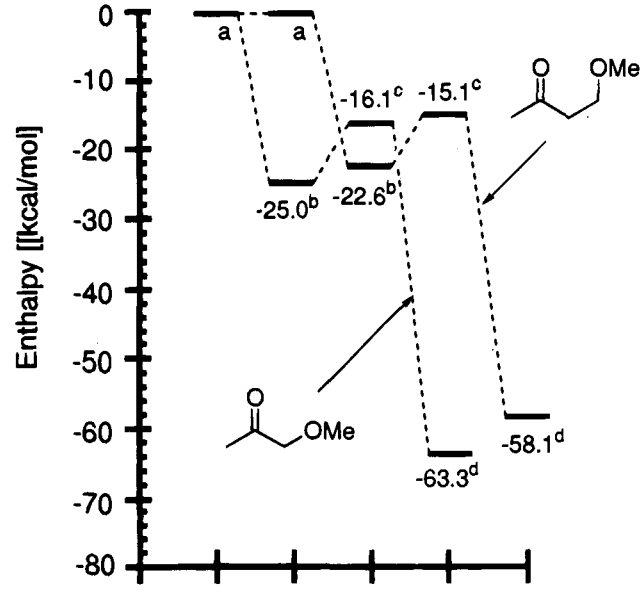


Figure 10. Two conformations of the TS in the addition of organometallics (R−M) to β-alkoxy carbonyl compounds.

models such as **A** should be employed most cautiously in predicting the *level* of diastereoselectivity.

As to the β-chelate reactions, various TS models including chair, boat, their twisted forms, and non-chelation paths have been discussed to explain the observed, diverse selectivity.[5] Unfortunately, the decisions as to what model is to be employed have been made solely on an arbitrary basis. The present studies determined for the first time that there are two chelation pathways for the β-chelation reaction, among which one (chair TS) is selective and another (boat TS) nonselective (Figure 10). For Me_2Mg, the nonselective boat pathway is energetically favorable and thus accounts for the experimental data. On the other hand, it may be possible, with the aid of suitable experimental variables, to change the relative activation energies of the chair and the boat TSs. In fact, the chair TSs have been proposed by experimentalists as working models to explain the reactions of titanium[5a] or borane[5b,5c] reagents, and it is possible that such nontraditional reagents may somehow stabilize the chair TS (or destabilize the boat TS).

Whereas the stereochemical discussion in the paragraph above shows that the chelation pathway can account for the high and low selectivities in α- and β-chelation reactions, the calculated energetics also endorse the common speculation that some reactions may proceed via non-chelation pathways. Namely, it has been shown experimentally that the β-chelation reaction is much slower than the α-chelation reaction and hence a non-chelation pathway (which is expected to be non-stereoselective) may effectively compete with the chelation pathway.[7,8] The energetics obtained in the present calculations supported this common conjecture. As summarized in Figure 11, the stability of the starting β-chelate (as well as the product β-chelate) is less than that of the α-chelates. It is therefore possible that the net low reactivity of the β-chelate (and hence the possible intervention of non-chelation pathways) is due to unfavorable chelate formation in solution.[7,8]



[a]Reactants. [b]αCPLX1 or βCPLX1. [c]αTS1 or βTS1a. [d]αPRD1 or βPRD1.

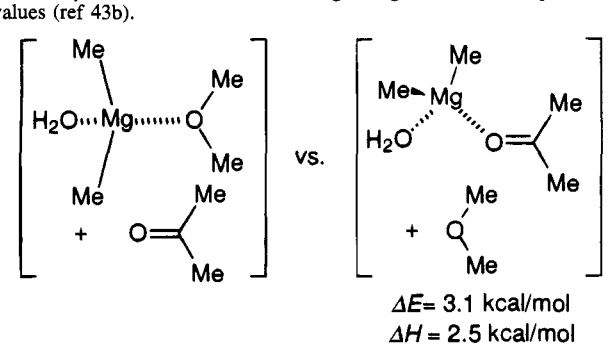
Figure 11. Enthalpy profiles in the Me_2Mg addition to methoxyacetone and 4-methoxy-2-butanone at the MP2(FC)/6-31+G*//HF/6-31G* level with the ZPE correction by a factor of 0.91. The enthalpies (0 K) are relative to the reactants.

Parenthetically, the present studies suggest a reason for the difference of reactivity between methoxyacetone and methoxyacetaldehyde. As shown by the enthalpy diagram shown in Figure 12 (based on the data in Table 1), the ketone enjoys better stabilization upon complex formation than the aldehyde owing to higher basicity of the ketone carbonyl oxygen. On the other hand, the enthalpy difference for the TSs relative to that of reactants is smaller. This difference of the enthalpy profile makes the activation enthalpy from the complex to the TS higher for the ketone, making the ketone less reactive than the aldehyde.

Finally, while the kinetic importance of a metal/carbonyl π-complex has been suggested occasionally in (chelation-controlled) carbonyl addition reactions,[34] the IRC analysis in Figures 3 and 8 did not support such a speculation. This agrees well with the recent experimental studies for a β-chelate and a simple carbonyl compound,[45] which indicated that π-complexation is not a kinetically important event. This analysis also extends to α-chelation-controlled additions as revealed by the snapshots in Figure 3, where no π-complex was found as a minimum. It can be readily perceived from the formula below that the relative orientations of the π-orbital and the neighboring

(41) As shown in Schemes 1 and 2, the chelate formation may proceed via monocoordination first to the basic ethereal oxygen (see footnote 39), followed by rapid intramolecular second ligation. In such an event, the kinetics of the chelate formation may be insensitive to the electronic environment of the carbonyl group. On the other hand, the thermodynamic stability of the chelate is expected to be subject to *p*-substituent effects (this time, however, with a negative ϱ^+ value (−1.35, see ref 38)). Unfortunately, the current level of sophistication of theoretical methods does not allow explicit treatment of solvent molecules in such systems.

(42) It is known experimentally[43] and theoretically[44] that etheral oxygens are more basic than carbonyl oxygens. We confirmed this for the Me_2Mg-(H_2O) case (see below) at the MP2(FC)/6-31+G*//HF/6-31G* level. In these calculations, coordination of $Me_2Mg(H_2O)$ to Me_2O is preferred to that to acetone by a few kcal/mol, which is in good agreement with experimental values (ref 43b).



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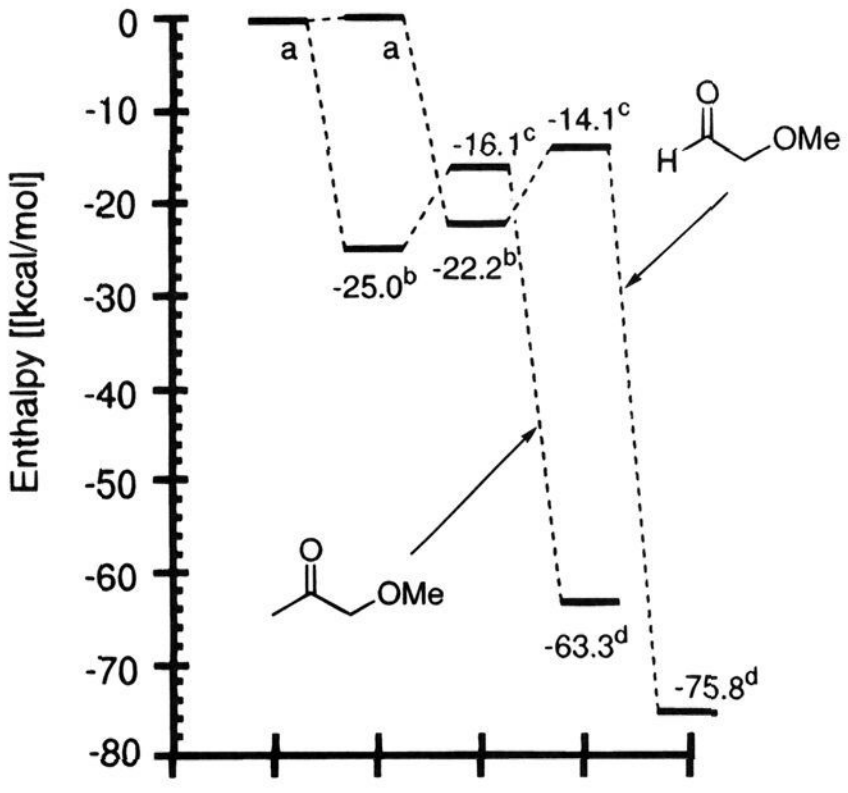
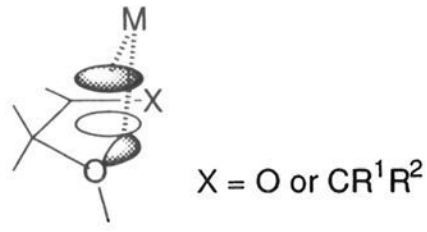


[a]Reactants. [b]αCPLX1 or αCPLX2. [c]αTS1 or αTS2. [d]αPRD1 or αPRD2.

Figure 12. Enthalpy profiles in the Me_2Mg addition to methoxyacetone and methoxyacetaldehyde at the MP2(FC)/6-31+G*//HF/6-31G* with the ZPE correction by a factor of 0.91. The enthalpies (0 K) are relative to the reactants.

nonbonding orbital of the α-alkoxy group are not at all suitable for bidentate coordination to a single metallic center. The π-complexation in α-chelation is expected to be also unimportant in an olefinic equivalent, namely, an organometallic addition to an allylic alcohol derivatives (CR^1R^2). There has been reported some experimental support of this conjecture.[46]



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Supplementary Material Available: Tables of Cartesian coordinates for the structures of representative stationary points and a table of energies and structural parameters for intermediates obtained by the SCRF calculations of some reactions (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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