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An ab initio study of the enolboration of 3-pentanone mediated by boron monochlorides L_2BCl

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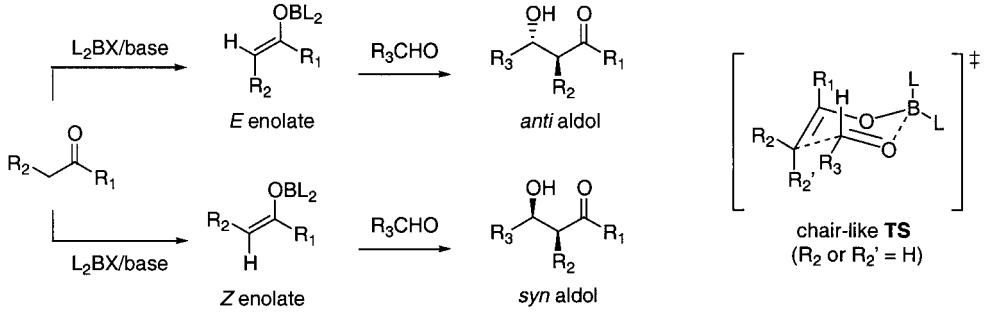
Abstract—Using ab initio methods at the HF/6-31G** level, we have studied the mechanism of the enolboration of 3-pentanone mediated by boron monochlorides L_2BCl (L=H, methyl and isopropyl) and trimethyl amine. The size of the L group has been found to have a decisive influence on the configuration (*E* or *Z*) of the formed boron enolate. Thus, whereas our calculations predict that dimethylboron chloride yields the *Z* enolate with high stereoselectivity, diisopropylboron chloride is found to yield predominantly the *E* enolate. The difference in behavior is due mainly to steric features related to the conformational bias of the respective ketone–boron chloride complexes formed reversibly in the first step of the process. These findings, which are in good agreement with experimental results in aldol reactions with L_2BCl reagents, provide a compelling theoretical explanation for the stereochemical outcome of such reactions.

The aldol reaction[1] is a powerful and general method for the stereocontrolled construction of carbon–carbon bonds. The influence of the relevant parameters of the reaction, i.e. type of heteroelement counterion, configuration and substitution pattern of the enolate, base used, solvent, additives, etc. has been studied experimentally in great detail. Among the many enolate types investigated, boron enolates have proved to be particularly versatile because of their good reactivity and excellent stereoselectivity.[2] The latter has been accounted for by assuming that the aldol addition step takes place through a cyclic, chair-like transition state[3,4] in which the boron atom is bound to the enolate and aldehyde oxygen atoms (Scheme 1). The comparatively short boron–oxygen bonds give rise to a compact atom arrangement which maximizes the internal induction and hence the stereoselectivity. In agreement with this mechanistic view, *Z* enol borinates give rise to *syn* aldols while *E* enolborinates are precursors of *anti* aldols.[2] Therefore, controlling the *E*/*Z* configuration of the enolate is of paramount importance.

Several methodologies have been developed to achieve this stereochemical control. For instance, the stereoselective formation of *syn* aldols via *Z* enolates can be performed with boron triflate reagents L_2BOTf (L=alkyl group) in the presence of a tertiary amine.[5] H.C. Brown and his group carried out further investigations in this field using reagents of general formula L_2BX (X=Cl, Br, I). They found that, for X=Cl, the size of the alkyl ligand had a decisive influence on the stereochemical outcome of the



Scheme 1. Enolization of ketones with L_2BX reagents and aldolization transition state.

Keywords: ab initio calculations; boron enolates; dialkyl boron monochloride; aldol reaction; stereoselectivity.
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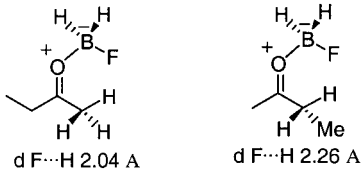


Scheme 2. F···H distances in two isomeric complexes of butanone with BF_3.

aldol reaction.[6] Thus, reagents L_2BCl with a relatively small L group (e.g. *n*-butyl or the conformationally rigid 9-BBN system) generated mainly *syn* aldols via the *Z* enolate. In contrast, an increase in the bulk of the L groups caused an increase in the percentage of *anti* aldols, presumably formed via *E* enolates. It turned out that, for L=Chx (cyclohexyl), *anti* aldols were formed with high stereoselectivity. Dicyclohexylboron chloride, Chx_2BCl, has in fact been widely used by several researchers for the stereoselective synthesis of *anti* aldols.[2,7]

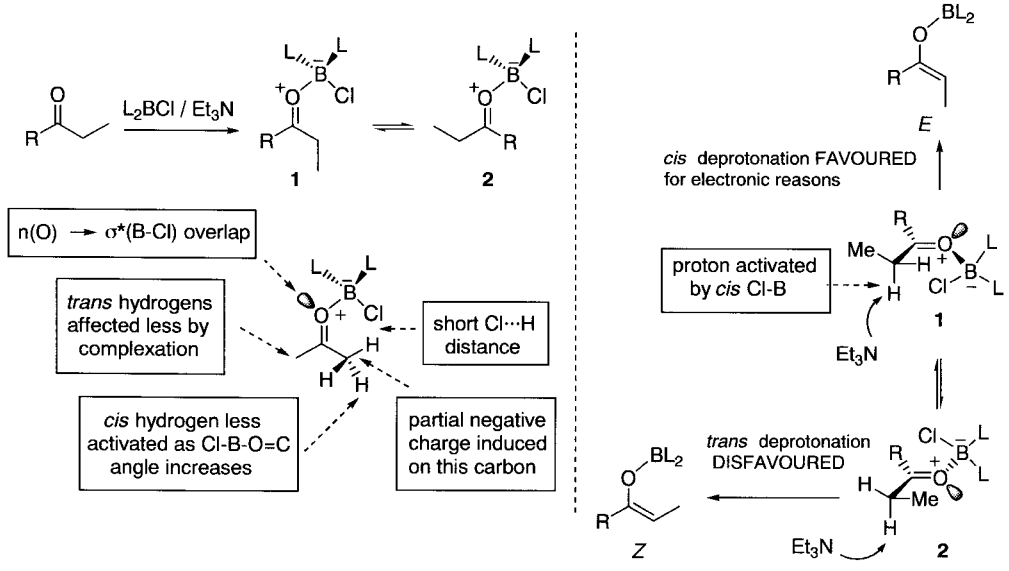
In order to explain the predominant formation of *E* enolates using Chx_2BCl, Paterson and Goodman proposed a mechanistic model based on a theoretical study of the complexation of aldehydes and ketones with BH_2F. The most stable conformation was found to be that in which the boron–fluorine bond eclipses the carbonyl group (see Scheme 2 for the two butanone–BH_2F complexes).[8] This preference was attributed to a stabilizing anomeric effect[9] involving the uncomplexed lone electron pair on the oxygen atom and the σ^*_{B-F} orbital. This type of stabilization, which reaches its maximum value when the C=O–B–F dihedral angle is 0°, had been previously observed in theoretical studies on aldehyde–BF_3 complexes[10] and was confirmed by Goodman in a later study.[11] Furthermore, Goodman postulated the existence of an attractive interaction between the fluorine and the α-H atoms, which leads to a shortened F···H distance. In the case of butanone (Scheme 2), these distances were calculated to be 2.04 and 2.26 Å, much less than the sum of the van del Waals radii of H and F (note also that the F···H distance is shorter for the complex where the boron is proximal to the methyl group). The combination of both electronic effects was postulated as an explanation for the higher stability of the eclipsed conformation.[8a]

Taking all this into consideration, Paterson and Goodman proposed that in the complexation step previous to enolate formation with L_2BCl, the chlorine atom tries to situate itself in an eclipsed orientation with respect to the carbonyl group, i.e. the dihedral C=O–B–Cl angle tends to be as small as possible.[8b] Furthermore, if two α positions are available for enolization, the chlorine atom should be located proximal to the carbon atom which can best support the partial negative charge induced on it as a consequence of the short H···Cl distance. Since the ability to support a negative charge is related to the degree of substitution in the order Me>Et>*i*Pr≅*t*-Bu, the complexation process in the case of ethyl ketones should predominantly yield complex **1** rather than **2** (Scheme 3; R is assumed to be bulkier than ethyl). Along these lines, the induced partial negative charge should activate the hydrogen atom with the C–H bond parallel to the carbonyl π orbital towards deprotonation. The aforementioned authors therefore concluded that *cis* deprotonation of **1** (i.e. proximal to the boron atom) to yield the *E* enolate should be electronically favored over *trans* deprotonation of **2** to the *Z* enolate.

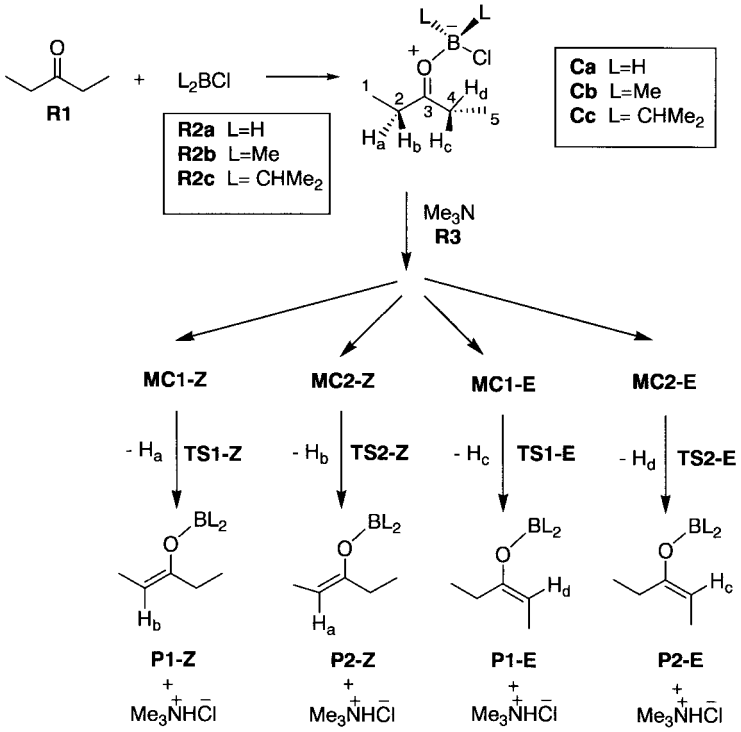
In the present paper, we present the results of our ab initio studies on the mechanism of the enolboration of 3-pentanone mediated by three different dialkylboron monochlorides L_2BCl (L=H, Me, $CHMe_2$). Our purpose was to gain a deeper understanding of the influence of steric and electronic features on the configuration of the enol borinate formed.

1. Methods and models

The geometrical optimizations of stationary points along the potential energy surface (PES) were made at the HF level with the 6-31G** basis set.[12–16] All calculations were carried out with the GAUSSIAN 98 suite of programs.[17] Berny analytical



Scheme 3. Stereoelectronic control of the enolboration process according to Paterson and Goodman.



Scheme 4. Pathways for the enolboration process mediated by L_2BCl reagents of variable steric size.

gradient optimization routines[18] were used for optimization. An eigenvalue following algorithm[19] was used for locating the transition structures (TSs). The stationary points were characterized by frequency calculations in order to verify that minima and TSs have zero and one imaginary frequency. The nature of each TS was verified by using the second-order González–Schlegel integration method[20] to trace the intrinsic reaction coordinate (IRC)[21] from the TS to the two lower energy structures it connects. Energy values were computed at 0°C, since this is a common temperature for conducting these enolization experiments.[2] The ZPE and the corresponding thermal corrections have been taken into account. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[22] Optimized geometries of all the structures are available from the authors.

In order to avoid excessively lengthy calculations, we have worked with simplified models of a somewhat reduced molecular size. For instance, the L group was taken to be H or Me to represent small alkyl groups. For a bulky alkyl group such as cyclohexyl, the isopropyl group (Me_2CH, *i*Pr) was considered a suitable surrogate as it has comparable rotational features and gives rise to a similar steric crowding in the vicinity of the boron atom (the isopropyl group would not be a good model for the apparently more similar 9-BBN moiety, however, as the latter is conformationally much more rigid and has thus a lower effective bulk). As regards the base, the commonly used tertiary amines Et_3N or $EtNMe_2$ were replaced by Me_3N.

2. Results and discussion

The enolboration process comprises two consecutive steps, the first one being the reversible formation of a complex between the ketone and the Lewis acid L_2BCl (R=H, Me, $CHMe_2$). The second and rate-limiting step corresponds to the abstraction of one of the hydrogen atoms at C-α to give the final enol borinate (Scheme 4).

An exploration of the PESs for the enolborations enabled us to find the following stationary points: the reagents **R** and complexes **C** (first step), the molecular complexes **MC**, the transition structures of the deprotonation processes **TS**, and the final enolates **P** (second step). Scheme 4 shows the stationary points along the corresponding reaction channels while Table 1 gives their total and relative energies. Fig. 1 shows the geometries of the ketone–boron complexes **Ca** ($ClBH_2$), **Cb** ($ClBMe_2$) and **Cc** ($ClBiPr_2$), and Table 2 presents their main geometrical parameters. For **Cc**, the internal rotations of the isopropyl groups were taken into account, with only the least energetic conformation being used for the calculations.

The formation of complexes **Ca–c**, which are more stable than the starting molecules (see Table 1), *takes place without a measurable activation barrier*. As shown in Fig. 1, the boron atom in L_2BCl coordinates with the carbonyl oxygen atom, and the boron–chlorine bond tends to eclipse the C=O bond. An increase in the C=O and B–Cl bond lengths, as compared to the analogous bond lengths in the reactants, is observed as a consequence of the O···B interaction. This is in agreement with the postulated anomeric effect (interaction between the lone pair on the oxygen and the antibonding σ^*_{B-Cl} orbital). However, even though the anomeric effect reaches its maximum for a dihedral C=O–B–Cl angle with a value of zero, previous studies on the preferred geometries of ethyl ketone complexes have shown that this angle differs markedly from 0°. This is probably

Table 1. HF/6-31G** total energies (au) and relative energies (kcal/mol, in parentheses, relative to the sum **C**+**R3**), including zero-point energies and thermal corrections, for the stationary points of the reaction between 3-pentanone (**R1**), L_2BCl (**R2**) and Me_3N (**R3**)

	R2a	R2b	R2c
C	−755.228127	−833.265382	−989.274272
MC1-Z	−928.379946 (−1.2)	−1006.416538 (−0.8)	−1162.424788 (−0.4)
MC2-Z	−928.380810 (−1.8)	−1006.416436 (−0.7)	−1162.425809 (−1.0)
MC1-E	−928.379792 (−1.1)	−1006.416479 (−0.8)	−1162.423734 (−0.3)
TS1-Z	−928.338510 (+24.8)	−1006.376710 (+24.2)	−1162.376494 (+29.9)
TS2-Z	−928.337009 (+25.7)	−1006.369782 (+28.5)	−1162.376642 (+29.8)
TS1-E	−928.338453 (+24.8)	−1006.367440 (+30.0)	−1162.381619 (+26.4)
P1-Z	−928.384504 (−4.1)	−1006.430775 (−9.7)	−1162.434515 (−6.5)
P2-Z	−928.383179 (−3.2)	−1006.430865 (−9.8)	−1162.431155 (−4.4)
P1-E	−928.385121 (−4.5)	−1006.430583 (−9.6)	−1162.432250 (−5.1)

Total energies (hartrees) of the reactants are: **R1**=−269.892389; **R2a**=−485.328234; **R2b**=−563.370093; **R2c**=−719.375203; **R3**=−173.149874.

due to the existence of attractive interactions between the complexed boron Lewis acid and the α or β protons.[11] In fact, the dihedral C═O–B–Cl angles in complexes **Ca**–**c** have significant values which, interestingly, clearly decrease when progressively bulkier L groups are used (see Table 2). It is also worth mentioning that attractive interactions[8,11] between the chlorine and the hydrogen atoms of one of the ethyl groups of 3-pentanone are now predicted to exist for all three complexes. In fact, an increase of the Cl···Ha interaction is observed as the value of the C═O–B–Cl dihedral angle decreases.[23] Thus, while this distance is 3.12 Å for complex **Ca**, it is about 2.82 Å for complex **Cb** and 2.72 Å for **Cc**. In the latter two cases, the distance is thus less than the sum of the van der Waals radii of H and Cl. As a result of these conformational preferences, small boron ligands L (R=H, Me) tend to arrange themselves onto one of the two faces of the carbonyl group (face A, Fig. 1). Therefore, steric approach of the base from the other face (B) becomes easier. In contrast, bulky L groups ($CHMe_2$) point towards either carbonyl face (see **Cc** in Fig. 1); thus, the steric hindrance to the approach of the base is similar from both directions.

As shown by the energy barrier values (Table 1), the rate-limiting step is the abstraction of one of the hydrogen atoms at C-α of the ketone complex by the nitrogen atom of the base to yield the enolate via the corresponding TS. Four reaction channels are available for each complex (Scheme 4). However, a preliminary HF/6-31G study of the PESs ruled out the reaction path corresponding to the abstraction of proton H_d through transition structure **TS2-E**. This process involves a very high energy barrier due to the steric crowding exerted by the chlorine atom and the boron ligands towards the approach of the base. In consequence, only the remaining three channels (along **TS1-Z**, **TS2-Z** and **TS1-E**) were further investigated.

The **MC**s and **TS**s of the various deprotonation processes are shown in Figs. 2–4. For **Ca** (Fig. 2, ketone complex with

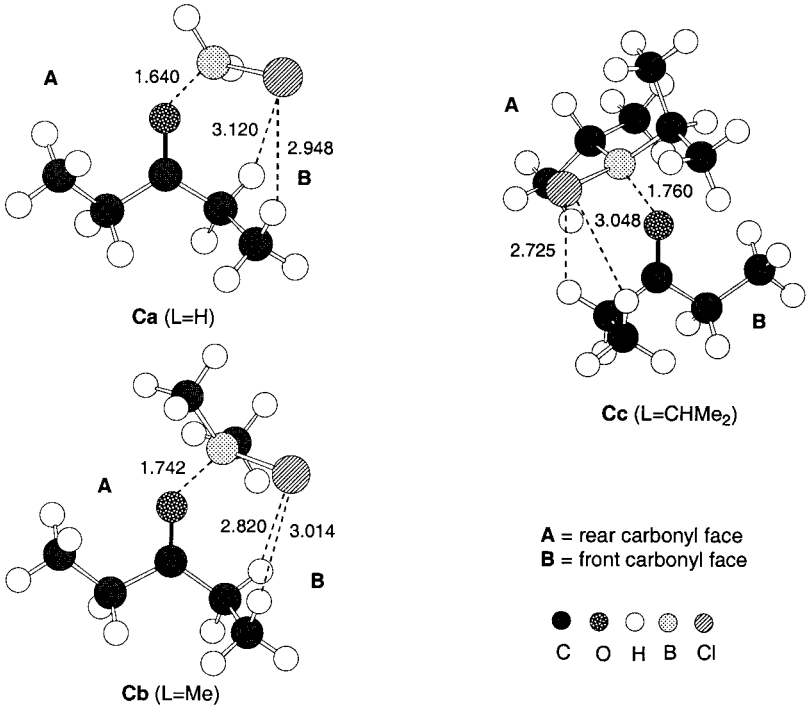


Figure 1. HF/6-31G** optimized geometries of complexes **Ca**, **Cb** and**Cc**. Bond lengths are given in Å.

Table 2. HF/6-31G** geometric parameters (lengths in Å, angles in deg) for complexes **C**

	Ca	Cb	Cc
O–B	1.640	1.742	1.760
B–Cl	1.949	1.890	1.892
C=O	1.242	1.213	1.212
Cl···H_α	3.120	2.820	2.725
Cl···H_β	2.948	3.014	3.048
C=O–B–Cl	−69.0	−50.3	22.9

$ClBH_2$), all three energy barriers are found in a very narrow range (about 1.5 kcal/mol, see Table 1). We thus concluded that no significant stereochemical discrimination is to be expected for this enolization reagent.[24] This lack of stereoselectivity is related to the small steric hindrance exerted by the hydrogen atoms bound to the boron. This makes approach of the base to both carbonyl faces more or less equally feasible.

The situation is different in the deprotonation of **Cb** (Fig. 3, ketone complex with $ClBMe_2$). The energy barrier for **TS1-Z** (25.0 kcal/mol) is much lower than those for **TS2-Z** (29.3 kcal/mol) or **TS1-E** (30.8 kcal). These high-energy differences indicate that only transition structure **TS1-Z** is meaningful in this case. The approach of the base from face B is much less hindered than from face A, where the boron-bounded methyl groups are located. In consequence, formation of the *Z* enolate is predicted to be much favored over formation of the *E* enolate.

With the bulky isopropyl groups on the boron atom of **Cc** (Fig. 4, ketone complex with $ClBiPr_2$), a reversal in the energy barrier values is observed. Transition structure **TS1-E** leading to the *E* enolate now exhibits the lowest energy barrier (26.7 kcal/mol), whereas those leading to *Z* enolates (**TS1-Z** and **TS2-Z**) display appreciably higher values (>30 kcal/mol). Faces A and B now exhibit a similar steric hindrance, which gives rise to similar energy barriers

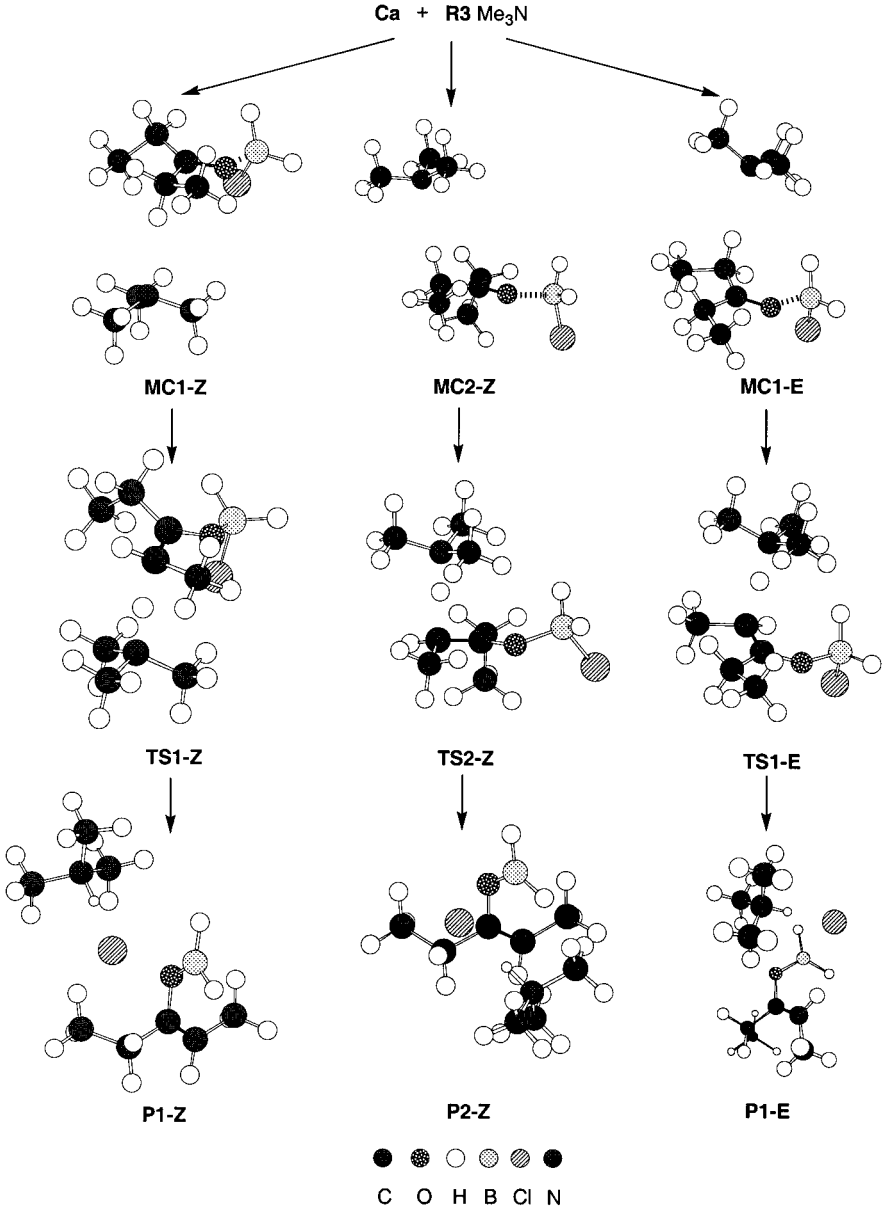


Figure 2. Molecular complexes, **TS**s and products corresponding to the deprotonation reaction between complex **Ca** (R=H) and trimethylamine **R3**.

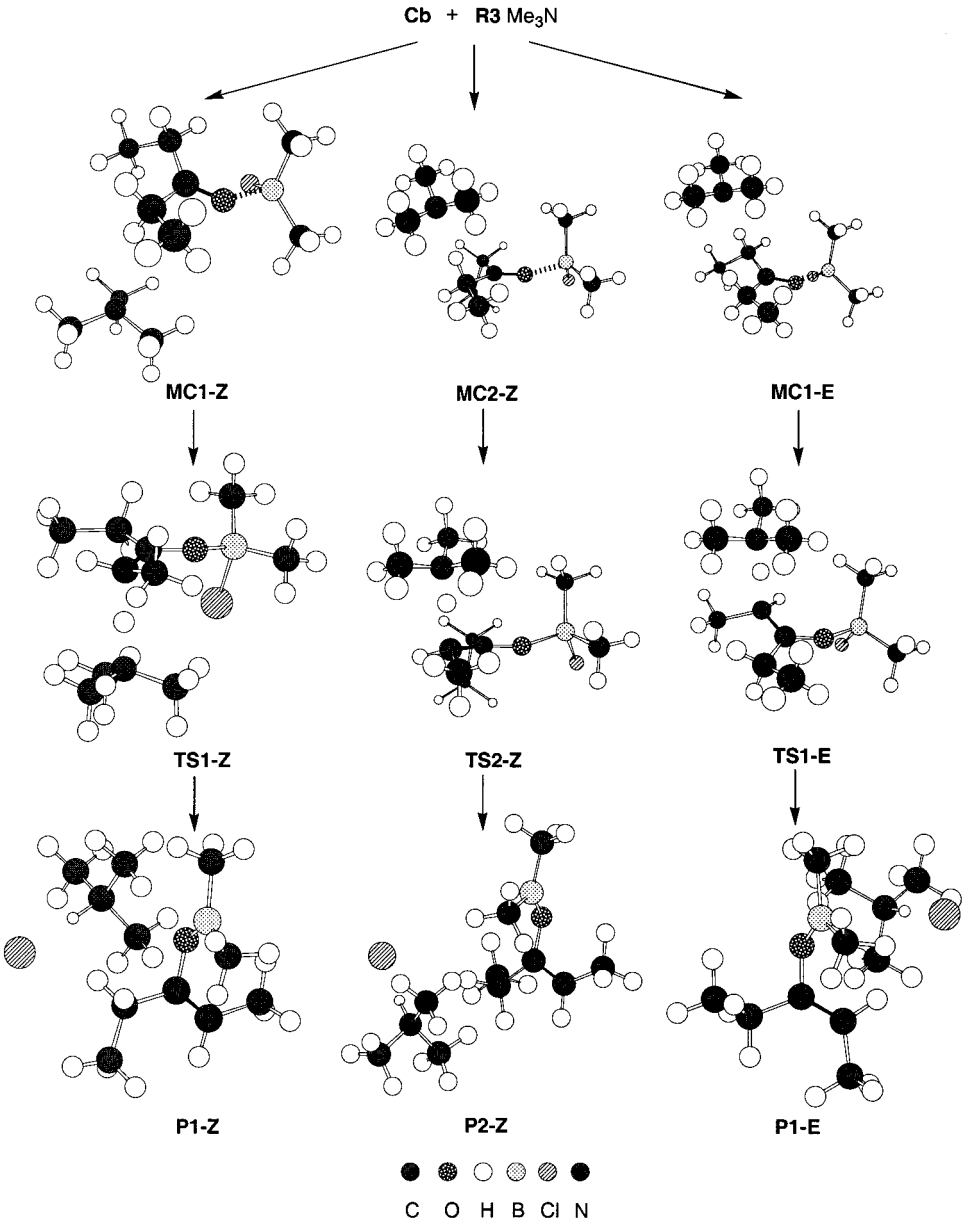


Figure 3. Molecular complexes, **TS**s and products corresponding to the deprotonation reaction between complex **Cb** (R=Me) and trimethylamine **R3**.

for transition structures **TS1-Z** and **TS2-Z**. However, due to the particular conformational bias of complex **Cc**, the approach of the base through transition structure **TS1-E** has no excessive steric crowding to overcome and is now the preferred pathway.

These energy results indicate that the formation of *Z* enolates with L_2BCl is favored for small alkyl L groups (L≠H). This is in agreement with experimental data reported by H.C. Brown and his group (>97% of *Z* enolate for L=*n*Bu).[6] On the other hand, the formation of the *E* enolate is favored when L is bulky (R=$CHMe_2$), a fact which also fits nicely with experimental evidence (95% of *E* enolate for L=Chx).[6]

The selected geometrical parameters for the **TS**s are given in Table 3. In all cases, the length of the breaking C_2–H or C_4–H bond is about 1.47–1.56 Å while that of the forming N–H bond is about 1.20–1.29 Å. When the base approaches from either carbonyl face, the progressively increasing steric crowding causes an increase in the length of the breaking C–H bond and a decrease in the length of the forming N–H bond.[25]

The imaginary frequency values for the **TS**s are between 1383i and 1753i cm^{-1}. These high values indicate that these processes are associated with light atom motions.

A further result of our studies deserves mention. The results obtained for the calculation of either the Mulliken or natural charges[22] at C_2 and C_4 in complexes **Cb** and **Cc** (deprotonation at these two carbon atoms leads to the *Z* and *E* enolates, respectively, see Scheme 4) do not corroborate the previous assertion[8] that an increase of the size of the boron-bonded ligands L, which is associated with a narrowing of the C=O–B–Cl dihedral angle, would also give rise to an

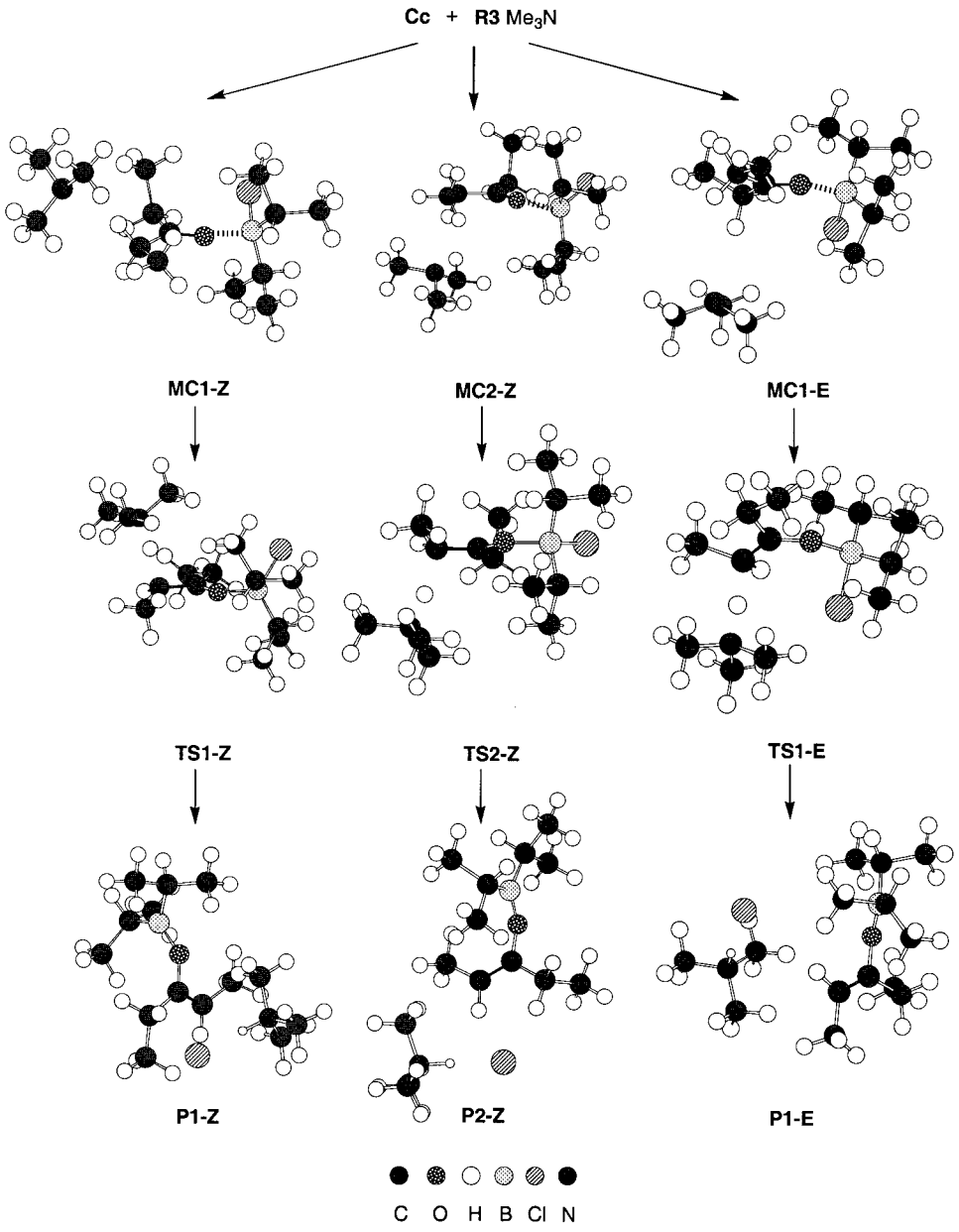


Figure 4. Molecular complexes, **TS**s and products corresponding to the deprotonation reaction between complex **Cc** (R=$CHMe_2$) and trimethylamine **R3**.

increase in the partial negative charge supported by C_4. In fact, the computed partial negative charges at these two carbon atoms are essentially the same (about −0.55) for small (L=Me) and for bulky ligands (L=$CHMe_2$). Thus, even if electronic factors might not be completely excluded as regards the control of the stereochemical outcome of the enolization, the steric interactions between the boron ligands L in the ketone–boron chloride complexes and the deprotonating base play the dominant role in controlling the relative values of the energy barriers for deprotonation.

Table 3. HF/6-31G** geometric parameters (lengths in Å) for the transition structures corresponding to the reaction between complexes **C** and Me_3N

	Ca (L=H)			**Cb** (L=Me)			**Cc** (L=$CHMe_2$)		
	TS1-Z	**TS2-Z**	**TS1-E**	**TS1-Z**	**TS2-Z**	**TS1-E**	**TS1-Z**	**TS2-Z**	**TS1-E**
C_2–H	1.472	1.496		1.465	1.532		1.558	1.527	
C_4–H			1.499			1.537			1.481
N–H	1.283	1.259	1.249	1.288	1.223	1.221	1.205	1.235	1.261
C_2–C_3	1.409	1.402		1.406	1.405		1.408	1.407	
C_3–C_4			1.403			1.401			1.406
C=O	1.264	1.267	1.264	1.265	1.263	1.263	1.257	1.261	1.261
O–B	1.523	1.536	1.528	1.547	1.561	1.563	1.566	1.563	1.554
B–Cl	1.954	1.904	1.911	2.014	1.949	1.951	1.961	1.973	2.002

3. Conclusions

We have performed an ab initio HF/6-31G** study of the mechanism of enolboration of 3-pentanone with various reagents of general formula L_2BCl in the presence of the tertiary amine Me_3N as the deprotonating base. The PESs of all reactions have been explored, and all stationary points have been located and characterized. These results allow us to propose an explanation for the behavior of ketones during enolboration with dialkylboron chlorides L_2BCl and tertiary amines. We have shown that, with comparatively small ligands L other than H,[24] deprotonation at C_2 (see Scheme 4 for 3-pentanone numbering) is markedly favored and leads to the formation of the *Z* enolate. As the size of the boron ligands increases, the steric crowding at C_4 diminishes because of the conformational change experienced by the ketone–L_2BCl complex. At the same time, the hydrogen atoms at C_2 are now subjected to increased steric crowding. As a result, the reaction pathway which yields the *E* enolate via deprotonation at C_4 is now the energetically favored one.

We therefore conclude that the preferred conformation adopted by the ketone–boron chloride complex in the first step of the process is controlled by both steric and electronic factors. However, the stereoselective formation of either the *E* or the *Z* enolate is controlled mainly by the steric size of the boron ligands, which dictate the preferred direction of approach of the deprotonating base.

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23. Rotation of the dihedral O=C–C_4–C_5 angle also caused breakdown of these hydrogen bonds and a parallel destabilization of the complexes.
24. Monochloroborane $ClBH_2$ has never been experimentally used for enolborations but only for olefin hydroborations (chlorodicyclohexylborane is just prepared in this way from cyclohexene). Most likely, it would react with aldehydes or ketones as a reducing agent, rather than as an enolboration reagent.
25. With our calculations, neither additional TSs nor intermediates were detected after the deprotonation TS itself. The former would be related to the B–Cl bond breaking process and the formation of $Me_3NH^+Cl^-$. This does not mean that this step has no reaction barrier but the detection of such TSs involving charged species would demand a simulation of solvent effects. This is, however, very difficult to put into practice with the complicated model molecules used in this study. Furthermore, it would not essentially change the conclusions obtained in the present work.