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Graphical Abstract

Origin of stereocontrol in the Matteson reaction: importance of attractive electrostatic interactions

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Origin of stereocontrol in the Matteson reaction: importance of attractive electrostatic interactions

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This paper is dedicated to the memory of Professor Jonathan Williams, one of the most creative chemists of his generation, and just a wonderful human being.

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ABSTRACT

The Matteson reaction involves treatment of a chiral boronic ester with (dichloromethyl)lithium in the presence of ZnCl_2 which leads to an α -chloroboronic ester with very high diastereoselectivity. The origin of selectivity has now been investigated using modern computational analysis. The explanation for selectivity was previously based on steric repulsions in the transition state but the new study has identified a novel $\text{Cl}\cdots\text{H}$ electrostatic interaction which is only present in one of the two possible transition states. It is believed that this attractive interaction is critical in controlling the stereochemical outcome of the process. Furthermore, this more complete model can now be used to rationalize the disparity in reactivity (C-migration vs O-migration) occasionally observed in diastereomeric boron ate complexes, and why substrates devoid of the key hydrogen bond react with low stereocontrol.

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1. Introduction

Organoboronic esters are versatile building blocks in modern synthesis since the boron moiety can be transformed into a variety of functional groups.^{1,2} Many of these transformations are initiated by nucleophilic addition to the electrophilic boron atom (ate complex formation), followed by 1,2-migration.³ The migration proceeds with retention of stereochemistry at the migration origin and inversion at the migration terminus, making the transformation stereospecific.⁴ It is this stereospecificity that has made boronic esters such valuable entities in asymmetric synthesis.^{4,5} Within this class of transformations, the Matteson reaction is the archetypal example and best known.^{6–14} In the Matteson reaction a chiral auxiliary is embedded in the diol moiety of the boronic ester substrate and subsequent treatment with (dichloromethyl)lithium in the presence of ZnCl_2 leads to an α -chloroboronic ester with very high diastereoselectivity (e.g. in Scheme 1A for $\text{R} = i\text{Pr}$ dr = 97:3).¹⁴ Subsequent treatment with a Grignard reagent gives the homologated boronic ester. Although pinanediol was originally used as the auxiliary, it was superseded by C2-symmetric 1,2-dialkylethanediol ($\text{R} =$ isopropyl, cyclohexyl). The overall process involves two 1,2-migrations of alkyl groups from a tetracoordinated boron to an adjacent chlorine-bearing carbon atom. Of the two steps, it is the first step which determines the stereoselectivity of the process since the second step is stereospecific. In the first step there is a choice over which

of the two diastereotopic chlorine atoms aligns anti periplanar to the migrating group.

Scheme 1: Matteson reaction and proposed models to explain the diastereoselectivity observed.

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Different models have been put forward to account for the high diastereoselectivity observed. Corey proposed that initial coordination of ZnCl_2 occurs trans to the bulky R group for steric reasons (Scheme 1B).¹⁵ This leads to two possible transition states for 1,2-migration but **TS₂** was deemed to be more favorable, since **TS₁** suffers from steric repulsion between the two chlorine atoms. An alternative model, proposed by Midland and supported by density functional methods, focused on the alignment of the non-participating chlorine atom relative to the metal (Scheme 1C).¹⁶ In this scenario, two transition states were identified as having the non-participating chlorine anti to the metal (**TS₂** and **TS₃**). Of these, the preferred transition state places the Lewis acid on the less sterically hindered position (anti to the bulky R group), ultimately leading to the same model proposed by Corey.¹⁵ Both models suggested steric reasons for the origin of stereocontrol in the Matteson reaction. We have now reinvestigated the mechanistic basis for the observed diastereoselectivity using a higher level of theory. Herein we report that an attractive hydrogen bonding interaction, in addition to the steric effects noted above, is also likely to contribute to the stereoselectivity observed.¹⁷ This new model also now accounts for some unusual observations of the Matteson reaction that were encountered but could not be explained by the existing models.

2. Results and Discussion

Our investigation began by modelling the Matteson homologation of boronic ester **1** with (dichloromethyl)lithium, in the presence of ZnCl_2 (Scheme 2). Since high stereoselectivity has been reported with ZnCl_2 and not with LiCl ,¹⁸ the lithium cation was not modelled explicitly, in analogy with other related 1,2-migrations.¹⁹ Density functional theory calculations were performed with Gaussian using the M062X/6-311G(d,p) + LanL2DZ level of theory, with a polarisable continuum model of solvation (PCM, THF).²⁰

Scheme 2. Calculated transition states for the Matteson reaction of **1** with LiCHCl_2 .

Based on Corey's model,¹⁵ we placed the Lewis acid trans to the R group of the ester to minimize steric interactions, which then gave rise to two transition states which differed by which of the two diastereotopic chlorines was antiperiplanar to the migrating methyl group (**TS₄** and **TS₅**). In both cases (and as observed by

Midland¹⁶) the calculated transition state structures indicated a concerted asynchronous mechanism, with significant elongation of the C–Cl bond (2.55 Å and 2.53 Å, in **TS₄** and **TS₅** respectively) but with only minimal migration of the methyl group. Because of this concerted asynchronous mechanism, chloride abstraction by the Lewis acid renders the migration terminus more cationic-like and the zincate more anionic-like. Indeed, in both transition states the migration terminus is almost trigonal planar (angles sum to ~354°), thus suggesting a partial carbocation character. The polarized nature of the transition state was confirmed by Natural Bond Orbital (NBO) analysis which revealed partial positive charges on the chlorine atom (due to mesomeric stabilization) and on the hydrogen atom directly attached to the migration terminus. Furthermore, a partial negative charge was calculated on both the halogen atoms of ZnCl_2 due to the chloride abstraction. These charges result in an important electrostatic interaction between the partially negatively charged chloride of ZnCl_2 and the partially positively charged hydrogen atom. However, this Cl··H interaction, not considered in previous models,^{15,16} is only available in **TS₅**, the lower energy transition state, and not present in **TS₄**. Indeed, the Cl··H bond distance in **TS₅** (2.80 Å) is shorter than the sum of their relative Van Der Waals radii (1.75 Å + 1.10 Å).²¹ Furthermore, upon comparing **TS₄** with **TS₅** a formal O–Zn bond rotation is observed which places one chloride of ZnCl_2 closer in proximity to the partially positive hydrogen atom. The attractive hydrogen bonding interaction present in **TS₅**, together with the repulsive steric/electronic interactions between the chlorine atoms in **TS₄**,^{15,16} results in a very significant difference in energy between **TS₄** and **TS₅** ($\Delta G = 7.4$ kcal/mol), leading to the high stereocontrol observed.

To explore the importance of the attractive hydrogen bonding interaction, we performed calculations on the Matteson reaction where the key hydrogen atom was replaced by a methyl group. Thus, we studied the (known) reaction of **1** with (dichloroethyl)lithium, in the presence of ZnCl_2 (Scheme 3A). Interestingly, replacing the interacting hydrogen with a methyl group, transition state **TS₆** appears geometrically similar to **TS₇** since they can almost be superimposed by simply swapping the Me with the Cl atom. This can be rationalized as a chlorine atom is isosteric with a methyl group²² and because there is no attractive Cl··H interaction. However, the difference in energy was now substantially smaller: $\Delta G = 2.2$ kcal/mol for **TS₆/TS₇** vs 7.4 kcal/mol for **TS₄/TS₅**. Indeed, while (dichloromethyl)lithium is the reagent of choice in the Matteson reaction, employing (dichloroethyl)lithium results in variable levels of selectivity and the sense of asymmetric induction is also unpredictable, making this reaction of limited synthetic utility.²³ Typical literature examples for this type of reaction are shown in Scheme 3B, highlighting the unpredictability of the reaction. Note, in this case Matteson used the pinanediol as the auxiliary; there are no examples with the C2-symmetric diol ligands.²³ The limited success in the synthesis of the corresponding tertiary boronic esters can therefore be attributed, at least in part, to the lack of the attractive Cl··H interaction favoring one transition state over the other.

The inclusion of this electrostatic interaction not only provides new insight into the origin of stereocontrol, but it also supports experimental evidence that is difficult to rationalize based on simply steric effects. For instance, it has been reported that the α -chloro-boronic ester **2** reacts with MeMgBr to furnish the desired C-migration product **3** whereas the diastereoisomer **4** gave predominantly the O-migration product **5** (Scheme 4).¹³ The differing behavior of the two diastereomers can be rationalized using the new model.

Scheme 3. A) Calculated transition states for the Matteson reaction of **1** with $\text{LiC}(\text{Me})\text{Cl}_2$. B) Examples of Matteson reactions with $\text{LiC}(\text{Me})\text{Cl}_2$ showing very different levels of diastereoselectivity.²³

Scheme 4. Different fate of diastereomeric α -chloro-boronic esters **2** and **4** during homologation.¹⁴

For diastereoisomer **2**, the transition state **TS_C** for 1,2-migration, in which the carbon substituent of the migrating group

aligns antiperiplanar to the chloride leaving group, enjoys chelation of the metal anti to the *i*Pr group, binding of the leaving group to the metal and the stabilising interaction between the halide and the C–H bond. However, in **TS_C** for 1,2-migration of diastereomer **4**, where the migrating carbon group aligns antiperiplanar to the chloride leaving group, the stabilising interaction between the halide and the C–H bond is lost. In order to regain this stabilising interaction, rotation around the C–B bond occurs, resulting in the alignment of the chloride antiperiplanar to the oxygen, which therefore migrates (**TS_O**). It is believed that contra-thermodynamic oxygen migration occurs instead because of the stabilising interaction between the halide and the C–H bond leading to borinic ester **5**. This rationale was supported by further computational analysis. Using the diastereomeric α -chloro-boronic esters **6** and **7** as model substrates in the reaction with methylmagnesium bromide, the transition states for the C-migration and the O-migration were calculated (Scheme 5). For consistency with the experimental conditions employed, MgBr_2 was used as Lewis acid promoter.

Scheme 5. Calculated transition states for the C-migration and O-migration for the α -chloro-boronic esters **6** and **7**.

It was found that for substrate **6** methyl migration was preferred over O-migration by 4.2 kcal/mol. However, for the other diastereoisomer **7** the situation is reversed, with the methyl migration being higher in energy by 1.5 kcal/mol, thus O-migration can be expected, which is in agreement with the experimental results.¹⁴ The different outcomes can be rationalised by considering the stabilizing $\text{Br}\cdots\text{H}$ interaction. For substrate **6**, the C-migration transition state **TS₈**, in which the methyl migrating group aligns antiperiplanar to the chloride leaving group, benefits from coordination of the magnesium anti to the methyl substituent of the diol backbone, binding of the leaving group to magnesium and the stabilising $\text{Br}\cdots\text{H}$ interaction. However, this $\text{Br}\cdots\text{H}$ interaction is not available for the diastereomer **7**. In order to maintain the stabilising $\text{Br}\cdots\text{H}$ interaction, one of the oxygens of the boronic ester has to align antiperiplanar to the leaving group, thus favouring O-migration as observed in **TS₁₁**. The same trend was observed replacing MgBr_2 with ZnCl_2 , thus extending the validity of the model to other Lewis acids.

This analysis also accounts for the diastereomeric enrichment in the second step of the Matteson reaction shown in Scheme 1A. The major diastereoisomer undergoes C-migration, whereas the minor diastereoisomer undergoes O-migration, leading to a different product, thereby enriching the mixture further in favor of the major isomer.

3. Conclusion

In the Matteson reaction, a modern computational analysis of the favoured transition state has revealed a key Cl⋯H electrostatic interaction between one chlorine atom of ZnCl₂ and the hydrogen atom of the (dichloromethyl)lithium moiety. This interaction is particularly favorable in the concerted asynchronous transition state since as the reaction proceeds the chlorides of ZnCl₂ become more negative and the hydrogen becomes more positive. Such an interaction is analogous to the well-established formyl C–H hydrogen bond to electronegative elements popularized by Corey.²⁴ The intermediacy of the Cl⋯H electrostatic interaction helps to rationalize why diastereomeric ate complexes behave differently (C-migration vs O-migration) under identical reaction conditions and why substrates devoid of the key hydrogen atom involved in such interactions lead to low and unpredictable selectivity.²³ It is likely that this more complete model will also account for other hitherto inexplicable outcomes of the otherwise reliable Matteson reaction.

4. Experimental section

Calculations were performed using the Gaussian09 suite of programmes.²⁵ Geometries were optimized with the DFT method using M06–2X functional as implemented in Gaussian, using 6–311G(d,p) as basis set for all the atoms, except for Zn (LanL2DZ). All calculations were carried out using the PCM model of solvation with tetrahydrofuran as the solvent. All geometry optimizations were full, with no restrictions. All stationary points located in the potential energy hypersurface were characterized as minima (no imaginary frequencies) or as transition states (one and only one imaginary frequency) by vibrational analysis. The analysis also provided zero-point vibrational energy corrections and thermal corrections to various thermodynamic properties. Full Cartesian coordinates for the optimised geometries are reported in the Supporting Information.

Conflict of interest

The authors declare no conflict of interest.

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