Pergamon

Tetrahedron 57 (2001) 8125–8128

TETRAHEDRON

Understanding the high diastereofacial discrimination in nucleophilic additions to nitrones: the first ab initio study on the nucleophilic addition reactions of chiral nitrones with Grignard reagents

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Received 10 May 2001; revised 4 July 2001; accepted 26 July 2001

Abstract—The nucleophilic addition of methyl magnesium bromide to a C-(2-pyrrolidinyl) nitrone has been studied by ab initio molecular orbital (HF/6-31+G*) and density functional theory (B3LYP/6-31+G*//HF/6-31+G*) calculations via location of the two diastereomeric transition states. The overall reaction is exothermic and proceeds via precomplexation of the nitrone with the organometallic reagent. The calculations confirm that chelation is the main factor governing the experimentally confirmed preference for the *Si* attack leading to *syn adducts*. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

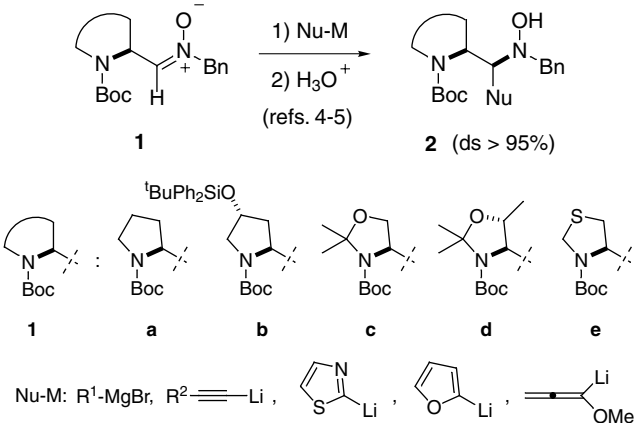
The nucleophilic reactions to C=N bonds in general[1] and to nitrones in particular[2] are subjects of intense current interest. In previous reports from this laboratory,[2a] it has been demonstrated that it is possible to change the stereochemical outcome of the nucleophilic additions to nitrones only by changing the reaction conditions (use of Lewis acids) in the case of α-alkoxy nitrones,[3] or by changing the protecting groups of the starting material in the instance of α-amino nitrones.[4]

The case of α-amino nitrones and, particularly, C-(2-pyrrolidinyl) nitrones **1** is rather interesting due to the total syn stereoselectivity that they show in every nucleophilic addition studied not only by us[5] but also by other groups[6] (Scheme 1).

In these systems, the nucleophile atacks on the Si face of the nitrone group. Since discussion of nucleophilic addition mechanisms to C=X unsaturated systems advanced mostly on the basis of the product stereochemistry, a carbamate directing effect may be ruled out as the source of such preferential attack due to the fact that X-ray structures of the obtained products showed in all cases a strong hydrogen-bond interaction between the hydroxyamino group and the carbamate carbonyl group.[7] Fig. 1 shows seven structures overlayed thus demonstrating the structural similarity between compounds **2**.

The only significant geometry differences between the compounds shown in Fig. 1 are concerned with the five-ring conformation, which does not affect to the intramolecular hydrogen bonding and should reflect only the intrinsic requirements of a pyrrolidine (or 1,3-oxazolidine) skeleton. According to a proposal based on product-like transition state, we invoked[8] a chelate model A (Fig. 2) for the preferential formation of syn compound **2**.

Now, in order to determine the reliability of model A, we



Scheme 1. R^1=Me, Et, Ph, Bn, Vinyl, Allyl; R^2=Me_3Si^-, MeO_2C^-.

Keywords: nitrones; Grignard reagents; nucleophilic additions; theoretical calculations.

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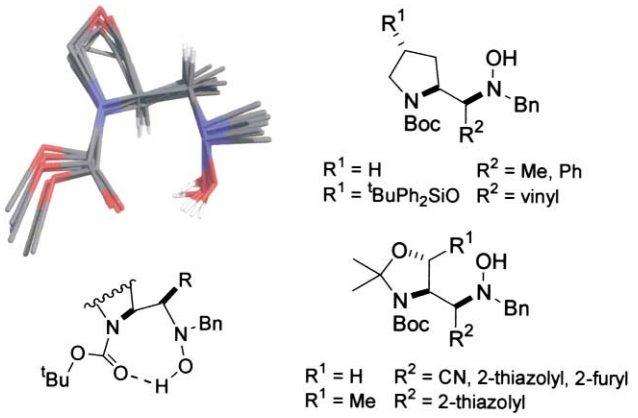


Figure 1. Overlay of X-ray structures corresponding to **2**. Only common atoms are shown for clarity.

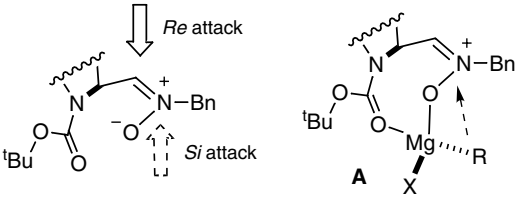
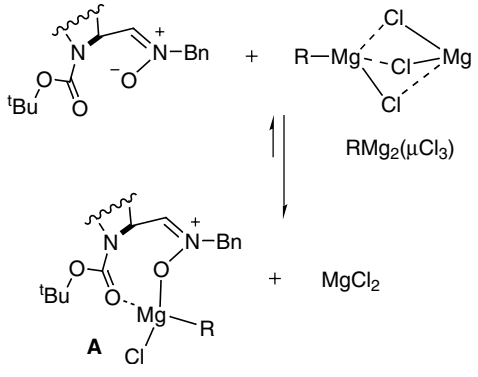


Figure 2. Proposed preferential model (**A**) for nucleophilic additions of Grignard reagents to C-(2-pyrrolidinyl) nitrones.

have undertaken an ab initio study of the nucleophilic addition of methyl magnesium chloride to nitrone **1a**. A preliminary semiempirical study (PM3) confirming this approach has been previously reported.[5]

In this study, we assume a mechanism in which the Grignard reagent acts as a monomer giving rise, in the first stage of the reaction, to a chelate (A), rather similar to the structures shown in Fig. 1. After formation of the complex, the nucleophilic attack occurs by the less hindered face. The assumption of this mechanism is based on (i) the similarity between A and structures shown in Fig. 1, (ii) experimental evidences of the formation of complexes of type A between nitrones **1a**–**d** and $MgBr_2$[9] and (iii) previous reports[10] on the structure of RMgCl in solutions of THF. In this regard, it has been recently reported[10] that $RMg_2(\mu Cl_3)$ is the dominant species in THF solutions of RMgCl. From an experimental point of view, it is reasonable to postulate that $MgCl_2$ can be displaced by the nitrone to form the chelate A (Scheme 2).



Scheme 2.

2. Computational methods

All critical points were fully optimized by analytical gradient method using the GAUSSIAN 98 suite of programs.[11] Due to the size of the molecules under investigation, we restricted our geometry optimizations to the HF/3-21G and HF/6-31+G* levels of theory. The initial structures were guessed from X-ray data and then optimized by using the PM3 semiempirical Hamiltonian.[12] The final structures from the PM3 optimization were used for ab initio calculations at the HF/3-21G level of theory. The obtained full optimized structures at such a level were further used for calculations at HF/6-31+G* level of theory. Stationery points have been located without any geometry restriction and have been characterized through the calculation of the force constants matrix by ensuring that they correspond to minima (representing equilibrium structures) or saddle points (representing transition structures) on the PES; i.e. they have zero or one and only one imaginary frequency, respectively. In the case of transition structures, the corresponding eigenvector involved the expected formation of the new C–C bond, the cleavage of the C–Mg, the shortening of the Mg–O and the lengthening of the C=N bonds. The activation Gibbs energies have been computed at 298.15 K. Optimized geometries of all stationery points are available from the authors in PDB format. Single point calculations at HF/6-31G*//HF/3-21G and B3LYP/6-31+G*//HF/6-31+G* levels of theory have also been carried out in order to assess electron correlation effects.

In this work, MeMgCl has been selected as the Grignard reagent. For representing chiral C-(2-pyrrolidinyl) nitrone **1a**, *tert*-butoxycarbonyl and benzyl groups have been replaced by methoxycarbonyl and methyl groups, respectively. These systems are somewhat simpler than the nitrones used experimentally but likely embody the needed features for the discussion.

3. Results and discussion

We begin our discussion by examining in detail the reaction profile for the nucleophilic addition of MeMgCl to nitrone **1a**. There are two possible nucleophilic attacks: (i) by the Re face, leading to the anti adduct and (ii) by the Si face leading to the syn adduct. The two possible reaction pathways and the stationery points optimized at the highest level (HF/6-31+G*) are presented in Fig. 3.

We found for each diastereotopic pathway, two minima corresponding to the starting chelate complex and the product, and one transition state connecting these points. The calculated free energies for reactants (R), chelate complexes (C) for Re and Si attacks, transition states (TS) for both attacks, and syn and anti products (P) are summarized in Table 1.

To avoid confusion, the starting complex and transition state corresponding to a Re attack will be denoted C-Re and TS-Re, respectively. The starting complex and transition state corresponding to a Si attack will be referred to as C-Si and TS-Si, respectively. The obtained products from Re and Si

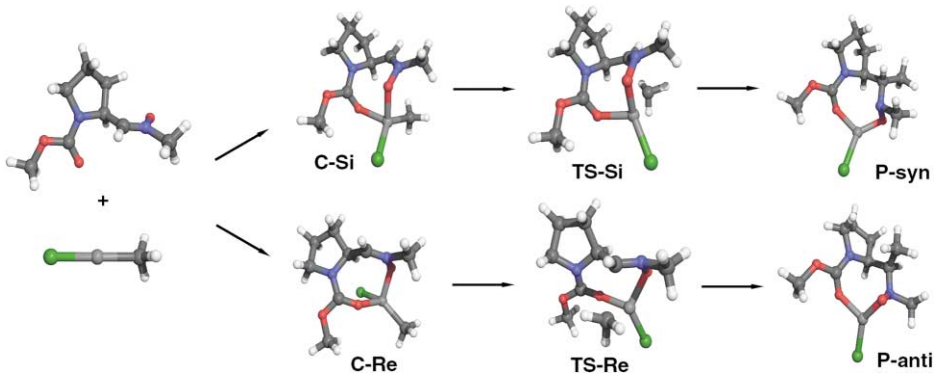
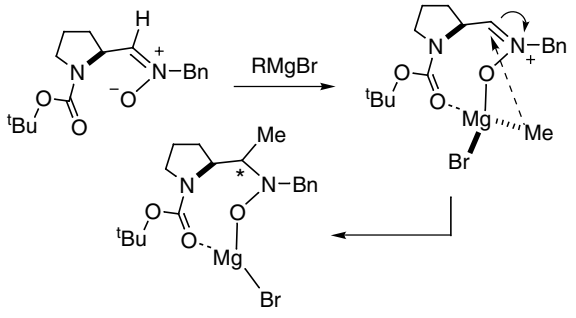


Figure 3. Optimized geometries (HF/6-31+G*) for the equilibrium and transition structures for the nucleophilic addition of MeMgCl to **1**.

Table 1. Calculated free energies (hartree) of the reagents, chelate complexes, transition structures and products for the nucleophilic addition of MeMgCl to **1a**

	HF/6-31G*[a]	HF/6-31+G*	B3LYP/6-31+G*[b]
Nitrone	−644.297818	−644.327453	−648.229767
MeMgCl	−698.753189	−698.756636	−700.263043
C-Si	−1343.093098	−1343.120944	−1348.516686
C-Re	−1343.099639	−1343.127768	−1348.524699
TS-Si	−1343.061885	−1343.086048	−1348.496380
TS-Re	−1343.059382	−1343.083453	−1348.495297
P-syn	−1343.157906	−1343.179747	−1348.565242
P-anti	−1343.154728	−1343.176084	−1348.562737

[a] Single point calculation using HF/3-21G optimized geometries.
[b] Single point calculation using HF/6-31+G* optimized geometries.



Scheme 3.

attacks correspond to P-anti and P-syn structures, respectively.

The detailed reaction scheme and a schematic reaction profile including the relative free energies are also given in Scheme 3 and Fig. 4, respectively.

The formation of stable chelate complexes without energy barriers prior to the addition step has been proposed and demonstrated previously for nucleophilic additions to carbonyl compounds.[13] In the case of nitrones **1**, the hypothesis is strongly supported by the X-ray structures of hydroxylamines showing intramolecular hydrogen bonds (Fig. 1).

Both processes are exothermic and the transition states were found to be below of reactants in energy. Only optimization at HF/6-31+G* shows for TS-Re an energy value slightly above the reactants. The syn product was found to be more stable in all calculations with the only exception of optimization at HF/3-21G level, which gave the anti adduct 3 kcal/mol below the syn one.

According to these results, the reaction is favored both thermodynamically and kinetically showing higher stabilization of products (about 60 kcal/mol) and negative or almost zero activation energies. The significant stabilization of the initial complexes by chelation of the carbamate

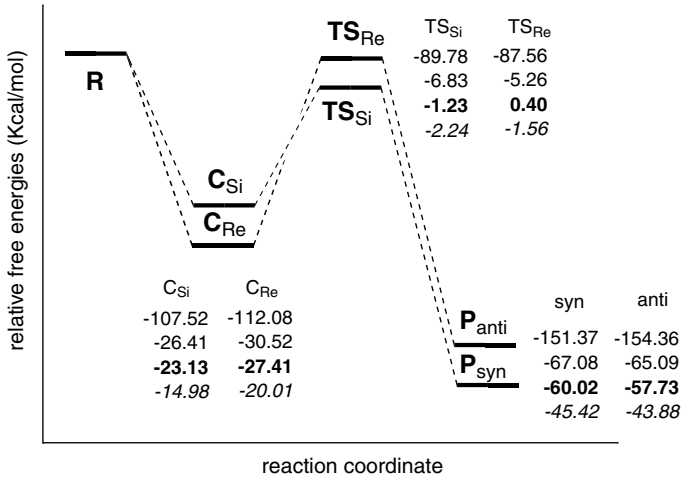


Figure 4. Relative free energies (referred to reactants **R**) for the reaction of **1a** with MeMgCl. Free energies are given in kcal/mol relative to the reagents (normal typeface: HF/3-21G; underlined: HF/6-31G*//HF/3-21G; bold: HF/6-31+G*; italic: B3LYP/6-31+G*//HF/6-31+G*).

group and the nitrone oxygen allows this thermodynamically favored feature. In fact, the chelation in TS-Si significantly influences the approaching direction of the methyl group to the nitrone carbon.

On comparing the transition states TS-Re and TS-Si, that leading to the syn adduct (TS-Si) shows in all cases the lowest energy. Thus, the reaction by the Re face has more activation energy (0.40 and −1.56 kcal/mol using HF and DFT methods, respectively) than that by the Si face (−1.23 and −2.24 kcal/mol using HF and DFT methods, respectively). By comparing the evaluated methods, it can be concluded that qualitatively similar results were obtained from single point calculations and optimization procedures. After optimization at HF/6-31+G* level, the energy difference between transition states was 1.63 kcal/mol, thus predicting a 16:1 syn/anti ratio. Similarly, single point calculations at HF/6-31G*//HF/3-21G showed the transition states to be separated by 1.57 kcal/mol (predicted syn/anti ratio 14:1). On the other hand, single point calculations using density functional methods (B3LYP/6-31+G*//HF/6-31+G*) only showed a difference of 0.68 kcal/mol (predicted syn/anti ratio 3:1). Thus, while HF/6-31+G* calculations predict a clear dominance of the syn isomer (which is experimentally observed), single point calculations using DFT methods only suggest a slightly more favorable formation of the same syn adduct.

The geometry of the transition states are similar regardless of their intrinsic properties. Similar values are found for the C–C forming bonds (2.325 Å for TS-Si and 2.357 Å for TS-Re), the C–Mg breaking bonds (2.328 Å for TS-Si and 2.304 Å for TS-Re) and the C–N bonds evolving from double to single (1.299 Å for TS-Si and 1.294 Å for TS-Re). Also, similar attack trajectories are observed for the incoming methyl group according to the Dunitz–Burgi model.[14] However, in TS-Re (less stable than TS-Si), the change in orientation of the pyrrolidine ring, forced by the chelate, makes that unfavorable steric and electronic interactions arise between the incoming methyl group and the nitrogen atom of the ring. These interactions are avoided by slightly deforming the transition structure, since the attack trajectory is maintained. This fact could explain the energy differences between the transition structures. It is worth noting that the chelate structure is maintained throughout the reaction path, thus pointing out the importance of the formation of the starting complexes as well as the directing effect of the chelation.

4. Conclusions

In summary, we have presented the first ab initio study of a nucleophilic addition reaction of a Grignard reagent with a chiral nitrone, and have shown that the first order saddle points located for the reaction feature a chelation of the magnesium atom between the nitrone oxygen and the carbamate group. In fact, the most important mechanistic finding is that such a chelation is maintained throughout the reaction path, thus exerting a directing effect on the stereoselectivity of the nucleophilic attack. The calculated results show differences on the activation barriers for the corresponding diastereotopic nucleophilic attacks that are in good agreement with the experimental observations, although the diastereoselectivity predictions are clearly dependent on the method (HF or B3LYP) used.

Acknowledgements

We thank MEC (Madrid, Spain, Project PB97-1014) and DGA (Zaragoza, Spain, Project P079/99-C) for financial support.

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