Theoretical Study on the Regioselectivity of Tetrazolylimines with Alkyl Grignard Reagents

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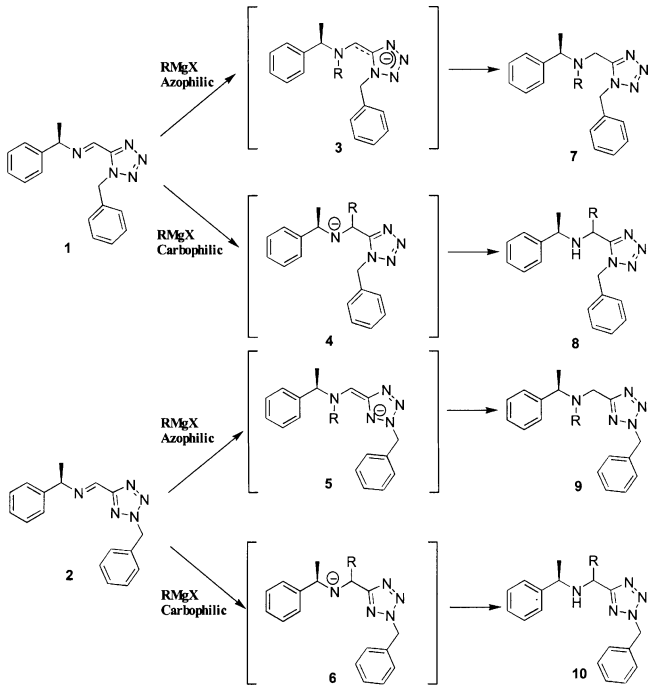
The alkyl Grignard addition reaction on 1-benzyltetrazolylimine proceeds to give N-alkylated products (azophilic addition) and, in contrast, the same reaction on 2-benzyltetrazolylimine produced predominantly C-alkylated products (carbophilic addition). In this report we described theoretical explanations for this experimental finding on the basis of the frontier molecular orbitals and the electrostatic nature of the reactants and the reaction intermediates.

Introduction

Numerous tetrazole derivatives possess various biological activities due to the fact that, in many cases, a tetrazole functional group serves successfully as a metabolically stable isostere for a corresponding carboxylic acid.[1] Recently in connection with the development of nonpeptidic antagonists of the vasoactive octapeptide angiotensin II, there has been renewed interest in the chemistry of tetrazoles.[2] As part of our research programs for designing enzyme inhibitors and receptor antagonists, we needed various tetrazole analogs as amino acid isosteres.[3]

Previously, we reported our experiment result that the addition of alkyl Grignard reagents on 1-benzyltetrazolylimine occurred at the nitrogen atom to give corresponding N-alkylated tetrazole amines (azophilic product) (**7**), while the same reagents on 2-benzyltetrazolylimine exclusively attacked the imino carbon (carbophilic product) (**10**) (Scheme 1 and Table 1).[4] First of all, this azophilic addition on the imine system is not common although there are few examples known in rather special cases such as the azophilic addition of Grignard reagents to the α-imino ester.[5,6] The rarity of this phenomenon and, in our case, a different behavior of two regioisomers prompted us to investigate the reaction theoretically. In the present paper, we will discuss our results based on the frontier molecular orbital (FMO) and the electrostatic nature of the starting materials and the possible reaction intermediates.



Scheme 1

Computational Methods

All computational works were performed on Silicon Graphics Computer (O_2 R5000) using SYBYL (v. 6.3, Tripos, Inc., St. Louis) program. In order to obtain optimal conformations for 1- or 2-benzyltetrazolylimine, corresponding intermediates and products, Grid search was performed.[7] For three rotatable single bonds with grid steps of 60 degrees, we calculated 216 different conformers. After we selected the lowest energy conformer, the geometry was reoptimized using the semi-empirical method with PM3 method. For anionic intermediate, we calculated the E isomers of anion states (**3**) and (**5**) without MgX. For alkyl Grignard reagents, semi-empirical calculations were carried out with MOPAC using PM3 [8]and ZINDO method.[9]

Table 1. Nucleophilic addition of Grignard reagents to 1 and 2-benzyltetrazolylimines

R^1MgX	Entry	**7** : **8**	Yield[a] (%)	Entry	**9** : **10**	Yield (%)
EtMgBr	1a	100 : 0	85	2a	24 : 76	54[b]
BnMgCl	1b	100 : 0	76	2b	5 : 95	75

[a] Yields after purification by chromatography on silica gel preparative TLC. [b] The ratio of two diastereomers is 3 : 7.

Results and Discussion

Frontier Molecular Orbital Interaction. First, we examined the frontier molecular orbital interactions of the reaction intermediates (**3**) and (**5**), as we expected that the azophilic addition might be preferred due to the anion stabilizing nature of the tetrazole group.

According to the PM3 calculation on two isomers, the LUMO energy of 1-benzyl-tetrazolylimine (**1**) was lower by 0.46 eV than that of 2-benzyltetrazolylimine (**2**). When the alkyl Grignard reagent attack as a nucleophile, it will attack the electrophilic site where the LUMO coefficient would be larger. When we compare the size of orbitals, the LUMO coefficient of nitrogen is slightly larger than that of carbon although there was no significant difference in the LUMO coefficients between the nitrogen atom and the carbon atom (entries **1** and **2** in Table 2). This result generally indicated that in both isomers the azophilic addition is slightly favorable.

In the case of the azophilic attack, the developing anion could be stabilized by the tetrazole ring. Therefore, we calculated the heats of formation of the anion intermediates from two isomers (**3, 4, 5, 6**) and found out that the heats of formation of tetrazole anion states (entries **3a** and **3b**, **5a** and **5b** in Table 2) (azophilic addition) were lower than that of nitrogen anion states (entries **4a** and **4b**, **6a** and **6b** in Table 2) (carbophilic addition). However, these results were not enough to explain the difference between 1- and 2-benzyltetrazolylimine toward the azophilic addition.

Nonetheless, the molecular orbital calculation showed that the electrons are more delocalized in the reaction intermediate **(3)** derived from the azophilic addition on 1-benzyltetrazolylimine **(1)** than in 2-benzyltetrazolylimine **(2)** and it also showed that the LUMO energy of (**3**) is lower than that of (**5**). Furthermore, it showed that the LUMO energy of 1-benzyltetrazolylimine (**1**) is lower in the tetrazole anion state (entries **3a** and **3b** in Table 2) than the imino anion state (entries **4a** and **4b** in Table 2), whereas, in the case of 2-benzyltetrazolylimine (**2**), the opposite is true. These two effects seemed to explain the trend that in the case of 1-benzyltetrazolylimine (**1**) the azophilic addition is more preferred over the carbophilic addition.

We then examined the interaction between orbitals from nucleophiles and electrophiles. A mixing of the occupied orbitals on the nucleophile with the unoccupied orbitals on the electrophile has been proposed to explain the reactivity between a nucleophile and an electrophile.[10] The stabilization energy (δE) of the transition state, gained by mixing of orbitals is given as

$$\delta E = \underbrace{\frac{Q_{nuc}Q_{elec}}{\varepsilon R}}_{A} + \underbrace{\frac{2(C_{nuc}C_{elec\beta})^2}{E_{HOMO}-E_{LUMO}}}_{B}$$

C_{nuc}: the HOMO coefficients on the nucleophilic site.
C_{elec} : the LUMO coefficients on the elctrophilic site.
β: the resonance integral.
E_{HOMO}-E_{LUMO}: the energy gap between the HOMO of the nucleophile and LUMO of the electrophile.
Q_{nuc} and Q_{elec}: the electron populations in the atomic orbitals on the nucleophile and electrophile respectively.
ε: the local dielectric constant.
R: the distance between the nucleophile and electrophile.

The resonance integral β was assumed to have a value of 5.83 for C-N bond and 6.22 for a C-C bond (1.75 Å).[11] The term A in the above equation is the electrostatic contribution to the stabilization of the transition state, while term B represents the frontier molecular orbital contribution.

The regioselectivity, in general, can be predicted by the comparison of δ*E* for each attacking site. The site where the greatest stabilization of the transition state can be accommodated (δ*E* is most highly negative) will be the attacking site. The energy gained by the FMO contribution (δ*E*) for each attacking site suggests that the azophilic addition is generally favored over the carbophilic addition in all cases (δE_N - $\delta E_c < 0$) (Table 3). It also shows that the preference for azophilic addition is slightly greater in the case of 1-benzyltetrazolylimine than the corresponding 2-benzyltetrazolylimine. This FMO result is similar to that of the azophilic addition of alkyllithium reagents to fluorenimines.[12]

In summary, the molecular orbital calculation seems to suggest that the Grignard reagents (HOMO) will attack preferentially the imino nitrogen over the imino carbon in both isomers but it is not enough to explain the difference of regioselectivity between two regioisomers.

Table 2. The result of semi-empirical calculation of reactants and anionic intermediates from Grignard addition on 1 and 2-benzyltetrazolylimine

Entry	HF (kcal)	HOMO	LUMO	N LUMO coefficient	C LUMO coefficient
1	189.55	-9.84	-0.65	0.45733	0.39923
2	192.37	-9.71	-0.19	-0.27845	0.21721

Anionic intermediates

Azophilic addition

R^1MgX	Entry	HF (kcal)	HOMO	LUMO	Entry	HF (kcal)	HOMO	LUMO
EtMgBr	3a	90.65	-3.43	2.64	5a	108.16	-2.99	2.89
BnMgCl	3b	125.03	-3.55	2.56	5b	137.15	-3.07	2.84

Carbophilic addition

R^1MgX	Entry	HF (kcal)	HOMO	LUMO	Entry	HF (kcal)	HOMO	LUMO
EtMgBr	4a	99.20	-3.67	2.86	6a	124.02	-2.66	2.35
BnMgCl	4b	131.48	-3.74	2.85	6b	150.36	-3.25	2.15

Table 3. The difference of stabilization energy of the transition states from azophilic and carbophilic addition

R^1MgX	1-benzyltetrazolylimine			2-benzyltetrazolylimine		
	δE_{azo}	δE_{carbo}	δE_N- δE_C	δE_{azo}	δE_{carbo}	δE_N- δE_C
EtMgBr	-0.811	-0.475	-0.336	-0.377	-0.163	-0.215
BnMgCl	-0.533	-0.312	-0.221	-0.247	-0.106	-0.141

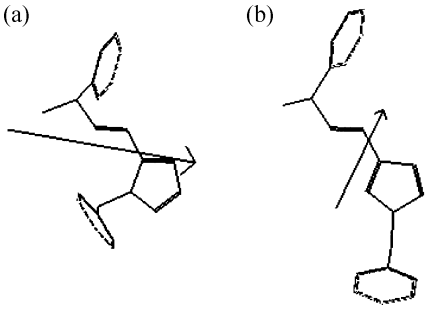


Figure 1. The direction and size of dipole moment of (a) 1-benzyltetrazolylimine (size: 4.64 debye) and (b) 2-benzyltetrazolylimine (size: 2.19 debye).

Electrostatic Interaction. Therefore, we examined dipole moment[13] to see its role on the regioselectivity of the reaction. The direction of dipole moment of 1-benzyltetrazolylimine (**1**) was found to be toward the tetrazole ring, while that of 2-benzyltetrazolylimine (**2**) was found to dissect the plane formed by the carbon atom and the tetrazole ring (Figure 1).

In the case of reaction intermediates, we had to consider four possible anion states (**3**), (**5**) & (**4**), (**6**) as depicted in Scheme 1. However, we considered only the E form of anion states (**3**) and (**5**) because of their thermal stability as well as in the corresponding starting conformations. The analysis shows that in the anion state (entries **3c** and **3d** in Table 4) the electron density is more populated in the tetrazole ring than on the imino nitrogen atoms (entries **4c** and **4d**). The size of dipole moment of the 1-benzyltetrazole anion states (entries **3c** and **3d**) was about two times bigger than that of the nitrogen anion state (entries **4c** and **4d**). In the case of the 1-benzyltetrazole, intermediate (**4**) resulted from the carbophilic attack, the dipole moment directed into carbon atom, while in the intermediate (**3**) resulted from the azophilic attack, the dipole moment directed into the tetrazole ring. Therefore, the Grignard reaction on 1-benzyltetrazolylimine (**1**) will most likely occur at the imino nitrogen to go through more stable anionic intermediate and eventually to give the azophilic addition product. In contrast, in the case of 2-benzyltetrazolylimine (**2**) the electron density is higher at the imino nitrogen atom (entries **6c** and **6d**) than in the tetrazole ring (entries **5c** and **5d**). Furthermore, the size (7.42 debye) and the direction of the dipole moment seem to support the carbophilic addition to be more favorable in the case of 2-benzyltetrazolylimine (Figure 2).

Table 4. The size (debye) and direction of dipole moment

	Azophilic addition					
R^1MgX	Entry	Size	Direction	Entry	Size	Direction
EtMgBr	3c	9.48	Tet.	5c	5.30	C-tet.
BnMgCl	3d	10.45	Tet.	5d	4.83	C-tet.
	Carbophilic addition					
R^1MgX	Entry	Size	Direction	Entry	Size	Direction
EtMgBr	4c	6.18	C-tet.	6c	7.42	Imino N.
BnMgCl	4d	3.29	C-tet.	6d	6.98	Imino N.

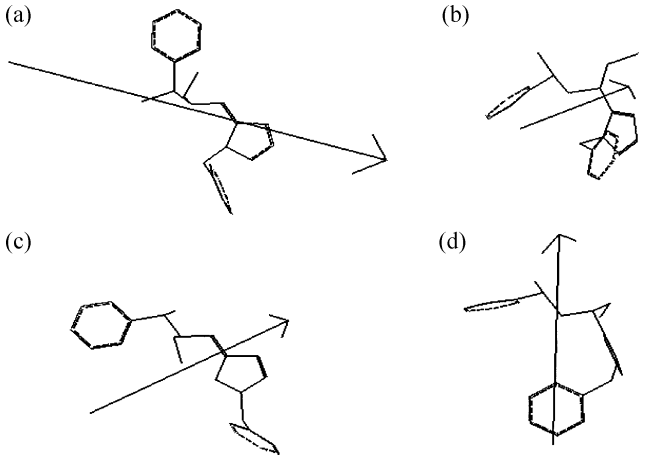


Figure 2. The direction and the size of possible anionic intermediates resulted from azophilic and carbophilic attack on two isomers. (a) the tetrazole anion state of 1-benzyltetrazolylimine by azophilic addition (size: 9.48 debye), (b) the nitrogen anion state of 1-benzyltetrazolylimine by carbophilic addition (size: 6.18 debye), (c) the tetrazole anion state of 2-benzyltetrazolylimine by azophilic addition (size: 5.30 debye), (d) the nitrogen anion state of 2-benzyltetrazolylimine by carbophilic addition (size: 7.42 debye).

Conclusions

The theoretical study revealed that the electrostatic contribution seems to be more important than the FMO contribution in determining the regioselectivity. The direction and size of dipole moment in the states of both starting and reaction intermediates support this conclusion well. Therefore, we may conclude that the alkyl Grignard reaction on 1-benzyltetrazolylimine (**1**) prefer the azophilic addition because of the stabilizing effect of the tetrazole anion (**3**). In contrast, in the case of 2-benzyltetrazolylimine (**2**) the normal carbophilic addition is preferred due to the lack of such tetrazole anion stabilizing effects.

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