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Computational Study on the Reactivity of Tetrazines toward Organometallic Reagents

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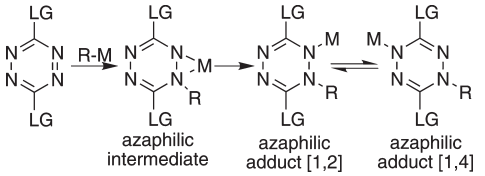

The possible reaction pathways between methyllithium and disubstituted 1,2,4,5-tetrazines (bearing methyl, methylthio, phenyl, and 3,5-dimethylpyrazolyl groups) were investigated by means of the density functional theory B3LYP/6-31G* method. Solvation was modeled using the supermolecule approach, adding one tetrahydrofuran molecule to the complexes. Comparison of the calculated energies and structures for the alternate azaphilic and nucleophilic addition pathways showed that the azaphilic addition is kinetically favored over nucleophilic addition, while thermodynamically the nucleophilic addition is usually preferred. The coordination of the tetrazine molecule with methyllithium was found to play a crucial role in the process. These findings provide the first rationale for the experimentally observed unique reactivity of tetrazines toward polar organometallic reagents, suggesting the presence of a kinetically controlled process.

Introduction

The chemistry of tetrazines has gained increased attention in the past few decades[1] mostly due to their applications in organic synthesis,[2] crop protection,[3] and materials science.[4] Their basic structural feature, the electron-deficient heterocyclic core, is the key to their most extensively utilized transformation, the "inverse electron-demand" Diels−Alder reaction, which provides an attractive route to pyridazines,[5] pyrroles,[6] pyrazoles,[7] and other condensed[8] and strained[9] heterocyclic ring systems. This reactivity has also been actively exploited recently in natural product synthesis[10] and bioconjugation studies.[11]

The electron-deficient nature of the heteroaromatic ring makes it susceptible to nucleophilic attack. There are several

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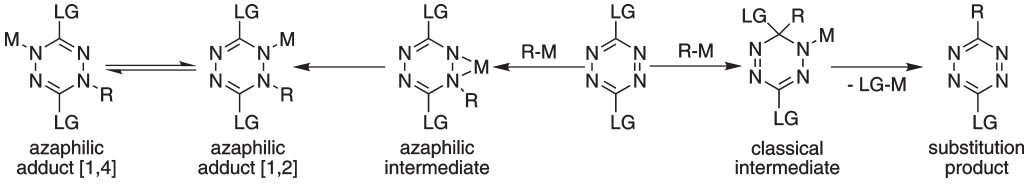
SCHEME 1. Azaphilic Addition and Classical Nucleophilic Substitution



reports on the addition of nucleophiles onto the ring[12] or substitution of leaving groups (LG), such as chloro, methylthio, or dimethylpyrazolyl with nitrogen, oxygen, or sulfur nucleophiles.[13] Although the analogous introduction of carbon nucleophiles would also be of synthetic importance, there are only a very limited number of known examples utilizing potassium cyanide, malonates,[14] or nucleophilic heterocyclic carbenes.[15]

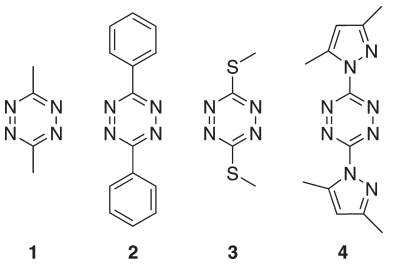
The use of polar organometallic reagents as carbon nucleophile, such as lithium, magnesium, or zinc organic derivatives, leads to the addition of the organic group onto a ring nitrogen atom.[16] This transformation, coined "azaphilic addition", is quite unprecedented for other heterocyclic systems. Unlike for the classical nucleophilic addition, where the incoming reagent attacks at a ring carbon atom, in the azaphilic addition the incoming nucleophile is attached to a ring nitrogen atom and the formed intermediate is usually stabilized by a 1,3-shift of the metal (or M = H following aqueous workup) (Scheme 1).

Our objective was to obtain an explanation for this unique reactivity of the tetrazines using computational calculations as an aid. Since experimental evidence suggested that the coordinating ability of the substituent on the tetrazine ring has a marked effect on the kinetics of the azaphilic addition,[16a] we selected a series of tetrazines for our studies, bearing substituents with varying coordinating ability: 3,6-dimethyltetrazine (**1**), 3,6-diphenyltetrazine (**2**), 3,6-bis(methylthio)tetrazine (**3**), and 3,6-bis(3′,5′-dimethylpyrazolyl)-tetrazine (**4**) (Scheme 2). As a nucleophile, methyllithium was selected for the sake of computational simplicity. Both azaphilic addition and classical nucleophilic substitution (not experimentally observed) pathways were studied up to the formation of the appropriate intermediates (Scheme 1, "azaphilic intermediate" and "classical intermediate").

Theoretical Model

The study of reaction modes of carbon nucleophile modeled by methyllithium and various tetrazines was carried out by determining the structures corresponding to ground-state and transition-state geometries on the reaction energy hypersurfaces. The organometallic reagents reported to add to tetrazines[16] are butyllithium and phenyllithium, but for computational simplicity we have used methyllithium as a model nucleophile. Ether-type solvents, especially tetrahydrofuran, have proved to be advantageous for azaphilic addition;[16a] therefore, specific solvent-related interactions were taken into account by incorporating one tetrahydrofuran molecule into the applied model using the supermolecule approach. It can be argued that lithium cation prefers to be 4-fold coordinated, but the addition of even a second THF molecule to our model complexes is sterically hindered and would also lead to prohibitively long computational times. Although our model carbon nucleophile, methyllithium, is present in oligomeric form in tetrahydrofuran,[17] we presume that its monomeric form, present through dissociation equilibria, is the reactive species and a good model for the reactions of less associated butyllithium and phenyllithium.

SCHEME 2. Tetrazine Derivatives Used in the Computational Study



All calculations were performed using the Gaussian 03 program package.[18] The geometries of complexes of methyllithium, one molecule of tetrahydrofuran, and the studied tetrazines as well as corresponding transition states and complexes of products were fully optimized using Becke's hybrid B3LYP functional[19] and the standard split-valence d-polarized 6-31G* basis set.[20] Earlier studies have shown that such combinations offer an adequate description of properties and reactions of tetrazines.[21] Harmonic frequency analysis was used to confirm

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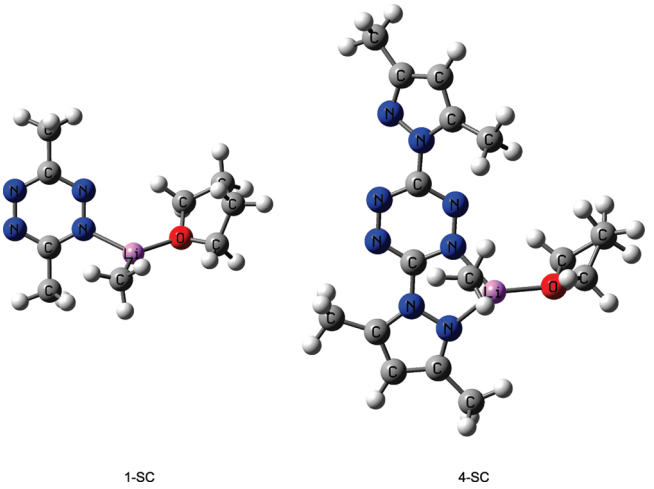

FIGURE 1. Starting complexes showing the coordination of methyllithium with noncoordinating (**1**) and coordinating (**4**) substituents.

that the found structures correspond to either minima (number of imaginary frequencies equals zero) or transition states (number of imaginary frequencies equals one). Unscaled frequencies were also used for calculation of the values of Gibbs free energy for the standard state of 1 atm at 298.15 K and for comparison with experiment[16a] also at 195.15 K. The lowering of the temperature does not change the qualitative outcome, as can be seen from the Supporting Information (Table 1S), and we have used the results at 298.15 K in our further discussions. Intrinsic reaction coordinate analysis[22] was used to confirm that the found transition states connect the desired minima.

Results and Discussion

Starting Complexes. Two fundamentally distinct ways were examined to describe the coordination of the polar organometallic reagent to the tetrazine molecule. Methyllithium can approach tetrazines either in the plane of the ring with its positively charged part pointing toward the ring nitrogens or perpendicular to the plane of the ring with its negatively polarized part oriented toward the electron-deficient core. The latter option was ruled out by preliminary calculations.

Tetrazines bearing substituents with modest or noncoordinating ability (**1**−**3**) can coordinate methyllithium by two adjacent ring nitrogens, denoted as N and N′ throughout the article, N being proximal to lithium (Figure 1, **1-SC**). The comparison of Li−N, Li−N′, and Li−C distances (Li−N: 2.03, 2.02, 2.00 Å; Li−N′: 2.83, 2.81, 2.76 Å; Li−C: 2.06, 2.06, 2.07 Å for **1**−**3**, respectively) reveals that the substituents have practically no influence on the structure of the starting complex. We were unable to locate an alternate complex of **3** with stronger S,N-coordination, due probably to the fact that it would result in a strained four-membered ring. The difference in Li−N and Li−N′ distances within the same complex can be attributed to the steric demand of the tetrahydrofuran, as nearly equal distance values were obtained in the absence of the solvent molecule.

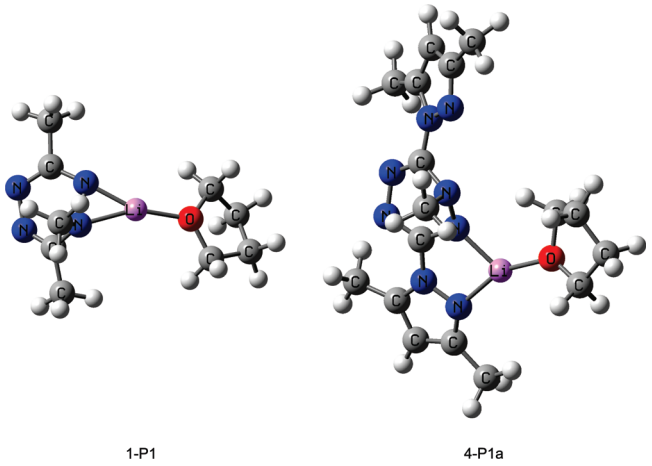

FIGURE 2. Azaphilic addition intermediates of tetrazines with noncoordinating (**1**) and coordinating (**4**) substituents.

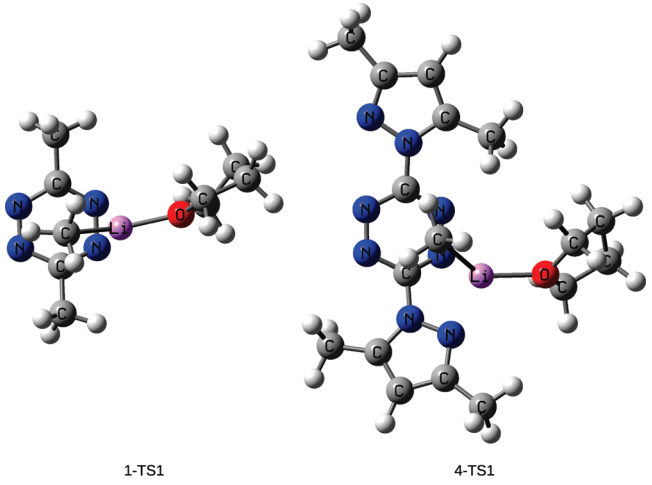

FIGURE 3. Azaphilic addition transition states of tetrazines with noncoordinating (**1**) and coordinating (**4**) substituents.

3,6-Bis(3′,5′-dimethylpyrazolyl)-1,2,4,5-tetrazine (**4**), having another strongly coordinating nitrogen in the pyrazole moiety, offers a more effective way of coordination, forming a five-membered ring with the participation of a nearby ring nitrogen (Figure 1, **4-SC**). This result is in accordance with experimental observations where salts of **4** and metal ions, showing the same type of coordination, were isolated.[23]

Azaphilic Addition Intermediates. The primary species formed in the azaphilic addition are the 1,2-adducts, which might be stabilized further by rearranging to the 1,4-forms. Azaphilic intermediates of the dimethyl (**1**) and diphenyl derivatives (**2**), where the tetrazine substituents do not take part in complexation, coordinate lithium by the two adjacent ring nitrogens, similarly to the starting complexes, though Li−N distances are smaller and the coordination to N′ is strongly increased (see Figure 2). In case of the methylthiotetrazine (**3**) both N,N′- and S,N-coordination modes were identified as stable P1 structures, though the N,N′-complex is favored by 10.6 kJ/mol.

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TABLE 1. Relative Energies of Azaphilic Addition (P1, TS1) and Classical Nucleophilic Substitution (P2, TS2) of Tetrazines with Different Substituents[a]

tetrazine	ΔG(P1)	ΔG(P2)	ΔG(TS1)	ΔG(TS2)	ΔG(P2) − ΔG(P1)	ΔG(TS2) − ΔG(TS1)
1	−90.9	−117.6	39.5	41.1	−26.7	1.6
2	−115.3	−123.0	34.1	39.1	−7.7	5.1
3	−135.1	−129.7	20.1	43.9	5.4	23.9
4	−159.6	−171.1	5.5	44.9	−11.5	39.4

[a]Starting complexes are taken as a zero point. TS1 and P1 denote the transition state and intermediate of the azaphilic reaction pathway, while TS2 and P2 denote the transition state and intermediate of classical nucleophilic substitution, respectively. All values are given in kJ/mol.

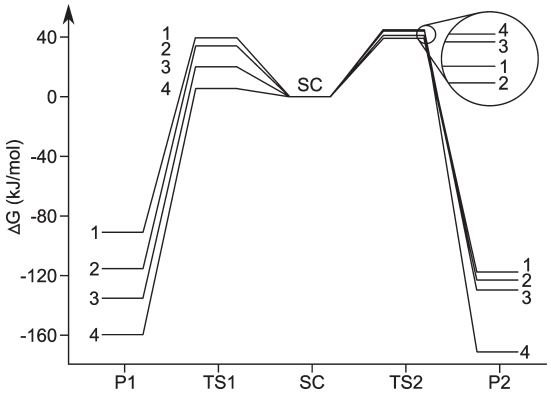

FIGURE 4. Reaction pathways of substituted tetrazines (**1**−**4**) with methyllithium. Starting complexes (SC) are taken as a zero point of the energy scale. TS1 and P1 denote the transition state and intermediate of the azaphilic pathway, while TS2 and P2 denote the transition state and intermediate of classical addition, respectively.

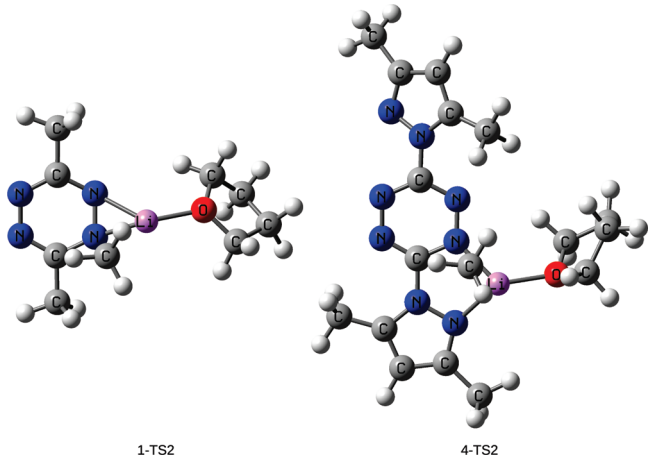

FIGURE 5. Classical nucleophilic addition transition states of tetrazines with noncoordinating (**1**) and coordinating (**4**) substituents.

For the pyrazolyltetrazine (**4**) two possible azaphilic intermediates were identified. In the more favorable one (**4-P1a**) the lithium is held in a five-membered chelate complex similar to those observed for the starting complex (**4-SC**), while the methyl group is shifted toward N′ (Figure 2). In the other possible intermediate, which is disfavored by 36.5 kJ/mol, the methyl group of the organometallic reagent is bound to the same tetrazine ring nitrogen as the lithium, resulting in a tetrahedral arrangement around this atom (**4-P1b**, see Supporting Information).

Transition States to Azaphilic Addition Intermediates. For tetrazines **1**−**3** methyllithium is coordinated in a similar side-on manner with its methyl group bending over the reacting nitrogen (Figure 3). For dipyrazolyltetrazine (**4**) the complex retains the five-membered ring also in the transition state (Figure 3). This behavior significantly lowers the activation energy in comparison with the other three tetrazine derivatives (see Table 1 and Figure 4). The activation energies of azaphilic addition show a marked dependence on the coordinating ability of the substituent: the stronger the coordinating ability, the lower the activation energy.

Classical (Nucleophilic Substitution) Intermediates. The intermediates along the classical (nucleophilic substitution) pathway show various types of coordination. In the methyltetrazine-derived intermediate (**1-P2**) lithium is coordinated by the two neighboring tetrazine nitrogens. In case of the classical intermediates derived from **2** and **3** we identified similar structures, but alternative minima were also located, where the substituents of the tetrazine ring act as coordinating groups. For 3,6-diphenyltetrazine (**2**) two intermediates are possible: either the lithium interacts with the phenyl group and tetrazine nitrogen, or a more stable (by 9.9 kJ/mol) N,N′-coordinated complex is formed. In case of 3,6-bis(methylthio)tetrazine (**3**) the intermediate possessing the S,N-coordination mode proved more stable than the analogous N,N′-coordinated structure by 6.7 kJ/mol. For the dipyrazolyltetrazine (**4**) the five-membered metallacyclic complex is retained in a similar way to that for its azaphilic intermediate.

Transition States to Classical (Nucleophilic Substitution) Intermediates. The transition-state structures (**TS2**) obtained for **1**, **2**, and **3** are very similar, with methyllithium moving over the plane of the tetrazine ring (Figure 5). The methyl group of the reagent is placed above the site of its attack, while lithium is placed over the adjacent ring nitrogen. The transition-state structure derived from the dipyrazolyltetrazine (**4**) is unique again since the five-membered bidentate coordination mode is maintained even in the transition state (Figure 5). However, this strong coordination prevents the methyl group from getting close to the site of its attack, the tetrazine carbon, and the activation energy is significantly higher than in the case of the azaphilic pathway. The activation energies of the classical (nucleophilic substitution) pathway are quite close to each other (within 6 kJ/mol) and not directly related to the coordinating ability of the substituents.

Summary

The azaphilic addition and classical nucleophilic substitution pathways of the reaction between disubstituted tetrazines and methyllithium were investigated using the DFT method. The influence of the tetrazine substituent on the reaction was modeled using four substituents with different coordinating ability (methyl, methylthio, phenyl, and 3,5-dimethylpyrazolyl groups in positions 3 and 6). The transition

state leading to the azaphilic addition intermediate was found to be lower in energy for all tetrazine derivatives than the transition state leading to the classical (nucleophilic substitution) intermediate. At the same time the classical intermediates were found in general to be more stable than the azaphilic intermediates, the only exception being the bis(methylthio)tetrazine derivative. The activation energy of azaphilic addition also showed considerable dependence on the coordinating ability of the tetrazine substituent, the activation free energy ranging from 5.5 to 39.5 kJ/mol, while for the classical pathway the range of activation energy was quite narrow (39.2 to 44.9 kJ/mol). On the basis of the calculated energies and structures we can propose that the unique reaction of polar organometallic reagents with tetrazines, known as azaphilic addition, is a kinetically controlled process. The key to this experimentally observed selectivity lies in the coordinating power of the tetrazine and its substituent, which strongly influence the structures and energies of most stationary states on the potential energy surface except for the transition state of nucleophilic substitution. This understanding might also open up the way to design and synthesize such coordinating substituents that might alter the selectivity of the reaction between tetrazines and organometallic reagents.

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Supporting Information Available: Geometries for all discussed structures. This material is available free of charge via the Internet at http://pubs.acs.org.