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Insights into the diastereoselective control in the sulfa-Michael addition of thiols to nitroalkenes: stereoelectronic effect in the cyclic chelated transition state

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ABSTRACT

The diastereoselective control in the sulfa-Michael addition of nitroalkenes and lithium thiolates followed by protonation was investigated. Lithium thiolates first added to nitroalkenes to afford cyclic lithium-chelated nitronates. The subsequent kinetic protonation of nitronates was proved to be the stereochemical determinant through the chelate-controlled six-membered half-chair transition state bearing two approximately 1,2-diaxial substituents due to stereoelectronic effect control. The stereoelectronic effect in the cyclic chelated transition state was probed and verified by tuning the steric bulkiness of the corresponding substituents. The reaction involving 1-nitrocyclohexene provided perfect support for the proposed diastereoselective control model. The current investigation provided not only comprehensive insights into the diastereoselective control in the sulfa-Michael addition of nitroalkenes and thiolates, but also an important role of the stereoelectronic effect in certain organic reactions involving cyclic chelate transition states.

1. Introduction

The sulfa-Michael addition (SMA), which is considered as the reaction of a sulfur nucleophile and carbon-carbon multiple bond electrophile activated by an conjugated electron-deficient group, has proven to be one of the most powerful strategies in constructing the sulfur-carbon bond,[1] and always plays a crucial role in the formation of key structural motifs of biologically active sulfur-containing compounds.[2] Meanwhile, when appropriately disubstituted activated π-systems serve as Michael acceptors, the SMA has the potential to introduce two vicinal stereogenic centers via only one transformation. Thus, extensive and intensive studies have been directed toward the development of the diastereoselective control of this transformation for quite a long time.[3] As we all know, conjugated nitroalkenes act as excellent Michael acceptors ascribing to their strongly electron-withdrawing capacity of the nitro group.[4] Furthermore, the nitro group is usually considered as masked functionality to be further converted to various useful functional groups, such as ketone, nitrile, nitrile oxide, and amino groups.[5] Additionally, the SMA adducts β-nitro sulfides are particularly versatile in synthetic chemistry since they can undergo a series of attractive transformations to provide diverse functionality.[6] Therefore, the diastereoselective sulfa-Michael addition of α,β-disubstituted nitroalkenes and thiols has been studied for many years. Although impressive advances have been made in organocatalyzed asymmetric SMA of nitroalkenes with thiols and thiolacetic acid in recent years,[1b,7] the diastereoselective control in the sulfa-Michael addition is still one of important issues and not clear completely.

In our recent study on the preparation of various disubstituted taurines, moderate to good diastereoselectivities were observed in the tertiary amine-catalyzed SMA of thiolacetic acid to α,β-disubstituted nitroalkenes with perfect yields.[8] Subsequently, we found that controlling the reaction time exerted remarkable impact on the diastereoselectivity in the triethylamine-catalyzed SMA between nitroalkenes and thiols. The SMA involving thiophenol and primary alkanethiols has been proven to be kinetic control at the beginning and thermodynamic control at the end and linear nitroalkenes generally produce *anti*-adducts as major kinetic products due to favorable steric and stereoelectronic effects.[9] In our continuous interest on the diastereoselective control in the SMA of nitroalkenes without any chiral auxiliary or

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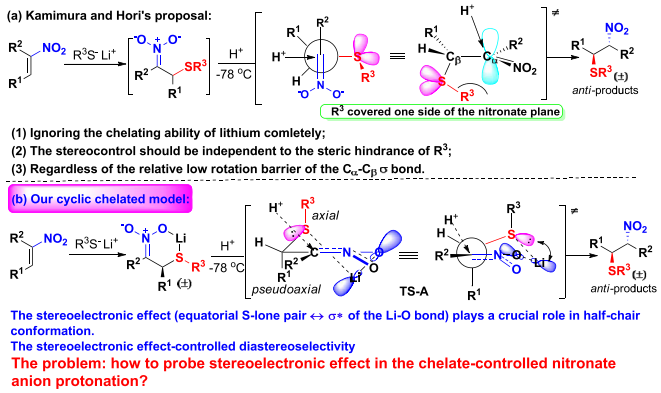
catalysts, we have investigated the diastereoselective formation of *anti*-β-nitro sulfides in reactions of nitroalkenes with sulfur nucleophiles, lithium thiolates R^3SLi, followed by protonation at −78 °C according to literature report due to their synthetic applicability.[10] Although Hori et al. assumed a concept of 'the *endo* alkoxy effect' which insisted that the substituent R^3 on the sulfur atom should take the *cis* position to the nitro fragment to cover one side of the nitronate plane to minimize the repulsion between *S*-lone electron pairs and the anion orbital in terms of computational consideration, their arguments were proposed on the basis of certain unconvincing hypothesis involving regardless of the chelating ability of lithium and the steric impact of substituent group R^3 on the sulfur atom (Scheme 1).[11] Furthermore, Apeloig et al. reported that low rotation barriers for adjacent σ-bonds in carbanions stabilized by the nitro group via ab initio calculations.[12] Thus, interconversion of the conformations at the stereogenic center of carbanions in nitronate anion intermediates could take place by rotating about the C_α–C_β σ-bond of the nitronate anion intermediates. Therefore, the origin of the stereocontrol in the conjugate addition reactions of sulfur nucleophiles R^3SLi to α,β-unsaturated acyclic nitroalkenes followed by protonation at −78 is still a riddle.



Scheme 1. Proposed transition state models for diastereoselective sulfa-Michael additions of lithium thiolates and nitroalkenes followed by protonation.

In order to reveal the origin of the *anti*-selectivity and to find out the dominated elements in the stereocontrolled process, we proposed a cyclic transition state **TS-A** (Scheme 1) for the protonation of nitronate anions, which will be proved to be the stereochemical determinant in this transformation, incorporating with the consideration of chelation control of lithium and stereoelectronic effect control. Although **TS-A** would be expected to be stabilized by the stereoelectronic effect, stereoelectronic and steric requirements imposed an approximate 1,2-diaxial substituted half-chair conformational bias to **TS-A** (Scheme 1). Especially, one of two *S*-lone pair orbitals has to occupy the equatorial direction in **TS-A** to share an antiperiplanar relationship with the σ* antibonding orbital of the Li–O bond. Nevertheless, all the experimental evidences provided by literature[10,11] seem to support the prediction made by **TS-A**. However, the problem is that ***how to further probe the stereoelectronic effect in the protonation reaction of the chelate-controlled nitronate anions experimentally***? We successfully tackled the problem by extrapolating from the diastereoselective change through tuning the steric hindrance of substituent groups R^1 and R^3. Herein, we present our results and hope that the results provide a potentially valuable guide to analyze the stereoelectronic factors that control the diastereoselectivity in chelate-controlled addition reactions.

2. Results and discussion

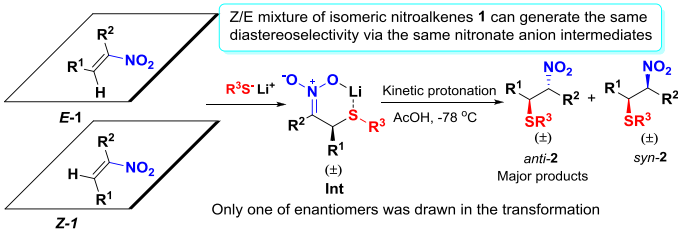
2.1. The stereochemical determinant step

The original motivation of our study was to understand the diastereoselectivity of conjugate addition reactions of sulfur nucleophiles R^3SLi to α,β-unsaturated acyclic nitroalkenes. The stepwise addition reactions consisted of two processes. Initial conjugate addition of nucleophiles to Michael acceptors gave rise to nitronate anion intermediates, which were protonated or further trapped with other electrophiles. Inagaki et al. argued that the stereospecific conjugate addition of lithium thiophenoxides to α,β-unsaturated carboxylic acid derivatives could be achieved via rapid protonation prior to conformational change in the corresponding intermediates.[3a] However, Morig et al. maintained that the stereoselection of enolate protonation was responsible for the diastereoselective 1,4-conjugate addition to α,β-unsaturated esters[13] and the geometry of the enolate anion intemediates should be relatively unaffcted the stereocontrol.[14]

To discern the stereochemical determinant in the sulfa-Michael addition of thiols to nitroalkenes, we should apply both (*E*)- and (*Z*)-nitroalkenes as Michael acceptors. Most of the available procedures for the synthesis of nitroalkenes, such as Henry reactions involving base mediated condensation of nitroalkanes with aldehydes followed by subsequent dehydration, are known to provide thermodynamically more stable *E* isomers, independently of the nitro compound precursors.[15] However, *Z* isomers can be prepared indirectly from the corresponding *E* derivatives. Treatment of (*E*)-2-nitro-2-butene (**1a**) and (*E*)-2-nitro-3-phenyl-2-propene (**1b**) with sodium benzeneselenolate followed by kinetically protonation with acetic acid afforded *anti*-nitroselenides. After H_2O_2-promoted *syn*-elimination of benzeneselenenic acid, *E*-**1a** and *E*-**1b** were converted into Z/E mixtures (4:1) and (2:3) of isomeric nitroalkenes, respectively.[4c,16]

Subsequently, the sulfa-Michael additions were performed with (*E*)-isomers and Z/E mixtures of nitroalkenes **1a** and **1b** as substrates. Not surprisingly, the *E*/*Z* mixtures provided almost the same diastereoselectivities comparing with their corresponding pure *E* isomers (Table 1, entries 1 vs 2, 3 vs 4). The experimental evidences clearly indicated that the same nitronate anion intermediates should be generated as a pair of enantiomers in each of reactions. The subsequent protonation is responsible for the generation of the diastereoselectivity. In other words, kinetic protonation of nitronate anions is the stereochemical determinant in the Michael addition of thiolates R^3SLi to α,β-disubstituted nitroalkenes. That is, the diastereoselectivity is controlled by the subsequent protonation process rather than the first Michael addition step.

Table 1
Diastereoselective sulfa-Michael addition of thiophenol to nitroalkenes **1a,b**



Entry	1	R^1	R^2	R^3	*Z*/*E*	2	Dr[a] (*anti*:*syn*)	Yield[b] (%)
1	*E*-**1a**	Me	Me	Ph	0/1	**2a**	91:9[c]	75
2	*Z*/*E*-**1a**	Me	Me	Ph	4/1	**2a**	92:8	67[d]
3	*E*-**1b**	Ph	Me	Ph	0/1	**2b**	75:25[c]	70
4	*Z*/*E*-**1b**	Ph	Me	Ph	2/3	**2b**	76:24	77[d]

[a] Dr values were determined by ^1H NMR.
[b] Isolated yield by column chromatography.
[c] The dr ratios were completely in accord with Kamimura's report [Ref 10].
[d] 0.22 mmol scale for the starting nitroalkenes in 2 mL dry THF.