What is the mechanism of amine conjugate additions to pyrazole crotonate catalyzed by thiourea catalysts?†‡

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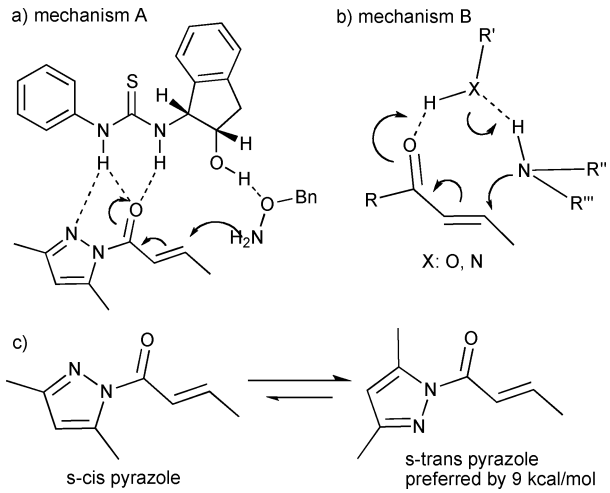
Aminoindanol-derived thioureas catalyze proton transfer and do not stabilise anions in an asymmetric conjugate addition to pyrazole crotonate. Calculations show that the urea H-bonds play different roles in the preferred transition state and in the one leading to the minor enantiomer in the mechanism of hydroxy-thiourea catalyzed conjugate additions to pyrazole crotonates.

Introduction

Hydrogen bond activation of carbonyl compounds constitutes an important mechanism of organocatalysis.[1,2] Thioureas, that are able to enhance the reactivity of electrophilic substrates,[3–6] have also been applied to reactions of carbonyl compounds.[7–12] Even though these catalysts have been successfully applied in conjugate 1,4 additions to acylimines[2,7] and nitro-olefins,[4,5,13] additions to acrolein derivatives are less common[9–12] Recently, Sibi and Itoh[9] have described the enantioselective addition of hydroxylamines to pyrazole crotonate derivatives catalyzed by chiral aminoindanol-derived thiourea catalysts,[5,11] a reaction that can be used for the preparation of β-amino acids. Nevertheless, high enantiomeric excesses are only obtained when bulky hydroxylamines are used as nucleophiles.

In the original work[9] stereochemistry was explained as a consequence of a H-bond between the hydroxyl group of the chiral catalyst and the oxygen in the nucleophile (Scheme 1a, mechanism A). This model qualitatively explains the stereochemistry of the product, but is only one of the possible patterns of H-bonds between the catalyst and the reaction transition state, and assumes that O=C-N-N group ring adopts the *s-cis* conformation in order to form the largest possible number of H-bonds with the substrate. Studies on the mechanism of addition of amines to α,β unsaturated carbonyl compounds show that water[14] and secondary amines[12] can catalyze the reaction by a proton switch mechanism (Scheme 1b, mechanism B). This mechanism is similar to that proposed in our studies of polymerisation.[15] The catalyst used by Sibi and Itoh can also use this mechanism, since it possesses a hydroxyl group. In this paper we study the mechanism of the reaction in order to elucidate the role of the catalyst and the impact of the different possible mechanisms on the enantioselectivity. Our mechanistic study also investigates the two possible conformations of the pyrazole ring (s-*cis* and s-*trans*, Scheme 1c).



Scheme 1 Mechanisms and pyrazole conformations.

Computational details

The mechanism of the reaction was first studied on a simplified model of the catalyst. Transition state and starting material structures were located using Gaussian03.[16] in toluene with B3LYP[17] functional and 6-31G**[18] basis set. Solvent effects were included by PCM model[19] The cavity for this PCM calculation was defined according to the UFF scheme. Vibrational contributions to Gibbs free energy were calculated at this level of theory. For each optimized structure, single point energy was calculated (MPWB1K[20,21]/6-31G**) with solvent (toluene) included implicitly by PCM model and UAKS[22] cavity definition. This energy was added to the Gibbs energy correction calculated previously. This correction contains the contribution of the translational entropy, that is overestimated[23] by the employment of the ideal gas approximation (accurate treatment of this contribution to the entropy is beyond the scope of this work[24]). Cancellation of error is expected when comparing Gibbs free energy barriers of transition states of identical molecularity (so the most important conclusions of this work are not affected), but this error has to be considered when comparing transition states or supramolecular structures composed of a different number of molecules, or when considering absolute ΔG values. Energy barriers are relative to the corresponding starting materials, in all cases.

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Studies on the enantioselectivity required the inclusion of the complete structure of the catalysts. Because of the large size of the system, and the necessity of considering different conformations of groups in the transition states, hybrid QM/MM ONIOM calculations were performed. Transition state structures were located using Gaussian03. The high level layer was treated with the B3LYP/6-31G** level of theory, and the low level layer was studied using the molecular mechanics UFF.[25] method. Vibrational contributions to Gibbs free energy were calculated at this level of theory. Extrapolated energy calculated by the ONIOM method might be affected by errors derived from the construction of the interface between layers. Therefore, single point energies on the complete optimized structures were calculated using pure DFT method. The calculation was performed using the Jaguar 7.0[26] program at the M05-2×[21,27]/6-31G** level of theory. This functional was chosen considering its reliability when reproducing long range interactions.[27] Solvent effects (trifluorotoluene) were included implicitly using a self-consistent reaction-field method as implemented in Jaguar 7.0[28] (dielectric constant: 9.28; probe radii: 2.525). Gibbs free energy corrections from previous calculations were added to the value of the solvation free energy.

Studies on the model system

First, we investigated the reaction mechanism for the Michael addition of O-methylhydroxylamine to pyrazole acrylate derivatives. These molecules were used as models of the different hydroxylamines used in the experimental work and of pyrazole crotonate. Previous studies on amine Michael addition to acrolein[12,29] reveal that lower activation barriers are obtained for an s-*cis* conformation of the acrolein, and in the case of s-*trans* conformation the reaction requires of the presence of an additional amine molecule to transport the proton. Our calculations on the addition of hydroxylamines to pyrazole crotonate derivatives also show the preference for the reaction on the C-C s-*cis* conformation of the electrophile (TS-1 and TS-2; Fig. 1). Concerted proton transfer in these transition states precludes the formation of zwitterionic species. The effect of the conformation of the pyrazole ring has also been investigated, and the most stable transition states correspond to the s-*trans* pyrazole orientation (TS-1). Transition states in which two hydroxylamines participate have also been found, but higher ΔG‡ values were obtained (TS-3 and TS-4; it is necessary to consider that entropy contribution for these transition states has been overestimated—see computational details—in comparison to TS-1 and TS-2). In these transition states, the second amine molecule has an active role in the transportation of the proton, according to a "proton switch" mechanism.[12,29]

In contrast to the results of the calculations on acrolein, addition to the s-*trans* C=C-C=O requires only one amine molecule (TS-5). Attempts to find transition states with the participation of more than one molecule were unsuccessful. QRC trajectory calculations[30] reveal that, in S-5, the nucleophile's proton is transferred to the pyrazole nitrogen leading to a zwitterionic product.

For the catalyzed reaction, the thiourea derived from aminoethanol was used as a model for the catalysts. Results are shown in Fig. 2. The Gibbs free energy of the formation of the complexes between the model catalyst and the substrate reveals that this complex formation is endothermic (3.4 kcal/mol), and, therefore, the energy barriers are referred to the isolated catalyst, substrate and nucleophile. (This thermodynamic parameter is affected by the inaccuracy in the calculation of the translational entropy—see computational details; enthalpies and zero-point energies of the complex formation are negative.)

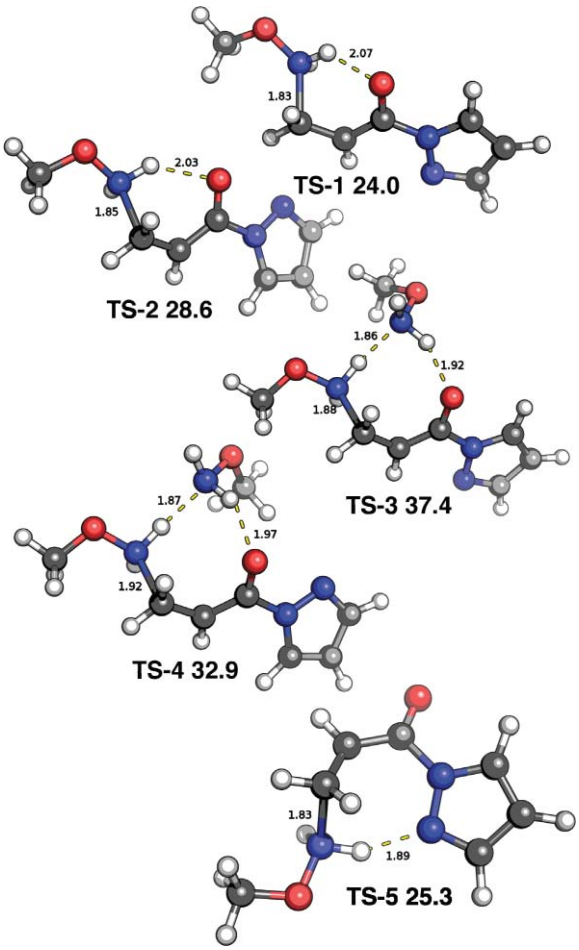


Fig. 1 Transition states for the uncatalyzed addition of methoxyamine to pyrazole acrylate. ΔG‡ energies expressed in kcal/mol; distances in Å.

Two different mechanisms have been considered, and for each mechanism, *cis* and *trans* conformations were studied around the α-C-β-C bond and the C(O)-imidazole N bond. In all transition state structures corresponding to mechanism B (TS-6 to TS-10 in Fig. 2), the hydroxy group of the catalyst is responsible for the proton switch mechanism. For mechanism A transition state structures, the amine proton is transferred to the electrophile oxygen (TS-11 to TS-14), or towards the imidazole nitrogen (TS-15), preventing the accumulation of charge in the transition states. This has been confirmed by means of QRC trajectory calculations.[30]

ΔG activation barriers calculated for the catalyzed transition state are smaller than the values obtained for TS-1 to TS-6. The preference for the catalytic pathways is even clearer if one considers that the inaccuracies in the calculation of translational entropy erroneously penalizes the catalytic transition states with respect to TS-1, TS-2 and TS-5 structures.

Transition states corresponding to mechanism A are 3–4 kcal/mol less stable than structures corresponding to mechanism B,

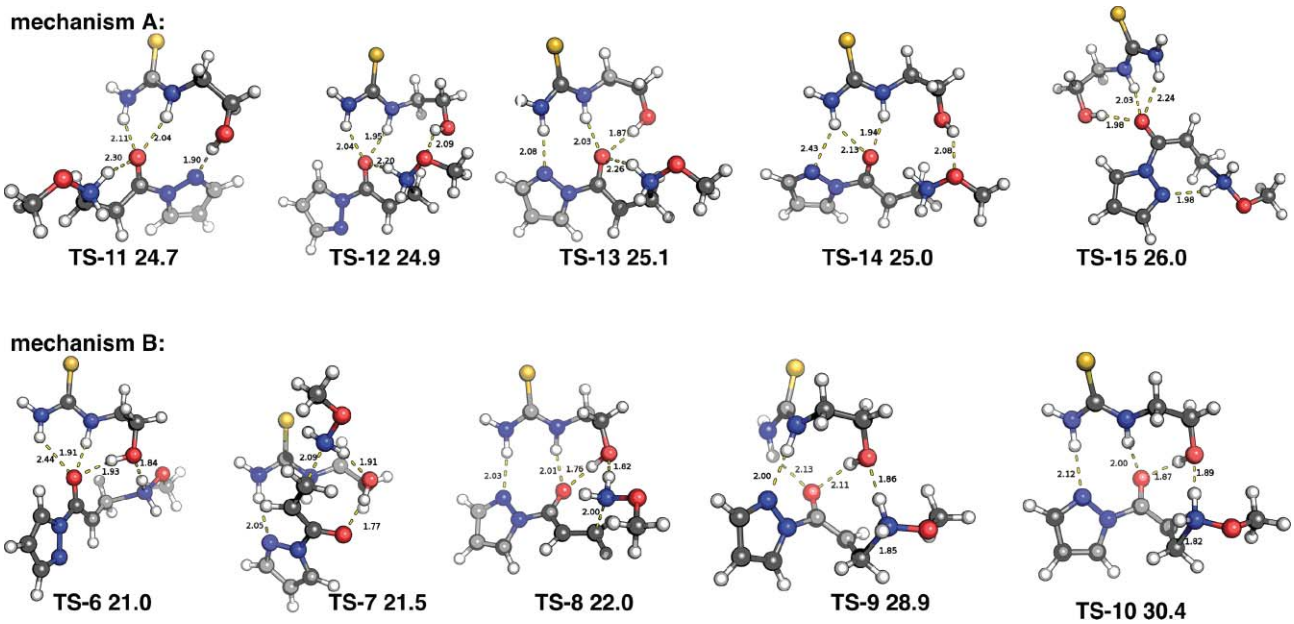


Fig. 2 Structure of transition states found for the model reaction. ΔG‡ energies expressed in kcal/mol; distances in Å.

in which the hydroxyl group of the catalyst is active in the proton switch mechanism. Structures with the α-C-β-C *trans* conformation (TS-9 and TS-10) are less stable than those with *cis* conformation. TS-8 shows the O=C-N-N group in the s-*cis* conformation, whereas TS-6 and TS-7 have this group in the s-*trans* conformation. These two structures have different H-bonds to the thiourea group: the carbonyl group in TS-6 and the pyrazole nitrogen for TS-7.

The pyrazole s-*trans* conformation of the substrate is 5.6 kcal/mol more stable than the s-*cis* conformation. This contrasts with the small energy difference observed between structures TS-6 and TS-7 or TS-8, and between complexes of the pyrazole s-*cis* and s-*trans* conformation (1.5 kcal/mol, see supporting information) indicating that H-bonds are more effective in the stabilization of the transition state and substrate with the pyrazole s-*cis* and s-*trans* substrate. Probably H-bonding prevents repulsion between oxygen and pyrazole nitrogen in the s-*cis* conformation. This is confirmed by the energy difference observed for mechanism B transition structures for s-*cis* and s-*trans* substrates catalyzed by methanol (see supporting information). In these transition structures, which lack the thiourea H-bond donors, the energy difference (5.9 kcal/mol) is similar to that observed in the substrates. Finally, as methyl substituents in the pyrazole ring might affect this relative stability, calculations of mechanism-B-like transition structures were repeated for acryloyl-3,5-dimethyl-pyrazole. The energy difference between the substrate conformations is raised to 9.0 kcal/mol, but the barrier for the pathway for TS-3 is raised to only 2.4 kcal/mol and to 1.9 kcal/mol for TS-2, relative to the barrier for TS-1.

Calculations on real catalysts

To test the feasibility of this mechanism, we performed ONIOM calculations[31] using the complete catalyst structure, reserving the expensive QM calculations for those atoms directly involved in the reaction. In Fig. 3, atoms in the high-level layer are represented

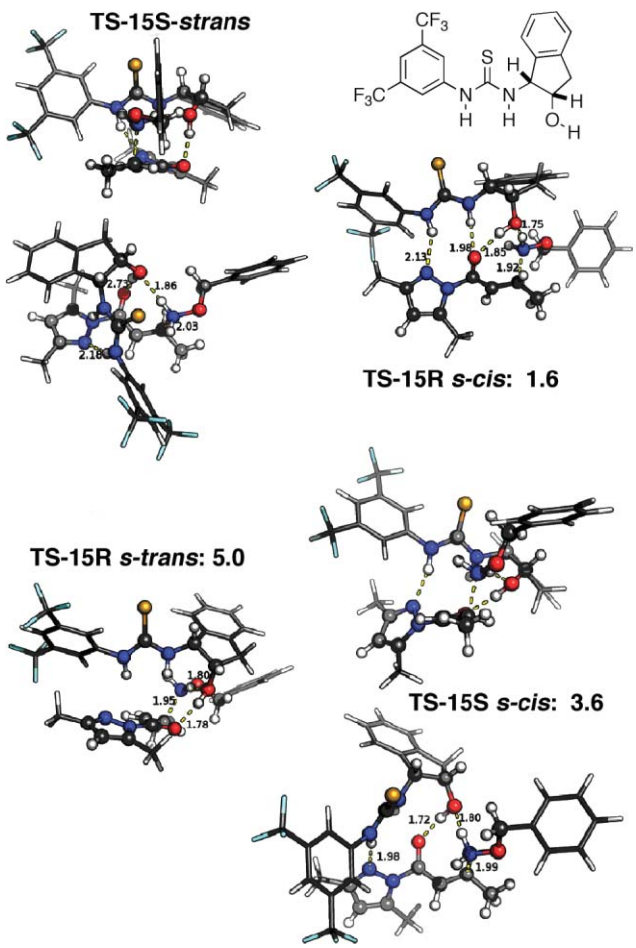
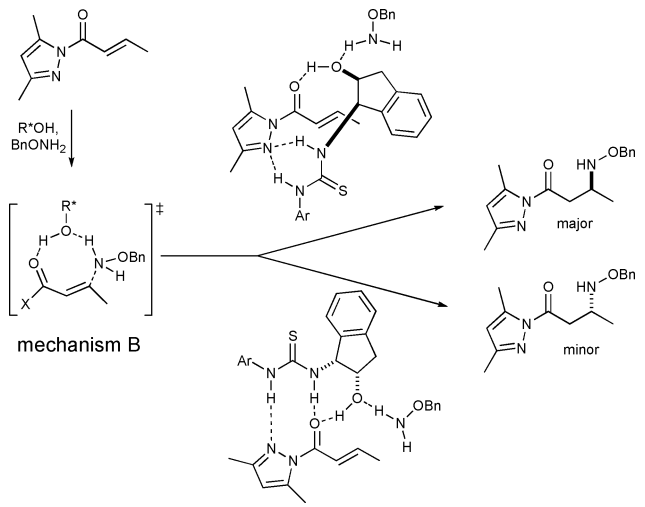


Fig. 3 Transition states obtained for the *cis* aminoindanol catalyst. ΔΔG‡ energies expressed in kcal/mol; distances in Å. Two views of TS-15*S* s-*trans* and TS-15*S* s-*cis* are included for clearer visualization.

by a "ball and stick" model, and atoms in the low-level layer are drawn by a wire model. Because of the energy differences between structures in mechanism A and B, only mechanism-B-like processes were included in this study. For the *cis* (1R,2S) aminoindanol-derived catalyst (Fig. 2), which shows a large enantioselectivity in the addition of O-phenylhydroxylamine (72% e.e., favoring the S product), four transition structures were obtained. Both R and S products can be generated from the O=C-N-N s-*cis* and s-*trans* conformation of the substrate. In the case of the R s-*trans* transition state (TS-15*R* s-*trans*), the rigidity of the indanol group in the catalyst precludes the adoption of the right conformation of the catalyst for the formation of H-bonds with the thiourea. This transition state is 5.0 kcal/mol less stable than the corresponding S transition state (TS-15*S* s-*trans*). When substrate s-*cis* conformations are considered, the transition state leading to the minor R product (TS-15*R* s-*cis*) shows a free energy difference of 1.6 kcal/mol compared with (TS-15*S* s-*trans*), in good agreement with experimental results (calculated e.e.: 88%; experimental e.e.: 72%, Scheme 2).



Scheme 2 Competing pathways: mechanism B (proton switch) is preferred for both major and minor products. The pattern of hydrogen bonding in the pathways leading to each is very different.

Higher enantioselectivities were observed when bulkier substituents in the nucleophile were employed. We repeated the calculations using O-(*tert*-butyldimethylsilyl) hydroxylamine. The energy difference between transition states corresponding to TS-15*S* s-*trans* and TS-15*R* s-*cis* is increased to 2.1 kcal/mol (calculated e.e: 94%; experimental e.e.: 94%).

We also tried to test the robustness of mechanism B by calculating the energy differences for a catalyst that gives poor enantioselectivity. These calculations might allow us to discover the origin of the lack of enantioselectivity in order to improve the design of future catalysts. We chose for this study the *trans* (1R,2R) aminoindanol derived catalyst (see supporting information), which yields poor enantioselectivity (19% e.e.). For this catalyst, the most stable transition structure (TS16-*S* s-*trans*) (Fig. 4) corresponds to an s-*trans* conformation in which the urea group establishes a H-bond with the pyrazole N atom. In the case of the analogous R transition state (TS16-*R* s-*trans*) this H-bond is missing since the catalyst is not able to adopt the right

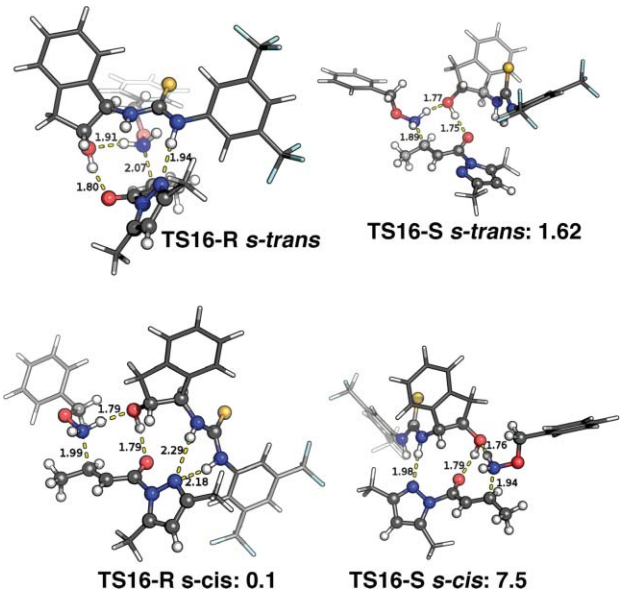


Fig. 4 Transition states obtained for the *trans* aminoindanol catalyst. ΔΔG‡ energies expressed in kcal/mol; distances in Å.

conformation. Remarkably, for the transition structures obtained for the s-*cis* conformation of the substrate, the urea H-bonds were formed with the pyrazole N atom, and not with the carbonyl oxygen. These bifurcated H-bonds between urea groups and sp^2 N atoms have already been proposed to explain the catalytic activities of thiourea groups in reactions on imine groups.[6] The very small free energy difference calculated for TS16-*R* s-*cis* transition state (0.1 kcal/mol, calculated e.e.: 11%) is in good agreement with the poor enantioselectivity observed.

Conclusions

We have shown that aminoindanol-derived thioureas are able to catalyze the conjugate addition of hydroxylamines to pyrazole-crotonate derivatives. The contribution of the uncatalyzed reaction is negligible. This is clear from the calculated ΔG barriers. The relative stability of s-*cis* and s-*trans* conformation in the substrate for the pyrazole ring is important, since the energy difference observed in favor of s-*trans* conformation in the starting materials is maintained for the transition structures. Nevertheless, this effect is reduced by the more efficient H-bond stabilization of the s-*cis* transition structures. This effect, observed in the model calculations, is crucial for the explanation of the stereoselectivity, since different enantiomers are generated from the s-*trans* and s-*cis* conformation of the pyrazole ring in the substrate (Scheme 2). The likelihood of this mechanism is reinforced by the good agreement between the observed enantioselectivity and the calculated enantioselectivity. We expect that, using these results, it will be possible to design catalysts which are able to form efficient H-bonds with the s-*trans* conformation and which will be even more enantioselective catalysts.

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