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JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Cinchona Urea-Catalyzed Asymmetric Sulfa-Michael Reactions: The Brønsted Acid–Hydrogen Bonding Model

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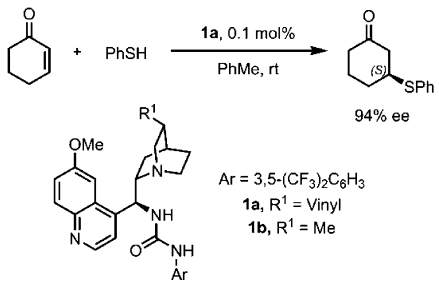
Supporting Information

ABSTRACT: The cinchona alkaloid-derived urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones was studied using density functional theory (DFT). Deprotonation of the thiol gives a protonated amine that activates the electrophile by Brønsted acid catalysis, while the urea group binds the nucleophilic thiolate by hydrogen bonding. These results demonstrate the generality of the Brønsted acid–hydrogen bonding transition state (TS) model for cinchona alkaloid catalysis that we recently showed to be favored over Wynberg's widely accepted ion pair–hydrogen bonding model and represent the first detailed mechanistic study of a cinchona urea-catalyzed reaction. The conformation of the catalyst methoxy group has a strong effect on the TS, an effect overlooked in previous mechanistic studies of reactions catalyzed by cinchona alkaloids.

We recently reported that Wynberg's cinchonidine-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones is explained by a new Brønsted acid–hydrogen bonding model, differing from the ion pair–hydrogen bonding model originally proposed by Wynberg, a pioneer in organocatalysis.[1]

We have now investigated an asymmetric conjugate addition reaction catalyzed by a cinchona alkaloid-derived urea (cinchona urea) reported by Singh and co-workers in 2010 (Scheme 1).[2] They proposed that their reaction proceeded via a Wynberg ion pair–hydrogen bonding type mechanism (Mode A, Figure 1). Other enantioselective transformations catalyzed by cinchona ureas include aldol,[3−5] cascade,[6] conjugate addition,[2,7−20] electrophilic bromination,[21] Mannich,[22] oxidation,[23] and Strecker[24] reactions. In these reactions, when comparison data have been reported, cinchona urea catalysts yield similar[6,7] or better[2−5,8−18,20,23,24] levels of enantioselectivity than their thiourea counterparts.

Scheme 1. Singh's Cinchona Alkaloid-Derived Urea-Catalyzed Asymmetric Conjugate Addition of Aromatic Thiols to Cycloalkenones



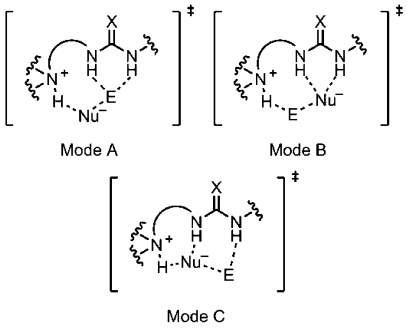


Figure 1. TS variants in (thio)urea-tertiary amine organocatalysis. X = S or O; E = electrophile, e.g., enone; Nu^- = nucleophile, e.g., thiolate.

Three different modes of activation have been proposed to explain thiourea-tertiary amine organocatalysis (Figure 1, X = S). Mode A was proposed by Takemoto,[25] Mode B by Pápai,[26] and Mode C by Wang.[27] These differ by how the three hydrogen-bond donors in the catalyst interact with basic sites on the nucleophile and electrophile. Experimental and computational work has provided some evidence for the validity of Modes A,[28−31] B,[26,32−35] and C.[27]

The only study of cinchona ureas is by Csámpai and co-workers, who used DFT to calculate $\Delta E^{\ddagger}$ for various cinchona (thio)urea catalysts in the enantioselective Michael addition of nitromethane to 1,3-diphenylpropenone.[36] Only Mode B was considered in their computational work, and transition states (TSs) leading to the minor product were not calculated. Given that urea is a much weaker acid than thiourea (pK_A = 26.9 and 21.1, respectively, in DMSO),[37,38] cinchona urea and thiourea catalysts may not proceed via the same mechanisms. Predicting the mechanism and stereochemical outcome of a cinchona urea-catalyzed reaction by extrapolation from previous thiourea mechanistic studies is therefore difficult.

We have studied Singh's cinchona urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones. The first

Received: May 17, 2016
Published: July 9, 2016

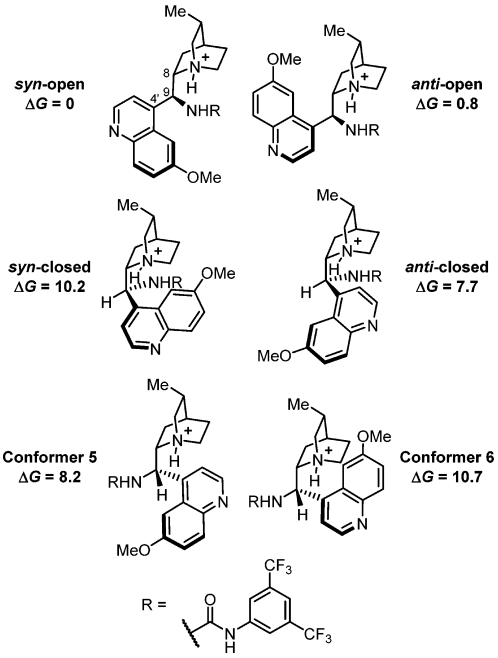
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DOI: 10.1021/jacs.6b05074
J. Am. Chem. Soc. 2016, 138, 9041−9044

step in this reaction is formation of the thiolate by the quinuclidine base leading to a thiolate−quinuclidinium ion pair.[1,26,27] This is followed by rate determining C−S bond formation.[39] In order to determine which catalyst activation mode (Figure 1, X = O) is preferred and to explain the observed stereoselectivity, we located TSs for the C−S bond forming step at the M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d)-IEFPCM(toluene) level of theory[40−44] using Gaussian 09[45] (see Supporting Information for full computational details). To simplify our calculations, the vinyl group on the quinuclidine ring was replaced by a methyl group (catalyst **1b**, Scheme 1).[46,47]

The conformations of the protonated urea catalyst were explored. Six principal conformations were generated from rotation about the C8−C9 and C9−C4′ single bonds (Scheme 2). Rotation about the C8−C9 bond interconverts the open,

Scheme 2. Principal Conformations of Protonated Catalyst 1b[a]



[a]All energies in kcal mol^{-1}.

closed, and final class of conformers.[47] *Syn* and *anti* refer to the orientation of the quinoline ring with respect to the heteroatom at C9. Our calculations show that the open conformations are strongly favored over the other C8−C9 bond rotamers and that the *anti*-open and *syn*-open conformers are close in energy. A *syn* orientation of the two N−H groups is preferred over the *anti* arrangement. These results are in agreement with Melchiorre who studied the conformational preferences of a cinchona amine[48] and Sunoj who studied the conformational preferences of a cinchona thiourea.[49] However, the *anti*-open TS conformation is favored over the *syn*-open TS arrangement by 3.2 kcal mol^{-1} (**TS-1** and **TS-3**, respectively, Figure S1). Therefore, only TSs that adopted the *anti*-open conformation were considered further.

A total of 78 unique prereaction complexes were located, the lowest energy of which involves close association of the thiolate and alkylammonium ions and hydrogen-bonding interactions from the urea group to the thiolate (Figure 2). The alkylammonium ion also interacts with the enone. The two

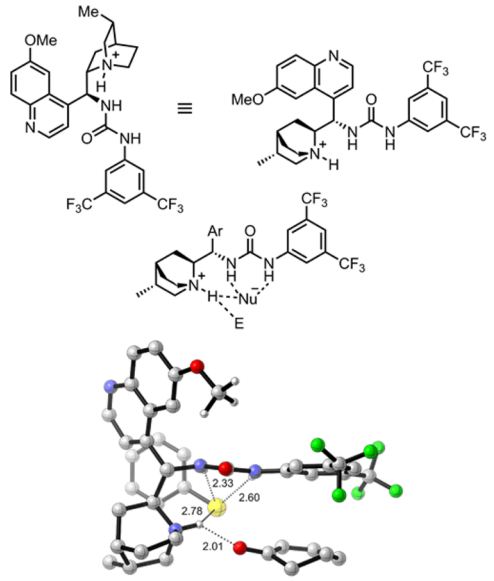


Figure 2. Lowest energy prereaction complex in the cinchona urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones. M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d)-IEFPCM(toluene). Noncritical hydrogen atoms omitted for clarity.

lowest energy TSs leading to the major and minor products via Mode B are shown in Figure 3. **TS-B(major)** is the lowest energy

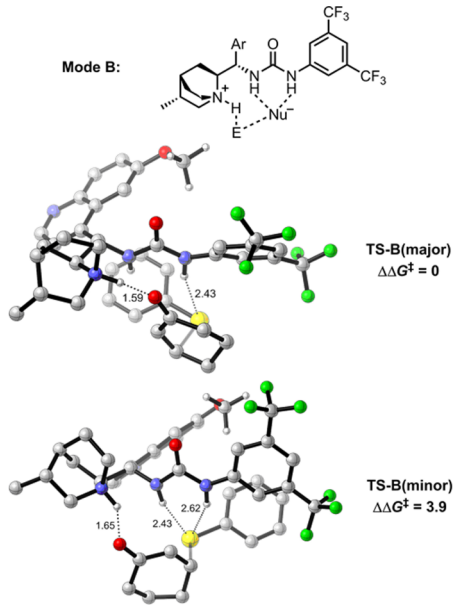


Figure 3. Mode B C−S bond-forming TSs in cinchona urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones. M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d)-IEFPCM(toluene). Noncritical hydrogen atoms omitted for clarity. All energies in kcal mol^{-1}.

TS and leads to the major product observed experimentally. From the lowest energy prereaction complex, the free energy barrier to **TS-B(major)** is 10.9 kcal mol^{-1}. Axial attack on the half-chair cyclohexenone is preferred over equatorial attack by 3.3 kcal mol^{-1}. **TS-B(minor)**, which leads to the minor product via Mode B, is destabilized relative to **TS-B(major)** by 3.9 kcal mol^{-1}. No obvious steric interactions contribute to this

DOI: 10.1021/jacs.6b05074
J. Am. Chem. Soc. 2016, 138, 9041−9044

difference in energy, but the geometry adopted by the substrate in **TS-B(minor)** results in a longer and less directional interaction from the quinuclidinium ion to the enone oxygen relative to **TS-B(major)** (N−H···O distance = 1.59 and 1.65 Å and N−H···O angle =151° and 143° in **TS-B(major)** and **TS-B(minor)**, respectively). Furthermore, a staggered conformation about the developing C−S bond is observed in **TS-B(major)**, and an eclipsed conformation is found in **TS-B(minor)** (CSCH dihedral = 69° and 6°, respectively). In contrast to **TS-B(minor)**, only one NH···S interaction is present in **TS-B(major)**, but the remaining urea NH interacts with the π system of the thiolate instead.

The two lowest energy TSs leading to the major and minor products via Mode A are shown in Figure 4 (**TS-A(major)** and **TS-A(minor)**). **TS-A(minor)** is destabilized relative to **TS-A(major)** by 0.8 kcal mol^{-1}. Both Mode A TSs are strongly disfavored relative to **TS-B(major)**.

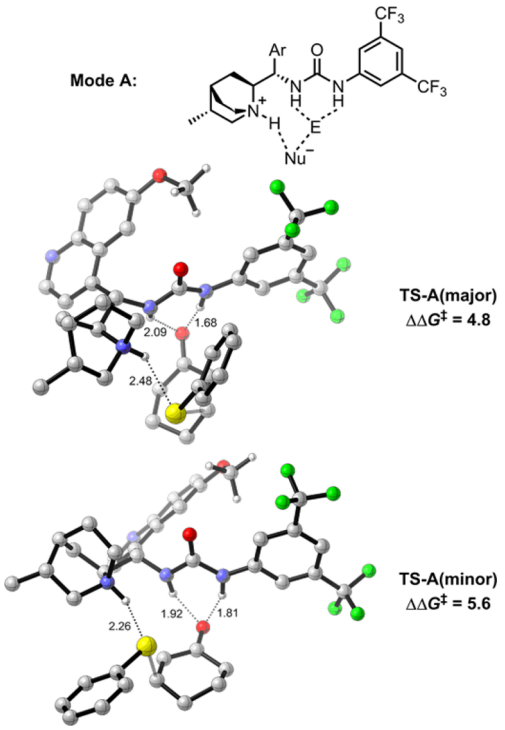


Figure 4. Mode A C−S bond-forming TSs in cinchona urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones. Free energies relative to **TS-B(major)**. M06-2X/def2-TZVPP-IEFPCM(toluene)//M06-2X/6-31G(d)-IEFPCM(toluene). Noncritical hydrogen atoms omitted for clarity. All energies in kcal mol^{-1}.

Mode B is preferred over Mode A because the developing alkoxide in the C−S bond-forming TS is stabilized to a greater extent by proton transfer from the quinuclidinium ion in Mode B than it is by the hydrogen-bonding interactions from the urea group in Mode A. The Mulliken atomic charge on the enone oxygen in **TS-B(major)** is −0.48 (calculated by M06-2X/def2-TZVPP-IEFPCM(toluene)).

The conformation of the quinoline ring's methoxy group has a strong effect on the TS energy. Starting from **TS-1** (Figure S1), rotation of the methoxy group by ∼180° so that the methyl group is oriented away from the urea oxygen gives a second TS (**TS-2**, Figure S1) that is 2.8 kcal mol^{-1} higher in energy and differs only in the conformation of the methoxy group. This is due to the unfavorable electrostatic interaction between the lone pairs of the methoxy and urea group oxygens. In Csámpai's study of the Michael addition of nitromethane to 1,3-diphenylpropenone catalyzed by cinchona urea catalysts, the methoxy group is in the less favored conformation.[36] This result highlights the need for a thorough approach to the conformational sampling of TSs in computational mechanistic studies.

TSs that adopted Wang's activation Mode C (Figure 1) could not be located, in agreement with work by Kótai et al., who could not locate this activation mode in their study of a bifunctional squaramide-catalyzed Michael addition.[35] Our attempts to find TSs of this nature optimized to Mode A TSs. Wang and coworkers proposed that activation Mode C explained the outcome of the direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam and chalcone catalyzed by a cinchona thiourea.[27] To examine the generality of their model, they also studied the Michael addition of nitromethane to chalcone catalyzed by a cinchona thiourea. However, in this further work, Mode B was not considered; closer examination of the TS reported for Mode C shows that it actually corresponds to Mode A, which raises doubts over the generality of activation Mode C. In these TSs, the methoxy group is in the less favored conformation.[50]

Urea catalyst **1a** yields higher levels of enantioselectivity than its thiourea counterpart (92% and 88% ee, respectively, under the same unoptimized conditions).[2] We performed calculations on the thiourea system and higher levels of selectivity are predicted for it ($\Delta\Delta G^{\ddagger}$ = 8.1 kcal mol^{-1} between major and minor TSs) relative to the urea catalyst. However, the self-association of bifunctional catalysts of this type has been well documented.[51−56] Upon self-association, the monomer, dimer, and higher aggregates can act as distinct catalysts with different selectivities.[54] In Singh's original paper,[2] the enantioselectivity of the reaction catalyzed by both the thiourea and urea catalysts decreases with increasing catalyst loading or decreasing temperature, suggesting catalyst aggregation is occurring.[52,54] The complexation energy of the thiourea is expected to be larger than the urea given the difference in their acidity.[37,38] A thiourea derivative was found to have a larger dimerization constant in solution compared to its urea counterpart.[57] Therefore, we propose that the urea catalyst performs better in Singh's reaction because it suffers from less aggregation. We also propose that the interaction between the methoxy group of the quinoline ring and the (thio)urea sulfur or oxygen helps prevent catalyst aggregation by increasing the steric demands around the sulfur or oxygen. This is supported by Singh's data which shows a large drop in enantioselectivity upon removal of this methoxy group for two thiourea catalyst systems (88% drops to 30% and −70% drops to −44%). This implies that if the steric environment around the sulfur or oxygen is increased further, no aggregation will be possible and concentration-independent enantioselectivities will be observed. This is seen in the new thiourea-based dimeric cinchona alkaloid catalyst system developed by Song.[56]

In summary, in the cinchona urea-catalyzed asymmetric conjugate addition of aromatic thiols to cycloalkenones, after initial proton transfer, the protonated amine activates the electrophile by Brønsted acid catalysis, and the urea group binds the nucleophile by hydrogen bonding. These results demonstrate the generality of our Brønsted acid−hydrogen bonding TS model for cinchona alkaloid catalysis and represent the first detailed mechanistic study of a cinchona urea-catalyzed reaction. The conformation of the quinoline ring's methoxy group has a strong effect on the TS energy, an effect overlooked in previous mechanistic studies of reactions catalyzed by cinchona alkaloids.

DOI: 10.1021/jacs.6b05074
J. Am. Chem. Soc. 2016, 138, 9041−9044

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05074.

Computational details and data and complete ref 45 (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to The English-Speaking Union (Lindemann Trust Fellowship to M.N.G.), Girton College, Cambridge (Research Fellowship to M.N.G.) and the NSF (CHE-1361104 to K.N.H.) for financial support. Computational resources were provided by the UCLA Institute for Digital Research and Education (IDRE) and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (OCI-1053575). Part of this work was performed using the Darwin Supercomputer of the University of Cambridge High Performance Computing Service (http://www.hpc.cam.ac.uk/), provided by Dell Inc. using Strategic Research Infrastructure Funding from the Higher Education Funding Council for England and funding from the Science and Technology Facilities Council. We thank Yu-hong Lam for helpful discussions regarding this work.

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DOI: 10.1021/jacs.6b05074
J. Am. Chem. Soc. 2016, 138, 9041−9044