Published in final edited form as:

ACS Catal. 2016 July 1; 6(7): 4616–4620. doi:10.1021/acscatal.6b01384.

Anion-Abstraction Catalysis: The Cooperative Mechanism of α -Chloroether Activation by Dual Hydrogen-Bond Donors

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Abstract

We provide here a detailed mechanistic characterization of the electrophile-activation step in a representative thiourea-catalyzed enantioselective reaction proposed to involve generation of ion-pair intermediates. Comparison of catalyst-promoted substrate epimerization with catalytic alkylation points to the participation of a common intermediate in both pathways and provides conclusive evidence for anion abstraction via an S_N1 -like pathway involving the cooperative action of two catalyst molecules.

GRAPHICAL ABSTRACT

Keywords

reaction mechanism; organocatalysis; anion-binding catalysis; anion-abstraction catalysis; ion-pairing catalysis

Dual hydrogen bond (H-bond) donors such as chiral urea, thiourea, and squaramide derivatives have gained prominence as important catalysts for a variety of highly enantioselective transformations involving ion-pair intermediates.^{1,2} As a general principle,

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures and characterization data, derivation of the rate law for epimerization, NMR kinetic procedures and data, Eyring analysis, discussion of relative rates, coordinates and energies for DFT structures (PDF)

Notes

The authors declare no competing financial interests.

the H-bond donor forms a stereodifferentiated environment around a reactive cationic intermediate by binding its counteranion, thereby controlling stereoselectivity of subsequent nucleophile addition.¹ Several distinct strategies for accessing the intermediate ion-pair complex have been proposed. These include: association of the H-bond donor to a pre-formed ion pair (Scheme 1A),^{2f} Brønsted acid co-catalysis, wherein the H-bond donor enhances the acidity of a weak acid by stabilizing its conjugate base (Scheme 1B),^{2d} and anion abstraction from a neutral substrate (Scheme 1C).^{2c} This last manifold has been invoked to explain a broad range of enantioselective reactions, but the detailed mechanism of neutral electrophile activation by H-bond donor catalysts remains poorly understood.

With the aim of gleaning insight that might ultimately guide the design of improved anion-abstraction catalysts, we recently undertook a detailed kinetic analysis of the enantioconvergent amido-thiourea-catalyzed alkylation of racemic α -chloroisochroman (**2**) with silyl ketene acetal nucleophiles (such as **3**, Scheme 2).³ This study revealed an unusual cooperative mechanism wherein the catalyst rests as a nonproductive dimeric aggregate (**1a•1a**) under typical reaction conditions (0.1 M in substrate, 10 mol% of catalyst); deaggregation is necessary before two molecules of the catalyst recombine with the substrates to enable rate-determining C–C bond-formation. While this analysis illuminated some of the causes for low catalyst efficiency, the specific roles of the two catalyst units in electrophile activation could not be determined through this kinetic investigation alone. Herein we describe advanced mechanistic characterization of the thiourea-catalyzed substitution reaction and report decisive evidence for anion abstraction via an S_N1-like pathway.

The alkylation reaction in Scheme 2 engages racemic chloroether ($\pm$)-**2** to produce a highly enantioenriched substitution product in high yield.^{2c} We initiated the mechanistic investigation by probing the basis for this stereoconvergence. Two limiting mechanisms could account for the catalytic conversion of both enantiomers of **2** to the same enantiomer of alkylation product **4**. In an S_N2 reaction manifold, the thiourea catalysts could effect direct activation of the chloride leaving group to enable stereospecific, invertive displacement (Scheme 3A).⁴ Within this mechanism, racemization of **2** by either a catalyst-independent (Scheme 3A-i) or a catalyst-promoted (Scheme 3A-ii) pathway must be rapid relative to alkylation in order to achieve >50% conversion through a dynamic kinetic resolution.^{5,6} In contrast, in an S_N1 reaction manifold, reversible catalyst-mediated ionization of the α -chloroisochroman **2** to form an oxocarbenium•chloride ion pair would activate the substrate to subsequent stereoselective nucleophile attack from either face of the prochiral oxocarbenium ion (Scheme 3B).^{4,7} Reversible collapse of the ion pair would lead to racemization of the substrate on the reaction time scale.⁸ We endeavored to design a set of experiments that would distinguish between each of these mechanistic possibilities.

We first sought to determine whether thiourea catalyst **1a** induces racemization of **2** under conditions relevant to catalysis. Enantioenriched α -chloroisochroman, **2**, could not be accessed, so it was not possible to track racemization by monitoring loss of optical activity. However, NMR spectroscopic techniques did afford methods for monitoring chemical exchange of the diastereotopic protons of racemic ($\pm$)-**2** over a range of timescales.⁹ The ¹H NMR signals for diastereotopic protons H^a/H^b or H^c/H^d (Figure 1A) do not coalesce in the

absence or presence of catalyst **1a**, even at temperatures as high as 70 °C in toluene-*d*₈, indicating that racemization must be slower than the differences in the Larmour frequencies of these protons (i.e. $k_{\text{rac}} < \sim 10^2 \text{ s}^{-1}$) at these temperatures.

In order to monitor chemical exchange on the slower spin–lattice relaxation (T_1) timescale, we applied a selective inversion–recovery (SIR) experiment.^{10,11} Competitive magnetization transfer by nuclear Overhauser effect (nOe) pathways could be minimized by studying the epimerization of α -chloroisochroman-*d*₃ (as a mixture of diastereomers **5a** and **5b**, Figure 1A) as a proxy for racemization. With these considerations, chemical exchange could be readily detected in the presence of catalyst.¹² The SIR data obtained over a range of total catalyst concentrations, $[1]_{\text{T}}$, were fit in order to extract values for the 1st-order rate constants, k_{obs} , and the spin-lattice relaxation constant, T_1 .¹³ In this manner, it was possible to establish that the rate of epimerization is correlated directly with $[1]_{\text{T}}$ with both thiourea **1a** and its urea analog, **1b** (Figure 1B, C). No epimerization occurs in the absence of catalyst. This result effectively rules out a stereospecific mechanism for catalytic alkylation that relies on catalyst-independent substrate racemization (Scheme 3A-i).

On the basis of the epimerization rate data alone, the S_N1 mechanistic manifold (Scheme 3B) cannot be distinguished from an S_N2 mechanism involving catalyst-mediated α -chloroisochroman racemization (Scheme 3C). However, racemization of **2** through an S_N1 mechanism should be inhibited by exogenous chloride sources.⁴ In contrast, racemization through an S_N2 mechanism should be promoted by an increased concentration of an exogenous chloride nucleophile. Accordingly, the SIR experiments were repeated with the addition of tetraoctylammonium chloride or hydrogen chloride (such that $[\text{Cl}^-] = [1]_{\text{T}}$). In both cases, the exogenous chloride sources suppressed epimerization completely within the limits of detection.

Taken together, the data are most consistent with an S_N1 mechanism for substrate racemization, wherein catalyst-promoted substrate ionization leads to formation of an oxocarbenium•chloride ion pair. Substrate epimerization and alkylation share the same kinetic dependence on catalyst and α -chloroether, indicating that the two processes share a common transition-state stoichiometry. Direct comparison of the rate laws reveals that epimerization catalyzed by **1a** or **1b** is 10^1 – 10^3 times faster than alkylation ($k_{\text{rel}} = k_{\text{epi}}/(k_{\text{cat}} \cdot [\mathbf{3}]) \sim 4$ – 13 for **1a**; $k_{\text{rel}} = k_{\text{epi}}/(k_{\text{cat}} \cdot [\mathbf{3}]) \sim 150$ – 440 for **1b**),¹⁴ as would be necessary for alkylation via either the dynamic kinetic resolution manifold in Scheme 3C or the stereoablative S_N1 mechanism in Scheme 3B. While the two possibilities are indistinguishable based on the kinetic data, the fact that the highly electrophilic oxocarbenium•chloride ion pair is generated in the epimerization implicates it as an intermediate in the alkylation as well. Accordingly, we propose that the alkylation reaction proceeds via the anion-abstraction ion-pairing mechanism depicted in Scheme 3B.

Analysis of the α -chloroether epimerization kinetics also sheds light on the mechanism by which dual H-bond donors effect anion abstraction. Catalysts **1a** and **1b** have been shown to exist predominantly in dimeric states under the conditions examined in this study.³ The apparent 1_{st}-order dependence of epimerization on $[1]_{\text{T}}$ (Figure 1B) is therefore indicative of the transition structure for anion abstraction engaging two molecules of catalyst. The

deviation from 1_{st}-order dependence on $[\mathbf{1b}]^T$ is analogous to the kinetic behavior observed for alkylation with both $\mathbf{1a}$ and $\mathbf{1b}$,³ wherein a shift to a deaggregated monomeric resting state results in a 2_{nd}-order dependence on catalyst at low $[\mathbf{1b}]_T$.¹⁵

Two different mechanisms for cooperative anion abstraction consistent with this kinetic analysis are depicted in Figure 2. Anion abstraction via “4H”-binding would involve simultaneous association of both dual H-bond donor motifs directly to chloride during the abstraction event. This type of 4H-anion binding is observed between thiourea $\mathbf{1a}$ and chloride in the solid state.³ Cooperative anion abstraction via “2H”-binding could proceed via association of one H-bond donor to another, resulting in a stronger dual H-bond interaction with the anion. A 2H-activation mode has been invoked by Smith and others to describe reactions enabled by designed, linked H-bonddonor catalysts for activation of carbonyl compounds.¹⁶ Both mechanisms in Figure 2 proceed through the same transition state stoichiometry and are, therefore, kinetically indistinguishable. We probed the 4H- and 2H-ground state $(\mathbf{1})_2 \cdot \text{Cl}^-$ complexes computationally using density functional theory (DFT), and found that they are remarkably similar in energy across different functionals, basis sets, and solvation models.¹⁷ As such, it is likely that both activation modes are energetically accessible; the dominant pathway may depend on the specific reaction parameters. The development of dimeric catalysts specifically linked in ways that enforce either of the two proposed activation modes may shed light on the operative mechanism and is expected to lead to more active catalysts with enhanced anion-abstraction capabilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This work was supported by the NIH (GM-43214) and by fellowships to D.L. (NSERC PDF), D.D.F. (Eli Lilly and Co.) and C.R.K. (NSF DGE1144152). The authors thank Dr. Sarah E. Reisman (Caltech) and Dr. Stephan J. Zuend (BASF) for contributions to the early stages of this project and for numerous helpful discussions, and Dr. Eugene E. Kwan for helpful discussions.

ABBREVIATIONS

Ar^F	3,5-bis(trifluoromethyl)phenyl
DFT	density functional theory
E	generic electrophile
nOe	nuclear Overhauser effect
SIR	selective inversion–recovery

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A. 4H-Anion-Abstraction **B. 2H-Anion-Abstraction** **Figure 2.**

Two potential cooperative modes of chloride abstraction. E = generic electrophile

A. Binding Pre-Formed Ion Pairs^b **B. Brønsted Acid Co-Catalysis^c** **C. Anion-Abstraction Catalysis^d**

^a Ar^F = 3,5-bis(trifluoromethylphenyl). ^b See ref 2f. ^c See ref 2d. ^d See ref 2c, 3.

Scheme 1. Activation modes in anion-binding catalysis by dual H-bond donors.^a

Scheme 2.
Model system for mechanistic analysis.

Scheme 3. Possible Mechanisms for α -Chloroisochroman Activation.