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Steric Effects of pH Switchable, Substituted (2-pyridinium)urea Organocatalysts: a Solution and Solid Phase Study

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Abstract

The study of hydrogen bonding organocatalysis is rapidly expanding. Much research has been directed at making catalysts more active and selective, with less attention on fundamental design strategies. This study systematically increases steric hindrance at the active site of pH switchable urea organocatalysts. Incorporating strong intramolecular hydrogen bonds from protonated pyridines to oxygen stabilizes the active conformation of these ureas thus reducing the entropic penalty that results from substrate binding. The effect of increasing steric hindrance was studied by single crystal X-ray diffraction and by kinetics experiments of a benchmark reaction.

Keywords

urea catalysis; organocatalysis; hydrogen bonds

Introduction

Organocatalysts have proved their utility in the decades since their development as reaction accelerants.^{1–6} Ureas and thioureas are common hydrogen bonding (HBing) motifs for organocatalysts. Early studies of ureas have focused on co-crystallization for molecular recognition,⁷ and have since developed into a field of its own.^{8–10} Urea organocatalysis¹¹ followed soon after. Schreiner and coworkers developed a more active thiourea catalyst¹² by incorporating two electron-deficient arenes to strengthen the HB donors. This catalyst is commercially available, and used as a benchmark for novel HB catalysts.^{13–16} Analysis of Schreiner's catalyst suggested that C-H...S=C HBs from the flanking electron-deficient arenes kept the structure in a planar and active conformation, with both NH donors pointing away from the sulfur of the thiocarbonyl.¹⁷ In a complementary approach, Seidel introduced a protonated, 2-pyridyl thiourea.¹⁸ There, an intramolecular hydrogen bond between the pyridinium NH and the sulfur of the thiocarbonyl enhanced preorganization while simultaneously strengthening the urea NH HB donors. The protonated 2-pyridyl urea/thiourea catalysed reactions between *trans*- β -nitrostyrene (BNS) and indole reached full conversion almost 100 times faster than a comparable, neutral, thiourea organocatalyst. Employing an internal acid to preorganise catalyst structure and enhance activity has also

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Declaration of interest

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been exploited by Mattson,¹⁴ with internal Lewis acids, and Kass,¹³ through *N*-methyl pyridinium enhanced C-H HBs.

Recently developed chiral HB organocatalysts^{19–23} have enabled enantioselective reactions, based on pioneering work by Jacobsen,²⁴ Connon,²⁵ Rawal,²⁶ and others. Many of these bifunctional organocatalysts impart enantioselectivity by appending chiral groups to the periphery of the scaffold near the active site. The chiral group interacts with the substrate through various noncovalent interactions (e.g. sterics, HBing, ion pairing). Here we present a systematic investigation of how increasing steric occlusion at the active site of urea-based organocatalysts influences catalyst activity.

Materials and Methods

The effect of sterics on urea organocatalyst activity was investigated by solid-state and solution studies. The size of the substituted group was systematically increased near the active site, and the active catalyst conformation was promoted with an intramolecular pyridinium HB to the urea oxygen. When increasing the substituent size, one must also consider the role of attractive London-dispersion forces. However, it has been shown that intermolecular dispersion is diminished in solution.²⁷ The catalysts were inspired by the work of Seidel's pyridinium activated thiourea.¹⁸ A charged, pyridinium was used to activate the ureas, preorganise their conformation, and facilitate crystallization for solid-state studies. Preorganization in this system serves two purposes: it orients the urea NH protons away from the carbonyl, and allows the steric environment to be controlled by substituting the pyridines. The other urea NH is kept in the “down” conformation by a weak CH HB from the phenyl ring.^{7,17}

The starting material for the phenyl derivative (**3c**, Figure 1) was synthesized via a Suzuki-Miyaura cross coupling between 2-amino-3-bromopyridine and phenylboronic acid. The pyridines required for the synthesis of the hydrogen and methyl derivatives (**3a/b**) were commercially available. The ureas were formed by mixing the appropriate 2-aminopyridine with phenyl isocyanate. After purifying the free-base ureas (**2a/b/c**) using flash chromatography, each urea was protonated by bubbling HCl gas through a MeOH solution of the free-base. The chloride salts of the protonated ureas (**1a•Cl**, **1b•Cl**, **1c•Cl**) were purified by recrystallization, and then subjected to anion metathesis with NaBARF (sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate). The BARF salts of the ureas were also purified by recrystallization from CHCl₃, and dried on vacuum before use.

Results and Discussion

The three free-base scaffolds (**2a/b/c**) each had revealing ¹H NMR spectra (CDCl₃): The N1-C_{urea} bond rotates such that the pyridine nitrogen accepts an intramolecular HB from the proton on N2 of the urea (Figure 1), shifting the urea N2H peak significantly downfield (**2a**: 11.79 ppm, **2b**: 12.14 ppm, **2c**: 12.06 ppm). However, when the pyridine is protonated with HCl, the N2H signal shifts upfield to (**1a•Cl**: 9.95 ppm, **1b•Cl**: 11.40 ppm, **1c•Cl**: 11.01 ppm), and the N1H proton signal shifts downfield (**1a•Cl**: 13.52 ppm, **1b•Cl**: 11.86 ppm, **1c•Cl**: 11.94 ppm) presumably due to HBing to the chloride counteranion, and from the

electron-withdrawing nature of the pyridinium. Once protonated, the $N_{Py}H$ signal appears very far downfield (**1a**·Cl: 15.10 ppm, **1b**·Cl: 15.65 ppm, **1c**·Cl: 15.86 ppm), consistent with an aromatic intramolecular hydrogen bond.

Single crystal X-ray diffraction was used to determine the preferred conformation of the free bases and the protonated ureas with different guests in the solid state. Analysis of crystal structures of the protonated ureas with different guests indicated that subtle steric interactions influence the conformation of the guest. Crystal structures of the free bases further validate the solution NMR data (Figure 2). Indeed, intramolecular HBing ($N_{Py} \cdots HN2$, **2a**: 1.89(2) Å, 142(2)° **2b**: 1.892(15) Å, 139.6(14)° **2c**: 1.914(17) Å, 141.8(15)°) puts the urea NH protons into an “up, down” conformation for all three free bases. In this conformation the ureas are only capable of donating one HB to a single guest. Therefore, the free base conformation should be inactive as a catalyst as stronger activation is anticipated when multiple HBs are operable.

The free bases were protonated with TFA to observe the effect of protonation on conformation and guest binding. The crystal structures (Figure 3) showed that the pyridine nitrogen was protonated and that sterics have a strong influence on the guest binding conformation. In all three cases (**1a**·TFA, **1b**·TFA, and **1c**·TFA) the trifluoroacetate anion (TFA^-) accepts HBs from the urea NH protons, yet each anion adopts a different conformation due to the steric influences of the catalysts. The hydrogen derivative (**1a**·TFA) donates two monodentate urea NH HBs to each of the TFA^- oxygens ($\angle N1H \cdots O$ 1.833(16) Å, 170.9(19)°; $\angle N2H \cdots O$ 1.970(16) Å, 167.9(17)°). The TFA^- is rotated such that the O-C-O plane deviates from the urea N-C-N plane by only 4.29(5)°. This binding conformation was expected due to inspiring work by Kilburn and coworkers on an analogous thiourea binding anions.²⁸ During their work, they showed that a single methyl group *ortho* to the urea changes the binding mode for the anion. Here, the methyl derivative (**1b**·TFA) donates two HBs to a single bifurcated HB acceptor of the TFA^- ($\angle N1H \cdots O$ 2.014(19) Å, 151.3(17)°; $\angle N2H \cdots O$ 1.851(19) Å, 160.7(17)°).

Here, the TFA^- is rotated 56.75(14)° from coplanarity. The phenyl derivative (**1c**·TFA) also donates two HBs to only a single oxygen of the TFA^- . In this crystal structure, the TFA^- is almost completely orthogonal to the urea at 84.88(17)°. The structures illuminate that protonation changes the conformation of the ureas and increased steric hindrance around the active site leads to increased orthogonality in guest binding.

The BARF salts (**1a**·BARF, **1b**·BARF, and **1c**·BARF) were synthesized to increase solubility in organic solvents, and to minimize competitive HB interactions with the anion. A crystal structure of **1a**·BARF (Figure 4) was obtained to determine if the urea would retain its preorganization without a HBing counter anion in the active site. As predicted, **1a**·BARF does not appreciably HB to the BARF anion, and the structure retains its active “down, down” preorganised conformation. **1a**·BARF dimerizes in an antiparallel head-to-head fashion, leaving the active site open. This dimerization arrangement has also been observed in similar 2-pyridyl amide structures,²⁹ suggesting a potential application in crystal engineering.

The reaction between *N*-methylindole and BNS is a prototypical choice to screen urea organocatalysts,^{30–32} and was employed here as well. Chloroform was chosen as the solvent to ensure the intramolecular HB remained operable, as well as to encourage HBing between the nitro group on BNS and the urea. A 6 mol % catalyst loading was chosen to allow comparison to other reports in a similar range of catalyst concentrations.^{13,14,16} **1a**·BARF is the most active catalyst (Figure 5), accelerating the reaction with a $k_{\text{rel}} = 23.4$, followed sequentially by **1b**·BARF ($k_{\text{rel}} = 3.7$) and **1c**·BARF ($k_{\text{rel}} = 1.0$). In contrast, the free bases displayed negligible conversion (< 1%) for **2a**, **2b**, and **2c** after 48 hours under the same conditions. Previous reports have already demonstrated that the reaction does not proceed through Brønsted acid catalysis.³³

Due to the lack of activity from the free-base containing reactions, it is evident that protonation of the pyridine is crucial to catalyst activity. Protonation eliminates the intramolecular $\text{N}_{\text{Py}} \cdots \text{HN2}$ HB and forces the urea into an a “down, down” conformation, activating and preorganizing the urea through a $\text{N}_{\text{Py}}\text{H} \cdots \text{O}=\text{C}$ HB. Furthermore, the same reaction catalysed with Schreiner’s thiourea under the same conditions resulted in only minimal conversion after 72 hours ($6.0 \pm 0.2\%$). As such, pyridyl urea organocatalysts show promise for the future development of efficient HB organocatalysts.

It has been proposed in the past that *ortho*-substituted aryl thioureas lack the preorganization to act as effective catalysts, and show negligible activity.¹⁷ The rationale for this lies in the low calculated barrier of rotation for *ortho* substituted thioureas. However, the molecules studied in this work contain a better HB donor ($\text{N}_{\text{Py}}\text{-H}^+$) and a better HB acceptor (the urea oxygen). Therefore, the ureas studied herein should have a higher barrier to rotation than non-pyridinium based thiourea organocatalysts, which rely on comparatively weaker C-H HBs to the sulfur of a thiocarbonyl. The higher barrier to rotation will keep these ureas in the active conformation, and will minimize the entropic penalty usually incurred from substrate binding.

The TFA^- crystal structures (Figure 3) and kinetics data (Figure 5) can be used to rationalize the effect sterics have on catalyst activity. The effect of sterics on an electron dense transition state becomes apparent when considering the TFA^- as a nitro-group transition-state analogue. As noted above, **1a** donates two monodentate HBs to each oxygen in **1a**·TFA within the ideal range ($< 2 \text{ \AA}$, $170 \pm 10^\circ$). Additionally, the CO·H angles (CO·HN1 $114.4(6)^\circ$, CO·HN2 $109.7(6)^\circ$) indicate optimal interactions with lone pair electron density on the TFA^- ($115 \pm 10^\circ$).³⁴ In contrast, **1c**·TFA displays bidentate HBing to the TFA^- , with longer contacts (N1H·O $2.207(14) \text{ \AA}$, N2H·O $2.033(19) \text{ \AA}$) and less favourable angles (N1H·O $152.2(19)^\circ$, N2H·O $161.2(18)^\circ$). Only one of the TFA^- CO·H angles (CO·HN1 $139.5(6)^\circ$, CO·HN2 $120.5(6)^\circ$) is somewhat favourable. A similarly destabilised binding mode is present in **1b**·TFA, albeit to a smaller extent. This distance from the substituted carbon on the pyridine to the carbonyl carbon of the TFA^- is $4.5431(18)$, $4.994(2)$, and $5.204(2) \text{ \AA}$ for **1a**·TFA, **1b**·TFA, and **1c**·TFA respectively. As the substituent on the pyridine increases in size, the guest is pushed farther away, and forms weaker HBs. Even when binding an anionic guest, **1b** and **1c** are unable to form ideal contacts, where **1a** can. More favourable HB contacts in the solid-state correlate with increased catalytic activity.

The acidity of the urea NH protons could also influence catalytic activity.³⁵ It is possible that the attenuated activity of **1b**·BARF and **1c**·BARF is influenced by a significant change in the urea NH HB strength. Experimentally measuring the pK_a of the urea NH protons was not tractable as the conformation of these ureas are pH sensitive and the pyridinium-NH has a lower pK_a than the urea NH protons. Therefore, the proton affinity of the urea nitrogens (N1 and N2) were calculated computationally in the gas phase at the B3LYP/6-31++G(d,p) level of theory. The resultant proton affinities for the N1 nitrogen on **1a**, **1b**, and **1c** are 1047.0, 1051.6 and 1069.9 kJ·mol⁻¹, respectively. For N2, the proton affinities of **1a**, **1b** and **1c** are 1124.0, 1128.6, and 1142.5 kJ·mol⁻¹, respectively. These small range of proton affinities (22.9 kJ·mol⁻¹ for N1, and 18.5 kJ·mol⁻¹ for N2) suggest that the various substitutions have a negligible effect on the acidity, and HB donating ability, of these ureas (compare the proton affinities for the structurally similar ammonia and methylamine,³⁶ = 47.7 kJ·mol⁻¹ which have aqueous pK_as of 9.2³⁷ and 10.6³⁸ respectively.). Thus, the steric influence in these ureas has the largest influence on binding.

A co-crystal of the BARF salt with BNS provided further insight into the reaction being studied. A diffraction quality crystal of **1c**·BARF·BNS was obtained by slowly evaporating a 1:1 solution of **1c**·BARF and BNS in CHCl₃. Despite the ubiquity of reactions involving BNS in the literature, this is the first example of BNS cocrystallized with an organocatalyst, and one of only two other examples of ureas hydrogen bonding to a nitro group.^{7,39} The BNS binds to the urea as expected, with the nitro group oxygens HBing to the urea NHs (Figure 6). However, the HBs are not ideal due to the steric influence of the phenyl ring in **1c**·BARF. The average torsional angle between the plane of the nitro group and the urea NCN plane is 21.53(27)° (for strong HBs these would be coplanar, 0°). The lack of favourable guest binding modes in the **1c**·BARF and **1c**·TFA crystal structures highlights that increasing the sterics proximal to the active site inhibits substrate binding. Unfavourable binding reduces the Lewis acidic activity of these organocatalysts.

Here, model organocatalysts were designed and synthesized to study the effect of sterics on the activation of BNS. 2-pyridyl ureas were chosen to allow the catalyst to be activated by pH changes (through both preorganization and increased HB donation). Crystal structures provided insight into the binding mode of these ureas, indicating that repulsive steric interactions are detrimental to ideal binding. Calculations of the proton affinities showed that the acidity, and therefore the HB ability of the ureas, is not largely influenced by sterics. In contrast, the kinetic results show that the most sterically hindered urea was the poorest catalyst. Therefore, sterics play a large role in the activity of urea organocatalysts. These results can be extrapolated to organocatalysts with chiral auxiliaries: enantioselective catalyst design should properly balance the desired stereocontrol with the detrimental effect of sterics.

Supplementary Material

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Figure 1.
 Synthesis of urea organocatalysts

Figure 2. Crystal structures of **2a** (top), **2b** (middle) and **2c** (bottom) highlighting the intramolecular HB observed in the free-bases.

Figure 3.

Crystal structures of **1a**·TFA (top), **1b**·TFA (middle), and **1c**·TFA (bottom), highlighting the effect of steric hindrance on guest binding geometries.

Figure 4. Crystal structure of **1a·BARF** (BARF anions omitted for clarity). The urea retains its preorganization even when paired with a weakly coordinating anion.

Figure 5.

Kinetic data of the reaction between *N*-methylindole (75 mM) and *trans*- β -nitrostyrene (25 mM) catalysed by **1a-BARF**, **1b-BARF**, **1c-BARF**, and uncatalysed.

Figure 6.
Crystal structure of **1c·BARF·BNS** (BARF anions omitted for clarity), displaying the unfavourable offset binding of BNS in the active site.