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## Acceleration of a Dipolar Claisen Rearrangement by Hydrogen Bonding to a Soluble Diaryl Urea

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Summary: The Claisen rearrangement of 6-methoxy allyl vinyl ether is catalyzed by a soluble diaryl urea, and evidence is presented that the urea stabilizes a dipolar transition state by hydrogen bonding.

We have recently prepared the soluble diaryl urea 1a and shown that it increases the stereoselectivity of radical allylation reactions of several sulfoxides. For example, allylation of 2 in the absence of 1a provided 3-*trans* and 3-*cis* in a ratio of 2.5/1, while the ratio increased to 7/1 when 1 equiv of 1a was added.<sup>1a</sup> This modest increase in selectivity was comparable to the effects exerted by protic solvents (such as CF<sub>3</sub>CH<sub>2</sub>OH) or traditional Lewis acids (such as ZnBr<sub>2</sub>).<sup>1b</sup> The major effect of 1a may be steric shielding of one face, as illustrated by complex 4. To investigate possible effects of 1a on non-radical reactions, we are surveying several types of reactions that are prone to acceleration by protic solvents or Lewis acids. This Letter reports significant accelerations that we have observed in Claisen rearrangements and attributes these accelerations to hydrogen bonding.



The rate of the Claisen rearrangement of 6-phenyl allyl vinyl ether (5a) at 100°C increased slowly but steadily upon addition of increasing amounts of 1a; when 1 equiv of 1a was added, the reaction was accelerated by a factor of about 4 (Table 1, upper entries).<sup>2</sup> The rate of rearrangement of 6-methoxy allyl vinyl ether (5b)<sup>3</sup> at 80°C (Table 1, lower entries) increased even more—up to a factor of 22 when 1 equiv of 1a was added. Significant accelerations in the rearrangement of 5b were noted even when catalytic amounts (0.1 or 0.4 equiv) of 1a were added. At 50°C, a factor of 34 increase in the rate of rearrangement of 5b was estimated<sup>4</sup> when 1 equiv of 1a was added.

Claisen Rearrangements	Substrate	T (°C)	equiv 1a	k (x 10 <sup>-5</sup> s <sup>-1</sup> )	k <sub>rel</sub>
$ \begin{bmatrix} 3 \\ 0 \\ 1 \\ 6 \end{bmatrix}^{4} \underbrace{\qquad}_{5} \underbrace{\qquad}_{5} \underbrace{\qquad}_{6} \begin{bmatrix} 0 \\ 0 \end{bmatrix} $	5a 5a 5a 5a	100 100 100 100	none 0.2 0.5 1.0	0.4 0.7 1.3 1.8	1 1.7 3.1 4.2
Ř Ř	 5 b	80	none	0.6	1
5a R ≖ Ph (all <i>E</i> ) 5b R = OMe ( <i>E</i> / <i>Z</i> = 2.6/1)	5 b 5 b 5 b	80 80 80	0.1 0.4 1.0	1.6 3.1 13.7	2.7 5.0 22.4

Table 1. Rearrangements of 5a,b with 1a in  $C_6D_6$ 

Control experiments provide insight into the origin of the accelerating effect of urea 1a (Table 2). Replacement of urea 1a by N,N-dimethyl urea 6 (no hydrogen bonds possible) completely negated the accelerating effect, while benzanilide 7 (one hydrogen bond possible) gave a small acceleration. The addition of 5 equiv of DMSO actually sped up the reaction a little; however, when the same amount of DMSO was added to the reaction containing urea 1a, the accelerating effect of the urea was lost. The thiourea analog 1b was not as effective as 1a in promoting this rearrangement.<sup>5</sup> Rearrangement of the allylic regioisomer of 5b (4-methoxy allyl vinyl ether,<sup>3a</sup> not shown) in the presence of 1a provided the isomeric product (5-methoxy-4-pentenal, not shown), thus suggesting that the rearrangement in the presence of 1a does not proceed through an ion pair.

	Additive	$k (x \ 10^{-5} \ s^{-1})$	k <sub>rel</sub>	
	none	0.6	1	
	1 equiv 6	0.6	1.0	
	l equiv 7	1.0	1.6	
	5 equiv DMSO	1.2	1.9	
	5 equiv DMSO and	0.8	1.3	
	1b	nd*	34	
	*Not deter	mined, see reference	ce 5	
C <sub>8</sub> H <sub>17</sub> O <sub>2</sub> C		`CO₂C8H17 (	C <sub>8</sub> H <sub>17</sub> O <sub>2</sub> C	Ph Ph
			7	1
	0		1	

**Table 2.** Control Experiments with **5b** at  $80^{\circ}$ C in C<sub>6</sub>D<sub>6</sub>

Some time ago, we and Coates discovered that Claisen rearrangements of electron rich allyl vinyl ethers like 5b were significantly accelerated (20-70 fold) when conducted in protic solvents, and we postulated that hydrogen bonding in the transition state was responsible for this acceleration.<sup>3</sup> We now propose the *bis*-hydrogen bonded transition state model<sup>6</sup> 8 as an explanation for the accelerating effects of the urea 1a on the Claisen rearrangement of 5b. Thioureas are about  $10^6$  times more acidic than analogous ureas,<sup>7</sup> yet thiourea 1b has a weaker accelerating effect than urea 1a. This suggests that hydrogen bonding, not acidity, is crucial for acceleration. Interestingly, aryl ureas do bind anionic molecules (sulfonates) with higher association constants than analogous aryl thioureas, but the effect is modest (a factor of two or three).<sup>10b</sup>

bis-Hydrogen Bonded Transition State Model 8



That bis- rather than mono-hydrogen bonding<sup>8</sup> is important is suggested by the small effect of benzanilide 7 on the rearrangement. It is also consistent with the calculations of Jorgensen,<sup>9</sup> which suggest that the acceleration of Claisen rearrangements by water<sup>3b</sup> is due in large part to the formation of hydrogen bonds in the transition state between the substrate and two separate water molecules. In contrast, the calculations suggest that the starting allyl vinyl ether forms only a single hydrogen bond. In our case, the association of the urea **1a** with both the starting material and the product must be very weak—addition of 1 equiv of **1a** to each compound does not give any noticeable shifts in the <sup>1</sup>H-NMR spectra in C<sub>6</sub>D<sub>6</sub>. DMSO is expected to bind the urea with a reasonable association constant,<sup>10</sup> and this indeed inhibits the accelerating effect of the urea **1a**.

These results may bear on the mode of action of the chorismate mutase family of enzymes. These enzymes accelerate the rearrangement of chorismic acid to prephenic acid, and each enzyme studied to date is thought to form a *bis*-hydrogen bond to the enol ether oxygen of chorismic acid.<sup>11</sup> This *bis*-hydrogen bond is probably partially responsible for the enzymatic acceleration of the rearrangement. Like 5b, chorismic acid is thought to rearrange through a transition state with dipolar character.<sup>12</sup> Therefore, the rearrangement of 5b promoted by urea 1a serves as a very crude solution model for the *bis*-hydrogen bonding effects of the chorismate mutase family of enzymes.



These results suggest that simple diaryl ureas have heretofore unrecognized potential to accelerate organic reactions. While the *bis*-hydrogen bonded model must currently be regarded as speculative, it is provocative that urea **1a** has now mimicked (on a stoichiometric basis) the effects of protic solvents in two completely unrelated reactions. Aryl ureas and related molecules are in vogue as hosts for molecular recognition, and our results suggest these types of molecules should be tested for their potential to alter rates and stereoselectivity of organic reactions.<sup>13</sup>

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## **References and Notes**

- a) Curran, D. P.; Kuo, L. H. J. Org. Chem. 1994, 59, 3259. b) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. J. Org. Chem. 1994, 59, 3547.
- 2. Procedure for conducting the Claisen Rearrangement of enol ether 5a in the presence of additive: A 0.2 M stock solution of enol ether 5a in C<sub>6</sub>D<sub>6</sub> was prepared and routinely stored in the refrigerator. In each run, 0.60 mL of enol ether 5a in C<sub>6</sub>D<sub>6</sub> solution was transfered by syringe to a 5 mL flask containing weighed amount of additive. The mixture was stirred to homogeneity and then transfered to an NMR sample tube and sealed. A <sup>1</sup>H-NMR spectrum was recorded every 6 h for catalyzed reactions (or 12 h for uncatalyzed reactions) until about 70% of enol ether 5a was consumed. Plots of ln A/A<sup>0</sup> versus time were linear with high correlation coefficients (> 0.9990). The rate constant was calculated using a first order rate law with the assumption that the aldehyde was generated exclusively.
- a) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. J. Am. Chem. Soc. 1987, 109, 1160. b) Claisen rearrangements can also be significantly accelerated by using water as the solvent: Brandes, E.; Grieco, P. A.; Gajewski, J. J. Org. Chem. 1989, 54, 515.
- 4. Rearrangement of 5b with no additive was too slow at 50°C to measure, so the control rate constant was calculated from the activation parameters in ref. 3a. These activation parameters reproduced the observed rate constant at 80°C within 10%, so we feel that the estimate at 50°C is reliable.
- 5. The thiourea decomposed slowly under the reactions conditions, so rate constants were not calculated. The accelerating effect was estimated from the conversion at early reaction time, when the decomposition of 1b was less than 10%.
- 6. For acceleration of Diels-Alder reactions through bis-hydrogen bonding to a bis-phenol, see: Kelly, T. R.; Meghani, P.; Ekkundi, V. S. Tetrahedron Lett. 1990, 31, 3381. Stoichiometric amounts of ureas 1a and 1b provide only very small rate increases (1.5-2.0) in Diels-Alder reactions between cyclopentadiene and acrolein, methyl vinyl ketone and phenyl vinyl sulfoxide.
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- a) The association constant of 1a with phenyl vinyl sulfoxide is 469 M<sup>-1</sup>, and with tetramethylenesulfoxide it is 1,000 M<sup>-1</sup> (L. H. Kuo, Ph.D. Thesis, University of Pittsburgh, 1995).
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