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VIP *Very Important Paper*

Urea- and Thiourea-Catalyzed Aminolysis of Carbonates

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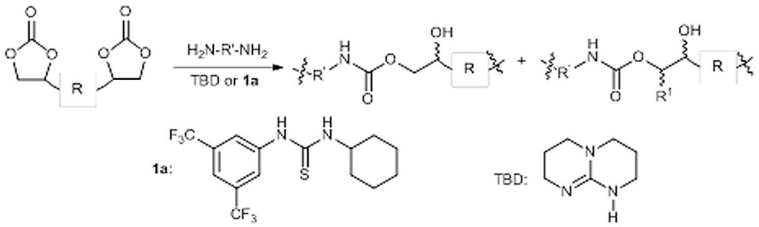
The aminolysis of (poly)carbonates by (poly)amines provides access to non-isocyanate polyurethanes (NIPUs) that are toxic-reagent-free analogues of polyurethanes (PUs). Owing to their low reactivity, the ring opening of cyclic carbonates requires the use of a catalyst. Herein, we report that the more available and cheaper ureas could advantageously be used for catalyzing the formation of NIPUs at the expense of the thiourea analogues. In addition, we demonstrate a medium-range pK_a of the (thio)urea and an unqeual substitution pattern is critical for controlling the efficiency of the carbonate opening.

Introduction

Polyurethanes (PUs) are the 6th most widely used polymers,[1] but the use of the toxic isocyanates for their syntheses raises increasing health and environmental concerns.[2] For this reason, the development of isocyanate-free alternatives to PUs is currently intensely investigated. While the long-known aminolysis of carbonates allows the preparation of non-isocyanate polyurethanes (NIPUs) whose properties may match those of PUs in many cases,[3–8] the limited reactivity of amines towards carbonates requires the use of catalysts for activating the amine and/or the carbonate. As a consequence, the aminolysis of carbonates has been investigated thoroughly.[9–18] In particular, it has been reported that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and the cyclohexylphenyl thiourea **1a** allow the efficient preparation of NIPUs (Scheme 1).[9,17] Interestingly, at low catalyst loading, **1a** outperformed TBD, hence allowing for the large scale preparation of NIPUs. However, the problem with the use of **1a** as catalyst lies in 1) its price and 2) the absence of commercial sources that may hamper its broad use.



Scheme 1. TBD or thiourea-catalyzed carbonate aminolysis.

On the basis of this observation, we investigated the possibility of using more affordable thiourea catalysts. In addition, as substituted ureas are generally more readily available than the corresponding thiourea derivatives, we have also screened a series of urea derivatives to evaluate their catalytic activity in the aminolysis of carbonates. The results of this study as well as the rationalization of the observations are presented and discussed in this article.

About a decade ago, Wittkopp and Schreiner reported that substituted thioureas are able to catalyze Diels–Alder reactions via "Lewis acid-type catalysis" and that the catalytic activity depends on the substitution pattern.[19] In particular, it was shown that the 3,5-bis(trifluoromethyl)phenyl group is among the best substituent not only because of the electron withdrawing effect of the CF_3 substituents, but also because of additional interactions involving the *ortho*-protons.[20]

To ascertain this hypothesis in the (thio)urea catalyzed aminolysis of carbonates, we synthesized a series of thiourea derivatives and their urea analogues (Table 1) bearing cyclohexyl, phenyl, and bis(trifluoromethyl)phenyl groups, and evaluated their performance towards the ring opening of propylene carbonate (PC) with cyclohexylamine. The choice of the two partners relies on earlier studies that demonstrated that the limited reactivity of cyclohexylamine was most appropriate for revealing catalytic efficacy.[9]

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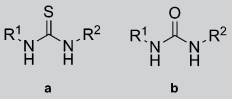
Table 1. Substitution pattern of the thiourea (a) and urea (b) derivatives used in the study and association constants (K) with propylene carbonate.



Substituents	(Thio)urea	pK_a[a]	K[a] [M^{-1}]
R^1 = 3,5-$(CF_3)_2C_6H_3$	**1a**	13.2	12
R^2 = cyclohexyl	**1b**	17.8	nd
R^1 = R^2 = cyclohexyl	**2a**	20.3	0.67
	2b	nd	0
R^1 = R^2 = Ph	**3a**	13.4	nd
	3b	18.7	nd
R^1 = R^2 = 3-$(CF_3)C_6H_4$	**4a**	10.9	1.4
	4b	16.1	nd
R^1 = R^2 = 3,5-$(CF_3)_2C_6H_3$	**5a**	8.5	121
	5b	13.8	nd
R^1 = 3,5-$(CF_3)_2C_6H_3$	**6a**	10.7	nd
R^2 = Ph	**6b**	16.1	nd

[a] The pKa values were calculated according to the method developed by Schreiner and co-workers. nd = not determined.

Results and Discussion

Synthetic procedures

Urea derivatives **1b**–**6b** were synthesized in a one-step procedure by reacting the commercially available isocyanate with the corresponding amine. The symmetrical thiourea derivatives **2a**–**5a** were readily prepared by condensation of two equivalents of the appropriate amine with thiophosgene. The non-symmetrically substituted thioureas **1a** and **6a** were synthesized according to a two-step process. The first step involved the synthesis of the thiocyanate by reaction of the amine and thiophosgene before the second amine was added. The experimental details are available in the Supporting Information.

The pK_a values of the organocatalysts screened in this study were determined using the method developed by Schreiner and coworkers.[21,22] The pK_a values found for the new organocatalysts investigated in this study are in agreement with the trend determined earlier. As expected, the pK_a value of **4b** (pK_a = 16.1) matches with the expectations because the contributions of the CF_3 groups to the pK_a are additive regardless their position.[21] For this reason, similar pK_a values were determined for **4b** and **6b**. The pK_a values of **1a** and **1b** differ by 4.6 units. This observation is consistent with the electronic effect of S versus O that was shown to induce a pK_a change of 4 to 6 pK_a units.[21]

In parallel with the pK_a determinations, an attempt to estimate the association constants between the (thio)ureas and the model carbonate was undertaken (Table 1). Unfortunately, the NMR titration method used for the calculation of the affinity constants (K) was only possible for **1a**, **2a**, **4a**, **5a**, and **2b**, as the other thioureas and ureas were insoluble in $CDCl_3$ the association cannot be measured in more competitive (H-bonding) solvents.

Upon adding various amounts (x equiv.) of PC to a solution of 1 equivalent catalyst in $CDCl_3$, ^{1}H NMR titrations followed by nonlinear regression were carried out and allowed the calculation of the association constants. The detailed calculations are provided in the Supporting Information.

The addition of increasing amounts of PC to a solution of **5a** in $CDCl_3$ induces significant peak shifts in the ^{1}H NMR spectrum with an important downfield shift of the NH urea protons ($\Delta\delta$ = 0.91 ppm) and a moderate downfield shift for the *ortho*-

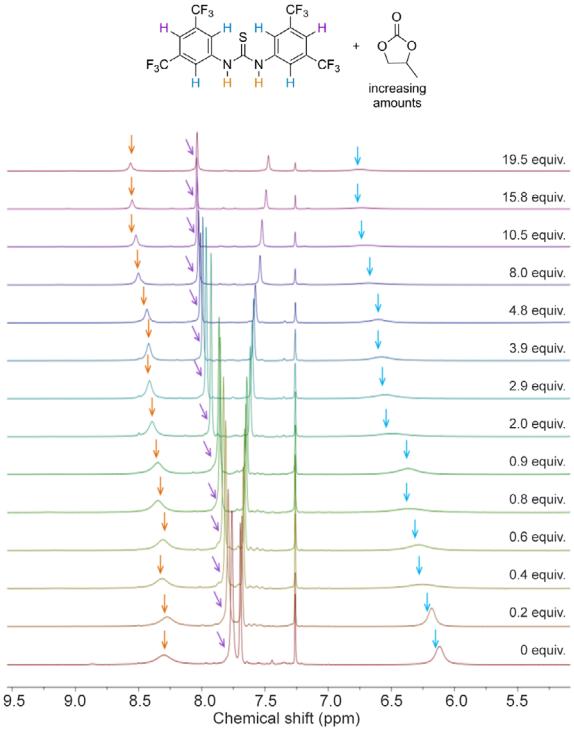


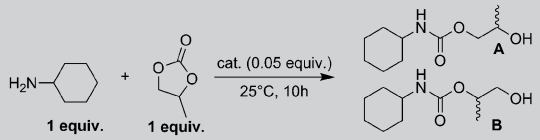
Figure 1. ^{1}H NMR titration of **5a** with increasing amounts of PC in $CDCl_3$.

and *para*-protons with $\Delta\delta$ = 0.23 and 0.11 ppm, respectively (Figure 1). Similar changes had already been observed by Schreiner and coworkers upon studying the complexation of γ-valerolactone with **5a**;[20] **5a** is the only catalyst for which a shift of the *para*-protons is observed. For the other thiourea derivatives (**2a**, **4a**, and **6a**), only the NH chemical shift was sensitive to complexation. As for **1a**, the chemical shifts of both the NH and *ortho*-protons underwent a noticeable change in the chemical shifts. For the thiourea derivatives investigated, the affinity constants were moderate but varied with the highest K value for the most acidic **5a** (K = 121 M^{-1}) and the lowest K value (K = 0.67 M^{-1}) for the least acidic **2a**. Hence, ^{1}H NMR titrations provide a useful tool to confirm the pK_a determination obtained by titration, so as to predict catalytic activity.[23]

Catalysis and correlation with pKa values

The catalysis experimentswere carried out at 25 °C for 10 h. As established previously,[9] cyclohexylamine and propylene carbonate were chosen for this study as they are virtually unreactivein the absence of catalyst (conv. < 9% after 1 h). Cyclohexylamine and PC were mixedtogether in a 1:1 ratio before the organocatalyst (5 mol%) was added. The progress of the reaction was monitored by GC–MS analyses (PC conversion, Table 2).

Table 2. Thiourea (a) and urea (b) catalyzed aminolysis of CP.



(Thio)urea substituents	(Thio)urea	Conv. [%] $t = 0.5$ h	$t = 1$ h
	none	5	9
$R^1 = 3,5\text{-}(CF_3)_2C_6H_3$, R^2 = cyclohexyl	**1a**	55	**66**
	1b	42	48
$R^1 = R^2$ = cyclohexyl	**2a**	17	26
	2b	5	21
$R^1 = R^2 = Ph$	**3a**	44	51
	3b	47	**53**
$R^1 = R^2 = 3\text{-}(CF_3)\ C_6H_4$	**4a**	40	52
	4b	60	**67**
$R^1 = R^2 = 3,5\text{-}(CF_3)_2C_6H_3$	**5a**	28	41
	5b	65	**70**
$R^1 = 3,5\text{-}(CF_3)_2C_6H_3$, $R^2 = Ph$	**6a**	55	**64**
	6b	65	**71**

Monitoring of the reaction was performed after 0.5 and 1 h respectively. After 1 h, the conversion slows down and reaches a plateau. Using a thiourea catalyst, the highest conversions were obtained with catalysts **1a** and **6a** (66 and 64%, respectively). Hence, non-symmetrical thioureas afford the best conversions. Slightly lower conversions of 51, 52, and 41% were obtained with **3a**, **4a**, and **5a**. Remarkably, the bis-cyclohexyl-substituted thiourea **2a** afforded much lower conversion with only 26% after 1 h. More interestingly, the urea catalysts also appeared to be excellent candidates for catalyzing the carbonate aminolysis reaction. Indeed, ureas **4b**, **5b**, and **6b** afforded the expected carbamates in 67, 70, and 71% conversion after 1 h, respectively. Hence, all the aromatic ureas investigated in our study proved more active catalysts than their thiourea counterparts. Owing to the large variety of commercially available ureas and isocyanate precursors, this unprecedented observation opens new perspectives in the catalyzed aminolysis of carbonates for the large scale synthesis of NIPUs. Figure 2 reveals that an optimal pK_a ranging between 14 and 16 is required for obtaining the highest PC conversion. More acidic or more basic (thio)ureas afforded lower conversions. Indeed, the cyclohexylamine is capable of deprotonating the most "acidic" (thio)urea derivatives [pK_a(cyclohexylamine) = 11.5 at 25 °C].[24] Consequently, the deprotonated catalyst is not able to activate the carbonate. Conversely, the less acidic catalysts do not activate the carbonyl strongly enough to allow nucleophilic attack of the amine. A more striking observation concerns the symmetry of the catalysts. Indeed, when two couples of catalysts with the same pK_a are compared, the non-symmetrical catalysts afford higher conversions. Hence, thioureas **4a** and **6a** exhibit similar pK_a values (10.9 and 10.7, respectively), but the symmetrical **4a** organocatalyst afforded a medium 52% conversion while the non-symmetrical catalyst **6a** gave 64%. A similar trend was noticed when comparing the ureas **4b** and **6b** even if the difference is minor. However, it appears that the substitution effect is more pronounced with thioureas than with ureas.

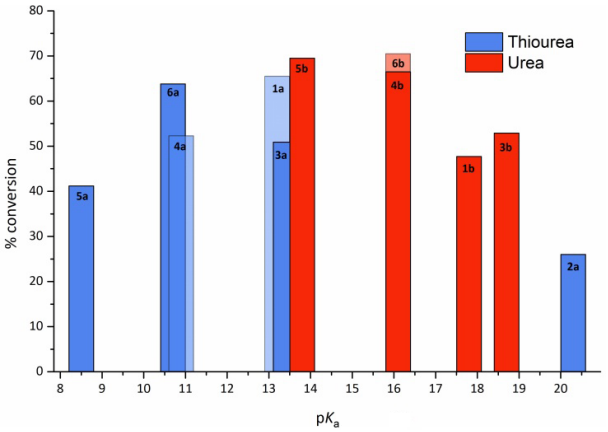


Figure 2. Evolution of the conversion of PC after 1 h versus pK_a.

Similar trends were established when comparing the conversion and the K values (Figure 3). The calculated association constants are low for most of the thioureas with $K < 2$ (**2a**, **4a**, **6a**). In addition, although **5a** displays the highest association constant it was not the best catalyst for the aminolysis of carbonates. The low pK_a of **5a** probably explains this observation.

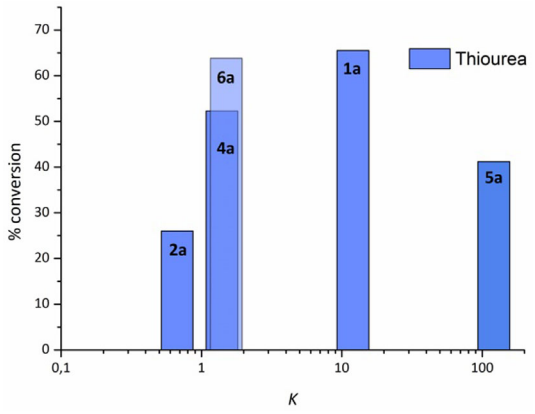


Figure 3. Evolution of the conversion of PC after 1 h versus the binding constant K.

Therefore, the conversion after 1 h detailed in Figure 3 is only 41% for **5a** versus 66% for **6a** that displays a 10× lower association constant. The highest conversions are obtained with association constants ranging between 1 and 12. Interestingly, the association constants between the carbonate and **4a** and **6a** are the same. Therefore, the CF_3 groups need not be necessarily located on the same aryl group to enhance the association constant value. A similar observation had already been made for the determination of the pK_a values.[21]

Although the catalytic binding event of the (thio)urea for the aminolysis of the carbonate reaction involves an interaction between the NH (thio)urea groups and the carbonyl of the carbonate as confirmed by ^{1}H NMR titration, the affinity constant of the catalyst for the substrate is not sufficient for explaining the catalytic effect of the (thio)ureas. Conversely, the pK_a of the thio(urea) accounts for a major part of the catalytic activity, provided it is not deprotonated owing to high intrinsic acidity.

Conclusions

This study demonstrates that readily available and affordable urea derivatives may advantageously replace thiourea derivatives or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in the aminolysis of carbonate reactions. This observation renders the non-isocyanate polyurethane (NIPU) synthesis more appealing as equally performant but cheaper catalysts may be used. The choice of the substitution pattern of the catalyst is mainly governed by its acidity. As urea derivatives are generally considerably less acidic than thiourea derivatives, they are less likely to be deactivated through deprotonation. The affinity constant of the catalyst and the carbonate as well as the relative positions of the substituents do not influence conversion much. Hence, a fine balance has to be met for catalyst pK_a adjustment and its ability for substrate complexation. This is clear because such ground state properties can only qualitatively correlate to transition state properties that are key to catalysis. Further developments towards the use of more soluble urea organocatalysts for NIPU syntheses are currently under investigation in our laboratories.

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Keywords: aminolysis · catalysis · polyurethanes · pk_a · reactivity

[1] L. Shen, J. Haufe, M. K. Patel, *Product overview and market projection of emerging biobased plastics* (PROBIP 2009). Commissioned by European Polysaccharide Network of Excellence (EPNOE) and European Bioplastics. Group Science, Technology and Society (STS), Copernicus Institute for Sustainable Development and Innovation, Utrecht University, Utrecht, the Netherlands, June 2009. Report No: NWS-E-2009-32.
[2] D. Bello, C. A. Herrick, T. J. Smith, S. R. Woskie, R. P. Streicher, M. R. Cullen, Y. Liu, C. A. Redlich, *Environ. Health Perspect.* **2007**, *115*, 328 – 335.
[3] B. Nohra, L. Candy, J.-F. Blanco, C. Guerin, Y. Raoul, Z. Mouloungui, *Macromolecules* **2013**, *46*, 3771 – 3792.
[4] M. S. Kathalewar, P. B. Joshi, A. S. Sabnis, V. C. Malshe, *RSC Adv.* **2013**, *3*, 4110 – 4129.
[5] O. Kreye, H. Mutlu, M. R. Meier, *Green Chem.* **2013**, *15*, 1431 – 1455.
[6] E. Delebecq, J.-P. Pascault, B. Boutevin, F. Ganachaud, *Chem. Rev.* **2013**, *113*, 80 – 118.
[7] G. Rokicki, A. Piotrowska, *Polymer* **2002**, *43*, 2927 – 2935.
[8] T. Bürgel, M. Fedtke, M. Franzke, *Polym. Bull.* **1993**, *30*, 155 – 162.
[9] M. Blain, L. Jean-Gérard, R. Auvergne, D. Benazet, S. Caillol, B. Andrioletti, *Green Chem.* **2014**, *16*, 4286 – 4291.
[10] A. Steblyanko, W. Choi, F. Sanda, T. Endo, *J. Polym. Sci. Part A* **2000**, *38*, 2375 – 2380.
[11] H. Tomita, F. Sanda, T. Endo, *J. Polym. Sci. Part A* **2001**, *39*, 3678 – 3685.
[12] H. Tomita, F. Sanda, T. Endo, *J. Polym. Sci. Part A* **2001**, *39*, 851 – 859.
[13] N. Kihara, T. Endo, *J. Polym. Sci. Part A* **1993**, *31*, 2765 – 2773.
[14] L. Annunziata, A. K. Diallo, S. Fouquay, G. Michaud, F. Simon, J.-M. Brusson, J.-F. Carpentier, S. M. Guillaume, *Green Chem.* **2014**, *16*, 1947 – 1956.
[15] H. Tomita, F. Sanda, T. Endo, *J. Polym. Sci. Part A* **2001**, *39*, 162 – 168.
[16] B. Nohra, L. Candy, J.-F. Blanco, Y. Raoul, Z. Mouloungui, *Eur. J. Lipid Sci. Technol.* **2013**, *115*, 111 – 122.
[17] R. H. Lambeth, T. J. Henderson, *Polymer* **2013**, *54*, 5568 – 5573.
[18] C. D. Diakoumakos, D. L. Kotzev, *Macromol. Symp.* **2004**, *216*, 37 – 46.
[19] A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407 – 414.
[20] K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919 – 5927.
[21] G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724 – 1727.
[22] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.
[23] A. R. Nödling, G. Jakab, P. R. Schreiner, G. Hilt, *Eur. J. Org. Chem.* **2014**, 6394 – 6398.
[24] R. Hrdina, C. E. Müller, R. C. Wende, K. M. Lippert, M. Benassi, B. Spengler, P. R. Schreiner, *J. Am. Chem. Soc.* **2011**, *133*, 7624 – 7627.

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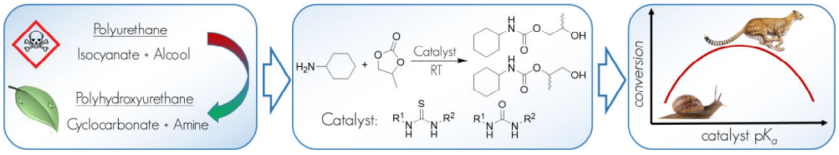

Catalyst substituted: Appropriately substituted ureas advantageously substitute thiourea catalysts in the ring opening of carbonates to afford non-isocyanate polyurethanes. A medium-range pK_a of the (thio)urea and an unequal substitution pattern is critical for controlling the efficiency of the carbonate opening

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