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## <sup>31</sup>P NMR Spectroscopically Quantified Hydrogen-Bonding Strength of Thioureas and Their Catalytic Activity in Diels–Alder Reactions

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The hydrogen-bonding strength of a variety of commonly employed thiourea catalysts was quantified by using a trialkylphosphine oxide as a <sup>31</sup>P NMR probe. Simple diarylthioureas and more complex bifunctional amine- and hydroxysubstituted thiourea derivatives were examined. Their catalytic activity was determined in a Diels–Alder reaction, and the obtained pseudo-first-order rate constants were correlated with the <sup>31</sup>P NMR chemical shifts. A linear correlation

### Introduction

Hydrogen-bond-donor catalysis in asymmetric organic synthesis has been a flourishing field over the last decades.<sup>[1,2]</sup> Amongst numerous catalysts applied, thioureas have distinguished themselves because of their straightforward, flexible preparation as well as their diverse reaction scope. They have found application as mild organic "Lewis acids",<sup>[3]</sup> as bifunctional amine catalysts capable of dual substrate activation,<sup>[4]</sup> and as co-catalysts in complex multicatalytic reactions.<sup>[5]</sup> Many efforts have been made to explore further catalyst structures, reactivities, and related mechanisms. On the contrary, only few systematic attempts have been made to probe the influence of fundamental properties, such as steric and electronic substituent effects, on the reactivity of thioureas.<sup>[6]</sup> A seemingly logical parameter affecting their reactivity are their  $pK_a$  values. Hence,  $pK_a$  scales for thioureas have been established and a link between the  $pK_a$  values and the catalytic activities has been proposed.<sup>[7,8]</sup>

Furthermore, structure–activity relationships between the  $pK_a$  values of three classes of tertiary amine–thioureas and their activity in Michael additions have been found (Figure 1).<sup>[8]</sup> The studies were limited to these classes of thioureas and more acidic, non-bifunctional thioureas such as Schreiner's catalyst remain unexamined. In contrast, some reactions, for example, Diels–Alder reactions<sup>[9]</sup> and

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between both variables was observed throughout the functionalized thioureas. The <sup>31</sup>P NMR probe correlation fared better in comparison to a  $pK_a$  correlation. Accordingly, the quantification presented herein by using a <sup>31</sup>P NMR probe offers an elegant way to estimate the catalytic activity of thiourea catalysts in hydrogen-bond-activated reactions such as the Diels–Alder reaction.

transfer hydrogenations,<sup>[10]</sup> have shown no correlation between  $pK_a$  values and thiourea catalyst reactivity. As a consequence, the Brønsted acidity of thioureas cannot be accounted as a sole measure of their catalytic activity.



Figure 1. Classes of thioureas investigated by Cheng regarding a structure–activity relationship between their catalytic activity in Michael reactions and their  $pK_a$  values.<sup>[8]</sup>

In previous work, we examined possible correlations between quantified strengths of Lewis acids by using NMR probes **4** and **5** (Figure 2) and their catalytic activity.<sup>[11,12]</sup>



Figure 2. Nitrogen-donor-based  ${}^{2}H$  NMR probes 4 and 5 for the quantification of metal halide and silicon based Lewis acids.<sup>[11,12]</sup>

Given that the activation mode of carbonyl functionalities by thioureas has been proposed to be similar to that of common Lewis acids,<sup>[3]</sup> we became interested in employing our approach for the quantification of thiourea efficacy. During our first experiments on this topic, Kozlowski et al. published an intriguing article, in which they pursued a similar strategy on the correlation between the catalytic activity of a few simple hydrogen-bonding donors and the blueshifts in the UV/Vis spectra inflicted by them upon coordinating a colorimetric sensor.<sup>[9]</sup> The colorimetric sensor used in this study was previously employed to quantify the strength of Lewis acids,<sup>[13]</sup> which encouraged us to use NMR probes to quantify the hydrogen-bonding strength of thioureas.

#### **Results and Discussion**

Upon Lewis acid complexation, previously used deuterium-labeled nitrogen-donor <sup>2</sup>H NMR probes **4** and **5** show a distinct <sup>2</sup>H NMR downfield shift,  $\Delta\delta(^{2}\text{H})$ , that is considered as a measure of the strength of the respective Lewis acid. As N–H··N hydrogen bonds are rather weak, probes **4** and **5** seemed less suitable to quantify the hydrogen-bonding strength of thiourea catalysts, and we shifted our focus on more Lewis basic probes. Phosphine oxides were introduced by Gutmann as Lewis acidity probes<sup>[14]</sup> and were reseized by Beckett to quantify mild boron-based Lewis acids;<sup>[15]</sup> furthermore, they are more Lewis basic than both **4** and **5**, resemble carbonyl groups, which are often targeted by thioureas, and offer an easy and fast application as a probe through <sup>31</sup>P NMR shift quantification.<sup>[16]</sup>

Therefore, we selected tri-*n*-butylphosphine oxide (6) as a  ${}^{31}P$  NMR probe. Upon hydrogen-bond formation between the oxygen atom of 6 and the acidic thiourea hydrogen atoms an electron density shift towards the thiourea is expected.<sup>[16]</sup> This should result in a downfield shift in the  ${}^{31}P$  NMR signal for 6a (Scheme 1).



Scheme 1. Working model for the quantification of thiourea hydrogen-bonding strength by <sup>31</sup>P NMR shifts.

In our initial attempt, we employed thioureas 7a, 8c, 7c, and 10 in titration experiments with phosphine oxide 6. These thioureas were expected to exhibit different hydrogen-bonding strengths, as a varying number of electron-withdrawing CF<sub>3</sub> groups<sup>[7b]</sup> and aryl substituents and a second thiourea subunit in proximity to the first are installed (Figure 3). All three features are known to lower the  $pK_a$  value of thiourea derivatives.<sup>[7]</sup> Phosphine oxide 6 was titrated by successively increasing the amount of thiourea by adding a thiourea stock solution and monitoring the <sup>31</sup>P NMR shift of the adduct of type **6a**. Indeed, the four thioureas inflicted varyingly strong <sup>31</sup>P NMR downfield shifts to yield the order 7a > 8c > 7c > 10 (Figure 4). In each case, saturation of the shift was observed, but the smaller the maximum shift value was the more equivalents of the thiourea were necessary to reach saturation. Such findings have been reported for simple metal halide Lewis acids<sup>[11]</sup> as well as for hydrogen-bond donors.<sup>[9]</sup>



Figure 3. Thioureas 7–11 and thiophosphoramide 12 used in the present study.



Figure 4. Plot of the <sup>31</sup>P NMR shift change  $\Delta\delta$ (<sup>31</sup>P) of phosphine oxide **6** upon titration with four different thioureas. **6**:  $\delta$ (<sup>31</sup>P, CH<sub>2</sub>Cl<sub>2</sub>) = 47.23 ppm.

Whereas the order of **7a**, **7c**, and **10** was expected from an empirical point of view as well as from the corresponding  $pK_a$  values (Table 1), **8c** > **7c** is surprising, as **7c** was found to possess a lower  $pK_a$  value than **8c**.<sup>[7]</sup> This comparison already showed a first discrepancy between the quanti-

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fied Lewis acidity and the  $pK_a$  values of hydrogen-bonddonor catalysts, which is in accordance with Kozlowski's observations.<sup>[9]</sup>

Table 1.  $\Delta\delta(^{31}P)$  NMR shift values upon coordination of the employed hydrogen-bond donors to **6**,  $k_{obs}$  values for the examined Diels–Alder reaction, Scheme 2, and p $K_a$  values.

Catalyst	$\Delta\delta(^{31}\text{P}) / \text{ppm}^{[a]}$	$k_{\rm obs}$ / $10^{-2} \min^{-1[b]}$	$pK_a^{[c]}$
none	0	$1.733 \pm 0.077$	_
7a	7.95	$3.947 \pm 0.046$	8.5
7b	7.51	$2.831 \pm 0.045$	≈9.7 <sup>[d]</sup>
7c	6.71	$2.061 \pm 0.127$	10.9
7d	6.01	$1.809 \pm 0.033$	12.1
8a	4.56	$1.746 \pm 0.079$	≈13.4 <sup>[d]</sup>
8b	6.10	$1.865 \pm 0.067$	_
8c	7.05	$2.821 \pm 0.016$	11.98
8d	1.75	$1.691 \pm 0.049$	≈18.0 <sup>[d]</sup>
9a	5.99	$1.912 \pm 0.020$	≈13.4 <sup>[d]</sup>
9b	5.52	$1.837 \pm 0.011$	_
9c	7.36	$3.182 \pm 0.059$	≈12.0 <sup>[d]</sup>
10	5.33	$1.766 \pm 0.024$	12.39
11	9.00	$2.370 \pm 0.133$	12.98
12	9.17	$4.278\pm0.217$	—

[a] Conditions according to GP1: **6** (2.29  $\mu$ mol), catalyst (up to 175 equiv.), absolute CH<sub>2</sub>Cl<sub>2</sub>, 2.0 mL final volume, see the Supporting Information for detailed information. [b] Reaction conditions according to GP2: 1.0 m **13**, 0.1 m **14**, 0.01 m catalyst, absolute CDCl<sub>3</sub>, 0.7 mL total volume, NMR tube, 300 K, see the Supporting Information for detailed information. [c] Taken from ref.<sup>[7]</sup> [d] Estimation based on ref.<sup>[7]</sup>

After having identified a suitable NMR probe in phosphine oxide 6, we examined a broader range of thioureas, including thiourea classes such as those introduced by Schreiner, 7a;<sup>[1h,3]</sup> Soós, 10;<sup>[17]</sup> and Ricci, 11,<sup>[18]</sup> which contain various structural elements and chiral scaffolds (Figure 3, Table 1). Thiophosphoramide 12 has been shown to be even more reactive than 7a in Diels-Alder reactions,<sup>[19]</sup> and it was subsequently included to add another strong hydrogen-bonding catalyst with a similar structure and binding motif. The shifts were determined by adding multiple equivalents of hydrogen-bond-donors 7-12 to probe 6 until no further shifts in the <sup>31</sup>P NMR signals were observed. Additionally, the influence of a trace amount of water was found to have a negligible effect on the  $\Delta\delta(^{31}\text{P})$ values (see the Supporting Information), by the addition of 1 µL of deionized water after the final measurement. Finally, the expected 1:1 complex stoichiometry between probe 6 and the thioureas, shown in Scheme 1, was verified by using Job's method<sup>[20]</sup> for some exemplary thioureas (see the Supporting Information).

The trend observed for the initially examined thioureas was continued for the new set of thioureas. Larger <sup>31</sup>P NMR downfield shifts were found for thioureas bearing more electron-withdrawing substituents. This is easily seen in the series of diphenylthiourea derivatives **7a–d**. An increased number of CF<sub>3</sub> substituents resulted in increased  $\Delta\delta(^{31}P)$  values, analogous to their  $pK_a$  values.<sup>[7]</sup> Another example of substituent effects on the  $\Delta\delta(^{31}P)$  values is noticeable in switching from **8d** [ $\Delta\delta(^{31}P) = 1.75$  ppm] over **8a** [ $\Delta\delta(^{31}P) = 4.56$  ppm] to **8c** [ $\Delta\delta(^{31}P) = 7.05$  ppm], and ending with **7a** [ $\Delta\delta(^{31}P) = 7.95$  ppm]. This order matches well with expectations based on the electron-withdrawing ability of the exchanged substituents. Inconsistent results were obtained for thiourea classes **8** and **9**. Whereas only a small influence of the different backbones on the  $\Delta\delta(^{31}\text{P})$  values was found for the pairs **8b/9b** (6.10/5.52 ppm) and **8c/9c** (7.05/7.36 ppm), a large discrepancy was found for **8a/9a** (4.56/5.99 ppm).

To probe the predictive power of the quantified thiourea Lewis acidities, a potential correlation between the latter and the catalytic activity of the thiourea catalysts was investigated. We chose the Diels–Alder reaction between cyclopentadiene (13) and methyl vinyl ketone (14) to determine rate constants (Scheme 2). Rate accelerations by Lewis acids in Diels–Alder reactions of  $\alpha,\beta$ -unsaturated carbonyls are based on the LUMO-lowering effect of electron-deficient Lewis acids<sup>[21]</sup> and, accordingly, the amount of rate acceleration is directly linked to the strength of a Lewis acid.<sup>[22]</sup> In that line, a correlation between the  $\Delta\delta$ (<sup>31</sup>P) values and the Diels–Alder reaction rate constants should be observed.



Scheme 2. Investigated Diels–Alder reaction to determine the catalytic activity of the thioureas and thiophosphoramide **12**.

The reactions were performed under identical conditions by using 10 equivalents of cyclopentadiene (13) and 10 mol-% of the thiourea catalysts to obtain pseudo-first-order kinetics with respect to 14. The reaction progress was monitored by <sup>1</sup>H NMR spectroscopy by integration of the methyl group of substrate 14 and the methyl groups of exo-15 and endo-15 (see the Supporting Information). Indeed, an exponential decrease in [14] was observed, which is indicative of pseudo-first-order kinetics. Only 8b showed slight deviations. In that case, reversible formation of an enamine between 8b and 14 or 15 might be possible through the primary amine functionality of 8b; however, similar behavior was not observed for 9b. Taking this into account, rate constants were calculated for all catalysts (up to 80% conversion), and very good  $R^2$  values of at least 0.9999 were obtained. At least three runs were conducted for every catalyst, and the mean values of the reaction rates are given in Table 1. In agreement with the NMR experiments, the influence of a trace amount of water was found to have a minor influence on the reaction rate constants (see the Supporting Information). The observed reactivities of the thiourea catalysts are rather small compared to those of common Lewis acids but nonetheless cover a broad range. For example, dialkylthiourea 8d does not catalyze the reaction, whereas thiophosphoramide 12 yields a significant rate acceleration.

Having data of both the quantified hydrogen-bonding strength and the catalytic activity in hand, we set out to determine a possible connection. A Hammett-type plot of



Figure 5. Hammett-type plot of the  $\ln(k_{rel})$  values of the Diels– Alder reaction versus the thiourea-induced <sup>31</sup>P NMR shifts. Compounds **11** and **12** were excluded from the linear fit. For calculation of the  $\ln(k_{rel})$  values, see the Supporting Information.

the measured rate constants versus the  ${}^{31}P$  NMR shifts is given in Figure 5.

Overall, a good linear correlation between both variables  $\ln(k_{\rm rel})$  and  $\Delta\delta(^{31}\text{P})$  was observed. Accordingly, a higher  $\Delta\delta(^{31}\text{P})$  value translates into a higher reaction rate and, hence, catalytic activity. Two outliers, **11** and **12**, were observed; their catalytic activities are smaller than the  $\Delta\delta(^{31}\text{P})$  values would suggest. A reason for this could be the effect of a possible threefold hydrogen bond, at least in the case of catalyst **12**. Despite this exception, the approach of using phosphine oxide **6** as a probe for the catalytic activity of structurally diverse thioureas seems valid. Yet, it should be noted that this correlation has to be seen as qualitative, considering the good but not excellent  $R^2$  value.

As mentioned above,  $pK_a$  values are often used as references for the activity of thiourea catalysts. Therefore, a comparison between correlations of both  $\Delta\delta(^{31}\text{P})$  as well as  $pK_a$  values with the  $ln(k_{rel})$  values was evoked (Table 1). The overlay of both plots is shown in Figure 6. The y axis for the  $\Delta\delta(^{31}P)$  values is inverted to match the pK<sub>a</sub> scale. The comparison shows a better correlation of the  $\ln(k_{rel})$ values with the  $\Delta\delta(^{31}\text{P})$  values ( $R^2 = 0.723$ , in this case including the value for 11 for accurate comparison) than with the p $K_a$  values ( $R^2 = 0.307$ ). Apparently, the <sup>31</sup>P NMR approach is more suitable for the evaluation of the catalytic activity of thioureas than the  $pK_a$  values. This finding is in line with reports by Schreiner<sup>[7]</sup> and Kozlowski,<sup>[9]</sup> in which it was concluded that  $pK_a$  values can be misleading and are only an incomplete measure for predicting catalytic efficacy. A possible reason may be the activation mode, as the Diels-Alder reaction examined by Kozlowski<sup>[9]</sup> and us is dominated by Lewis acid like behavior, whereas studies by Cheng<sup>[8]</sup> focused on reactions in need of an additional amine functionality to act as a Brønsted base in dual activation processes.



Figure 6. Overlay of plots of the  $\ln(k_{\rm rel})$  values of the Diels–Alder reaction between **13** and **14** and the <sup>31</sup>P NMR shifts (diamonds) as well as  $pK_a$  values (squares, Table 1). Dashed line: fit of  $\Delta \delta(^{31}P)$  values,  $R^2 = 0.72315$ , including **11**. Dotted line: fit of  $pK_a$  values,  $R^2 = 0.30673$ .

#### Conclusions

With the results presented herein we were able to identify a phosphine oxide based NMR probe that was able to qualitatively predict the reactivity of a broad range of structurally diverse thioureas by utilizing a simple and robust procedure. We obtained a satisfying correlation between hydrogen-bonding strength in terms of  $\Delta \delta(^{31}P)$  values, determined with the NMR probe, and the  $\ln(k_{rel})$  values of a Diels-Alder reaction. Our findings are in line with and expand on those of Kozlowski et al., namely, that at least for transformations such as Diels-Alder reactions that are governed by the LUMO-lowering strength of a thiourea, probes originating from Lewis acid quantification studies are more accurate than simple  $pK_a$  values. Additional functional groups, other than amines, such as a hydroxy group in 11 have a distinct effect on the reactivity of such thiourea-based catalysts and deviate for the amine-modified thioureas. Whether or not these conclusions hold true for other reactions as well will be the focus of ongoing studies in our groups.

### **Experimental Section**

**Supporting Information** (see footnote on the first page of this article): Experimental procedures for the NMR quantification and kinetic experiments, NMR spectra of previously unknown compounds, additional data and models for the calculation of reaction rate constants, and Job plots.

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