CF$_3$-groups Critically Enhance the Binding of Thiourea Catalysts to Ketones – a NMR and FT-IR Study

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Abstract

Substituted phenylthioureas have been established as efficient organocatalysts and substituents containing electron withdrawing CF$_3$ groups have been shown to enhance catalytic efficiency. The effect of the CF$_3$ groups on binding of catalysts to substrates in solution has however remained elusive. Here, we report on the effect of CF$_3$ substituted diphenylthioureas on the association with the substrate 1,3-diphenyl-2-propenone in solution by using a combination of nuclear magnetic resonance (NMR) and Fourier-transform infrared (FT-IR) spectroscopy. We use the ensemble-averaged chemical shift of the thiourea proton as function of substrate concentration to determine the association constants between catalyst and substrate. To experimentally discriminate between free and bound catalyst we use infrared absorption spectra, which show a red-shift of thiourea's N-H stretching vibration upon association with the substrate. With both methods, we find the association constant K to increase from ~1 L/mol to ~20 L/mol with increasing number of CF$_3$ substituents. This enhanced binding can explain the increased reaction rates observed for CF$_3$ substituted diphenylthiourea catalysts. For the efficient catalyst containing four CF$_3$-groups (Schreiner's catalyst), the strongest association is observed in toluene as a solvent, while the binding strength is somewhat weaker in dichloromethane, and association to the substrate is not detectable in acetonitrile. Our results thus demonstrate that even weak association between the thiourea catalysts and the ketone can facilitate efficient catalytic conversion. However, the association with the ketone substrates is very susceptible to competing interactions with the solvent.

I. Introduction

Hydrogen-bonding donors like thioureas have been established as efficient organo-catalysts.[1-10] In particular, the wide range of catalyzed reactions, including addition, allylation, Strecker, Michael- and Nitro-Mannich reactions,[11] renders thioureas promising catalysts, which are available at relatively low costs. In particular, substituted diphenylthioureas, pioneered by Schreiner and co-workers, have been

shown to provide fast reaction rates and high stereoselectivity for e.g. Diels-Alder reactions (Scheme 1).[1, 2]
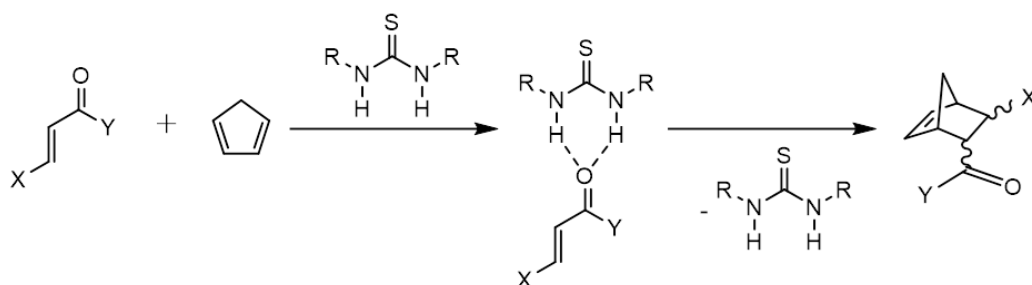
Scheme 1: *Reaction scheme of the thiourea catalyzed Diels-Alder cycloaddition. The catalyst hydrogen-bonds to the ketone, which activates the ketone. The catalyst can enhance the reaction rate and the stereoselectivity, which is determined by the electron density of the reactants and the nature of reaction (thermic or photolytic).*

Electron-withdrawing CF_3-groups have been demonstrated to enhance reaction rates and yields in diphenylthiourea catalysis.[2] The enhanced catalytic activity has been related to an increase in hydrogen-bond donor ability, i.e. a reduction of the pK_a values of thiourea's N-H groups.[12] Indeed, nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy experiments together with mass spectrometry and density functional theory calculations have shown that hydrogen-bonding between thiourea and ketones are the relevant interaction motif for catalysis. Remarkably, not only hydrogen-bond donation of the highly polar N-H group, but also of the ortho-proton of the phenyl group of phenylthiourea was suggested to contribute to the activation of the substrates.[13] Despite the importance of hydrogen-bonding, other contributions including dual activation, secondary interactions, and steric effects have been suggested to affect catalytic activity.[14]

Since catalyst-substrate aggregates are the relevant reactive intermediates, which determine amongst others e.g. reaction rates, energetic barriers etc., the binding strength between these thiourea catalysts and the substrates is important for catalytic activity. In principle, an enhanced catalytic activity may originate from stronger binding (substrate activation) or by the formation of more catalyst-substrate complexes. Even though these two effects are not completely independent – as a stronger hydrogen-bonding results in enhanced complex formation – the formation of catalyst-substrate bonds depends on the solvation of the catalyst, the substrate, and the complexes. For instance, reaction rates have been – rather counterintuitively – shown to be enhanced in hydrogen-bonded water, which has been ascribed to 'hydrophobic hydration'.[2, 15] Thus, to understand catalytic activity and to allow for a rational catalyst design, it is vital to understand solvation and study binding strength in solution.

Here, we report on the association[16,17] of diphenylthioureas with 1,3-diphenyl-2-propenone, relevant to Diels-Alder cycloaddition (Scheme 1), in solution. To study the effect of electron withdrawing CF_3-groups, we study the association of

diphenylthioureas with zero, two, and four CF_3 substituents at the phenyl rings. We determine the rather weak molecular association using the motionally averaged signals of the free and the bound catalyst in the NMR spectra, which shift upon hydrogen-bond formation. [18-20] The thus obtained association constants are confirmed, using the N-H stretching vibration of the catalyst in the infrared absorption spectra, in which the bound and free catalyst can be spectrally resolved. Our results show, that CF_3-groups indeed enhance the binding to 1,3-diphenyl-2-propenone, however, the association markedly depends on the solvent with rather weak association in toluene and dichloromethane and virtually no interaction between catalyst and substrate in acetonitrile.

II. Experimental Methods

Sample preparation
Diphenylthiourea (0CF-DPTU, Fluka, >98%), N,N′-bis[4-(trifluoromethyl)phenyl]-thiourea (2CF-DPTU, TCI, >97%), N,N′−bis[3,5−bis(trifluoromethyl)phenyl]−thiourea (4CF-DPTU, TCI, >98%) and 1,3-diphenyl-2-propenone (Sigma-Aldrich, >98%) were used without further purification. The deuterated solvents used for the NMR experiments dichloromethane (DCM-d2, Deutero, 99.6%), toluene (toluene-d8, Aldrich, 99.6%), and acetonitrile (ACN-d3, Merck, 99.96%) were dried over 4 Å molecular sieves, yielding water contents of ~20 ppm (determined for DCM using Coulometric Karl Fischer titration). To remove solid residuals from the molecular sieves the deuterated solvents were filtered using a 0.2 μm Omnipore membrane filter prior to sample preparation. The non-deuterated solvents dichloromethane (DCM, Fischer Chemical, 99.98%), toluene (Fischer Chemical, 99.8%), acetonitrile (ACN, Fischer Chemical, 99.99%), which were used for infrared experiments, were used without any further purification. Solutions were prepared by weight using an analytical balance, assuming that the solution density is that of the solvent. For the NMR experiments the concentration of the catalyst was kept constant at c_{cat}^0 = 0.01 mol/L (c_{cat}^0 = 0.015 mol/L for 0CF-DPTU) and the concentration of the substrate was varied from c_{subs}^0 = 0.005 mol/L to 0.4 mol/L. For the infrared experiments the catalyst concentration was kept constant at c_{cat}^0 = 0.02 mol/L and the concentration of the substrate was increased from c_{subs}^0 = 0.01 mol/L to 0.4 mol/L.

FT-IR experiments
FT-IR spectra were recorded using a Bruker Vertex 70 and the Nicolet 850 Magna IR spectrometer at a resolution of 4 cm^{-1}. The spectra were collected with a "Specac demountable Omni Cell" with the sample positioned between two CaF_2 windows separated by a 0.5 mm thick spacer.

NMR experiments
To study the strength of interaction between catalyst and substrate, we use NMR-spectroscopy, which provides information about the chemical environment. ^{1}H-NMR

spectra were recorded using a Bruker 300 MHz AVANCE III spectrometer. Spectra were referenced to the residual DCM peak at 5.32 ppm, the residual toluene peak at 2.09 ppm, or the residual acetonitrile peak at 1.94 ppm. To determine the chemical shift we used the chemical shift value at the peak maximum.

III. Results and Discussion

Molecular association using NMR spectroscopy
To study the origin of the different catalytic activities for CF_3 substituted diphenylthioureas, we explore the association of 0CF-DPTU, 2CF-CPTU, and 4CF-DPTU with 1,3-Diphenyl-2-propenone (association equilibria are shown in Scheme 2).
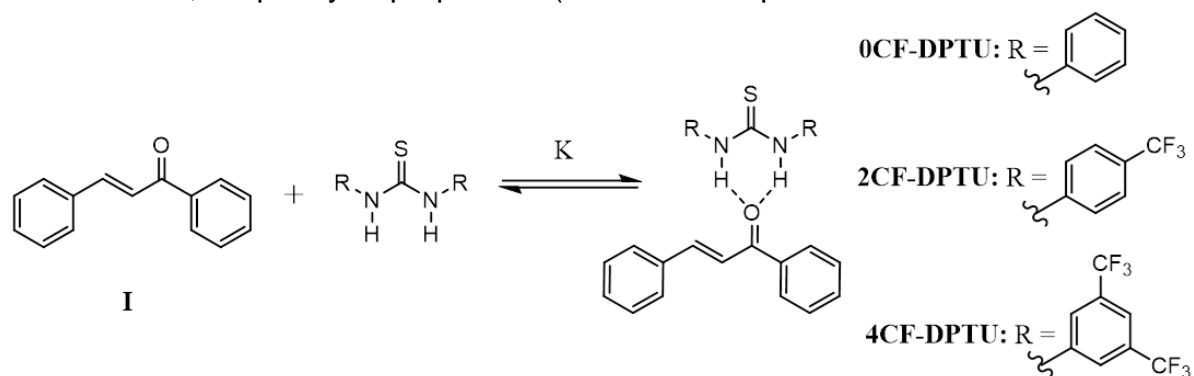
Scheme 2: *Investigated association equilibria between the thiourea catalysts and the substrate, which form a hydrogen-bonded catalyst-substrate complex.*

To detect molecular association, we record the ^{1}H-NMR spectra of solutions with constant thiourea concentration (c^0_{cat} = 0.01 mol/L) and varying substrate concentration (c^0_{subs} = 0 − 0.4 mol/L). As can be seen from the NMR spectrum (Fig. 1a) of a solution of only 1,3-Diphenyl-2-propenone, the substrate exhibits four narrow peaks – within the selected range at 7.7 − 8.2 ppm – due to the aromatic protons of the substrate. The spectrum for a solution of 4CF-DPTU contains two narrow peaks (at 7.94 and 7.80 ppm) due to the substituted phenyl groups and a broadened peak at 7.90 ppm due to thiourea's NH protons (Fig. 1b). As can be seen in Fig. 1c,d, also in the ternary mixtures the substrate and catalyst signals are observed, yet shifted with respect to their position in the binary solutions. The NH proton undergoes a marked downfield shift in the presence of the substrate. This de-shielding of the NH proton implies a reduction of the average electron density in the vicinity of the NH proton, consistent with hydrogen-bond-formation to the C=O group of the substrate. Note, that other protons e.g. of the ortho-proton of the phenyl-substituents undergo only a minor shift (see Figure S1, SI). This marked downfield shift is in line with earlier reports showing that the NH proton is very sensitive to changes in the electronic environment.[13]
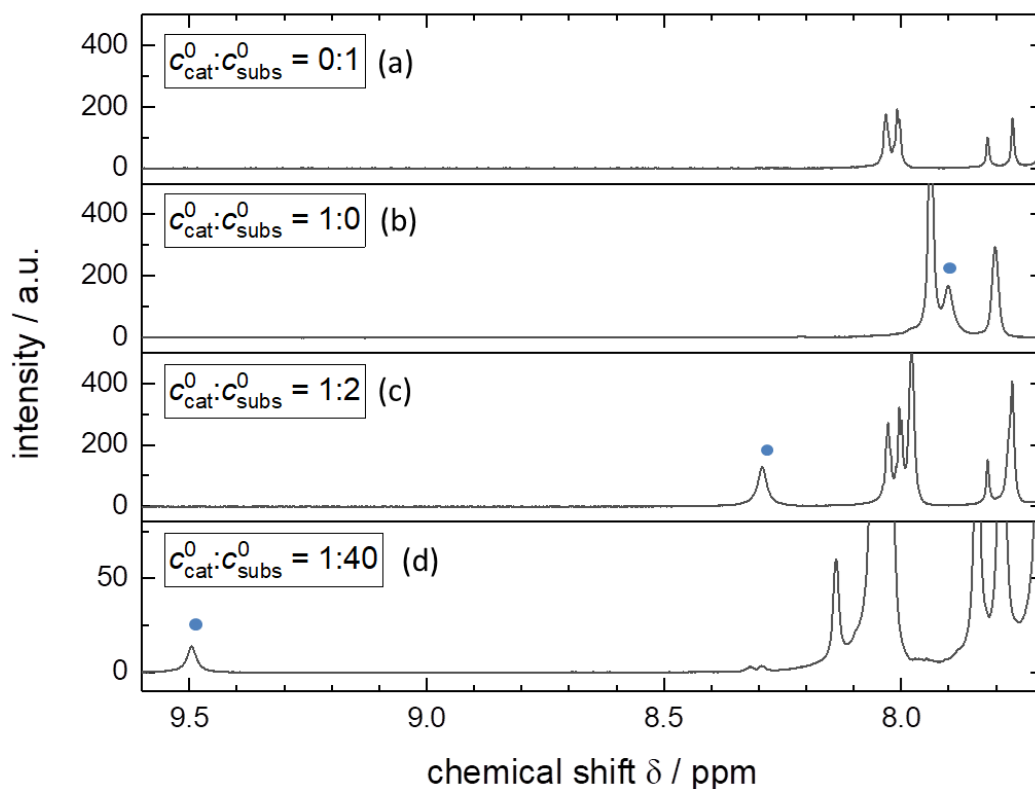
Figure 1. ^{1}H-NMR spectra for 4CF-DPTU (cat) and 1,3-Diphenyl-2-propenone (subs) mixtures in DCM at 7.7-9.1 ppm: (a) $c_{cat}^0 : c_{subs}^0 = 0{:}1$, (b) $c_{cat}^0 : c_{subs}^0 = 1{:}0$, (c) $c_{cat}^0 : c_{subs}^0 = 1{:}2$, and (d) $c_{cat}^0 : c_{subs}^0 = 1{:}40$. For visual clarity the NH proton peak is marked with blue filled circle.

To quantitatively compare the variation of the chemical shift for the studied thiourea catalysts, we analyse the chemical shift of the NH protons as a function of substrate concentration. As can be seen from Fig. 1, the chemical shift of the NH proton is most sensitive to the presence of the substrate. The extracted chemical shifts of the NH protons shown in Fig. 2 exhibit a marked increase with increasing substrate concentration for c_{subs}^0 < 0.2 mol/L, which levels off at higher concentrations of substrate for 4CF-DPTU. For 2CF-DPTU and 0CF-DPTU both the magnitude of the increase is lower and the curvature of the chemical shift as a function of c_{subs}^0 is less pronounced as compared to 4CF-DPTU, indicative of weaker interaction between the thioureas and the substrate. The observed chemical shift is however due to the motionally averaged signal of the free and the bonded catalyst. Hence, a change of chemical shift can be either caused by a stronger de-shielding upon hydrogen-bond formation (larger values of the chemical shift of the hydrogen-bonded complexes), or by a higher concentration of hydrogen-bonded complexes.
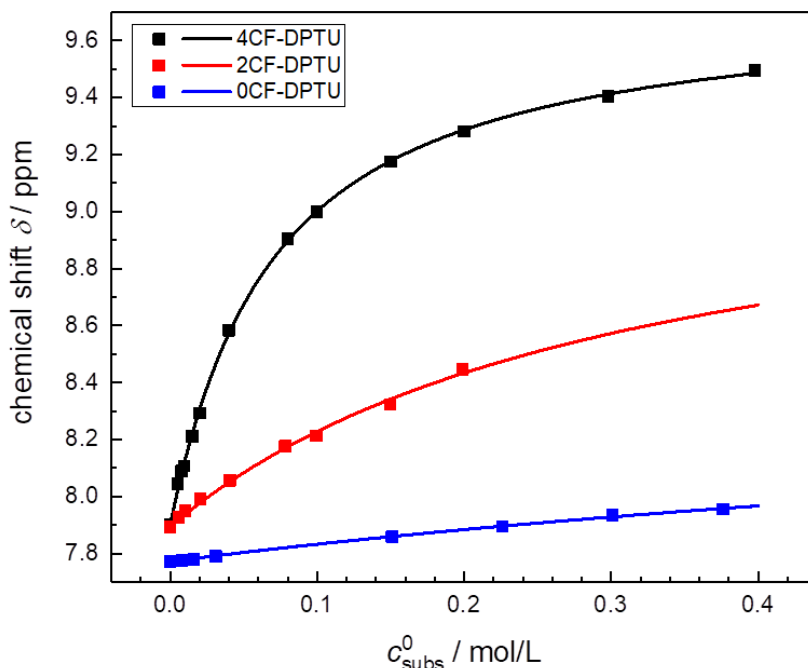
Figure 2. *Chemical shift of the NH protons as a function of substrate concentration c_{subs}^0 for 4CF-DPTU (black symbols), 2CF-DPTU (red symbols), and 0CF-DPTU (blue-symbols) in DCM. Solid lines show fits with the association model (eq. 2). The catalyst concentration is kept constant at $c_{\text{cat}}^0 = 0.01$ mol/L for 4CF-DPTU and 2CF-DPTU. For 0CF-DPTU the concentration of the catalyst ($c_{\text{cat}}^0 = 0.015$ mol/L) was higher to enable a better discrimination between the NH signals of the catalyst and the peaks of the substrate.*

To disentangle the effect of de-shielding and complex concentration to the observed signals, we fit an association model to the experimental ¹H-NMR data in Fig. 2. To this end, we assume a bimolecular association between the catalyst and the substrate molecule to form a hydrogen-bonded catalyst-substrate complex (scheme 2). The corresponding association equilibrium is given as:

$$K_{\text{NMR}} = \frac{[complex]}{[cat][subs]} \tag{1}$$

where [cat] and [subs] are the equilibrium concentrations of the free catalyst and the free substrate, respectively. [complex] is the concentration of hydrogen-bonded complexes. We assume the observed chemical shift δ to be the concentration weighted average of the chemical shift of the free catalyst, δ_{cat}, and of the chemical shift of the complex $\delta_{complex}$:

$$\delta = \delta_{\text{cat}}\frac{[cat]}{c_{\text{cat}}^0} + \delta_{\text{complex}}\frac{[complex]}{c_{\text{cat}}^0} \tag{2}$$

Mass conservation further gives:

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$$c_{\text{cat}}^0 = [cat] + [complex] \qquad (3)$$

We take the value for δ_{cat} from the $c_{\text{subs}}^0 = 0$ samples (δ_{cat}(4CF-DPTU) = 7.90 ppm, δ_{cat}(2CF-DPTU) 7.89 ppm, and δ_{cat}(0CF-DPTU) = 7.77 ppm). Thus, eqs. (1)-(3) excellently describe the experimental data (see solid lines in Fig. 2) with only two adjustable parameters, K_{NMR} and δ_{complex}. This suggests, that a bimolecular interaction dominates, as opposed to what has been found for other substrates in the solid state[21] and for asymmetric thiourea catalysts were different pathways are conceivable for a dual activation of the nucleophile and the electrophile.[22]

From the fits of eqs. (1)-(3) to the data, we obtain K_{NMR}(4CF-DPTU) = 15.8 $\pm$ 0.7 L/mol, K_{NMR}(2CF-DPTU) = 3.3 $\pm$ 0.3 L/mol, and K_{NMR}(0CF-DPTU) = 0.86 $\pm$ 0.03 L/mol [23] and for the chemical shift of the complex $\delta_{complex}$(4CF-DPTU) = 9.74 $\pm$ 0.02 ppm, $\delta_{complex}$(2CF-DPTU) = 9.27 $\pm$ 0.06 ppm, and $\delta_{complex}$(0CF-DPTU) = 8.54 $\pm$ 0.02 ppm,[23] respectively. Hence, the observed differences in de-shielding of the NH protons of different catalysts upon substrate addition (Fig. 2) are indeed a result of both, variation of the de-shielding upon complex formation for different catalysts (variation of $\delta_{complex}$ - δ_{cat}) and varying complex concentrations. Our results suggest that 4CF-DPTU forms the strongest hydrogen-bonds to the substrate, giving rise to the highest association constant. The thus obtained association constants are also consistent with the variation of the chemical shift of other protons of the catalyst and the chemical shift of the ^{13}C carbon of the C=O group of the substrate (see Figs. S2-S3, SI).

Association equilibria from FT-IR spectroscopy

Since the association equilibria as extracted from the NMR chemical shift may be biased by a substrate induced variation of the bulk properties of the solvent,[24] in particular for weak variation of the chemical shift (see 2CF-DPTU and 0CF-DPTU),[25] we use IR spectroscopy as an independent method to detect association.[26] In general, the NH stretching vibrations of the thiourea group are very sensitive to molecular associations, as the N-H stretching markedly red-shifts upon hydrogen-bond formation.[27]

In Fig. 3 we show the infrared absorption spectra for solutions of 0CF-DPTU (Fig. 3a), 2CF-DPTU (Fig. 3b), and 4CF-DPTU (Fig. 3c) with varying substrate concentration in DCM at frequencies characteristic to the NH stretching modes (~3150 – 3500 cm^{-1}). The absorption spectrum of 0CF-DPTU in DCM exhibits two vibrational modes at 3355 cm^{-1} and 3385 cm^{-1}. For alkyl substituted thioureas the presence of two N-H stretching bands has been explained by the presence of different conformers in solution, with distinctively different vibrational frequencies for the NH stretching mode.[28, 29] The two N-H stretching modes of N,N-diphenylthiourea (0CF-DPTU) have been suggested to stem from the trans-trans and trans-cis isomers.[30] Addition of the substrate hardly affects the infrared spectra at NH stretching frequencies, except for a minor reduction of the spectral amplitude of the two bands at 3355 cm^{-1} and 3385 cm^{-1} and a slight increase of the absorbance at 3180 – 3350 cm^{-1}.

The spectrum for a solution of 2CF-DPTU in DCM exhibits a single, yet asymmetric, band at 3370 cm^{-1} (Fig. 3b). The asymmetric band shape, in contrast to the clear double peak structure for 0CF-DPTU, suggests different conformational equilibria and/or faster conformational dynamics[31] for 2CF-DPTU, as compared to 0CF-DPTU. Upon addition of substrate to solutions of 2CF-DPTU, the N-H stretching bands at 3370 cm^{-1} decrease in amplitude and a broad absorbance at 3180 – 3350 cm^{-1} appears. Thus, our results indicate that upon addition of substrate, catalyst-substrate complexes are formed. Formation of complexes leads to the reduced concentration of free 2CF-DPTU molecules in solution giving rise to the decrease in the absorbance at 3370 cm^{-1}. A red-shifted NH stretching band due to hydrogen-bonded catalyst-substrate complexes can explain the absorbance at 3180 – 3350 cm^{-1}.

For solutions of 4CF-DPTU, we observe only a single symmetric absorption band at ~3375 cm^{-1}, which suggests that only one catalyst conformation can be detected on the timescale of the infrared experiments. This is consistent with NMR experiments, which have revealed that the trans-trans configuration of 4CF-DPTU prevails at room-temperature and the cis-trans isomer can only be observed at temperatures below 190 K.[13] The increasing amplitude of the red-shifted catalyst-substrate band at 3180 – 3350 cm^{-1} with increasing substrate concentration is most pronounced for 4CF-DPTU. Qualitatively, our results are in line with the association constants obtained from NMR: an increasing number of CF$_3$ groups results in enhanced association of DPTU with 1,3-Diphenyl-2-propenone and the associated complexes give rise to the hydrogen-bonded N-H stretching band at 3180 – 3350 cm^{-1}.
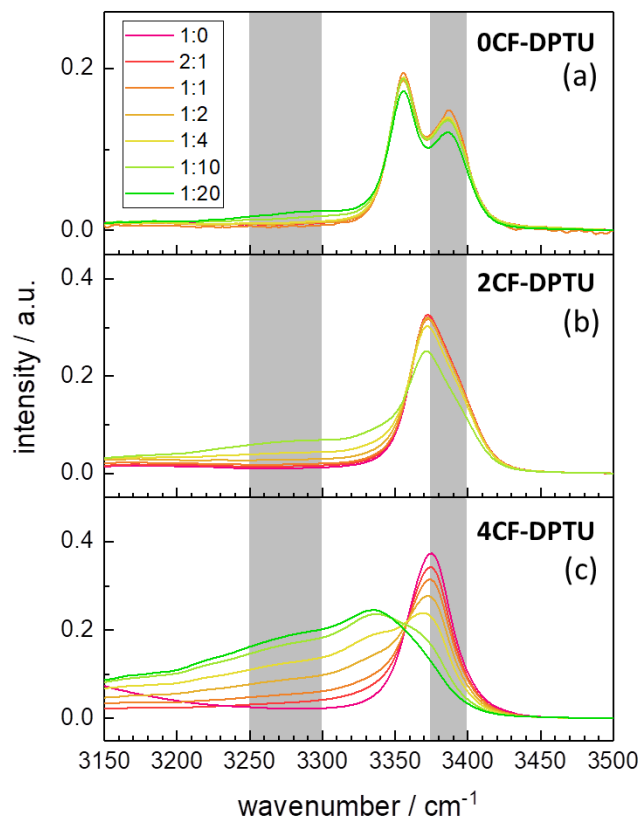

Figure 3: *Infrared absorption spectra for solutions of c_{cat}^0 = 0.02 mol/L (a) 0CF-DPTU, (b) 2CF-DPTU, and (c) 4CF-DPTU in DCM for different DPTU:substrate (1,3-diphenyl-2-propenone) ratios. Grey areas indicate the integration ranges used for the*

determination of the integrated absorbance of the free and the hydrogen-bonded catalyst (see text). The absorbance of the solvent and of 1,3-diphenyl-2-propenone has been subtracted from all spectra (for details see Figure S4, SI).

To quantitatively compare the infrared results to the findings from the NMR chemical shifts, we relate the infrared absorbances to molar concentrations. The absorbance of the free catalyst (A_{cat}) and of the complexes ($A_{complex}$) can be directly related to their molar concentrations, $[catalyst]$ and $[complex]$, via the extinction coefficients of free (ε_{cat}) and bound catalyst ($\varepsilon_{complex}$):

$$A_{cat} = \varepsilon_{cat} \cdot [cat] \cdot d \qquad (4a)$$
$$A_{complex} = \varepsilon_{complex} \cdot [complex] \cdot d \qquad (4b)$$

where d is the optical path length of the sample. To obtain the extinction coefficients, we rearrange eqs 3, 4a & 4b such:

$$\frac{c_{cat,0}}{A_{complex}} = \frac{1}{\varepsilon_{cat} \cdot d} \cdot \frac{A_{cat}}{A_{complex}} + \frac{1}{\varepsilon_{complex} \cdot d} \qquad (5)$$

that the inverse extinction coefficients can be obtained from the slope and the intercept of a linear regression ($\frac{c_{cat,0}}{A_{complex}}$ vs $\frac{A_{cat}}{A_{complex}}$). For this analysis, we use the integrated absorbance at 3375-3400 cm^{-1} for A_{cat} and the integrals at 3250 – 3300 cm^{-1} for $A_{complex}$ (see grey areas in Fig. 3). Note, that these frequency ranges do not cover the entire NH stretching bands shown in Fig. 3, in order to omit the spectral range where the contributions of free and bound catalyst overlap. Thus, also the obtained extinction coefficients are characteristic to the selected frequency range. In case of 0CF-DPTU the selected frequency range only covers the blue-shifted part of the split band. Given that the two bands stem from the presence of different conformers, we assume that the selected frequency range is representative of both conformers, which is valid for fast conformational exchange.

Using these values for $A_{complex}$ and A_{cat}, the linear relation of eq 5 describes the experimental quantities very well (Fig. 4). We note, that the slopes, which are proportional to the inverse extinction coefficients of the free catalysts, are similar for 2CF-DPTU and 4CF-DPTU. For 0CF-DPTU the slope is ~2 times higher, which can be explained by the double peak structure of the NH stretching band as this peak splitting results in a reduced apparent extinction coefficient for 0CF-DPTU within the selected frequency range.
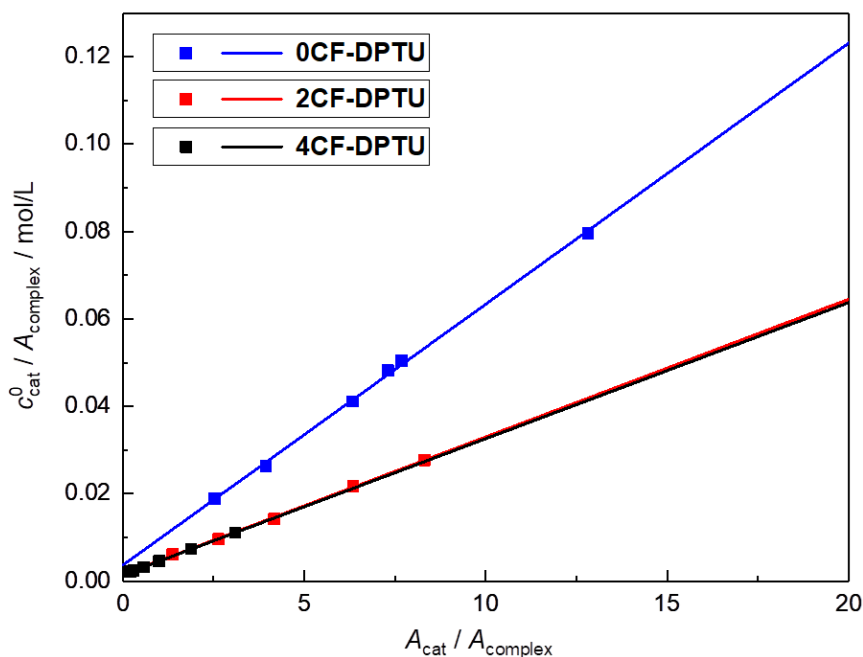
Figure 4: *Linear regression according to eq. 5 to obtain the extinction coefficient of the N-H stretching bands for the bound and the free catalyst.*

With the thus obtained values for ε_{cat} and $\varepsilon_{complex}$, we determine the degree of association α (see also Figure S5, SI):

$$\alpha = \frac{[complex]}{c_{cat}^0} \tag{6}$$

In line with our NMR results, α increases with increasing c_{subs}^0 and association is stronger with increasing number of CF_3 groups (Fig. 5). For a quantitative comparison to our NMR results we fit the bimolecular association model (eq 1) to the data in Fig. 5, which describes the variation of α with c_{subs}^0 well. The somewhat larger deviations of the data from the model at higher concentrations may stem from the partially overlapping IR bands of the free catalyst and the complex. We thus obtain the association constants K_{IR}, (K_{IR}(4CF-DPTU) = 10.2 ± 5.2 L/mol, K_{IR}(2CF-DPTU) = 2.0 ± 0.7 L/mol, and K_{IR}(0CF-DPTU) = 0.7 ± 0.4 L/mol).[23] In contrast to the NMR results (see $\delta_{complex}$ values above), we find no evidence for the spectra of the complexes to differ significantly for the three DPTUs (see Figure S6, SI).
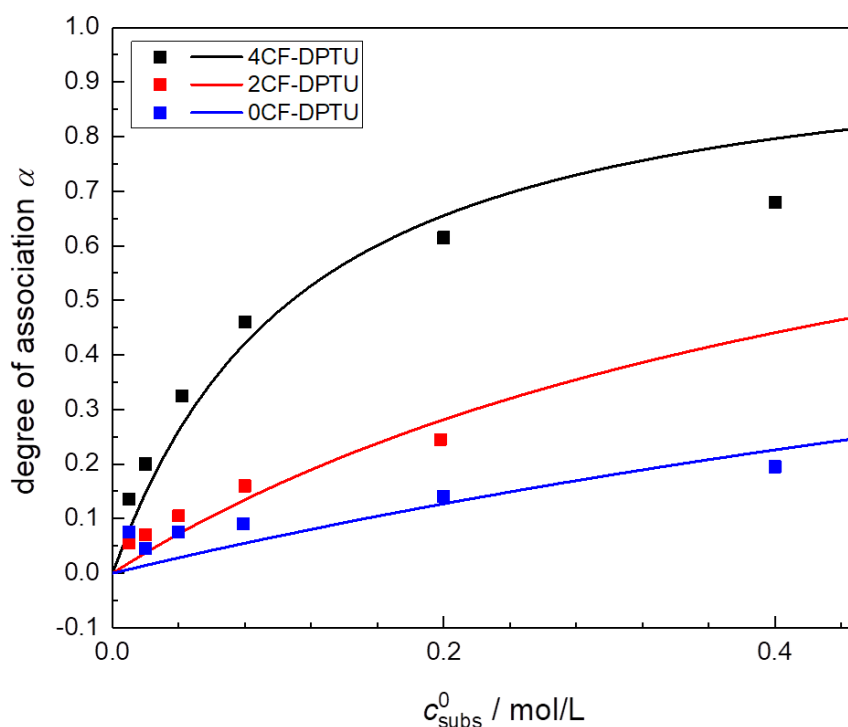
Figure 5: *Degree of association α, as obtained from the IR experiments (for details see text) for 4CF-DPTU (black symbols), 2CF-DPTU (red symbols) and 0CF-DPTU (blue symbols) in DCM (c_{cat}^0 = 0.02 mol/L). Solid lines show fits using the bimolecular association model (eq 1).*

As can be seen in Fig. 6, the association constants determined with both techniques agree well within the experimental error. More importantly, they correlate well with the reaction rates k_{rel} (relative increase of the reaction rate as compared to the absence of a catalyst) reported[2] for the Diels-Alder reaction of 1,3-diphenyl-2-propenone with cyclopentadiene (10-fold excess) in $CDCl_3$ catalyzed by 1 mol% 0CF-DPTU, 2CF-DPTU, or 4CF-DPTU. Thus, our results suggest that the enhanced catalytic conversion for CF_3 substituted DPTU catalysts originates from enhanced substrate binding. Our NMR experiments provide evidence for the enhanced association to originate – at least in part – from stronger N-H···O hydrogen-bonds, as the $\delta_{complex}$, which is predominantly effected by the local chemical environment, is shifted to higher values with increasing number of CF_3 groups. However, given the weak association of DPTU with 1,3-diphenyl-2-propenone, the chemical shift values of the complexes rely on extrapolation and are as such less certain. In fact, the N-H stretching bands, which are – similar to O-H stretching frequencies[32] – also a measure for the hydrogen-bond strength, are little affected by the presence of the CF_3 groups (see Figure S6, SI), indicative of different experimental sensitivities of NMR and IR. Nevertheless, the weak variation of the NH stretching band within the complexes across the studied DPTUs suggests that the intermolecular hydrogen-bond is not the sole cause for enhanced binding of 4CF-DPTU to the substrate. Additional, interaction of the ortho-proton of the phenyl group of phenylthiourea[13] with the substrate can comprise an

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additional interaction motif (see also Figure S1, SI) and also reduced solvation of the CF$_3$-substituted DPTU molecules may give rise to enhanced complex formation.
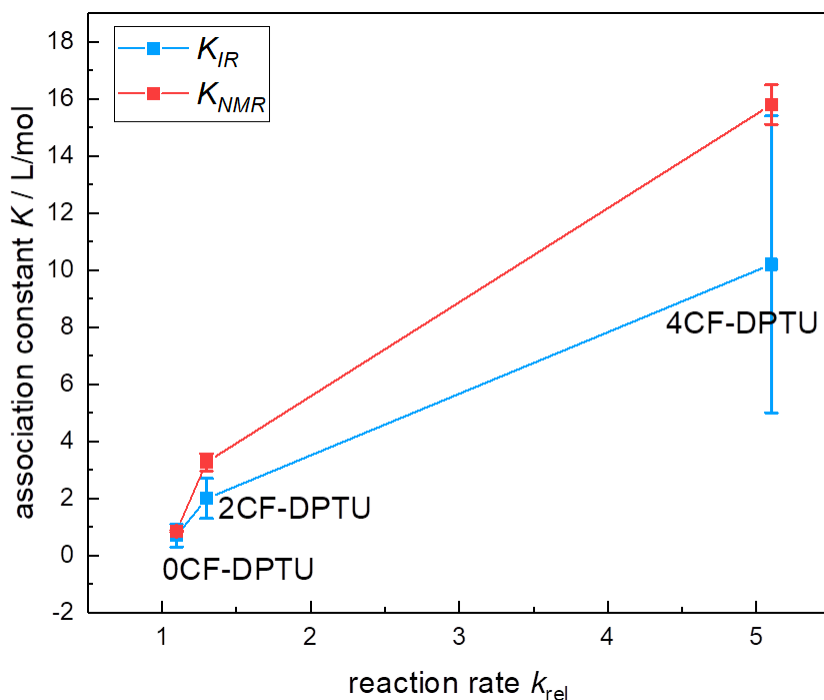

Figure 6: *Association constants K_{IR} and K_{NMR} vs relative rate constants of a Diels Alder reaction as reported in ref 2. Error bars correspond to K values for which the sum of the squared deviations increases by 100% when fitting eq (1) to the experimental data.*

Solvent effects

As differences in the solvation of the substrate, catalyst, and complexes in different solvents may give rise to different association, and thus different catalytic conversion, we investigate the effect of the solvent on the association.

Comparing our results for solutions in DCM to the association of DPTUs with 1,3-diphenyl-2-propenone in toluene, which is a commonly used solvent in catalysis, yet with lower polarity. Accordingly, we determine the K_{NMR} values from the ^{1}H-NMR chemical shifts (see Fig. S7, SI) in toluene.[33] As can be seen from the comparison of the determined values of the K_{NMR} (Tab. 1), the association strengths are comparable for 0CF-DPTU and 2CF-DPTU in toluene to those found in DCM. For 4CF-DPTU, however, association is enhanced in toluene as compared to DCM. The enhanced association of 4CF-DPTU with 1,3-diphenyl-2-propenone in toluene as compared to DCM points towards a less favorable interaction between the catalysts NH groups and the solvent in toluene as compared to DCM.

Conversely, in the highly dipolar solvent acetonitrile, we find the chemical shift of the NH protons DPTUs of all DPTUs to hardly vary with increasing concentration of 1,3-diphenyl-2-propenone (Fig. S8, SI). Hence, no appreciable association between the

DPTUs and the substrate in acetonitrile can be detected, which is further confirmed by the insensitivity of the catalysts NH stretching band to the substrate concentration in infrared absorption experiments (Fig. S9, SI). This suggests that the polarity of the solvent, as for instance determined via the $E_T(30)$ values,[34] is a reasonable estimate for the association strength of the DPTUs with ketones in organic (non-hydrogen-bonding) solvents. In general, binding of catalyst and substrate are markedly affected by the solvent, which suggests that solvation of the catalyst and substrate plays an important role for the formation of the reactive intermediates in catalysis. This is particularly apparent for 4CF-DPTU, for which association is strongly enhanced in toluene. [20]

Table 1: *Association constants, K_{NMR}, in DCM and toluene, as obtained from ^{1}H-NMR spectroscopy for the catalysts 0CF-DPTU, 2CF-DPTU and 4CF-DPTU, respectively.*

K_{NMR}	4CF-DPTU	2CF-DPTU	0CF-DPTU
CD_2Cl_2	15.8 $\pm$ 0.7 L/mol	3.27 $\pm$ 0.3 L/mol	0.86 $\pm$ 0.03 L/mol
Toluene	27.7 $\pm$ 1.3 L/mol	3.06 $\pm$ 0.1 L/mol	1.65 $\pm$ 0.2 L/mol

IV Conclusions

We use two independent techniques, NMR and FT-IR spectroscopy to quantify the association strength of diphenylthiourea-based catalysts with 1,3-diphenyl-2-propenone as a representative substrate in solution. We find bimolecular association to suffice to describe both infrared and NMR experimental findings. Despite the challenges in determining weak association equilibria, the interaction strengths determined by both methods agree very well. We find that with an increasing number of CF_3 substituents from 0CF-DPTU to 4CF-DPTU the association constant increases from ~1 L/mol to ~20 L/mol. This increase in molecular association correlates well with the reported increased catalytic activity of the DPTU-based catalysts. Our results suggest that the hydrogen-bond strength of the N-H···O=C bonds in the catalyst-substrate complexes is not the sole origin of the enhanced binding in solution for CF_3 substitued DPTUs but also the solvation of the catalyst, substrate and the complexes seem to contribute. The relevance of the solvation is supported by the marked dependence of the association equilibria on the solvent, with no detectable binding in solutions of acetonitrile and moderate interactions in toluene and dichloromethane.

Acknowledgements

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