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(Thio)urea Organocatalyst Equilibrium Acidities in DMSO

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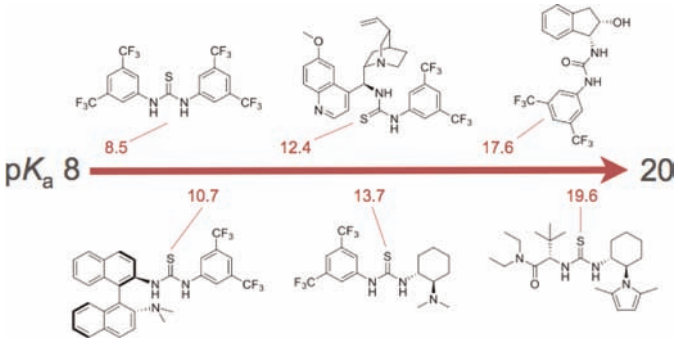
ABSTRACT



Bordwell's method of overlapping indicators was used to determine the pK_a values of some of the most popular (thio)urea organocatalysts via UV spectrophotometric titrations. The incremental effect of CF_3 groups on acidic strength was also investigated. The pK_a's are in the range of 8.5−19.6. The results may lead to a better understanding of noncovalent organocatalysis and may aid in future catalyst development.

The 3,5-bis(trifluoromethyl)phenyl moiety is a common structural motif in a great number of (thio)urea organocatalysts (Figure 1).[1] The apparently privileged role of the 3,5-bis(trifluoromethyl)phenyl moiety has been rationalized by its ability to increase the acidity of double H-bonding organocatalysts,[2] thereby strengthening the catalyst−substrate interactions that are akin to Lewis acid activation.[3] The 3,5-bis(trifluoromethyl)phenyl group also increases the polarity as well as the polarizability of a catalyst and, thereby, modulates the critical H-bonding interactions in the required transition state stabilization.[4] Much to our surprise, many of the pK_a values of common thiourea organocatalysts are unknown. The pK_a values of a selection of bifunctional dialkyl amino and cinchona-derived thioureas recently were determined in DMSO and correlated with their relative activity in some Michael addition reactions.[5] The tested catalysts were generally less acidic (pK_a = 13.2−21.1) than those reported here, and a structure-activity-enantioselectivity relationship could be established.[5] While hydrogen bonding interactions,

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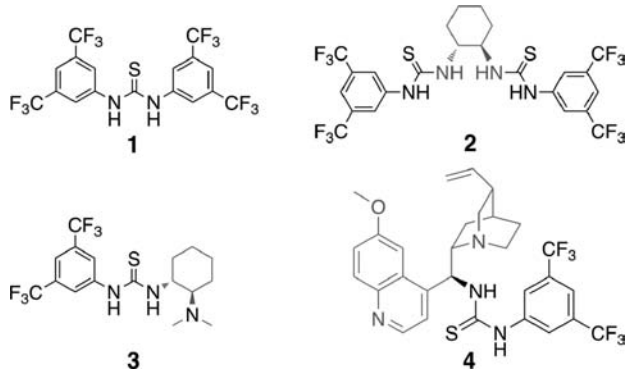

Figure 1. 3,5-Bis(trifluoromethyl)phenyl structural motif common to many organocatalysts.

and not proton transfer, play the key role in noncovalent organocatalysis,[6] it is quite clear that the availability of pK_a values for these catalysts helps in the understanding of catalytic activity and catalyst design, keeping in mind, however, that an equilibrium quantity has its limitations for a kinetic property such as transition state stabilization. As we demonstrated recently that the most common achiral catalyst, 3,5-bis(trifluoromethyl)phenyl thiourea (**1**) can readily be deprotonated with common bases such as diethylpropyl amine (DIPEA),[7] it is imperative to know the pK_a values of such catalysts to rationalize the underlying reaction mechanisms.

Although most organic reactions are being carried out in organic solvents, the first acidity scale was established in water with a limited practical pKa range of 0−12.[8] As many organic compounds are either sparingly soluble in aqueous media or significantly weaker acids than water, new acidity scales in organic solvents needed to be established. Polar non-H-bond-donor solvents proved to be very capable media for this purpose, since they suppress ion pairing,[9] and thus the obtained pK_a values were termed "absolute".[8,10] Bordwell and co-workers determined the pK_a values of over 1200 compounds in DMSO,[8] establishing an excellent basis for comparison. Inspired by this as well as Berkessel and O'Donoghue's report on the pK_a values of some important chiral Brønsted acid organocatalysts,[11] we decided to determine the acidic dissociation constants of some of the most popular (thio)urea organocatalysts in DMSO.

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Table 1. Indicators Used and Their pK_a Values in DMSO

no.	compound[a]	abbreviation	pK_a
1	9-cyanofluorene	CN-FH	8.3
2	2-bromo-9-(phenylsulfonyl)fluorene	2-Br-PhSO$_2$-FH	9.6
3	9-carbomethoxyfluorene	MeOOC-FH	10.35
4	4-nitrophenol	PNP	10.8
5	9-(phenylsulfonyl)fluorene	PhSO$_2$-FH	11.55
6	9-(ethylsulfonyl)fluorene	EtSO$_2$-FH	12.30
7	2-bromo-9-phenylthiofluorene	2-Br-PhS-FH	13.2
8	9-phenylthiofluorene	PhS-FH	15.4
9	9-^{i}propylthiofluorene	^{i}PrS-FH	16.9
10	9-phenylfluorene	Ph-FH	17.9
11	4-chloro-2-nitroaniline	4-Cl-2-NO$_2$-AN	18.9

[a] For further details see Supporting Information.

We adopted the spectrophotometric method of overlapping indicators, developed by Bordwell.[9] The basis of the pK_a determination is an acid−base equilibrium (eq 1) between an arbitrary weak acid (HA) and an appropriate indicator (HInd) that obeys Beer's law.

$$HA + Ind^- \rightleftharpoons A^- + HInd \quad (1)$$

A precondition for accurate measurements is a relatively similar acidity of the two participants; in our experience a pK_a difference no greater than 1.5 units is acceptable to keep the errors small. Addition of the weak acid yields a new equilibrium with a lower concentration of the indicator anion, resulting in a decrease of the UV absorption at a certain wavelength. In the absence of a proton source other than the weak acid, the following equation applies (charges were omitted for clarity).

$$\Delta[Ind] = \Delta[HA] \quad (2)$$

Since the initial amount of each species is known, the equilibrium constant (K_{eq}) of eq 1 can be calculated, which leads to the pK_a value of the weak acid in question:

$$pK_a = pK_{Ind} - \log K_{eq} \quad (3)$$

In order to achieve maximum accuracy, the concentration of the K-dimsyl base solution and the molar extinction coefficient of the indicator in use were determined in each titration. Dilution effects were taken into account, and moisture and oxygen exposure were minimized. Ion association was neglected due to the low concentration of participants (10^{-3}−10^{-4} M).[9] The (thio)urea derivatives investigated in this study were initially assumed to have pK_a values in the range of 9−18; hence a series of indicators covering the aforementioned range anchored to the Bordwell acidity scale was synthesized (Table 1). We used benzoic acid and *N*,*N*′-diphenylthiourea as test compounds to verify our approach. Benzoic acid is prone to self-association and the presence of water in solution has a serious influence on its pK_a value, so this resulted in being a challenging task. To our delight, repeated measurements with two different indicators showed close agreement with the literature values of these two test compounds (BzOH: 11.09 ± 0.07, *lit*. 11.0 ± 0.1; **8**: 13.38 ± 0.06, *lit*. 13.4 ± 0.1).[8]

We also measured one catalyst against three different indicators, furnishing basically the same pK_a value (see Supporting Information).

With a reliable method in hand we decided to investigate first the effect of the CF_3 groups on (thio)urea acidity (Figure 2). Bordwell's measurements already revealed that replacing the urea oxygen by a sulfur atom increases the acidity by 6 orders of magnitude; aryl substitution adds another 10^8 units to the acidity, which is due to DMSO lacking ion stabilizing effects. Thus, the ability of intramolecular charge distribution is critical to acidic strength, and unsubstituted (thio)urea (**5** and **6**) has a much higher pK_a value (26.9 and 21.1, respectively) than *N*,*N*′-diphenyl-(thio)urea (**7** and **8**) (18.7 and 13.4, respectively). Introducing CF_3 groups to the aromatic rings further increases acidity, owing to their strong σ-electron withdrawing ability. We find that the pK_a increase corresponds well with the overall number of CF_3 groups attached to the aromatic rings; each CF_3 group decreases the pK_a by approximately 1.2 pK_a units. The combined effect of four CF_3 groups thus results in a pK_a value of 8.5, which is well below the common expectation for a thiourea derivative. This low pK_a is in line with the literature value[2b] and underscores our finding that relatively weak organic bases (e.g., DIPEA) are able to deprotonate **1**.[7]

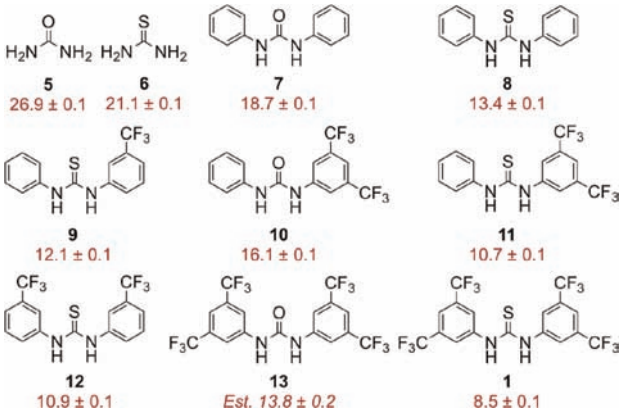

Figure 2. Substituent effects on a selection of achiral (thio)urea derivative pK_a values in DMSO.

Another conclusion is that both aromatic rings are involved in the stabilization of the anion, as indicated by the similar pK_a values of two isomeric thiourea compounds (Figure 2, **11**[2b] and **12**[1i]). A plausible explanation involves dynamic proton exchange between the two thiourea nitrogens, creating an average partial negative charge on both; this is in line with the fast H/D exchange of **1** in deuterated solvents (Mike Kotke, Dissertation, Justus-Liebig University Giessen, 2009). Most of the popular (thio)urea organocatalysts lack a second aromatic moiety, which would lead to somewhat higher pK_a values according to our hypothesis. Indeed, Wang's binaphthyl catalyst (Table 2, entry 1) inherits the acidic strength of the parent system

Table 2. pK_a Values of Some Popular Chiral (Thio)urea Organocatalysts in DMSO

entry	catalyst	structure	pK_a value
1	Wang[1a]	**14**	10.72 ± 0.02
2	Nagasawa[1b]	**2**	11.98 ± 0.09
3	Soós[1c]	**4**	12.39 ± 0.07
4	Schreiner-Zhang[1d]	**15**	12.54 ± 0.07
5	Jacobsen[1c]	**16**	12.57 ± 0.04
6	Ricci[1f]	**17**	12.98 ± 0.07
7	Tang[1g]	**18**	13.38 ± 0.03
8	Takemoto[1h]	**3**	13.65 ± 0.02
9	Ricci[1f]	**19**	17.63 ± 0.07
10	Jacobsen-like[a,12]	**20**	*18.3 ± 0.2*[b]
11	Jacobsen-List[c,13]	**21**	19.60 ± 0.01

[a] Jacobsen originally presented a large number of catalysts based on this general motif with various amino acids as well as variations in the substituents at the terminal amino group and the phenol moiety. [b] The pK_a presented is an apparent value, a result of the similar acidity of the thiourea group and the phenolic OH. [c] The depicted catalyst is the one prepared by List et al.;[13b] Jacobsen prepared various catalysts of this motif differing in the dialkyl substituents (Me, Ph, *i*-Bu) at the terminal amino group and the di-*ortho* substituents at the imidazol moiety (Me, Ph).[13a]

(−2.2 pK_a units), while the pK_a values of other commonly employed catalysts are 2−3 pK_a units higher (Table 2, entries 2−8). Without aromatic substituents the pK_a values converge to that of parent thiourea (Table 2, entry 10, 11). An important inclusion is that N-aryl thioureas have intrinsically lower pK_a values and may therefore be more useful as organocatalysts; exceptions are Jacobsen's catalysts **20** and **21** with pK_a's of 18.3 and 19.4. Intramolecular hydrogen bonds may also be responsible for an enhancement of acidic strength. For instance, while Nagasawa's thiourea **2** and the Takemoto catalyst **3** share the same chiral backbone, a second thiourea group is in close proximity to stabilize the incipient anion via H-bonding interactions in **2**, leading to a lower pK_a.

A survey of the literature yielded some examples where the increasing acidic strength of a series of catalysts had a beneficial effect on their activity in the given reactions.

Turnover frequencies (TOF) were calculated in each case to quantify catalyst performance. In a Morita−Baylis−Hillman reaction of 2-cyclohexen-1-one with phenylpropionaldehyde Takemoto's catalyst (**3**, pK_a = 13.65, TOF = 0.04 h^{-1}) exhibited moderate activity compared to that of Wang's (**14**, pK_a = 10.72, TOF = 0.17 h^{-1}).[1a] Similarly, in a vinylogous aldol addition of γ-butenolide to benzaldehyde, the best results were obtained with the Soós catalyst (**4**, pK_a = 12.39, TOF = 0.16 h^{-1}), and decreasing acidity of the thiourea moiety resulted in slightly lower reaction rates in the case of Takemoto's catalyst (**3**, pK_a = 13.65, TOF = 0.13 h^{-1}) and for a derivative of **3** without the CF_3 groups attached to the phenyl ring (pK_a = 17.0,[5] TOF = 0.08 h^{-1}).[14] The same three catalysts were involved in another study concerning an aza−Morita−Baylis−Hillman type reaction with turnover frequencies of 0.13, 0.19, and 0.16 h^{-1}, respectively.[15] This finding suggests that a thiourea derivative with an optimal pK_a value (∼13.7) may be suitable to achieve maximum acceleration in this transformation. It is quite clear, however, that the acidic strength of the (thio)urea moiety is only one of several key features defining catalytic properties. pK_a Values and catalyst activity do not necessarily correspond well, as shown in the case of transfer hydrogenations of nitroolefins.[16] This is not unexpected as catalyst−substrate interactions and transition-state stabilization can be energetically quite different.

In the current study we report the pK_a values of some of the most popular (thio)urea organocatalysts in DMSO. The UV-spectrophotometric indicators synthesized and used for this purpose were introduced by Bordwell; thus the obtained results are embedded within his extensive acidity scale. The strongly acidifying effect of CF_3 groups was also investigated and found to be very predictable by the number of groups attached to an aryl moiety. The data provided here are likely to contribute to future catalyst development and to a deeper understanding of noncovalent, hydrogen bonding organocatalysis.

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Supporting Information Available. Detailed description of the spectrophotometric titrations, synthetic protocols, and characterization of materials. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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