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Squaramide Equilibrium Acidities in DMSO

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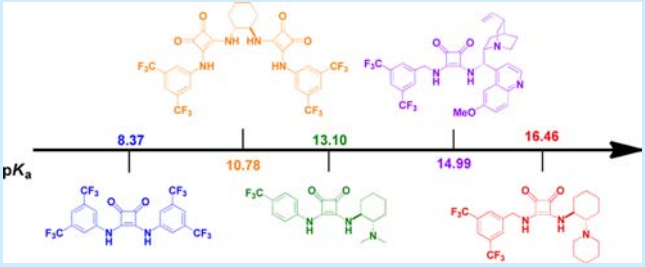
Supporting Information

ABSTRACT: A number of popular squaramide organocatalysts' acidities were determined by an overlapping indicator method in DMSO via UV spectrophotometric titrations. The pK_a values are in the range of 8.37−16.46. The results may be helpful for the rational design and development of squaramide type new catalysts.



Compounds possessing a hydrogen-bond donor motif associated with a chiral spacer framework, which are universally existent in nature, have become a prominent type of organocatalyst that enables the realization of a range of transformations with high efficiency and stereoselectivity.[1] Especially, chiral bifunctional (thio)urea-tertiary amines have received special attention owing to their double hydrogen-bonding interaction of the N−H bond, in which several functionalities, such as carbonyl, nitro, imine groups and vinyl sulfones, have been successfully activated.[2]

Squaramides, due to their structure feature of possessing both a hydrogen-bond acceptor at the carbonyl group and hydrogen-bond donor donated by the N−H group, have been designed as efficient receptors capable of not only recognizing anions and cations[3] but also forming complexes with a variety of neutral molecules.[4] In 2008, Rawal and co-workers applied a chiral squaramide-based organocatalyst derived from a cinchona alkaloid in the Michael addition of 1,3-dicarbonyl compounds to nitro olefins, which performed excellently in both chemical efficiency and stereocontrol compared to the results using the counterpart thiourea-based catalyst.[5] From then on, squaramides with different skeletons have been widely developed and proven efficient in a broad range of asymmetric transformations, including aldol,[6] Mannich,[7] Friedel−Crafts,[8] Michael addition,[9] Henry,[10] Morita−Baylis−Hillman,[11] Diels−Alder,[12] cycloaddition,[13] cascade reaction,[14] asymmetric cycloaddition of homophthalic anhydrides,[15] and so on.[16] It is worth mentioning that the squaramide catalyst exhibited superior activity evidenced by the fact that a very low catalyst loading was needed to complete the full conversion of the substrate. In fact, the crystallographic structure and computational data obtained by Rawal demonstrated that squaramide's two N−H bonds are coplanar with the rigid four-element-ring framework of the cyclobutendione unit.[5] Compared to the counterpart thioureas, the distances between the two N−H groups of squaramides are about 0.6 Å broader than in the case of thioureas. And the difference in value of the dihedral angles of the N−H bonds between squaramides and thioureas was ∼8°. These two natural differences were considered to be attributed to the "squara structure" of cyclobutendione.[5,16] In addition to the structure feature investigated above, the distinctly different pK_a values of N−H bonds between squaramide and (thio)urea compounds should be one of the most crucial parameters rationalizing the extraordinary performance of squaramides (Figure 1). However, to the best of our knowledge, the fundamental physical organic parameters of squaramides, i.e. the acidities, which are helpful for understanding the mechanism of asymmetric catalysis, are still unknown. It is worth noting that the absence of the corresponding pK_a values seriously limited the rational design and development of this emerging organocatalyst.

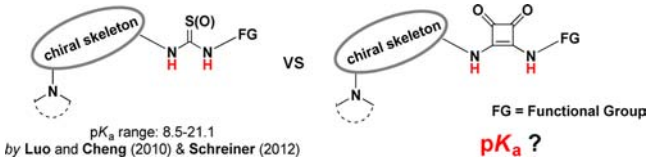


Figure 1. Situation of the pK_a values of bifunctional hydrogen-bonding catalysts.

In 2010, Luo and Cheng first determined the pK_a values of a series of chiral bifunctional thiourea catalysts in DMSO by an overlapping indicator method, in which a linear free energy relationship between the pK_a and both the reactivity and enantioselectivity of studied Michael reactions was found.[17] Subsequently, Schreiner et al. measured the acidities of some widely used thiourea and urea organocatalysts with the same method.[18] Furthermore, pK_a values of some widely used chiral Brønsted acid catalysts, such as phosphoric acids and super acids, were also reported by experimental methods.[19] In the

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present study, we reported the determination of the pK_a values of squaramide type catalysts.[20]

Eighteen squaramide catalysts, including achiral and chiral ones, were selected as the target compounds (Figure 2). The

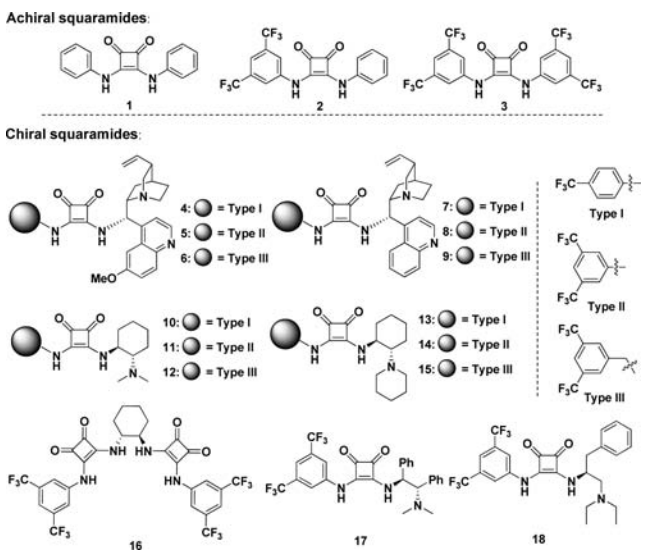

Figure 2. Studied squaramides.

pK_a values were measured in DMSO by the spectrophotometric method of an overlapping indicator.[21] A solution of an indicator containing a known concentration of its colored anion was titrated with a solution of squaramide whose anion absorbs at a different wavelength. The concentration of the indicator's anion is monitored by a UV/vis spectrophotometer after each addition of the squaramide solution (Figure 3). The equilibrium acidity of the squaramide could then be calculated according to eqs 1 and 2.

$$HA + In^- \underset{}{\overset{K_{eq}}{\rightleftharpoons}} HIn + A^- \quad (1)$$

$$pK_{HA} = pK_{HIn} - \log K_{eq}$$
$$= pK_{HIn} - \log ([HIn][A^-]/[In^-][HA]) \quad (2)$$

The determinations of the pK_a values were carried out under an atmosphere of argon. The treatment of DMSO and base (K-dimsyl basic solution) strictly followed that in literature.[21] The carbon acid indicators used in this study are shown in Figure 4. The results of the pK_a values of squaramides are shown in Table 1.

As shown in Table 1, the pK_a values of the studied squaramides cover the range 8.37−16.46. The electronic effect on acidity was then investigated. General information shows that the di-3,5-CF_3 substituted phenyl type squaramides have pK_a values lower than 11.9, indicating that they are more acidic than AcOH (pK_a = 12.3[30]). For the three achiral squaramides, in which both N-atoms were substituted with an aromatic group, fitting trifluoromethyl groups onto the aromatic ring sharply increases their acidities. Particularly, the pK_a values' decrements correspond to the increment of trifluoromethyl groups, in which each trifluoromethyl group strengthens the acidity of achiral squaramides by more than 1 pK_a unit. Owning to the lack of a second aromatic ring, most of the pK_a values of chiral squaramides are higher than **2**. With regard to the electron-withdrawing ability diminished by each type of

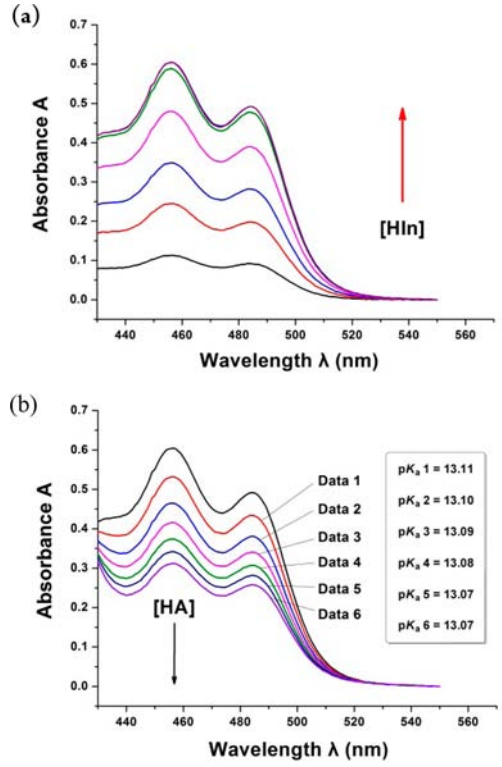

Figure 3. (a) Absorption spectra of the anion derived from 2-Br-PhS-FH for various added amounts of 2-Br-PhS-FH during the titration. (b) Absorption spectra of the anion derived from 2-Br-PhS-FH for various added amounts of squaramide **10** during the titration.

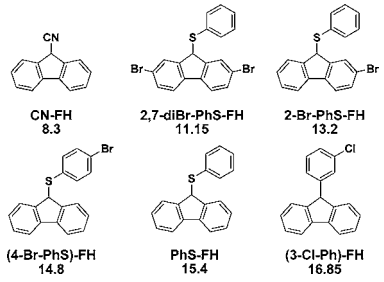

Figure 4. Indicators' structures and their pK_a values in DMSO.[22]

electronic tuning group, the pK_a values increase in the order type II < type I < type III.

We next examined the structural effect on the acidities of squaramides. It is not difficult to find that the squaramides with a cyclohexane-1,2-diamine motif (**11** and **14**) exhibit higher pK_a values than the squaramides with the other chiral skeletons (**5**, **8**, **17**, and **18**). With regard to **10**−**15**, the acidities of squaramides with cyclic tertiary-amine unit are higher than the corresponding acyclic tertiary-amine ones. Further inspection of the data shows that the pK_a gap between **11** and **14** (0.04 pK_a units) is smaller than the values in the other two pairs (0.2 pK_a units for **10** and **13**, 0.18 pK_a units for **12** and **15**), indicating that the structure effect on the acidity is weaker accompanied by the stronger influence of the electronic effect. Although it shares the same chiral skeleton with **10**−**15**, catalyst **16** has a remarkably lower pK_a value, which can be explained by the addition of the second squaramide moiety. And for the squaramides **4**−**9**, which possess cinchona alkaloid skeletons,

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Table 1. pK_a Values of Squaramides in DMSO

entry	squaramide	pK_a value	indicator
1	**1**	12.48 ± 0.05	2-Br-PhS-FH
2	**2**	10.55 ± 0.03	2,7-diBr-PhS-FH
3	**3** (Schmidt, 2013)[23]	8.37 ± 0.04	CN-FH
4	**4** (Du, 2010)[24]	12.17 ± 0.03	2,7-diBr-PhS-FH
5	**5** (Du, 2010)[24]	10.54 ± 0.04	2,7-diBr-PhS-FH
6	**6** (Jørgensen, 2010)[25]	14.99 ± 0.05	(4-Br-PhS)-FH
7	**7** (Du, 2010)[24]	12.18 ± 0.04	2,7-diBr-PhS-FH
8	**8** (Du, 2010)[24]	11.03 ± 0.03	2,7-diBr-PhS-FH
9	**9** (Rawal, 2010)[5]	15.13 ± 0.05	(4-Br-PhS)-FH
10	**10** (Du, 2011)[26]	13.10 ± 0.04	2-Br-PhS-FH
11	**11** (Rawal, 2010)[27]	11.83 ± 0.05	2,7-diBr-PhS-FH
12	**12** (Rodriguez, 2012)[28]	16.28 ± 0.05	(3-Cl-Ph)-FH
13	**13** (Rawal, 2010)[27]	13.30 ± 0.04	2-Br-PhS-FH
14	**14** (Rawal, 2010)[27]	11.87 ± 0.03	2,7-diBr-PhS-FH
15	**15** (Rawal, 2010)[29]	16.46 ± 0.05	(3-Cl-Ph)-FH
16	**16**	10.78 ± 0.03	2,7-diBr-PhS-FH
17	**17** (Rawal, 2010)[29]	11.42 ± 0.03	2,7-diBr-PhS-FH
18	**18**	11.57 ± 0.04	2,7-diBr-PhS-FH

the pK_a values decrease when the quinoline rings were substituted by 6′-methoxy groups.

The rapid development of chiral squaramide catalysis can be attributed to their excellent catalytic performance rather than the corresponding thiourea, which is generally considered due to its higher acidity. However, more quantitative information regarding the pK_a gap between squaramide and thiourea is still needed. Comparison of the pK_a value between squaramides and corresponding thiourea analogues was then conducted. It was found that the pK_a values of squaramides are lower than their thiourea analogues (Figure 5), in which 0.13−1.97 pK_a gap

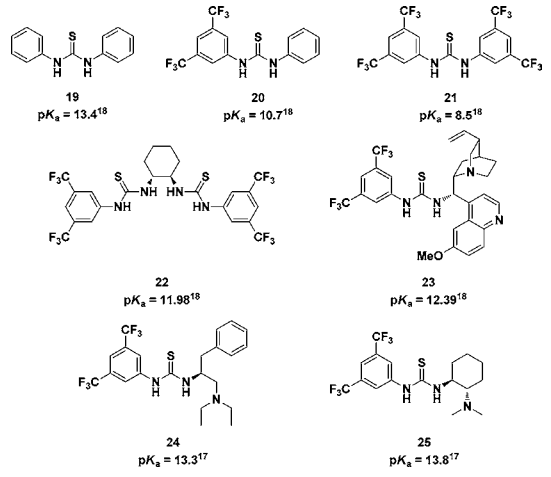

Figure 5. pK_a values of thiourea analogues in DMSO.

units were obtained. Although the magnitude of the pK_a gap between squaramide and thiourea is sharply dependent on the parent structure, the fact that squaramide is more acidic indicated that squaramide engages in stronger hydrogen bonds than the corresponding thiourea. This result may be one of the most important reasons explaining why lower loadings of squaramide catalysts can perform with even higher activity in completing a broad range of asymmetric transformations. To our delight, two good straight lines with R values of 0.995 and 0.932 were obtained in the regression analysis between the pK_a values of achiral squaramides and their thiourea analogues, and chiral squaramides and their thiourea analogues, respectively (Figure 6). This interesting correlation implies that the pK_a of squaramide may be estimated on the basis of the knowledge of the pK_a value of the corresponding thiourea.

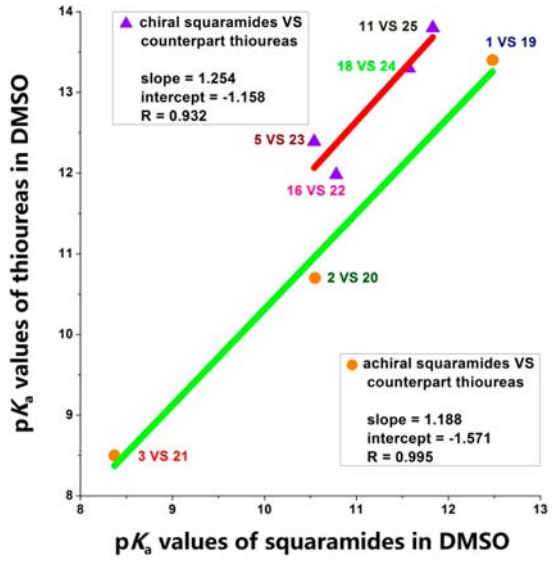

Figure 6. Correlation of pK_a values of squaramides with their thiourea analogues.

In summary, we have determined the pK_a values of 18 squaramide organocatalysts in DMSO by the classical overlapping indicator method. The pK_a values lie in the range 8.37 to 16.46. The acidifying effect of the catalysts' structure and substituted trifluoromethyl groups were investigated. Moreover, comparisons of the acidity values between squaramides and their thiourea analogues were also conducted. We believe that the data reported here will provide a basis for developing new hydrogen-bonding catalysts and will be helpful in obtaining deeper insight into the corresponding mechanisms.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, analytic data for all the new compounds, and Figures S1−S17. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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