Organic LETTERS

Letter

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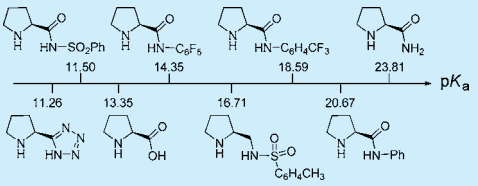
Equilibrium Acidities of Proline Derived Organocatalysts in DMSO

Zhen Li, Xin Li,* Xiang Ni, and Jin-Pei Cheng*

State Key Laboratory of Elemento-Organic Chemistry, Department of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Weijin Road 94th, Tianjin 300071, China

Supporting Information

ABSTRACT: Equilibrium acidities of proline and its derived organocatalysts were measured in DMSO by an overlapping indicator method via UV/vis spectrophotometric titration. The pK_a values are in the range of 11.17−23.81.



In the early 1970s, the proline catalyzed asymmetric intramolecule aldol reaction, the Hajos−Parrish−Eder−Sauer−Wiechert reaction, which is one of the highly enantioselective catalytic carbon−carbon bonding reactions, was reported by two industrial laboratories.[1] In 2000, inspired by class I aldolase enzymes and powerful aldolase catalytic antibodies, List, Lerner, and Barbas reported the first proline catalyzed asymmetric direct intermolecule aldol reaction, which triggered the understanding of the potential of aminocatalysts.[2] From then on, the asymmetric catalysis of proline and its derivatives, such as proline amide, has grown up at a dramatic pace. And a number of important asymmetric transformations, including aldol reaction, Mannich, Michael addition, amination, halogenation, alkylation, and tandem reaction, have been successful realized by proline and proline amide catalysis.[3]

With the development of new catalytic reactions, the mechanisms of the proline and proline amide catalysis have been also considered as urgent research content and studied in depth by experimental measurements and theoretical calcualtions.[4] It is believed that the proline and proline amide catalysis proceed through an enamine mechanism, in which the secondary amine moiety reacts with aldehyde or ketone to form enamine, while hydrogen of proline or proline amides provides the hydrogen bonding function to activate the electrophile (Figure 1). As it is known that the more acidic amide will lead to the formation of a stronger hydrogen bond, increasing acidities of amides should provide an effective strategy to improve the catalytic activities of proline amide type catalysis. Furthermore, the stronger hydrogen bonding would also be helpful for stereocontrol, leading to a better enantioselectivity. In fact, the proline amide derived organocatalysts with strongly electron-withdrawing groups were found to exhibit much higher catalytic activity and enantioselectivity than the corresponding chiral amide with electron-donating groups.[5] As is emphasized by Jørgensen in a recent review,[6] the acidity of the hydrogen-bond donor unit should be taken into consideration when designing new proline derived bifunctional aminocatalysts. However, to our surprise, there is only one theoretical study of proline amide derivatives' acidities in DMSO by DFT calculations, which have relatively large mean absolution deviation (0.98 pK units),[7] and no pK_a scales of proline and proline amides was determined by experimental method until now. Therefore, a systematic study of corresponding acidities by accurate measurement is highly desirable.

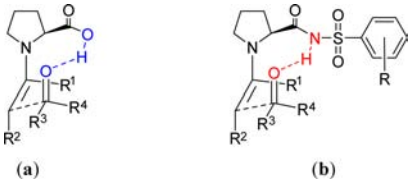


Figure 1. Mechanism of proline and proline amide catalysis.

Bordwell and co-workers had established the absolute acidity scale by an overlapping indicator method for a large number of compounds, which provides the most comprehensive pK_a data with a wide range of 30 pK units.[8] Because DMSO is one of the frequently used solvents in proline and proline amide catalyzed reactions,[9] the pK_a values of proline and proline amides in DMSO are important for the understanding of catalytic mechanism and rational design of efficient proline type organocatalyst. Recently, the research of the determination of chiral Brønsted acids' pK_as has attracted extensive attention.[10,11] At the same time, our group has also determined the pK_a values of a number of important thioureas and squaramides by classic overlapping indicator method.[12] Continuous our physical organic chemistry guided research program of asymmetric catalysis,[12,13] herein we reported the determination of the pK_a values of proline and its derivatives in DMSO.

As shown in Figure 2, **17** proline and its derivatives were selected as target compounds. Eight carbon acids, which has been considered as standard indicators using in previous study, were selected as indicators in this work and exhibited in Figure 3. The pK_a values were obtained in DMSO by an overlapping indicator method via UV/vis spectrophotometric titration according to our previous study.[12,14,15] Taking acid **14** as the

Received: January 16, 2015
Published: February 13, 2015

DOI: 10.1021/acs.orglett.5b00143
Org. Lett. 2015, 17, 1196−1199

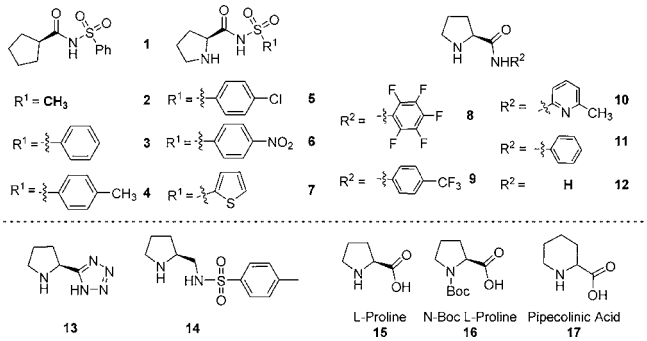


Figure 2. Studied proline derivatives in this work.

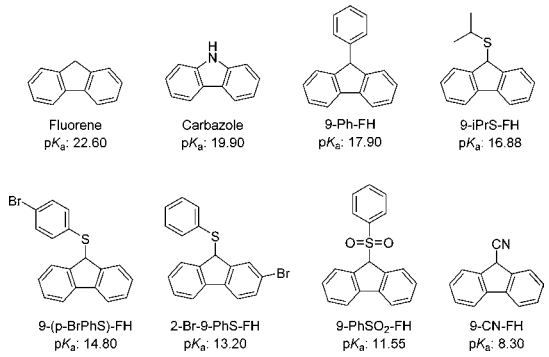


Figure 3. Indicator's structures and their pK_a values in DMSO.

example, a work calibration curve was obtained by titrating indicator solution into the base (K-dimsyl) solution (eq 1), in which both the spectra and the weight were recorded (Figure 4a). Acid **14** was added after dimsyl was consumed. Corresponding equilibrium between **14** and anion of indicator was achieved (eq 2). The concentration of indicator anion could be calculated by monitoring UV/vis spectra, and the concentration of the other three species could be derived from accurately weighed amounts of solution. Consequently, equilibrium constant K_{eq} could be calculated and the pK_a value of **14** was readily accessible for each addition of acid through eq 3 (Figure 4b). It should be noted that for carboxylic acids **15**–**17**, due to the interference of the equilibriums by homoconjugation[16] or homohydrogen bonding (eq 4),[17] a modified indicator overlapping method, which was developed by Bordwell with special mathematical techniques that take both equilibriums into account without modification of experimental procedure,[17c] was employed.

$$\mathrm{HIn} + \mathrm{dimsyl} \rightarrow \mathrm{In}^- + \mathrm{DMSO} \quad (1)$$

$$\mathrm{HA} + \mathrm{In}^- \overset{K_{eq}}{\rightleftharpoons} \mathrm{HIn} + \mathrm{A}^- \quad (2)$$

$$pK_{HA} = pK_{HIn} - \mathrm{Ig}K_{eq}$$

$$= pK_{HIn} - \mathrm{Ig}\frac{[HIn][A^-]}{[In^-][HA]} \quad (3)$$

$$\mathrm{HA} + \mathrm{A}^- \overset{K_{hb}}{\rightleftharpoons} \mathrm{AHA}^- \quad (4)$$

With the indicator overlapping method, the proline derived organocatalysts' pK_as were obtained with very small uncertainty (SD $\leq \pm$ 0.10 pK), and the results are summarized in Table 1. In general, the pK_a values covered the range from 11.17 to 23.81. As shown in Table 1, prolinetetrazole (**13**) and *N*-sulfonylated proline amides (**2**–**7**) exhibited the stronger acidities (11.17–11.57). This result indicates that **2**–**7** and **13** should be much more efficient proline type catalyst with dual-activation enamine mechanism. In fact, prolinetetrazole and *N*-sulfonylated proline amides indeed showed very good catalytic activity and enantioselectivity in a number of asymmetric transformations.[18] Careful examination of the data, we found

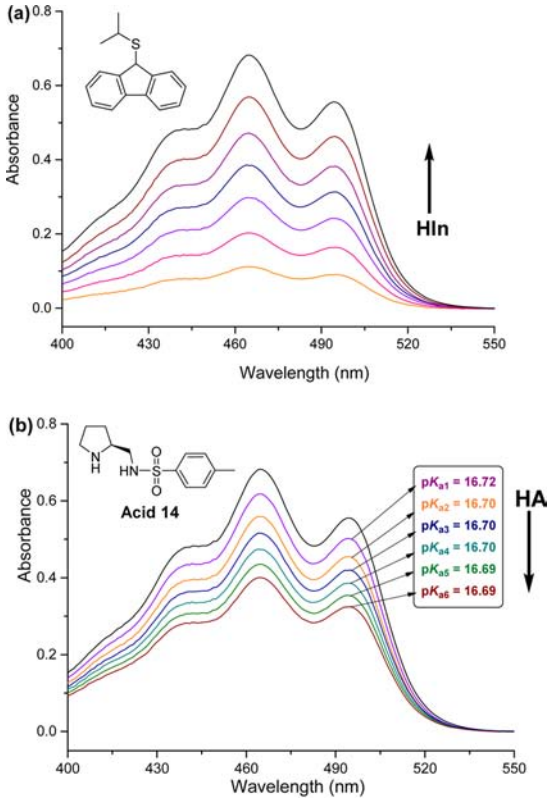


Figure 4. (a) UV/vis absorption spectra of indicator anion derived from 9-iPrS-FH for various added amounts of 9-iPrS-FH. (b) UV/vis absorption spectra of indicator anion derived from 9-iPrS-FH for various added amounts of acid **14**.

Table 1. pK_a Values of Proline Type Organocatalysts in DMSO

acid	pK_a	indicator[a]
1	8.47 ± 0.03	9-CN-FH
2 (Ley, 2005)[18b]	11.57 ± 0.01	9-PhSO$_2$-FH
3 (Ley, 2005)[18b]	11.50 ± 0.01	9-PhSO$_2$-FH
4 (Berkessel, 2004)[18a]	11.55 ± 0.01	9-PhSO$_2$-FH
5	11.39 ± 0.02	9-PhSO$_2$-FH
6 (Berkessel, 2004)[18a]	11.17 ± 0.02	9-PhSO$_2$-FH
7 (Nakamura, 2008)[18d]	11.40 ± 0.02	9-PhSO$_2$-FH
8 (Moorthy, 2009)[21e]	14.34 ± 0.03	9-(*p*-BrPhS)-FH
9 (Gong, 2005)[5]	18.60 ± 0.02	9-Ph-FH
10 (Gong, 2006)[5]	20.39 ± 0.03	carbazole
11 (Gong, 2005)[5]	20.67 ± 0.02	carbazole
12 (Gong, 2005)[5]	23.81 ± 0.09	fluorene
13 (Yamamoto, 2004)[18c]	11.26 ± 0.01	9-PhSO$_2$-FH
14 (Adolfsson, 2004)[22]	16.71 ± 0.02	9-iPrS-FH
15 (List, 2000)[2]	13.35 ± 0.04	2-Br-9-PhS-FH
16	11.56 ± 0.01	9-PhSO$_2$-FH
17 (List, 2000)[2]	13.40 ± 0.10	2-Br-9-PhS-FH

[a]FH, fluorene.

DOI: 10.1021/acs.orglett.5b00143
Org. Lett. 2015, 17, 1196–1199

that the pK_a values of **2**−**7** and **13** varied very little for different substituent groups. This observation is quite different from the calculation results.[7] Because the pK_a values of tetrazole and the conjugate acid of pyrrolidine are 8.2[8] and 11.1,[19] respectively (Figure 5a,b), we think that the current determined pK_a values

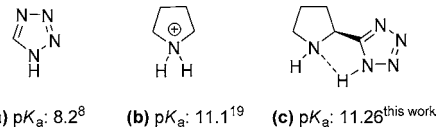


Figure 5. pK_a values of (a) tetrazole, (b) conjugate acid of pyrrolidine, and (c) prolinetetrazole.

of prolinetetrazole and *N*-sulfonylated proline amides are apparent acidities. A five-membered ring type structure formed by an intramolecular hydrogen bonding was proposed to interpret the observed similar pK_as (Figure 5c). To prove the possibility of the existence of intramolecular hydrogen bonding, a control compound **1** was synthesized, which exhibits much more acidic strength (pK_a = 8.47) than **3**. Moreover, Hammett correlation analysis of pK_a values versus corresponding substituent constants σ_p[20] for four *N*-sulfonylated proline amides was also conducted, which showed a good linearity with adjusted *R*-square value of 0.996 (Figure 6). The relative small

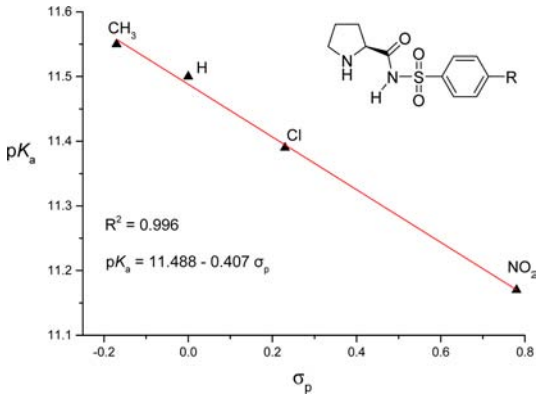


Figure 6. Correlation of pK_a values of four *N*-sulfonylated proline amides with Hammett parameters.

ρ value (−0.407) indicates that the acidities of *N*-sulfonylated proline amides are insensitive to the change of remote substituent, which also is auxiliary verification of the probability of intramolecular hydrogen bonding effect between pyrrolidine nitrogen and the amide group.[9a]

Further inspection of the data shows that proline amide (**12**) without substituent group appears much less acidic (entry 12, Table 1), which is similar to the acidities of urea (pK_a = 23.3)[8] and benzamide (pK_a = 23.35).[8] When amide was modified with aryl substituent group, the resonance effect, which could stabilize the negative charge, led to the enhanced acidity (**8**−**11**, entries 8−11, Table 1). Among the studied aromatic proline carboxamides, **8**, which attached with a more electron withdrawing pentafluorobenzene group, exhibited the most acidity.

We also carried out the determination of pK_a values of acids **15**−**17**. As exhibited in Table 1, the acidity of proline (entry 15, Table 1) is a bit weaker than benzoic acid (for benzoic acid, pK_a = 11.0).[17a] When the N atom was protected by electron withdrawing group *tert*-butoxycarbonyl, corresponding pK_a value decreased sharply from 13.35 to 11.56 (entry 16, Table 1). The almost same pK_a value of pipecolinic acid (entry 17, Table 1) indicates that the ring size of the studied acid is not the key element for the acidity.

With the obtained pK_a values of proline and proline amides, the analysis of the relationship between catalysts' acidities and stereoselectivities was investigated with the classical aldol reaction between acetone and *p*-nitrobenzaldehyde (Figure 7).[18,21] As shown in Figure 7, a good linear correlation with *R*-

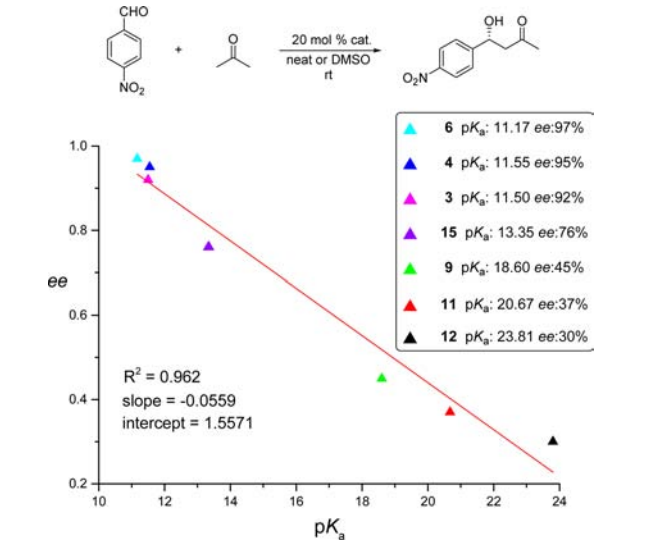


Figure 7. Correlation between pK_a values and stereoselectivities.

square value of 0.962 was obtained in the regression analysis between pK_a values of catalysts and aldol products' enantioselectivities. The inspiring correlation implies that the more acidic proline amide lead to the formation of a stronger hydrogen bond, in which the product's enantioselectivity is increased. This interesting finding should shed some light on the rational design of new proline amide type catalysts.

In summary, we have measured equilibrium acidities of proline and proline amide type organocatalysts in DMSO by an overlapping indicator method. The acidities of the studied organocatalysts cover a wide pK_a value range from 11.17 to 23.81. The relationship between catalysts' acidities and stereoselectivities was also investigated with a classical aldol reaction between acetone and *p*-nitrobenzaldehyde. It is believed that the pK_a data obtained in this work will be helpful for designing new proline derived hydrogen donating amino-catalysts.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of target compounds, UV/vis spectra for the titration. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*For X.L.: E-mail, xin_li@nankai.edu.cn.
*For J.-P.C.: E-mail, chengjp@nankai.edu.cn.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b00143
Org. Lett. 2015, 17, 1196−1199

■ ACKNOWLEDGMENTS

Financial support from the National Basic Research Program of China (973 Program, 2012CB821600), National Natural Science Foundation of China (21390400, 21421062, 21172112, and 21172118), the Program for New Century Excellent Talents in University (NCET-12-0279), and the State Key Laboratory on Elemento-organic Chemistry.

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DOI: 10.1021/acs.orglett.5b00143
Org. Lett. 2015, 17, 1196–1199