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Brønsted Acids

On the Acidity and Reactivity of Highly Effective Chiral Brønsted Acid Catalysts: Establishment of an Acidity Scale**

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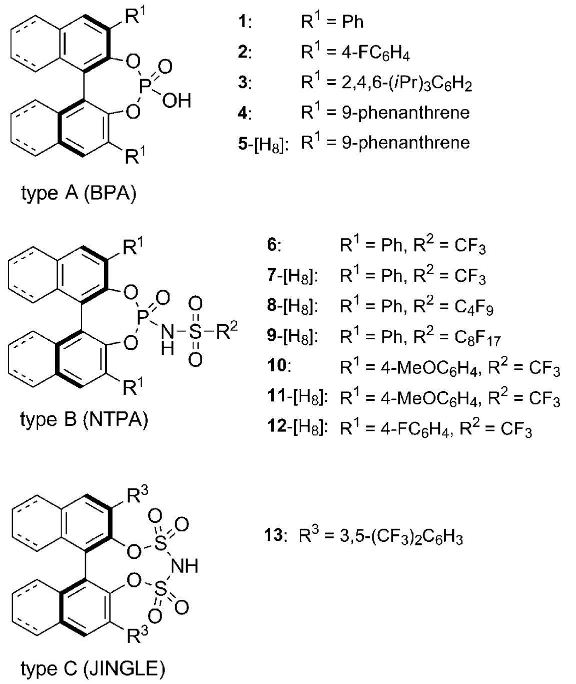
Chiral phosphoric acid diesters derived from 1,1′-bi-2-naphthol (binol) and their analogues are a highly efficient class of metal-free Brønsted acid organocatalysts.[1,2] Transfer hydrogenation as well as various addition reactions to aldimines and ketimines are among the most important reactions that can be carried out efficiently with these catalysts. The moderate acidity of these catalysts[3a] renders them ideal for the activation of basic imines by hydrogen bonding or ion pairing[3b] in a dual or bifunctional fashion. However, the activation of less basic carbonyl functionalities is more demanding, and only few enantioselective applications have been reported so far.[4] Therefore, the more acidic chiral binol-derived *N*-triflylphosphoramides (NTPAs)[5,6] were introduced and proved suitable for the activation of more challenging substrates.[4,7] Asymmetric C−C and C−X bond-forming transformations, such as Diels–Alder and [3+2] cycloaddition reactions, the Nazarov cyclization, asymmetric protonation, and Mukaiyama aldol reactions, have been carried out efficiently with chiral *N*-triflylphosphoramides in a variety of organic solvents, including halogenated as well as aromatic solvents, and more recently also in aqueous media. Furthermore, Brønsted acid organocatalysts based on bis(sulfonyl)imides were introduced by Berkessel et al. (JINGLE, Scheme 1)[8a] and Giernoth and co-workers (BINBAM).[8b]



1: $R^1 = Ph$
2: $R^1 = 4\text{-}FC_6H_4$
3: $R^1 = 2,4,6\text{-}(iPr)_3C_6H_2$
4: R^1 = 9-phenanthrene
5-[H$_8$]: R^1 = 9-phenanthrene

6: $R^1 = Ph, R^2 = CF_3$
7-[H$_8$]: $R^1 = Ph, R^2 = CF_3$
8-[H$_8$]: $R^1 = Ph, R^2 = C_4F_9$
9-[H$_8$]: $R^1 = Ph, R^2 = C_8F_{17}$
10: $R^1 = 4\text{-}MeOC_6H_4, R^2 = CF_3$
11-[H$_8$]: $R^1 = 4\text{-}MeOC_6H_4, R^2 = CF_3$
12-[H$_8$]: $R^1 = 4\text{-}FC_6H_4, R^2 = CF_3$

13: $R^3 = 3,5\text{-}(CF_3)_2C_6H_3$

Scheme 1. Types of chiral Brønsted acid organocatalysts. [H$_8$] denotes 5,6,7,8-tetrahydronaphthyl rings.

On the basis of reported data for achiral Brønsted acids, it was proposed that the acidity of these classes of compounds increases in the order: binol-derived phosphoric acid diesters (BPAs) < NTPAs < JINGLEs (Scheme 1). However, the pK_a values of these catalysts are not known. Furthermore, to date no correlation between the acidity and catalytic activity of the different Brønsted acids has been reported, in spite of their wide application in catalysis.

We therefore decided to determine the pK_a values of binol-derived phosphoric acid diesters and their analogues and correlate them with the catalytic activity of the catalysts to obtain an acidity and reactivity scale that would help users in Brønsted acid catalysis to choose the appropriate catalyst for a given transformation. Herein we present our results on the determination of the pK_a values in acetonitrile (AN) of a range of chiral Brønsted acids (Scheme 1) and discuss the relation between the acidity and catalytic properties of these compounds. Furthermore, we compare the results with a recent report,[9] which appeared during our studies.

The pK_a measurements were carried out by the previously described spectrophotometric titration method.[10] All experiments were performed in a glove box under an atmosphere of argon in AN with a water content below 10 ppm to avoid the distorting effect of water on pK_a values. The results of the pK_a measurements are summarized in Table 1. The acids can be divided according to their acidity centers into three groups: A) binol-derived phosphoric acid diesters (BPAs), with pK_a values in the range of 12–14, B) mixed imides of phosphoric and triflic acid (NTPAs), with pK_a values in the range of 6–7, and C) imides of sulfonic acids (JINGLEs), with pK_a values around 5.

As expected, the nature of the acidity center had the strongest influence on the acidity of the catalysts studied: the catalyst acidity increased in the order A (BPAs) < B (NTPAs) < C (JINGLEs). The next important influencing

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Table 1: Results of the pK_a measurements in AN in order of decreasing acidity.

Compound[a]	Assigned pK_a[b]	−log(k_i)	
		LLS[c]	NLS[d]
5-[H_8] (R^1 = 9-phenanthrene)	14.0	5.55	5.55
3 (R^1 = 2,4,6-*i*Pr_3-C_6H_2)	13.6		
4 (R^1 = 9-phenanthrene)	13.3		
1 (R^1 = Ph)	12.7	5.35	5.36
2 (R^1 = 4-F-C_6H_4)	12.5		
11-[H_8] (R^1 = 4-MeO-C_6H_4, R^2 = CF_3)	6.9		
9-[H_8] (R^1 = Ph, R^2 = C_8F_{17})	6.8	3.73	3.72
7-[H_8] (R^1 = Ph, R^2 = CF_3)	6.7		
8-[H_8] (R^1 = Ph, R^2 = C_4F_9)	6.7	3.60	3.60
10 (R^1 = 4-MeO-C_6H_4, R^2 = CF_3)	6.4	3.33	3.32
6 (R^1 = Ph, R^2 = CF_3)	6.4		
12-[H_8] (R^1 = 4-F-C_6H_4, R^2 = CF_3)	6.3		
13 (R^3 = 3,5-$(CF_3)_2$-C_6H_3)	5.2	2.85	2.89

[a] References describing the synthesis of the compounds are given in the Supporting Information. [b] The pK_a scale in AN is anchored to the value for picric acid (pK_a = 11.0).[11] [c] Values were obtained by the linearized least squares method. [d] Values were obtained by the nonlinear least squares method.

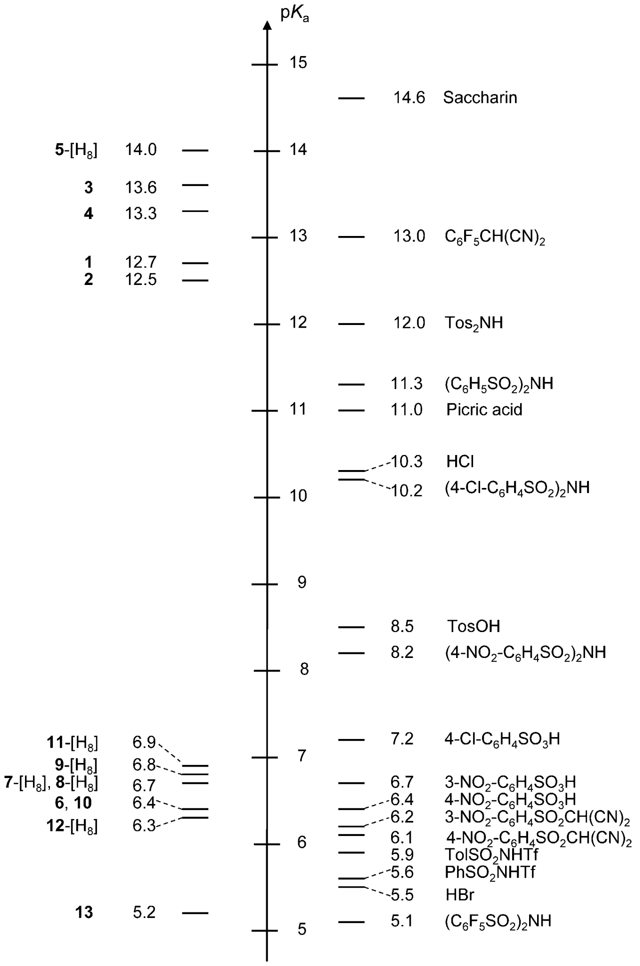

Figure 1. Comparison of pK_a data (values for the compounds in AN).[10,11] Tf = trifluoromethanesulfonyl, Tos = *p*-toluenesulfonyl.

factor was the aromatic or aliphatic nature of the outer binaphthalene rings. This influence can be seen in the pairs **4** and **5**-[H_8], **10** and **11**-[H_8], and **6** and **7**-[H_8], in which the average influence of the second aromatic ring is equivalent to 0.5 pK_a units. The acidity increase observed in the series **11**-[H_8], **7**-[H_8], **12**-[H_8] as well as in the series **3**, **4**, **1**, **2** corresponds to that expected from the electronic properties of the substituents R^1 (Scheme 1). The greater influence of substituent R^1 in group A than in group B can be explained by the delocalization of the negative charge in the anionic form of the acid: the higher the concentration of the negative charge at the acidity center, the more effect the substituent has. In group B, the charge is largely delocalized on the perfluoroalkanesulfonyl group. This phenomenon is also responsible for the much larger pK_a difference between **1** and 4-toluenesulfonic acid (4.2 pK_a units) than between **6** and *N*-trifluoromethanesulfonyl-*p*-toluenesulfonamide (TosNHTf; 0.5 pK_a units). The members of group B that differ only in the length of the perfluoroalkyl chain have almost equal acidities. Although the perfluoroalkyl chain is closer to the acid center than the R^1 substituent, it influences the negative charge of the anions only through an inductive effect. The type C catalyst **13** is the most acidic and differs in acidity from the type B catalysts by one order of magnitude.

For a better comparison, we compiled an acidity scale (Figure 1), in which we included the values of other known acids together with those of the chiral Brønsted acids. This scale will be useful for reaction planning and the further development of the field of asymmetric Brønsted acid catalysis.

Recently, Christ et al. reported pK_a values for similar acids in dimethyl sulfoxide (DMSO).[9] Only one of our acids (compound **3**) is included in their dataset, but all three groups of acids (A–C) are described. Most of the pK_a values in Ref. [9]—those for the weaker acids—agree well with our data and show a good correlation of the pK_a values of neutral OH, NH, and CH acids between AN and DMSO with a slope near unity and an intercept in the range of 10–13 pK_a units (pK_a values in DMSO are lower).[11] However, in contrast to our findings, three compounds belonging to groups B and C (compounds **5**, **7a**, and **7b** in Ref. [9]) have pK_a values that are very similar to those of compounds in group A. The pK_a range for groups A–C in Ref. [9] is between 1.7 and 4.2, in stark contrast with the range of close to 9 pK_a units found for our pK_a values in AN. Christ et al. conclude that the acidity differences between the different catalysts are not large and that the relative acidity of the catalysts may not be the only factor that influences their catalytic performance.[9] In fact, these three acids from groups B and C should have negative or near-zero pK_a values in DMSO. At first sight, it is astonishing that groups of acids which differ by 6–7 pK_a units in AN (differences that are fully rationalizable in terms of their structures) have almost identical pK_a values in DMSO. However, our past experience suggests that measurements of highly acidic acids in DMSO can provide pK_a values of 1–3 (even though the true pK_a value can be negative) if the ionization ratio of the measured species is not monitored.[12]

To investigate this discrepancy, we carried out some experiments in DMSO. Compound **6** was dissolved in DMSO, and the UV/Vis spectrum of its anion was observed because of

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complete ionization. A large excess of an acidic titrant (trifluoromethanesulfonic acid) was added to protonate the anion. However, it was impossible to detect any neutral acid form of the acid from the spectra. In contrast, the anion of **3** was readily protonated, as indicated by changes in the spectrum. These experiments demonstrate that the pK_a values of these two compounds are very different, and that the pK_a value of **6** in DMSO is most likely below zero (see the Supporting Information for details).

To evaluate the catalytic activity of the compounds studied and correlate it with the assigned pK_a values, we investigated the Nazarov cyclization[13,14] of a dienone (see Scheme 1 in the Supporting Information) according to a previously reported procedure.[14] This reaction is particularly suitable, as the corresponding product, a neutral cyclopentenone, does not contain basic sites that would bind the Brønsted acid or form ion pairs and thus lead to different catalyst concentrations or catalyst inhibition and hence unreliable measurements and statements. We monitored the performance of six catalysts by NMR spectroscopy to determine the conversion of the substrate (see the Supporting Information for full details).

On the basis of the recorded data, we calculated rate constants k_I for a first-order reaction by using two methods: linearized least squares (LLS) and nonlinear least squares (NLS; Table 1). The catalysts were chosen in such a way that all three groups were represented and the full range of measured pK_a values was covered. A plot of $-\log(k_I)$ values against the pK_a values revealed that the catalytic activity of the investigated Brønsted acids correlates with their acidity (Figure 2). The higher the acidity is (lower pK_a value), the higher the rate constant is (lower $-\log(k_I)$ value), in agreement with the findings described above. Weaker phosphoric acids have pK_a values 6–8 units higher and rate-constant values two orders of magnitude smaller than those of their triflamide analogues. Whereas the ability to promote enantioselective transformations is due to the catalyst structure, the ability to activate reactions and influence the reaction rate relies largely on the acidity of the catalyst. According to Figure 2, and in agreement with our earlier experimental observations,[7] the acids in groups B and C show a higher ability to activate and accelerate reactions as compared to those in group A.

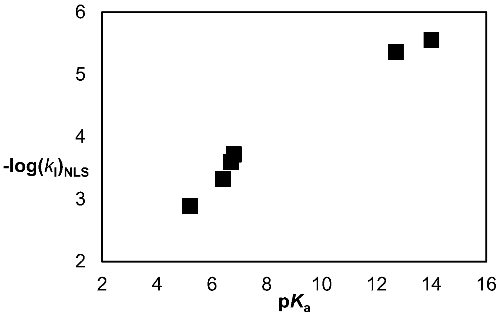

Figure 2. Correlation between the acidity (pK_a values) of the catalysts and their catalytic activity (negative logarithm of the rate constant).

In conclusion, we have determined pK_a values for a series of chiral Brønsted acids in AN on the basis of a UV/Vis spectrophotometric method. For the three groups of catalysts investigated, we can conclude that the binol-derived phosphoric acids that make up group A have a pK_a range of 12–14, the fluorinated *N*-sulfonylphosphoramides in group B have acidity values around 6–7 on the pK_a scale, and bis(sulfuryl)imides (group C) have pK_a values of approximately 5 in AN. For comparison, we compiled an acidity scale (Figure 1) that includes various other known acids as well as the chiral Brønsted acids and will be useful for the further development of the field of asymmetric Brønsted acid catalysis. Furthermore, our experiments clearly indicate a direct correlation of the catalytic properties of these acids with their pK_a values, whereby higher rate constants are observed for more acidic Brønsted acid catalysts. It is also evident from the present study that the big gap in acidity between *N*-triflylphosphoramides and phosphoric acids calls for the development of new chiral catalysts with adjusted catalytic properties.

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