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Theoretical Study on the Acidities of Chiral Phosphoric Acids in Dimethyl Sulfoxide: Hints for Organocatalysis

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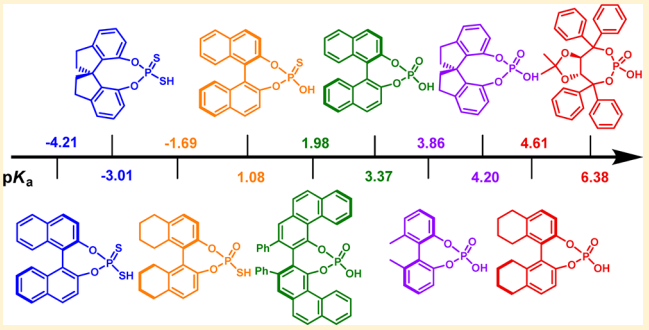
Supporting Information

ABSTRACT: The pK_a values of 41 chiral phosphoric acid-family catalysts in DMSO were predicted using the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method for the first time. The study showed that the calculated pK_a's range from −4.23 to 6.16 for absolute pK_a values and from −4.21 to 6.38 for relative pK_a values. Excellent agreement between the calculated and experimental pK_a's was achieved for the few available cases (to a precision of around 0.4 pK_a unit), indicating that this strategy may be suitable for calculating highly accurate pK_a's. A good linear correlation between the pK_a's for 3 and 3′ disubstituted phenyl BINOL phosphoric acids and the Hammett constants was obtained. The relationship between the acidities of phosphoric acid catalysts and their reaction activity and selectivity was also discussed. Knowledge of the pK_a values of phosphoric acids should be of great value for the understanding of chiral Brønsted acid-catalyzed reactions and may aid in future catalyst design.



INTRODUCTION

The use of chiral Brønsted acids as organocatalysts has been a huge advantage in asymemetric catalysis over the past decade.[1] Selected examples include (thio)urea,[2] squareamides,[3] TADDOL,[4] BINOL,[5] dicarboxylic acids,[6] phosphoric acids,[7] phosphoric amides,[8] bis(sulfonyl)imides,[9] and bis(sulfuryl)-imides.[10] Among them, chiral phosphoric acids derived from 1,1′-bi-2-naphthol (BINOL) and other axially chiral backbones have attracted special attention. Since the pioneering work by Akiyama[7a] and Terada[7b] in 2004, phosphoric acid-related catalysis has resulted in great progress in many enantioselective transformations, including Mannich,[11] Friedel−Crafts,[12] aza-Diels−Alder,[13] Pictet−Spengler,[14] Strecker,[15] cycloaddition,[16] aldol reactions,[17] Robinson-type annulation,[18] aza-ene-type reactions,[19] aza-Darzens,[20] transfer hydrogenations,[21] reductive aminations,[22] multicomponent and cascade reactions,[1t,23] and so forth.

Phosphoric acids usually act as bifunctional catalysts[1c,o,24] in which the appropriate acidity can capture electrophilic components through hydrogen-bond interactions without loose ion-pair formation, where the phosphoryl oxygen acts as a Lewis base site to capture another substrate and the bulky 3 and 3′ subsituents extend stereoselectivity. Numerous studies have demonstrated that the proper acidity is necessary to form the tight ion pairs that play an important role in controlling reaction activity and stereoselectivity. As revealed by some work,[7l,25,74−76] changing the acidity is an alternative strategy to improve the catalytic activity and stereoselectivity of a reaction because adjusting the volume of the 3 and 3′ subsituents to promote stereoselectivity does not always work. As a result, much effort has been devoted to modifying the BINOL backbone or developing new axially chiral backbones to improve the catalytic performance of phosphoric acids. Furthermore, intensive efforts have also been made to study the mechanism of phosphoric acid catalysis using either experimental or computational methods.[16d,26] However, the goal of gaining in-depth knowledge and using it for the design of new catalysts remains elusive and warrants further explorations. In this regard, the fundamental physical organic parameters of phosphoric acid catalysts, particularly pK_a, that are essential for designing new catalysts have been largely overlooked. As an example, Berkessel and O'Donoghue determined the pK_a values of nine phosphoric acids in DMSO.[27] Although they have gained reliable results by a classical overlapping-indicator spectrophotometric method, the limitation of the phosphoric acid type is obvious, especially considering that only the BINOL backbone was considered and the lack of sufficient quantities of known acids are far from meeting the demand of pK_a values. In another case, Seebach reported the pK_a measurements of TADDOLs and analogs in a mixture of MeO$(CH_2)_2$OH and water, contributing just one data point for TADDOL-derived phosphoric acids.[28]

It is well known that a variety of classic relationships, including the Brønsted relationship,[29] Hammett equation,[30] and Taft equation,[31] that laid the foundation for modern

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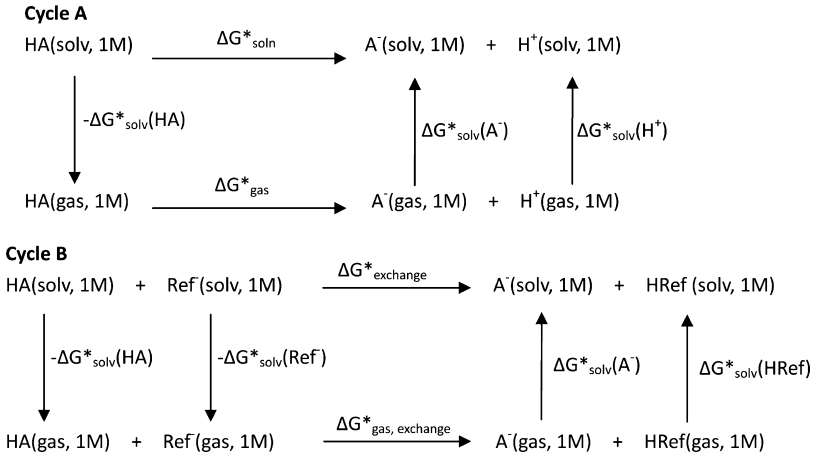
Scheme 1. Thermodynamic Cycles Employed in This Study



physical organic chemistry were established on the basis of equilibrium-acidity studies. Furthermore, knowledge of the accurate pK_a values of a catalyst is important for a mechanistic understanding and interpretation of selectivity.[26] Accordingly, an analysis of the acidity of Brønsted acids in linear free-energy relationships (LFER) was also introduced in the study of the structure−activity−stereoselectivity relationships in organocatalysis.[32,33] For example, Sigman and co-workers have observed that the reaction rate and enantioselectivity are directly correlated to a catalyst's acidity in a hetero-Diels−Alder reaction catalyzed by amide-derived catalysts.[32] Very recently, Luo and Cheng have experimentally determined the first pK_a scale for a range of asymmetric thiourea catalysts and disclosed the correlations between pK_a and catalytic activity and stereoselectivity.[33] It is worth noting that the above-mentioned LFER study undoubtedly provided a platform for improving catalyst performance and informing new catalyst design.

Because of the rapid development of computational chemistry, the pK_a's of organic acids in solution can currently be calculated with similar or greater accuracy than those obtained experimentally.[34,35] This provides an excellent chance to solve the problem of the missing data for phosphoric acid catalysts. Over the past years, this group has worked a great deal on the determination of acidity values by experimental methods[36] and theoretical calculations.[37] A great number of widely used functional compounds' pK_a's were measured (or calculated), and they were successfully used in many chemical aspects. Because of our continuous interest in fundamental physical organic parameters and on the basis of our recent developmental research in the area of organocatalysis,[38] herein we present the theoretical study on the pK_a values of chiral phosphoric acids.

Over the past 2 decades, enormous efforts have been made to develop theoretical protocols to calculate pK_a constants for complementing experimental techniques.[34,35,39] A number of approaches were reported that dealt with the solvation effects required for evaluating acidity/basicity in solution.[40−43] Among the various solvation models applied, the continuum-solvation models,[44] despite somewhat approximating for treating the solvent as a structureless continuum, are the most popular because of their high efficiency and simplicity. Recently, Truhlar[45] and co-workers have developed a universal-solvent model (SMD model) that uses a dielectric continuum to treat bulk electrostatic effects in combination with atomic-surface tensions to account for first-shell solvation effects to predict the free energy of solvation with reasonable precision.[35a,46]

Invariably, most theoretical protocols for predicting pK_a involve the representation of the acid-dissociation process using a thermodynamic cycle (Scheme 1).[47] The direct method[48] is extensively used in previous work for its simplicity. However, problems arise in the treatment of the solvated proton, whose chemical structure is often unknown and difficult to model theoretically. Usually, the experimental solvation free energy of a proton is introduced to account for this problem. With thermodynamic cycle A (Scheme 1), the free energy of acid dissociation in DMSO can be obtained through eq 1. The * symbol is used for a standard state of 1 mol/L in any phase.[49] The pK_a can be obtained through the thermodynamic relationship (eq 2).

$$\Delta G^*_{soln} = \Delta G^*_{gas} + \Delta G^*_{solv}(A^-) + \Delta G^*_{solv,DMSO}(H^+) - \Delta G^*_{solv}(HA) \quad (1)$$

$$pK_a = \frac{\Delta G^*_{soln}}{RT\ \ln(10)} \quad (2)$$

It should be noted that larger errors may occur when applying a direct method to pK_a predictions because the number of charged species is not conserved across the reaction and the associated uncertainties for estimating their solvation energies are much larger. Furthermore, the reliable experimental solvation free energy of a proton is still unconfirmed (values range from −252.89 to −273.3 kcal/mol, Results and Discussion). To solve the above-mentioned problems, the proton-exchange method (cycle B, Scheme 1) is used to gain more reliable pK_a values. With this cycle, the exchange free energy in DMSO is obtained through eq 3, where the experimental value of the reference acid is used. The pK_a is obtained through eq 4.

$$\Delta G^*_{exchange} = \Delta G^*_{gas,exchange} + \Delta G^*_{solv}(A^-) + \Delta G^*_{solv}(HRef) - \Delta G^*_{solv}(HA) - \Delta G^*_{solv}(Ref^-) \quad (3)$$

$$pK_a = \frac{\Delta G^*_{exchange}}{RT\ \ln(10)} + pK_a(HRef) \quad (4)$$

Taking advantage of the above-mentioned thermodynamic cycles, the pK_a's of 41 chiral phosphoric acids and their

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derivatives in DMSO were calculated, and the results are presented.

RESULTS AND DISCUSSION

General Information. To set a common ground for th easy expansion of the pK_a scales of phosphoric acids for various purposes in the future, we have mainly selected well-developed BINOL-derived phosphoric acids with different electronic and steric natures of their 3 and 3′ substituents to disclose the influence of the substituents. Meanwhile, phosphoric acids derived from various scaffolds have also been included in this study. Thus, an overview of phosphoric acids can be depicted.

Optimization of the Calculation Methods. A large database of pK_a constants for various organic acids in DMSO compiled by Bordwell[50] and co-workers has been widely used in chemistry. The pK_a values in DMSO usually serve as a reference because not only is DMSO itself a widely used solvent in catalysis[51] but also DMSO has good linear relationships between its acidities and those in other molecular/ionic solvents.[36b,52] As a result, many reliable predictions of the pK_a values in DMSO have been made in recent years. Along with parametrized PCM, Pliego et al.[53] calculated the pK_a values of organic acids with a root-mean-square (rms) error of 2.2 pK_a units. By utilizing the COSMO-RS procedure, Klamt et al.[54] calculated seven acids with an rms error of 1.76 pK_a units. Yates et al.[55] combined CBS-QB3 and CPCM to calculate the basicity of nucleophilic carbenes via a direct method in DMSO, water, and MeCN. Guo et al.[56] applied a PCM-based cluster-continuum approach to calculate the pK_a's of organic acids in DMSO with a precision of around 1.7 pK_a units. Following up on this, they reported an improved method based on IEF-PCM results with a UA0-cavity model to predict the pK_a values of organic acids with a precision of 1.4 pK_a units.[57] A similar protocol with a scaled-PCM model was used to calculate the pK_a values of C−H bonds in heterocyclic compounds with a precision of 1.1 pK_a units.[58] Trummal, Burk, Koppel, and co-workers also applied the IEF-PCM method to calculate the pK_a values of substituted phenols with a mean unsigned error (mue) of 0.6 pK_a unit.[59] Recently, Wang et al.[35d] calculated values for a variety of organic acids via a proton-exchange method in nonaqueous solvents, achieving a precision of less than 1.0 pK_a units. Very recently, Shi et al.[60] applied a CPCM model with DFT functional to calculate the values for a set of important (*S*)-proline amide derivatives with an rms error of 1.3 pK_a units.

Encouraged by the above-mentioned excellent work, we tried to establish a convenient calculation method for the purpose applying it to the theoretical study of the pK_a's of phosphoric acids. First, five chiral phosphoric acids with known pK_a's (Figure 1) were chosen to develop our calculation methods. Then, the performance of different theoretical models was evaluated with direct methods. As shown in Table 1 (for other methods see Table S1 in the Supporting Information), the PCM and CPCM models predicted pK_a values with large errors (MUE >7.9) under identical conditions. Even with a smaller basis set, the SMD model gave pK_a values with a MUE of 5.61 pK_a units (method d). Method g (SMD/M05-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)) with the SMD model predicted pK_a values with a MUE of 0.93 pK_a unit. Method h (SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)) delivered reasonable results with a MUE within a precision of 0.5 pK_a unit. It should be pointed out that the calculated results with direct methods strongly depend on the value of the solvation free energy of the proton. Because the solvation free energies of the proton in DMSO that were estimated from the TATB assumption[61] or cluster-pair approximation[62] are different in various reports[63] (values range from −252.89 to −273.3 kcal/mol), it is reasonable to optimize this value to minimize the error. In comparison to the values of known experimental pK_a's, the value of −268.34 kcal/mol[55] was found to provide the best result with a MUE of 0.33 pK_a unit.

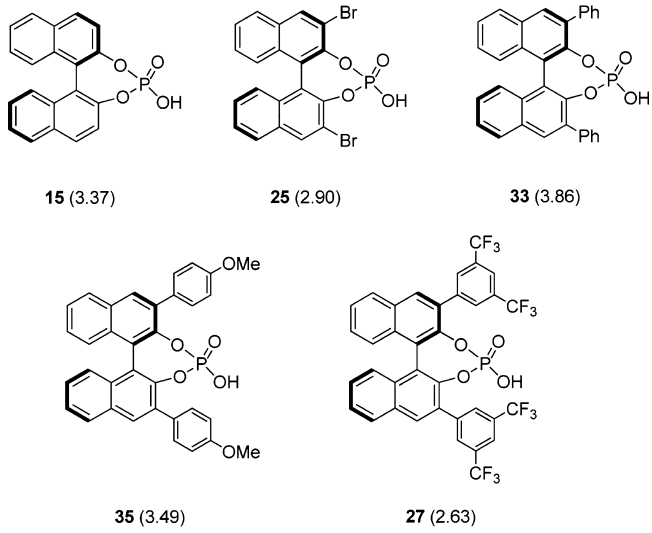

Figure 1. Five acids for the development of the method (experimental data from ref 27).

Next, to cancel out the uncertainty of the solvation energy of the proton, we examined these methods with the proton-exchange cycle. Acid **15** (pK_a^{exp} 3.37) was chosen as the reference acid. As shown in Table 2 (for other methods see Table S2 in the Supporting Information), all of the methods present better performance than that of the direct method. Again, method h with the SMD model (SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)) shows the best results.

Collectively, the pK_a values of the test acids predicted by the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method agree well with the experimental data. The SMD-solvation model was found to exhibit a potential advantage for predicting the solvation energy of such type molecules. It should be noted that some previous studies have demonstrated that a pure implicit method alone may be inadequate to account for the strong interaction between ionic species and solvent in the first layer and that better results may be obtained by including one or more solvent molecules in the explicit subsystem.[34a,64−66] Because the accuracy of our pK_a predictions is rather good, the addition of one or more explicit solute molecules was not considered further.

pK_a Values of Chiral Phosphoric Acids and Derivatives. With the optimal calculation method in hand, we turned our attention to the application of the established theoretical model to calculating the pK_a of frequently used phosphoric acid catalysts. As a result, the pK_a values of 41 chiral phosphoric acids were calculated (Figures 2 and 3). The pK_a values predicted by either the direct method or proton-exchange method agree well with the known experimental data, indicating that the calculations are reliable. We first focus on the relationship between the structure of parent acids and their corresponding pK_a values. In general, the pK_a values of different scaffold acids cover a range of about 11 pK_a units. Sulfur-

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Table 1. Performance of the Different Theoretical Models for Test Acids with Direct Methods

acid	pK_a (calc)[b]	pK_a (calc)[c]	pK_a (calc)[d]	pK_a (calc)[e]	pK_a (calc)[f]	pK_a (calc)[g]	pK_a (calc)[h]	pK_a (exp)[i]
15	−6.10	−0.29	−0.86	−0.91	−0.82	2.52	3.15	3.37
25	−8.39	−1.49	−1.79	−2.20	−2.06	1.38	2.11	2.90
33	−18.66	−11.30	0.13	−12.20	−11.96	2.77	3.33	3.86
35	−5.16	2.43	1.91	1.58	1.84	2.91	3.47	3.49
27	−15.44	−9.75	−11.21	−10.71	−10.46	2.00	2.63	2.63
MUE[a]	14.00	7.33	5.61	8.14	7.94	0.93	0.33	

[a]MUE is the mean unsigned error. [b]Calculated by B3LYP/6-31+G(d)/PCM/Bondi//B3LYP/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [c]Calculated by B3LYP/6-31+G(d)/CPCM/Bondi//B3LYP/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [d]Calculated by SMD/M06-2x/6-31+G(d)//B3LYP/6-31+G(d). [e]Calculated by M06-2x/6-31+G(d)/CPCM/Bondi//M06-2x/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [f]Calculated by M06-2x/6-31+G(d)/PCM/Bondi//M06-2x/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [g]Calculated by SMD/M05−2x/6-311++G(2df,2p)//B3LYP/6-31+G(d). [h]Calculated by SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d). [i]Experimental data from ref 27.

Table 2. Performance of the Different Theoretical Models for Test Acids with the Proton-Exchange Method

acid	pK_a (calc)[b]	pK_a (calc)[c]	pK_a (calc)[d]	pK_a (calc)[e]	pK_a (calc)[f]	pK_a (calc)[g]	pK_a (calc)[h]	pK_a (exp)[i]
25	1.08	9.95	2.43	9.24	9.37	1.60	2.33	2.90
33	−9.18	0.14	4.36	−0.76	−0.52	2.99	3.55	3.86
35	4.31	13.88	6.14	13.02	13.28	3.13	3.69	3.49
27	−5.97	1.70	−6.98	0.74	0.98	2.22	2.85	2.63
MUE[a]	6.07	5.52	3.31	5.60	5.57	0.74	0.33	

[a]MUE is the mean unsigned error. [b]Calculated by B3LYP/6-31+G(d)/PCM/Bondi//B3LYP/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [c]Calculated by B3LYP/6-31+G(d)/CPCM/Bondi//B3LYP/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [d]Calculated by SMD/M06-2x/6-31+G(d)//B3LYP/6-31+G(d). [e]Calculated by M06-2x/6-31+G(d)/CPCM/Bondi//M06-2x/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [f]Calculated by M06-2x/6-31+G(d)/PCM/Bondi//M06-2x/6-311++G(2df, 2p)//B3LYP/6-31+G(d). [g]Calculated by SMD/M05−2x/6-311++G(2df,2p)//B3LYP/6-31+G(d). [h]Calculated by SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d). [i]Experimental data from ref 27.

substituted phosphoric acids (**1**−**5**, **7**, and **9**−**11**) are more acidic than other phosphoric acids, and they can be found in the range from −4.0 to 2.0 (pK_a's from the proton-exchange method were used in the Results and Discussion, similar to below). Dithiophosphoric acids (**1**−**3**) are the strongest acids (pK_a <−3.0) among the analogues. The strong acidity of thiophosphoric acids can be attributed to the increased polarizability of sulfur (2.90) versus oxygen (0.802) and to a better stabilization of the conjugate base with a larger atom.[70] It can also be inferred that selenium-substituted phosphoric acids would be more acidic than thiophosphoric acids with the same scaffold (i.e., **8** (−1.21) versus **9** (1.08)). The acidic enhancement of such acids should undoubtedly extend the scope of phosphoric acid-catalyzed asymmetric transformations. This tendency is also consistent with the pK_a values of PhOH, PhSH, and PhSeH in DMSO (18.0, 10.3, and 7.1, respectively). Among the studied phosphoric acids, the diversity of the acidity is strongly dependent on the structure. Phosphoric acids derived from vaulted 2,2′-binaphthol (**14**), 3,3′-biphenanthrol (**12**), and 6,6′-biphenanthrol (**13**) have similar pK_a values in the range of 2.14−2.92.[7h,71] The first generation of phosphoric acids, BINOL phosphoric acid (**15**), has a benchmark pK_a of 3.37. Decreasing the conjugate system leads to weak acidity. For example, the pK_a's of biphenyl-2,2′-diol phosphoric acid (**16**), 6,6′-dimethylbiphenyl-2,2′-diol phosphoric acid (**17**), 1,1′-spirobiindane-7,7′-diol (SPINOL) phosphoric acid (**18**), H_8- BINOL phosphoric acid (**19**), and the TADDOL phosphoric acids (**21**, **22**) are 3.80, 3.86, 4.20, 4.61, 6.21, and 6.38, respectively. Among them, acid **22** is predicted to be the weakest acid. Not surprisingly, the TADDOL analogue (TEFDDOL) phosphoric acid **6** is rather acidic resulting from the equiping of four trifluoromethyl groups. By keeping these pK_a values of the parent acids in mind, one will be able to roughly infer the unknown pK_a's of other scaffold acids bearing the same substituents according to their different parent acids (Scheme 2).

Next, different 3 and 3′ substitutents of BINOL-derived phosphoric acids were carefully examined. Overall, the pK_a values of the calculated BINOL-derived acids have a range between 1.56 and 5.11. Although the 3 and 3′ substituents indirectly attach to the reaction center, the pK_a's of such acids vary according to the electronic and steric nature of the substituents. After the fine adjustment of the electronic nature of the substituents at the 3 and 3′ positions, the acidities of such acids can be tailor-made according to one's demand. For example, 3,3′-dipentafluorophenyl BINOL phosphoric acid (**23**) has a pK_a of 1.56. In practice, it will be more convenient if a quantitative relationship exists between the structure and acidity. Fortunately, we find a good correlation between the calculated pK_a's and the Hammett[72] substituent constants (Figure 4). It can be expected that a similar relationship should be applicable to other types of phosphoric acid scaffolds.

Application to the Analysis of Organocatalysis. With the obtained calculated acidities of different phosphoric acids and their derivatives, the analysis of the relationship between acidity and reactivity (enatioselectivity) was discussed. We first focus on the aspect of the phosphoric acid backbone. 2,2′-Diphenyl-[3,3′-biphenanthrene]-4,4′-diol (VAPOL)-derived acid **24** was introduced to an imine amidation reaction by Antilla[7h] in 2005. Acid **15** (95% yield in 16 h, <5% ee, pK_a 3.37) was found to be unsuitable for this transformation. Even with larger steric groups, BINOL-derived acids achieved only moderate enantioselectivity (60−71% ee). Acid **24** (95% yield in 1 h, 94% ee, pK_a 1.98) was found to be much more effective and stereoselective than the BINOL acids. In 2007, Antilla reported that phosphoric acids catalyzed the hydrogenation of α-imine esters using Hantzsch esters as hydride donors.[68a] In the catalyst screening, VAPOL-derived acid **24** (99% yield, 96% ee, pK_a 1.98) was also found to be much more effective and

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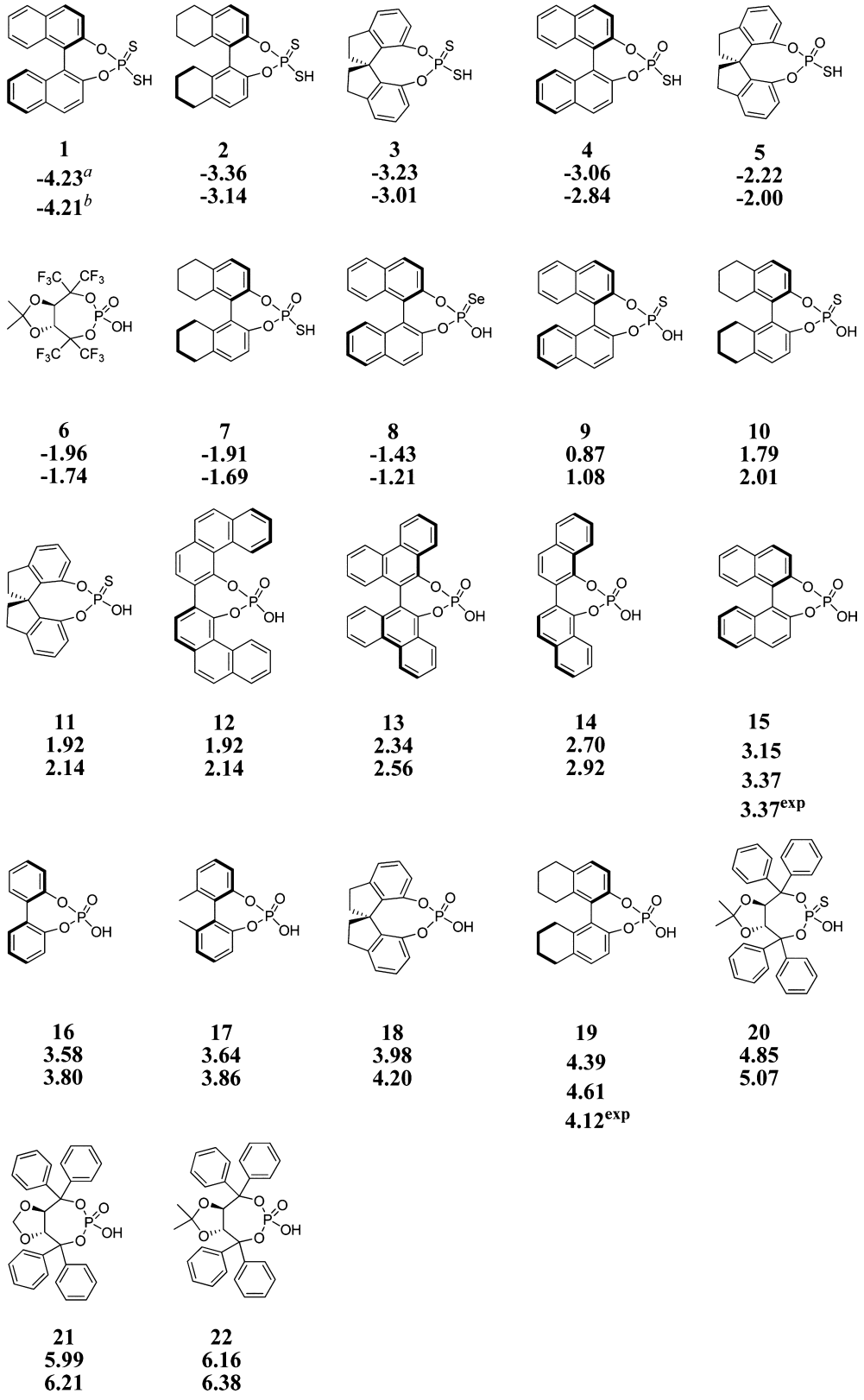

Figure 2. pK_a values of parent chiral phosphoric acids calculated by the direct method in the first row and the proton-exchange method in the second row.

stereoselective than BINOL-derived **32** (29% yield, 27% ee, pK_a 3.51) and VANOL-derived **26** (<5% yield, 17% ee, pK_a 2.77). These observations are consistent with the strength of our calculated pK_a's. Regarding the electronic effect, this case can be traced back to the original work carried out by Akiyama[7a,73] in 2004. In this study, acid **28** (pK_a 2.98) turned out to be the optimal acid in the Mannich-type reaction because of its high enantioselectivity and acceleration of the reaction rate. Because

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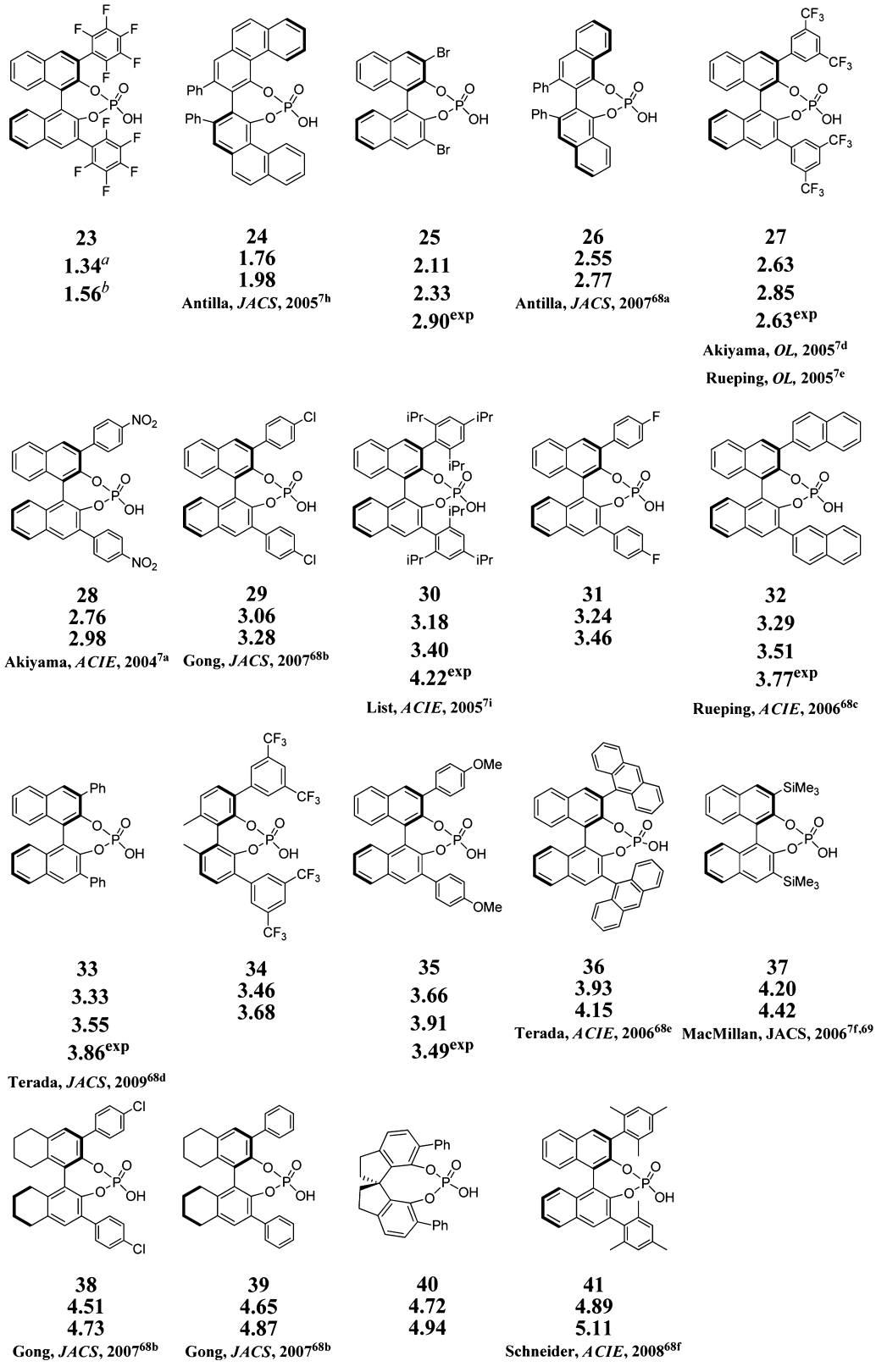

Figure 3. pK_a values of chiral phosphoric acids[67−69] calculated by the direct method in the first row and the proton-exchange method in the second row.

of its stronger acidity, this acid can bind its substrate tightly, resulting in a highly enantiomeric excess product. A novel TADDOL-derived chiral phosphoric acid was also used in the Mannich reaction by Akiyama.[7g] In this reaction, several TADDOL phosphoric acids were evaluated under identical conditions. Because of its weak acidity, **21** (pK_a 6.21) was found to be unsuitable for this transformation. When a phosphoric acid with an electron-withdrawing group (*p*-CF_3)

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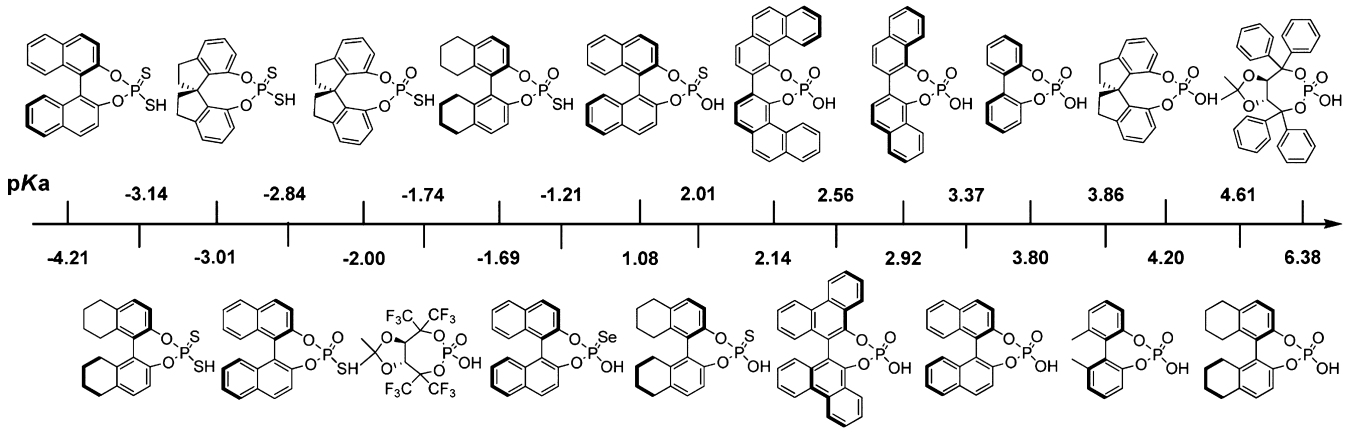
Scheme 2. Acidity Scale of the Parent Phosphoric Acids



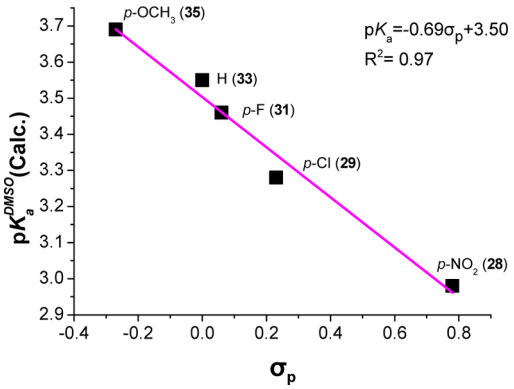


Figure 4. Correlation between the pK_a^{DMSO} (calc.) of BINOL-derived phosphoric acids and the Hammett substituent constants (σ_p).

was used, the product yield and enantioselectivity improved, as expected. A similar influence on the reaction activity and enantioselectivity by changing the catalyst acidity was also observed in other types of reactions, including Friedel–Crafts,[74] activation of enantiotopic C(SP^3)-hydrogen,[7n] hydrophosphonylation of imines,[75] and transfer hydrogenation.[76] It is worth noting that the observed LFER relationship among BINOL phosphoric acid catalysts can also be applied to the analysis of other types of chiral phosphoric acid-catalyzed reactions.

Although numerous phosphoric acid-catalyzed highly enantioselective reactions have been reported to date, the activation models are restricted to the activation of electrophilic carbon–heteroatom or heteroatom–heteroatom multiple bonds.[1i,m,7] However, the reactions involving C–C multiple-bond activation remain a challenge in the development of phosphoric acid-catalyzed transformations. This unfortunate limitation can perhaps be explained by the relative weak acidity (pK_a >1 in DMSO) of phosphoric acids. Recently, Toste and co-workers[7l] reported the first asymmetric additions to dienes utilizing a bis-sulfur-substituted phosphoric acid, which showed the potential synthetic approaches for utilizing phosphoric acids on the transformation of unactivated C–C multiple bonds. They demonstrated that the strong acidity of the catalyst is necessary to implement such a strategy. Our calculated pK_a's of dithiophosphoric acids (e.g., **2**, pK_a −3.14) are rather strong compared to those of phosphoric acids, which strongly supports Toste's experimental results. These interesting findings should shed some light on the rational design of new catalysts and the development of novel reactions.

CONCLUSIONS

The pK_a values of a series of widely used chiral phosphoric acid catalysts in DMSO were obtained with the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method, which has a precision of about 0.4 pK_a unit. Interestingly, Truhlar and Cramer's SMD model exhibits a potential advantage over that of other polarizable-continuum models when applied to larger molecule systems. The primary value of this study is that it provides the acidity scale of parent phosphoric acids, which can be used to order all related acids. Second, this study demonstrated that the pK_a values of 3,3′-disubstituted-phenyl BINOL phosphoric acids have a linear correlation with the Hammett substituent parameter. According to the line slopes and line intercepts, the acidities of any 3,3′-disubstituted-phenyl BINOL phosphoric acids can be easily estimated. Furthermore, this phenomenon can also be used in the analysis of other types of chiral phosphoric acids. Third, this study also suggests that sufur/bis-sulfur-substituted phosphoric acids can enhance the range of acidity, which will extend the application of phosphoric acid catalysts. In addition, examples of utilizing these pK_a scales to analyze problems in phosphoric acid-catalyzed reactions, such as reactivity and stereoselectivity, have been presented. The knowledge of these important and hard-to-obtain acidities in DMSO and the corresponding conclusions are of great value for providing important clues for the more definitive study of structure–activity trends and the guidance of more rational reaction design. We also expect that the mechanistic understanding of phosphoric acids-mediated catalysis will benefit from our continuing efforts.

EXPERIMENTAL SECTION

The structures of all species were obtained by full optimization using the B3LYP[77] functional in conjunction with the 6-31+G(d) basis set, and the nature of the stationary points was confirmed by frequency calculations at the same level of theory. For molecules that have more than one possible conformation, the conformation[7e,78] with the lowest free energy was singled out and used in the ensuing calculations.

Standard free energies of solvation in DMSO were determined using the polarizable-continuum model (PCM) and the conductor-polarizable-continuum model (CPCM) with bond radii at the B3LYP/6-31+G(d), M05-2x/6-31+G(d), and M06-2x/6-31+G(d) levels on the gas-phase geometries. The SMD free energy of solvation was calculated at the M06-2x/6-31+G(d), M05-2x/6-311++G(2df, 2p), and M06-2x/6-311++G(2df, 2p) levels.[79]

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All calculations were performed using the Gaussian 03[80] or Guassian 09[81] suite of programs. The selected five acids were used to evaluate the calculation methods, and the pK_a values of other acids were calculated under optimal methods.

■ ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates of the optimized structures and the complete listings for refs 80 and 81. 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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