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What are the pK_a values of organophosphorus compounds?

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Abstract—A first-principle theoretical protocol was developed, which could successfully predict the pK_a values of a number of amines and thiols in DMSO with a precision of about 1.1 pK_a unit. Using this protocol we calculated the pK_a values of diverse types of organophosphorus compounds in DMSO. The accuracy of these predicted values was estimated to be about 1.1 pK_a because phosphorus is in the same group as nitrogen and in the same period as sulfur. The theoretical predictions were also consistent with all the available experimental data. Thus, a scale of reliable pK_a values was constructed for the first time for organophosphorus. These pK_a values would be helpful to synthetic chemists who need to design the experimental conditions for handling deprotonated organophosphorus. On the basis of these pK_a values we also studied, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines.

1. Introduction

Organophosphorus are organic compounds that contain phosphorus as an integral part of the molecule.[1] Common examples for organophosphorus include phosphines, phosphinites, phosphonites, phosphites, phosphinous amides, phosphinous diamides, phosphinous triamides, phosphonium salts, phosphine oxides, phosphinates, phosphonates, and phosphates (Fig. 1).

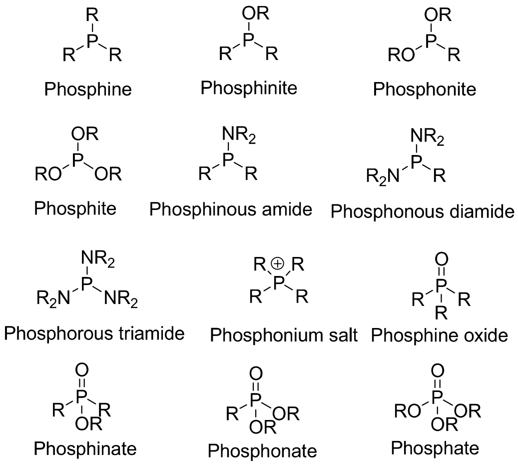

Figure 1. Common organophosphorus compounds.

Organophosphorus compounds have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.[2] They have also been used as nerve agents in chemical warfare (e.g., Sarin gas), and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma.[3] In academic researches organophosphorus compounds find important applications in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.).[4] The use of organophosphorus compounds as achiral or chiral ligands for transition metal-catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.[5] Furthermore, organophosphorus compounds can be used as flame retardants for fabrics and plastics, plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors.[1]

Several general methods have been developed for the synthesis of organophosphorus.[1,6] The two most popular of these are: reaction of an organometallic reagent with a phosphorus halide, and reaction of a metal phosphide with an organic electrophile. In the second method, a metal phosphide is often prepared by deprotonation of the corresponding P–H containing compound with a base[7] (e.g., *t*-BuOK, EtONa, NaH, etc. see Fig. 2 for some recent examples). This is successful only if the base is obtained from a compound that is a weaker proton acid than the phosphine. Thus, there is a strong need for organic chemists to know the solution-phase pK_a values of the P–H bonds in different organophosphorus, both for scientific curiosity and for practical reasons. Unfortunately, because phosphorus-centered anions are

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doi:10.1016/j.tet.2006.02.049

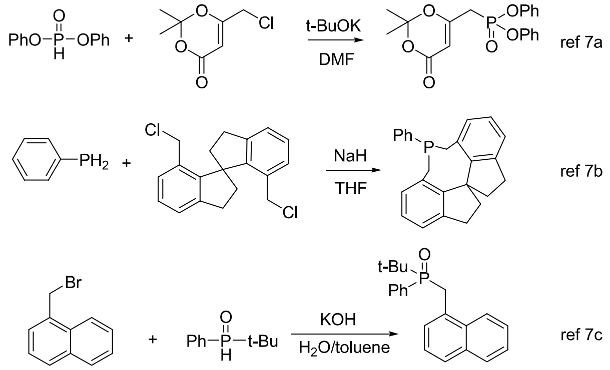


Figure 2. Some recent syntheses in which a metal phosphide reacted with an organic electrophile.

usually highly unstable species, it has been a formidable challenge to design experimental approaches to determine the pK_a's of organophosphorus. Up to now the solution-phase acidities of organophosphorus remain almost entirely unknown except for PH_3 (pK_a=29 in water); and there has not been a single pK_a value for any P–H bond in the famous Bordwell scale of acidities. Only Issleib and Kummel once reported the experimental solution-phase acidities of six phosphines in tetrahydrofuran.[8]

We recently launched a program to systematically investigate how to utilize the modern quantum-chemical methods to acquire useful, quantitative data for realistic, solution-phase organic chemistry. In the first step of the program, we developed a generally applicable, ab initio protocol to calculate the pK_a values of diverse organic acids in dimethyl sulfoxide (DMSO).[9] The first version of the protocol could reach a precision of about 2 pK_a units in the calculation of pK_a values of over 100 structurally-unrelated organic molecules. This protocol was utilized to predict the pK_a's of a variety of organosilanes in DMSO that have not been experimentally measured. In the present study, we attempted to improve our previous protocol so that it could more accurately predict the pK_a values of amines (for N–H bonds) and thiols (for S–H bonds) in DMSO that have been experimentally measured. Once this was accomplished, it would be legitimate to consider that the improved ab initio protocol was able to reliably predict the pK_a values of various organophosphorus compounds in DMSO that still remain largely unknown. The reason for this is that phosphorus is in the same group as nitrogen and in the same period as sulfur. If a method based on the first principles can successfully handle both nitrogen and sulfur, it should be able to handle phosphorus as well.

Armed with the carefully benchmarked theoretical protocol, we systematically calculated for the first time the pK_a values of various types of organophosphorus compounds in DMSO. The accuracy of these calculated values was estimated to be about 1.1 pK_a units, which is sufficient for most practical applications. With these pK_a values in hand, synthetic chemists can more rationally design the experimental conditions for the reactions that require the use of deprotonated organophosphorus. The availability of these pK_a values also enabled us to study, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines. Thus, it is truly valuable to have an extensive and reliable tabulation of the pK_a values for various types of organophosphorus. By supplying trustworthy and useful data that are difficult to obtain via the experiments, we also hope to better demonstrate that computational chemistry is becoming an enabling tool to make realistic predictions for synthetic organic chemistry.

2. Gas-phase acidities

Before we try to calculate the solution-phase pK_a value of an organophosphorus compound A–H, it is important to ascertain that we can reliably calculate its gas-phase acidity defined as the free energy change of the following reaction in the gas phase at 298 K, 1 atm.

$$A-H(g) \rightarrow A^-(g) + H^+(g) \tag{1}$$

However, up to now there have been only five experimental gas-phase acidity values reported for neutral organophosphorus (see Table 1), and it would not be sensible to use these five values to evaluate the performance of a particular theoretical approach. Thus, we included the gas-phase acidity data of 25 amines and 14 thiols in Table 1,[10] and we utilized the B3LYP/6-311++G(2df,p)//B3LYP/6-31+G(d) method to calculate the N–H, S–H, and P–H gas-phase acidities of these 44 compounds. In the calculation, the geometry of each species was optimized using the B3LYP/6-31+G(d) method. The electronic energy of the species was then calculated using the B3LYP/6-311++G(2df,p) method. The free energy of each species was calculated using the above electronic energy and zero-point vibrational energy, thermal corrections (0→298 K), and the entropy term obtained at the B3LYP/6-31+G(d) level (unscaled).

Comparing the experimental and theoretical gas-phase acidities, we obtained the following regression Eq. 2 (also see Fig. 3):

$$\Delta G_{\text{exp}} = \Delta G_{\text{theor}} + 0.6 \quad (r = 0.996,\ \text{sd} = 1.9,\ N = 44) \tag{2}$$

The slope of the regression equaled unity and the mean error (i.e., the intercept of the regression) was as low as 0.6 kcal/mol. The correlation coefficient (r) was 0.996 and the standard deviation (sd) was 1.9 kcal/mol for 44 compounds. Because the experimental errors of the gas-phase acidities are mostly about 2.0 kcal/mol (see Table 1), it was obvious that the theoretical predictions at the B3LYP/6-311++G(2df,p)//B3LYP/6-31+G(d) level were sufficiently accurate for N–H, S–H, and P–H gas-phase acidities.

3. Computing pK_a's of amines and thiols in DMSO

As mentioned previously, there has not been a single experimental pK_a value for organophosphorus in DMSO. Thus, it is impossible to evaluate the reliability of the theoretical predictions by comparing some of the predicted values with the corresponding experimental data. In order to

Table 1. The experimental (ΔG_{exp}) and theoretical (ΔG_{theor}) gas-phase acidities (kcal/mol)

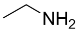
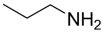
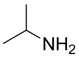
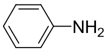
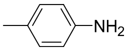
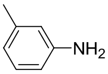
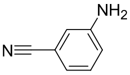
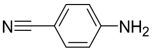
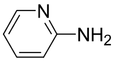
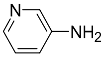
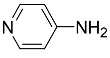
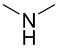
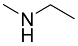
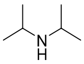
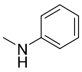
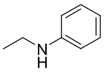
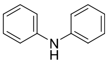
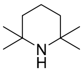
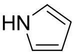
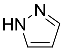
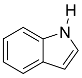
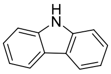
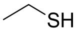
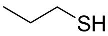
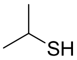
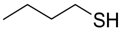
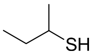
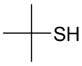
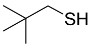
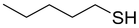
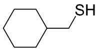
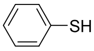
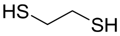
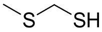
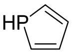
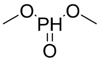
Compound	ΔG_{exp}	ΔG_{theor}
NH_3	396.9±0.4	395.5
$H_3C–NH_2$	395.7±0.7	394.5
	391.7±0.7	389.0
	391.0±3.0	389.4
	389.9±3.0	387.0
	369.6±2.0	367.3
	359.1±2.0	360.0
	360.1±2.0	361.5
	359.6±2.0	360.3
	345.7±2.0	346.4
	341.5±2.0	341.3
	355.6±2.0	355.5
	353.3±2.0	354.2
	349.8±2.0	350.9
	389.2±0.6	385.6
	387.4±2.0	384.0
	382.8±0.4	380.7
	357.5±2.0	358.1
	356.8±2.0	358.3
	343.8±2.0	344.5
	382.3±0.4	382.2
	350.9±2.0	352.6
	346.4±2.0	348.2
	341.9±2.0	343.5
	337.4±2.0	338.8
H_2S	344.4±3.0	343.8
$H_3C–SH$	350.6±2.0	349.8
	348.9±2.0	348.0
	347.9±2.0	347.3
	347.1±2.0	346.6
	347.4±2.0	347.8
	346.8±2.0	346.2

Table 1 (*continued*)

Compound	ΔG_{exp}	ΔG_{theor}
	346.2±2.0	346.5
	345.4±2.0	345.8
	346.2±2.5	348.5
	346.3±2.0	346.2
	333.8±2.0	332.3
	339.2±2.1	337.8
	343.0±4.0	340.3
PH_3	361.0±2.0	359.8
	353.0±2.3	350.7
	365.9±2.8	363.7
	331.0±3.0	330.7
	349.3±3.5	342.5

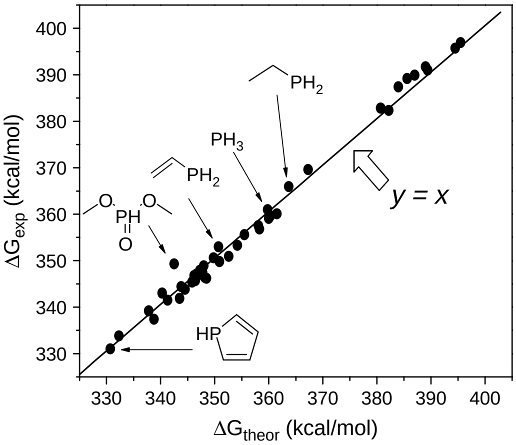


Figure 3. The correlation between the experimental and theoretical gas-phase acidities.

solve this problem we hypothesized that an ab initio method must be able to reliably handle phosphorus if the same method was known to be successful for handling both nitrogen and sulfur. The scientific basis for this hypothesis is that phosphorus is in the same group as nitrogen and in the same period as sulfur.

In Table 2 we collected a number of experimental pK_a values for amines and thiols in DMSO. Our mission was to develop an ab initio method that could accurately predict all the pK_a values in Table 2. In order to accomplish this mission, we firstly needed to derive the equations for the pK_a calculation. Thus, we considered the following proton-exchange reaction between an acid AH and aniline anion[9,11]

$$AH + C_6H_5NH^- \rightarrow A^- + C_6H_5NH_2 \quad (3)$$

Table 2. The experimental and theoretical pK_a values for 27 amines and 13 thiols in DMSO

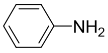
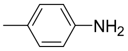
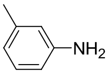
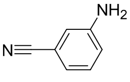
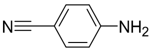
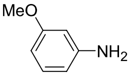
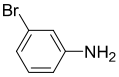
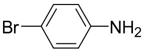
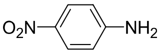
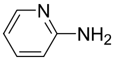
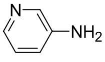
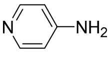
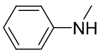
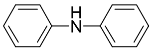
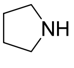
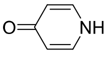
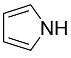
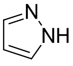
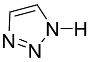
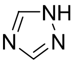
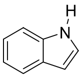
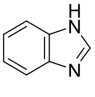
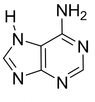
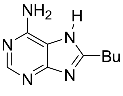
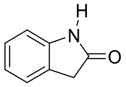
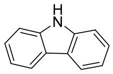
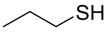
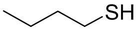
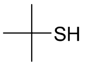
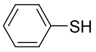
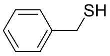
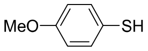
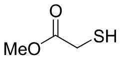
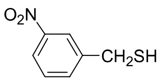
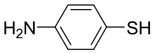
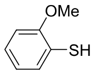
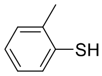
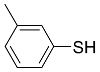
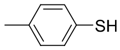
Compound	pK_a (exp)	$f=1.00$	$f=1.05$	$f=1.10$	$f=1.15$	$f=1.20$	$f=1.25$	$f=1.30$
	30.6	30.6	30.6	30.6	30.6	30.6	30.6	30.6
NH_3	41.0	38.6	39.0	39.3	39.7	40.1	40.5	40.8
	31.0	30.5	30.6	30.6	30.7	30.7	30.7	30.7
	31.0	30.8	31.0	31.0	31.0	31.0	31.1	31.0
	27.5	28.2	28.0	27.7	27.5	27.2	27.0	26.7
	25.3	25.7	25.5	25.2	24.9	24.6	24.3	24.0
	30.5	30.4	30.5	30.5	30.5	30.5	30.5	30.5
	28.4	29.0	28.9	28.8	28.6	28.4	28.3	28.1
	29.1	29.7	29.4	29.3	29.1	29.0	28.9	28.8
	20.9	21.9	21.6	21.4	21.0	20.8	20.4	20.0
	27.7	27.5	27.4	27.4	27.3	27.3	27.2	27.2
	28.5	28.7	28.5	28.4	28.3	28.2	28.1	27.9
	26.5	26.7	26.7	26.6	26.4	26.3	26.1	26.0
	29.5	31.2	31.3	31.2	31.3	31.2	31.2	31.1
	25.0	26.4	26.4	26.2	26.1	25.9	25.7	25.4
	44.0	41.4	41.7	41.9	42.2	42.4	42.6	42.8
	14.8	17.0	16.4	15.8	15.4	14.9	14.5	14.2
	23.0	23.6	23.6	23.5	23.6	23.5	23.5	23.5
	19.8	19.5	19.3	19.2	19.1	19.0	19.0	19.0
	13.9	13.3	12.9	12.5	12.2	11.9	11.7	11.5
	14.8	14.8	14.2	13.9	13.6	13.3	13.1	12.9
	21.0	22.2	22.0	21.9	21.8	21.6	21.5	21.3
	16.4	17.6	17.2	16.8	16.5	16.3	16.0	15.8
	14.2	14.0	13.3	12.7	12.2	11.7	11.2	10.8
	15.3	15.2	14.8	14.3	14.2	13.7	13.3	12.9

Table 2 (*continued*)

Compound	pK_a (exp)	f=1.00	f=1.05	f=1.10	f=1.15	f=1.20	f=1.25	f=1.30
	18.5	18.5	18.3	18.2	18.1	18.0	17.9	17.9
	19.9	21.5	21.3	21.1	21.0	20.8	20.6	20.4
	17.1	15.1	15.0	15.1	15.2	15.3	15.5	15.8
	17.1	14.5	14.4	14.4	14.6	14.8	15.0	15.2
	17.9	15.8	15.9	15.8	16.2	16.2	16.7	16.6
	10.3	10.7	10.4	10.1	10.0	10.0	10.0	9.9
	15.4	15.5	15.3	15.2	15.2	15.3	15.4	15.5
	11.2	12.3	12.0	11.7	11.7	11.6	11.6	11.7
	13.0	12.1	11.9	11.7	11.8	11.8	11.9	12.0
	14.2	13.8	13.5	13.3	13.2	13.1	13.0	13.0
	12.5	11.9	11.6	11.4	11.5	11.5	11.6	11.7
	11.4	14.4	14.3	14.2	14.2	14.2	14.2	14.2
	10.7	11.4	11.2	11.0	10.9	10.9	10.8	10.8
	10.6	10.9	10.6	10.4	10.3	10.3	10.3	10.3
	10.8	11.1	10.8	10.5	10.5	10.4	10.5	10.5
r	—	0.9898	0.9907	0.9915	0.9924	0.9927	0.9929	0.9926
sd	—	1.213	1.147	1.122	1.087	1.106	1.128	1.183

If the free energy change of the above reaction in the DMSO solution was defined as $\Delta G_{\text{exchange}}$, the p$K_a$ of the acid AH could be calculated by Eq. 4.

$$\mathrm{p}K_a(\mathrm{AH}) = \mathrm{p}K_a(\mathrm{C_6H_5NH_2}) + \frac{\Delta G_{\text{exchange}}}{2.303 \times RT} \quad (4)$$

It was noteworthy that here we chose aniline for the proton exchange reaction because we wished to develop a method that was the most effective for amines, thiols, and phosphines. Since the chemical properties of nitrogen, phosphorus, and sulfur are relatively close to each other in the periodic table, we envisaged that it was probably more sensible to calculate $\Delta G_{\text{exchange}}$ as a quantity relative to a well-defined nitrogen- or sulfur-containing compound such as aniline.

The experimental pK_a value for aniline is 30.6.[12] It is also known from the previous studies that the gas-phase free energy change of Eq. 3 can be fairly accurately calculated.[8,10] Thus, whether the theory can reproduce the experimental pK_a's mainly relies on the quality of the solvation energy calculations. In order to attain maximum accuracy, herein we utilized the most recent version of the polarized continuum model, that is, IEF-PCM (integral equation formalism PCM),[13] to calculate the solvation free energies. The central idea of this solvation model is the construction of a solvent-inaccessible cavity in which the solute molecule resides.[14] In practice, this solvent-inaccessible cavity is built as a union of overlapping spheres entered on the nuclei of atoms or chemical groups. The sphere radii are usually proportional to the atomic radii with a scale factor (f). For each combination of solvation model, scale of atomic radii, and solvent, the f value has to be specifically optimized.

In the present study, we chose Bondi's atomic radii[15] and the solvent here was DMSO. Our present mission was to find the optimal f value so that the standard deviation between the experimental pK_a's listed in Table 2 and the corresponding theoretical predictions reached the minimum. Using the IEF-PCM/Bondi model, we examined different f

values (f = 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30) in the calculation of pK_a's in DMSO. Comparing the experimental data and the theoretical predictions (see Table 2), we found that the predicted results in the present study were not very sensitive to the f values. Nonetheless, it was determined that a scale factor of 1.15 was the most desirable. The standard deviation and correlation coefficient between the theoretical and experimental pK_a values using this scale factor were 1.1 pK_a unit and 0.992 for 27 amines and 13 thiols, respectively (see Fig. 4).

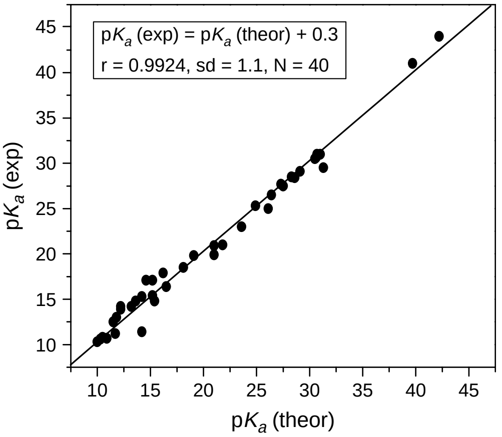


Figure 4. The correlation between the experimental and theoretical pK_a values for 27 amines and 13 thiols (f = 1.15).

4. Predicting pK_a's of organophosphorus in DMSO

Armed with the carefully benchmarked theoretical method that can predict the pK_a values of diverse amines and thiols with a precision of 1.1 pK_a unit, we systematically calculated the pK_a values of various types of organophosphorus compounds in DMSO (see Table 3). Because phosphorus is in the same group as nitrogen and in the same period as sulfur, we assumed that the error bar for the predicted pK_a values listed in Table 3 was also about 1.1 pK_a unit.

It was noteworthy that the predicted pK_a values in DMSO could now be compared with the experimental pK values in THF,[8] as a result of the recent finding by Streitwieser et al. that there was a good correlation between the pK's in THF with the absolute pK_a's in DMSO:[16]

$$pK(\mathrm{THF}) = -0.963 + 1.046\, pK_\mathrm{a}(\mathrm{DMSO}) \qquad (5)$$

Using the above empirical equation and the experimental pK values in THF (see Table 3), we calculated that the corresponding 'experimental' pK_a values in DMSO should be 35.6, 35.0, 33.1, 31.8, 24.3, and 21.7 for di-*tert*-butylphosphine, dicyclohexylphosphine, diethylphosphine, cyclohexylphosphine, phenylphosphine, and diphenylphosphine, respectively. It was gratifying to see that these values were in good agreement with our current predictions, which are 36.1, 34.6, 34.9, 29.6, 22.4, and 22.9, respectively. This confirmed that the predicted pK_a values in Table 3 were fairly accurate.

Thus, all the above analyses made us confident that we had constructed the first scale of reliable pK_a values for diverse organophosphorus compounds in DMSO (see Fig. 5). On the basis of this scale of data, it was found that the pK_a values of organophosphorus ranged widely from about +9 to +37. Since the pK_a value of NH_3 is 41.0, it is obvious that essentially all the organophosphorus can be deprotonated by the strong bases such as $NaNH_2$, $NaN(SiMe)_2$, LiN(*i*-Pr)$_2$, and *n*-BuLi. Except for monoalkylphosphine (pK_a ≈ 30), dialkylphophines (pK_a ≈ 35), phosphonous diamides (pK_a ≈ 37), and phosphonites (pK_a ≈ 33), most of organophosphorus can be deprotonated by the modestly strong bases such as *t*-BuOK (pK_a of *t*-BuOH is 32.2) and EtONa (pK_a of EtOH is 29.8). Finally, almost no organophosphorus can be deprotonated by the weak bases such as Et_3N (pK_a of Et_3NH^+ is 9.0) and pyridine (pK_a of pyridinium is 4.1).

5. Structural–properties relationships

5.1. Trivalent organophosphorus

Trivalent organophosphorus that possess a P–H bond include primary phosphines, secondary phosphines, phosphinites, phosphonites, phosphinous amides, and phosphonous diamides. The pK_a values of these compounds vary from 22.4 to 36.5. These values are lower than the pK_a's of their nitrogen counterparts (see Fig. 6).

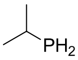
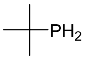
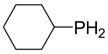
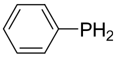
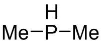
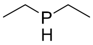
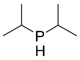
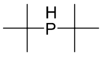
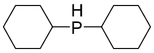
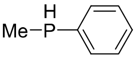
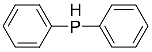
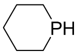
The pK_a of PH_3 is 24.1 in DMSO. This value is about 16 pK_a units lower than that of NH_3 (39.7). When an α-substituent is introduced, the pK_a values of $MePH_2$ (29.6), $MeOPH_2$ (27.3), and Me_2NPH_2 (28.2) are about 6, 3, and 4 pK_a units higher than that of PH_3. In comparison, the pK_a value of $MeNH_2$ (42.9) is only 3.2 pK_a unit higher than that of NH_3, while the pK_a values of $MeONH_2$ (36.5), and Me_2NNH_2 (35.9) are about 5 pK_a units lower than that of NH_3.

Change of the methyl groups to the phenyl groups in the α-substituents decrease the pK_a values of both phosphines and amines. From $MePH_2$ to $PhPH_2$ the pK_a value decreased by 7.2 pK_a units, while from $MeNH_2$ to $PhNH_2$ the pK_a value decreased by 12.3 pK_a units. From $MeOPH_2$ to $PhOPH_2$ the pK_a value decreases by 1.2 pK_a units, while from $MeONH_2$ to $PhONH_2$ the pK_a value decreased by 3.2 pK_a units. From Me_2NNH_2 to Ph_2NNH_2 the pK_a value increased by 0.6 pK_a units, while from Me_2NPH_2 to Ph_2NPH_2 the pK_a value remains the same.

5.2. Pentavalent organophosphorus

Pentavalent organophosphorus that possess a P–H bond include phosphine oxides, phosphinates, and phosphonates. These compounds in solution exist as an equilibrium mixture of two tautomeric forms (Scheme 1), a tetracoordinated P(V) form and a tricoordinated P(III) form. Previous studies have indicated that these equilibria are usually heavily shifted to the left.[17] The pK_a values of pentavalent organophosphorus vary from 9.0 to 26.9. It is not difficult to understand that the pK_a values of pentavalent organophosphorus are usually much lower than the pK_a values of trivalent organophosphorus. Furthermore, the pK_a's of different pentavalent organophosphorus decrease

Table 3. Theoretical gas-phase acidities (kcal/mol) and pK_a values in DMSO for diverse types of organophosphorus[a]

Compound	Gas-phase acidity	pK_a
PH_3	359.8	24.1
Me–PH_2	366.2	29.6
	363.7	29.3
	362.6	29.3
	361.7	29.8
	361.8	29.6 (32.3)
	346.9	22.4 (24.5)
 $\mathrm{Me{-}\overset{H}{P}{-}Me}$	370.9	34.8
	367.3	34.9 (33.7)
	365.1	35.0
	363.8	36.1 (36.3)
	364.0	34.6 (35.7)
	352.6	26.7
	343.7	22.9 (21.7)
	368.8	35.2
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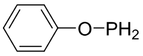
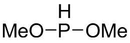
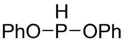
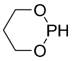
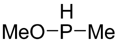
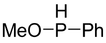
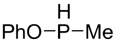
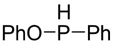
	352.0	26.1
 $\mathrm{MeO{-}\overset{H}{P}{-}OMe}$	367.1	33.6
 $\mathrm{PhO{-}\overset{H}{P}{-}OPh}$	350.4	28.2
	362.5	30.6
 $\mathrm{MeO{-}\overset{H}{P}{-}Me}$	368.0	33.7
 $\mathrm{MeO{-}\overset{H}{P}{-}Ph}$	349.9	26.1
 $\mathrm{PhO{-}\overset{H}{P}{-}Me}$	357.6	31.2
 $\mathrm{PhO{-}\overset{H}{P}{-}Ph}$	342.0	24.0
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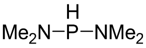
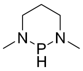
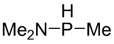
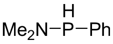
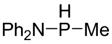
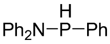
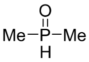
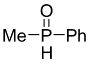
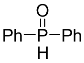
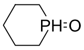
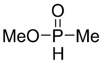
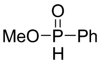
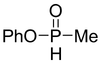
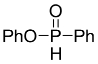
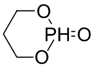
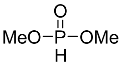
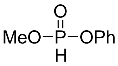
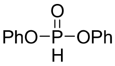
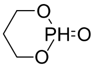
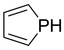
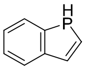
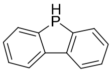
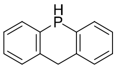
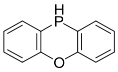
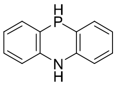
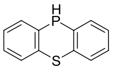
 $\mathrm{Me_2N{-}\overset{H}{P}{-}NMe_2}$	366.7	36.1
	361.3	31.7
 $\mathrm{Me_2N{-}\overset{H}{P}{-}Me}$	368.9	36.5
 $\mathrm{Me_2N{-}\overset{H}{P}{-}Ph}$	352.1	29.1
 $\mathrm{Ph_2N{-}\overset{H}{P}{-}Me}$	352.5	32.1
 $\mathrm{Ph_2N{-}\overset{H}{P}{-}Ph}$	340.0	23.7
 $\mathrm{Me{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Me}$	353.4	26.9
 $\mathrm{Me{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Ph}$	345.7	23.9
 $\mathrm{Ph{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Ph}$	337.8	20.6
	352.6	26.9
 $\mathrm{MeO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Me}$	345.4	22.0
 $\mathrm{MeO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Ph}$	342.2	20.3
 $\mathrm{PhO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Me}$	339.5	20.7
 $\mathrm{PhO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}Ph}$	334.6	17.9
	347.4	23.3
 $\mathrm{MeO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}OMe}$	342.5	18.4
 $\mathrm{MeO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}OPh}$	330.7	13.9
 $\mathrm{PhO{-}\underset{H}{\overset{\overset{O}{\|}}{P}}{-}OPh}$	324.0	9.0
	340.9	17.3
	330.7	9.9
	329.8	12.9
	330.0	15.2
	339.3	21.7
	339.8	22.3
	343.2	23.8
	337.7	20.7

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[a] The values in the parentheses are the experimental pK values in THF reported in Ref. 7.

roughly in the order: phosphine oxides > phosphinates > phosphonates.

The pK_a values for dimethylphosphine oxide is 26.9 (see Fig. 7). Changing one of the methyl groups to phenyl lowers the pK_a to 23.9. Changing both of the methyl groups to phenyl further lowers the pK_a to 20.6. Similar substituent

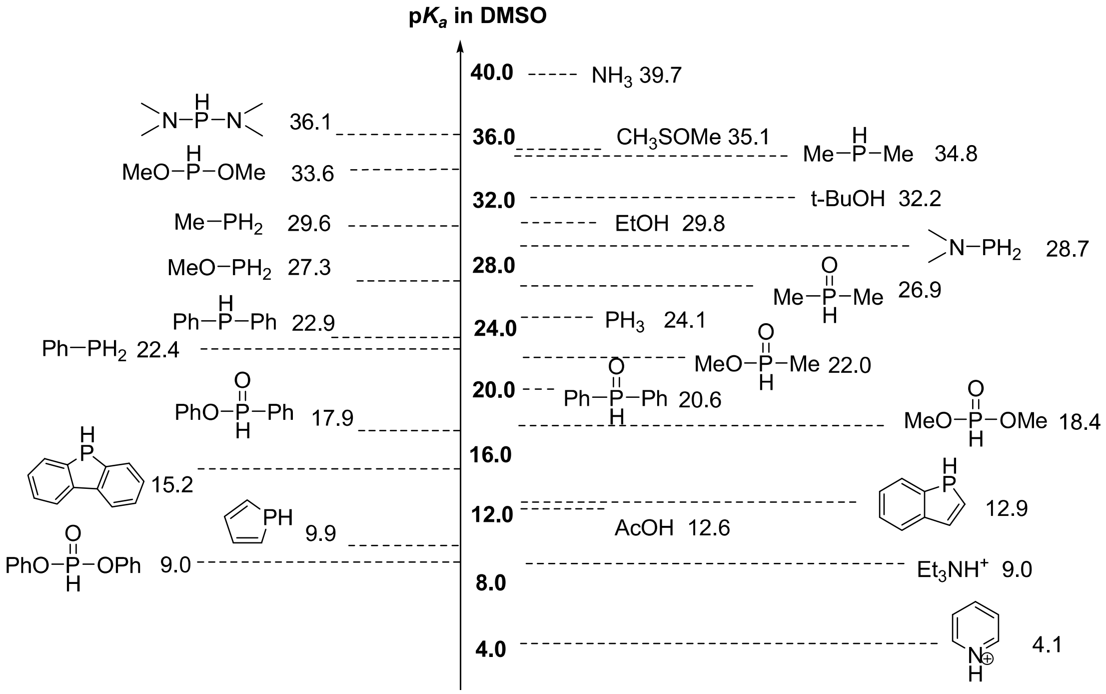


Figure 5. A scale of pK_a values for organophosphorus in DMSO.

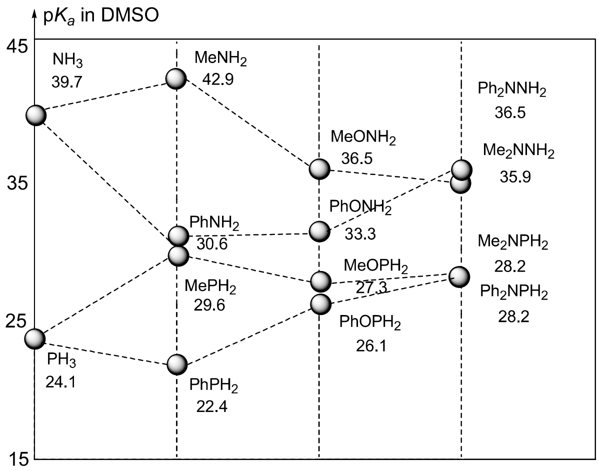
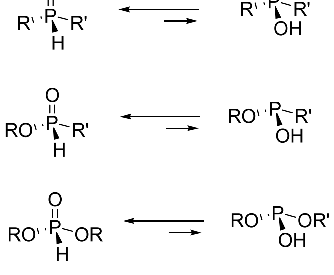


Figure 6. Comparing the pK_a values of trivalent organophosphorus and amines in DMSO.



Scheme 1.

effects are seen for phosphonates. Thus, changing one of the methyl groups in dimethyl phosphonate to phenyl lowers the pK_a from 18.4 to 13.9, while changing both of the methyl groups to phenyl further lowers the pK_a to 9.0.

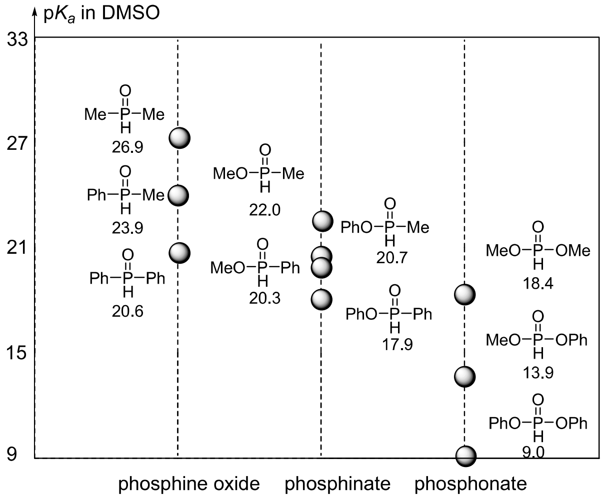


Figure 7. The pK_a values of pentavalent organophosphorus in DMSO.

In contrast to phosphine oxides and phosphonates, the pK_a values of phosphinates are much less sensitive to the substituents. The highest pK_a value (22.0) is predicted for methyl methylphosphinate, while the lowest pK_a value (17.9) is predicted for phenyl phenylphosphinate. The pK_a value of methyl phenylphosphinate is predicted to be slightly lower than that of methyl methylphosphinate by 1.3 pK_a unit. The pK_a value of phenyl phenylphosphinate is also predicted to be slightly lower than that of methyl phenylphosphinate by 2.8 pK_a unit. The pK_a values of methyl phenylphosphinate (20.7) and phenyl methylphosphinate (20.3) are very close. Nonetheless, it is important to remember that the error bar of the predicted pK_a values is about 1.1 pK_a unit.

5.3. Phosphorus heterocycles

Phosphorus heterocycles are peculiar compounds that have interested physical organic chemists for decades.[18] Very recently, phosphorus heterocycles have also become interesting to synthetic chemists as some of them, such as phosphabenzenes and phosphaferrocenes, have been found to be versatile ligands in highly efficient catalysts.[19] In the present study, we have predicted, for the first time, the pK_a values of a few interesting phosphorus heterocycles (see Table 3). The pK_a values of some phosphorus heterocycles, such as 9,10-dihydroacridophosphine and its derivatives (pK_a=20.2–23.3), are very close to their acyclic counterparts (e.g., diphenylphosphine, pK_a=22.9). However, the pK_a values of two phosphorus heterocycles (i.e., 1*H*-phosphole, pK_a=9.9; and 1*H*-phosphindole, pK_a=12.9) are remarkably lower than almost all the other organophosphorus.

The fact that the pK_a's of 1*H*-phosphole (9.9) and 1*H*-phosphindole (12.9) are about 10–13 pK_a units lower than that of diphenylphosphine (22.9) is actually surprising, because for the nitrogen cases the pK_a's of 1*H*-pyrrole (23.0) and 1*H*-indole (21.9) are only 2–3 pK_a units lower than that of diphenylamine (25.0). A careful examination of the optimized structure of 1*H*-phosphole reveals that the molecule is not a planar species (see Fig. 8). However, after deprotonation the phosphol-1-ide anion becomes planar. As recently discussed by Nguyen et al.,[20] 1*H*-pyrrole is probably not aromatic but the phosphol-1-ide anion is. Thus, the exceptionally low pK_a of 1*H*-phosphole is due to the aromatization effect during deprotonation. The same explanation can be applied to 1*H*-phosphindole, because before deprotonation this molecule is not planar, either (see Fig. 8). It is worth noting that Nief et al. once produced the phosphindolyl anion from 1-phenylphosphindole.[21] From the ^{31}P NMR analysis they found that the phosphindolyl anion had a higher basicity than the phospholyl anion. This experimental finding is consistent with our theoretical predictions, because pK_a of 1*H*-phosphindole (12.9) is calculated to be higher than that of 1*H*-phosphole (9.9).

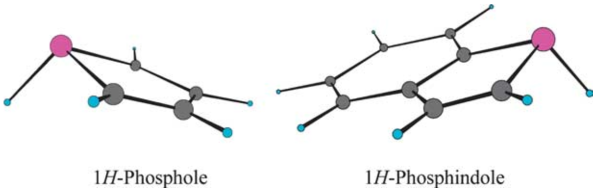


Figure 8. The optimized structures of 1*H*-phosphole and 1*H*-phosphindole.

6. Summary

A first-principle theoretical protocol was developed, which could successfully predict the pK_a values of a number of amines and thiols in DMSO with a precision of about 1.1 pK_a unit. Using this protocol we calculated the pK_a values of diverse types of organophosphorus compounds in DMSO. The accuracy of these predicted values was estimated to be about 1.1 pK_a because phosphorus is in the same group as nitrogen and in the same period as sulfur. The theoretical predictions were also consistent with all the available experimental data. Thus, a scale of reliable pK_a values was constructed for the first time for organophosphorus. These pK_a values will be helpful to synthetic chemists who need to design the experimental conditions for handling deprotonated organophosphorus. On the basis of these pK_a values we have also studied, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines.

7. Computational methodology

All of the theoretical calculations were conducted using the Omega programs[22] and the Gaussian 03 programs.[23] The conformation search for each compound was carried out by using Omega, which used rule-based torsion driving to generate multiple conformations under the Merck molecular force field. These conformations were then used as initial structures for the B3LYP/6-31G(d) calculations. The conformation with the lowest energy was used for all the following calculations.The gas-phase energy calculations were conducted using the standard B3LYP/6-311++G(2df,2p)//B3LYP/6-31G(d) method. The PCM solvation model was used in its integral equation formalism (IEF-PCM)[13] to calculate the solvation free energies in DMSO. Although it was demonstrated that the change of geometry by the solvation effect was usually not significant,[14] we performed geometry optimizations in the DMSO solution to calculate the solvation free energies. All the IEF-PCM calculations were performed at B3LYP/6-311++G(2df,2p) level (version=MATRIX INVERSION, cavity=PENTAKISDODECAHEDRA, Icomp=4, TSNUM=60, TSARE=0.4, radii=Bondi, alpha=1.00–1.30).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.049. The cartesian coordinates of the optimized molecules, the calculated electronic energies, thermal corrections to Gibbs free energies, and solvation free energies.

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