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Published on Web 05/15/2002

Estimating pK_a Values for Pentaoxyphosphoranes

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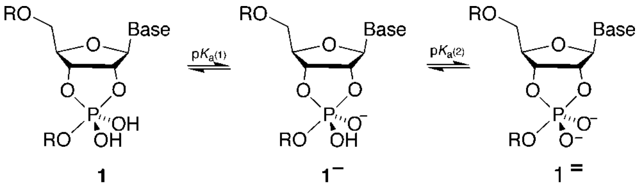
Received February 1, 2002

Abstract: pK_a values are estimated independently, by two entirely different methods, for the ionizations of the apical and equatorial OH groups of two representative hydroxyphosphoranes. A bond length−pK_a correlation based on crystal structures of cyclohexanol derivatives gives values of 13.5 ± 1.5 and 8.62 ± 1.87, respectively, for the apical and equatorial OH groups of tetracyclohexyloxyhydroxyphosphorane, and an ab initio molecular dynamics calculation gives values of 14.2 and 9.8 for the corresponding first ionizations of pentahydroxyphosphorane.

Phosphate transfer reactions involving diesters typically go by associative mechanisms,[1] involving pentacovalent transition states and, in at least some cases, intermediates. Such pentaoxyphosphorane intermediates **1** are of particular interest in the hydrolysis of RNA, and their lifetimes and protonation states are of paramount importance in understanding the mechanisms of action of ribonucleases.[2] So the pK_a values of the monoanion, as a base and as an acid, are a key to understanding the mechanisms of these reactions. They are not, however, directly accessible, because lifetimes of pentaoxyphosporanes are too short. Pentaalkoxyphosphoranes are isolable but rapidly hydrolyzed, but no pentaoxyphosphorane with a free OH group has been isolated.[3] The derived anions are less stable still: the current consensus is that a phosphorane monoanion in solution has a short but significant lifetime, but a phosphorane dianion only a borderline existence.[2]



Previous estimates (summarized by Perrault and Anslyn[2]) range from 6.5 to 11 for pK_a(1) and 11.3−15 for pK_a(2). We report two new, independent estimates—in remarkably close agreement—for pK_a(1) for both apical and equatorial OH groups of simple hydroxyphosphoranes, based on two completely different approaches: (a) a crystal structure correlation and (b) ab initio molecular dynamics calculations.

Methods and Results

Crystal Structure Correlation: pK_a Estimates for (Cyclohexyloxy)$_4$POH. There is a simple linear relationship between the length of a C−OX bond and the pK_a of the acid HOX:[4,5] the stronger the acid the longer the bond. This correlation can in principle be used to estimate pK_a values of compounds HOX too unstable to exist as the free acid or anion.[4,5] Such *structure−reactivity*[6] correlations are very general: they have been demonstrated for 14 of 15 classes of compounds tested, and have been extended to N−O and P−O bonds. The single exception, which may be said to prove the rule, is the system ArCHMe−OX, where the torsion angle between the plane of the aromatic ring and the C−OX bond is a second significant variable.[7] The (stabilizing) $\pi-\sigma^*_{C-OX}$ interaction responsible for the effects on bond length in this benzylic system is strongest for the best leaving groups XO$^-$, and for the (perpendicular) geometry where the π and σ^*_{C-OX} orbitals are parallel. Since this preference is in opposition to the usual steric preference (for the largest, methyl, group to be perpendicular to the plane of the ring) the conformation about the Ar−C(OX) bond changes for the most electronegative groups OX, so that the $\pi-\sigma^*_{C-OX}$ interaction makes an increased contribution to the lengthening of the C−OX bond.[7] This effect on conformation is limited to those systems where a strong π-type interaction affects the length of the C−OX bond directly. There is little or no dependence on torsion angle for $\sigma-\sigma^*_{C-OX}$ interactions.[4]

The sensitivity of the length of a C−O bond to pK_a depends on the substituents on C.[4] Good correlations have been established for acetals, and for derivatives of cyclohexanol and

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(1) Thatcher, G. R. J.; Kluger, R. *Adv. Phys. Org. Chem.* **1996**, *25*, 99−265.
(2) Perreault, D. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 432−450.
(3) Hanes, R. E.; Lynch, V. M.; Anslyn, E. V.; Dalby, K. N. *Org. Lett.* **2002**, *4*, 201−203.
(4) Kirby, A. J. *Adv. Phys. Org. Chem.* **1994**, *29*, 87−183.
(5) The method was recently used by White to estimate the pK of 2,4-dinitrobenzenesulfenic acid. Green, A. J.; Giordano, J.; White, J. M. *Aust. J. Chem.* **2000**, *53*, 285−292.
(6) Structure−*reactivity* correlations in general: because reactivity (the rates and equilibria of reactions of compounds R−OX) is typically correlated (by linear free energy relationships) with the pK_a values of the conjugate acids HOX of the leaving groups.
(7) Edwards, M. R.; Jones, P. G.; Kirby, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 7067−7073.

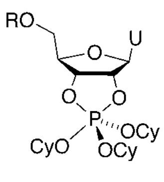
10.1021/ja025779m CCC: $22.00 © 2002 American Chemical Society

of primary alcohols,[8] with the sensitivity to the pK_a falling in this order. Higher sensitivity promises more accurate estimates of pK_a, because the standard deviation of the relevant bond lengths in accurate crystal structures, of the order of 0.003 Å, is of the same order of magnitude as the sensitivity coefficient of the correlation (i.e. ±0.003 Å corresponds to ±1 pK_a unit). A few attempts to make methoxymethoxyphosphoranes (containing $MeOCH_2O-P$ groups) convinced us that such systems were likely to be inconveniently unstable, so we chose to work with phosphoranes derived from secondary alcohols, and specifically cyclohexanol, for which good data and a good correlation (eq i) are available.[8]

$$\text{bond length (cyclohexyl}-\text{OX)} = 1.475 - (2.90 \times 10^{-3})\text{p}K_a(\text{HOX}) \quad \text{(i)}$$

There are no relevant crystal structures in the Cambridge Structural Database of phosphoranes derived only from simple primary or secondary alcohols.

To estimate the pK_a of the P−OH group of systems of interest to the bioorganic chemist we have prepared and tried to crystallize a series of pentaalkoxyphosphoranes from tricyclohexyl phosphite. Of most interest are structures close to **1**, and we have prepared various tricyclohexyloxyphosphoranes **2** derived from uridine (**U** = 3-*N*-methyl-uridyl), as well as simpler cyclic derivatives of ethan-1,2-diol and *cis*-cyclopentane-1,2-diol. Crystallization proved impossible for all these compounds, using either conventional methods or the Cambridge freeze-grow technique.[9] We eventually obtained crystals of the simplest system, pentacyclohexyloxyphosphorane [$(CyO)_5P$, **3**]. We report its structure and derived estimates of pK_a values for the apical and equatorial OH groups of $(CyO)_4POH$.[10]



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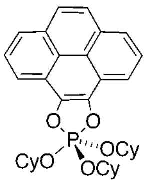

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We have a crystal structure for only one compound with a five-membered ring spanning apical and equatorial positions, the adduct **4** of tricyclohexyl phosphite and phenanthraquinone: [11] results for this compound are discussed briefly below.

Experimental Section

^1H and ^{31}P NMR spectra were recorded on a BRUKER Avance-DRX 400 spectrometer at 300 K, using tetramethylsilane and 85% H_3PO_4 as internal and external standards, respectively. Chemical shifts are reported in δ (ppm). All solvents used were very carefully dried, and reactions carried out in anhydrous conditions under argon. Tricyclohexyl phosphite was prepared as previously described[12] and recrystallized from acetonitrile. The carefully dried white crystalline solid (mp 53−54 °C) is extremely hygroscopic. Its spectroscopic properties and ^{31}P NMR chemical shift (δ 139.2 ppm) agree with previously reported values. Cyclohexyl benzenesulfenate was prepared in 60−75% yield, according to Chang et al.[13] (1,2-diol bis-benzenesulfenates can be prepared by using the same procedure). These compounds were not isolated but redissolved immediately after workup (estimated yields 57−68%) in dry pentane or dry DCM, and used immediately. To a cooled (−78 °C) solution of alkyl benzenesulfenate (10 mmol) in dry pentane or DCM (150 mL) was added, over a period of 1 h, a solution of tricyclohexyl phosphite (2.5 mmol) in 30 mL of dry pentane. After standing for a further 1 h the mixture was allowed to warm to room temperature and stirred for a further 2 h. Cooling to −78 °C precipitated diphenyl disulfide, which was removed by filtration. The filtrate was concentrated to 50 mL and the process repeated. The residues were washed with anhydrous propylene carbonate (3 × 50 mL) and acetonitrile (3 × 50 mL), and the combined extracts were evaporated to dryness. As the primary criterion of purity we used the peak in the ^{31}P NMR with the characteristic chemical shift of pentacovalent phosphorus. After purification the peak assigned to the desired phosphorane accounted for over 95% of phosphorus compounds present, and the ^1H NMR spectrum indicated that less than 5% of diphenyl disulfide remained.

Scheme 1. General Procedure for Preparation of Pentaoxyphosphoranes

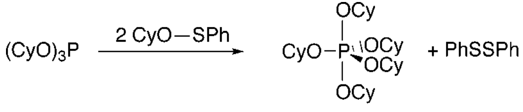

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Table 1. Observed Cyclohexyl−O Bond Lengths for Cyclohexyloxyphosphoranes **3** and **4**

	bond lengths (Å)	
molecule[a]	apical	equatorial
3(i)	1.443(4) 1.435	1.449(4) 1.459 1.460
3(ii)	1.438 1.429	1.451 1.452 1.444
3(iii)	1.440 1.435	1.447 1.445 1.443
3(iv)	1.443 1.443	1.449 1.452 1.454
mean	1.4383 ± 0.0050	1.45042 ± 0.0054
4	1.433(3)*	1.461(3) 1.466(4)

[a] Independent data for four molecules of **3** in the asymmetric unit.[10]

Pentacyclohexyloxyphosphorane (**3**) was eventually obtained as colorless crystals, mp <15 °C, by slow cooling from pentane. The literature mp[13] of **3** is 90−92 °C: we made no attempt to measure the melting point of the crystals we obtained at low temperatures. ^{31}P NMR: −73.68 ppm; sextet, $J_{^{31}P-^{1}H}$ 8.49 Hz. ^1H and ^{13}C NMR agreed with reported values.[13] (Other tricyclohexyloxyphosphoranes failed to crystallize, and were not fully characterized.)

3 crystallized in space group $P1$, with four molecules in the unit cell, giving 20 relevant C−O bond lengths from the one experiment (Table 1).[10] Of these eight involve apical and twelve equatorial oxygens, allowing independent estimates of the pK_a values of apical and equatorial P−OH groups. The mean (cyclohexyl)C−OP bond lengths (Table 1) are 1.436 ± 0.0044 and 1.450 ± 0.005 Å for bonds to apical

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(8) Amos, R. D.; Handy, N. C.; Jones, P. G.; Kirby, A. J.; Parker, J. K.; Percy, J. M.; Su, M. D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 549−558. Equation i is taken from this paper.

(9) Bond; A. D.; Davies, J. E.; Kirby, A. J. *Acta Crystallogr. E* **2001**, *57*, o1242−o1244.

(10) For full structural information see: Davies, J. E.; Kirby, A. J.; Roussev, C. D. *Acta Crystallogr. E* **2001**, *57*, o994−o995.

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(12) Saunders, B. C.; Stark, B. P. *Tetrahedron* **1958**, *4*, 169.

(13) Chang, L. L.; Denney, D. B.; Denney, D. Z.; Kazior, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 2293−2297.

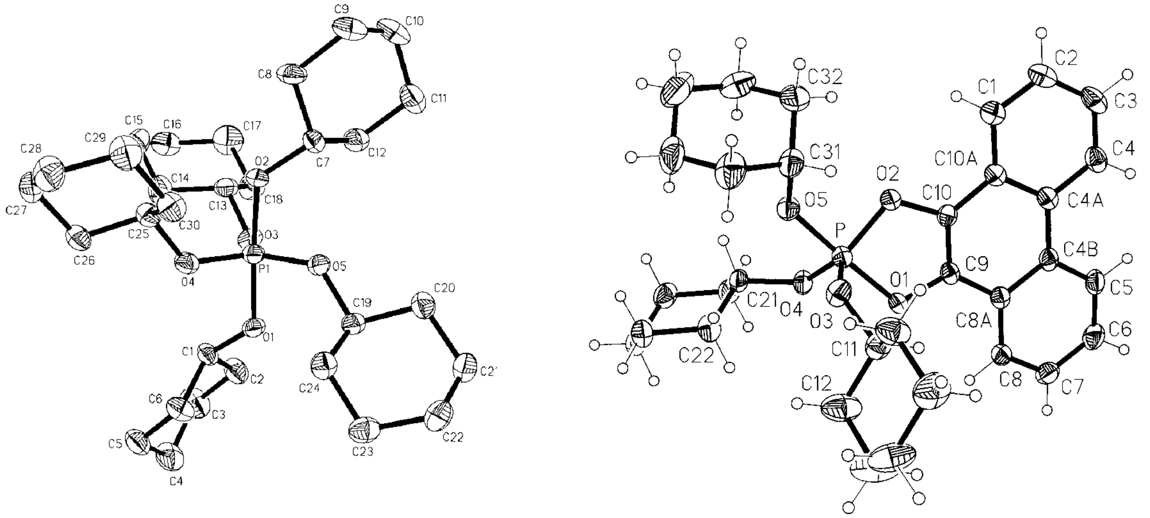

Figure 1. Molecular conformations of **3** (molecule 1 of 4 in the asymmetric unit)[10] and **4**,[11] showing displacement ellipsoids at the 30% probability level.

and equatorial O, respectively, corresponding (eq i) to pK_a values of 13.5 ± 1.5 and 8.62 ± 1.87 for the apical and equatorial OH groups of the tetracyclohexyloxyhydroxyphosphorane.

Tricyclohexyloxyphenanthren-9,10-dioxyphosphorane (**4**) was prepared by the addition of triisopropyl phosphite to phenthraquinone. The crystal structure (Figure 1)[11] shows that the C—O bond of the apical cyclohexyloxy group in the crystal is axial on the cyclohexane ring. The equatorial preference of an alkoxy group is relatively small, even for *tert*-butoxy (*A*-value 0.75[14]), so this inversion is reasonably explained as a crystal packing effect. The axial geometry does not vitiate the bond length−pK_a correlation, because our best information is that axial and equatorial cyclohexyl−OX bonds to the same OX leaving group do not differ significantly in length,[15] but phosphorane **4** also differs from **3** in two more important respects. Two of the oxygen atoms attached to P are phenolic, and thus substantially more electronegative than alkoxyl groups; and they are constrained apical−equatorial in a five-membered ring. We have no simple way of estimating how far either difference would affect the pK_a values of phosphorane P−OH groups. It may be presumed that more electronegative atoms will increase the acidity of geminal P−OH groups, by the generalized anomeric effect, and the relevant C−OP bonds are indeed significantly shorter than the corresponding bonds of **3**. But in the absence of more data the pK_a estimates (formally about 11 and 4, respectively[16]) we can derive for the apical and equatorial P−OH groups of structures, based on a single compound, can only be indicative.[17]

Density Function Based ab Initio Molecular Dynamics Calculations: P(OH)$_5$

The "Car−Parrinello" approach[18] has proved particularly suitable for simulating aqueous acid−base reactions, dominated as they are by solvent effects. An important element in this success is that the time scales for transfer of excess protons in water[19] and the dissociation of strong acids[20] are well within the 10 ps time-window accessible to current ab initio molecular dynamics (MD) simulation technology. Dissociation of weak acids, however, can only be studied by using special sampling methods. Previous work on water autodissociation[21,22] has shown that the free energy for breaking an OH bond can be computed by thermodynamic integration. In this approach an explicit order parameter q, such as the distance r between the leaving proton H^+ and the residual basic anion A^-, is fixed by mechanical constraint techniques. A series of constrained runs is performed at consecutive values of q bridging two states of interest. The mean force $f(q)$ is evaluated for each of the intermediate values of q. Numerical integration of these data gives an estimate of the potential of mean force $w(q)$ relative to its value $w(q_0)$ at some reference state q_0.

$$\Delta w(q) = w(q) - w(q_0) = -\int_{q_0}^{q} \mathrm{d}q'\, f(q') \qquad \text{(ii)}$$

The order parameter q can be a general function of particle coordinates. This feature is the basis for the constraint method used in the present calculation: as an alternative to imposing an AH distance constraint, proton abstraction is enforced by controlling the hydrogen coordination of n_H of anion A^-.[22] This has the advantage that all protons are treated on a strictly equivalent footing.

To maximize the duration of a run in real time, the spatial dimensions of the model were kept to a minimum, with one P(OH)$_5$ molecule solvated in an cubic cell of side $L = 9.86$ Å. Filled with pure liquid water this box contains 32 H_2O molecules. A single P(OH)$_5$ solute molecule must displace 3 water molecules to maintain ambient pressure, leaving 29 solvent molecules in the cell. This system (see Figure 2) was used for all protonation states, without further adjustment of solvent density. The temperature was kept at 300 K.[23] We verified that under these conditions, P(OH)$_5$ and monanion are stable on the

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[14] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

[15] Amos, R. D.; Handy, N. C.; Jones, P. G.; Kirby, A. J.; Parker, J. K.; Percy, J. M.; Su, M. D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 549−558.

[16] Nominally 11.03 ± 1.03, 4.82 ± 1.04, and 3.10 ± 1.38, based on standard deviations of bond length from the crystal structure solution.

[17] Published structures for the phenanthraquinone-triisopropyl phosphite adduct are not accurate enough to be useful in this context (Hamilton, W. C.; LaPlaca, S. J.; Ramirez, F.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 2268−2272. Spatley, R. D.; Hamilton, W. C.; Ladell, J. *J. Am. Chem. Soc.* **1967**, *89*, 2272−2278).

[18] Car, R.; Parrinello, M. *Phys. Rev. Lett.* **1985**, *55*, 2471.

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[20] Laasonen, K.; Klein, M. L. J. *Phys. Chem. A* **1997**, *101*, 98.

[21] Trout, B. L.; Parrinello, M. *Chem. Phys. Lett.* **1998**, *288*, 343. Trout, B. L.; Parrinello, M. *J. Phys. Chem. B* **1999**, *103*, 7340.

[22] Sprik, M. *Chem. Phys.* **2000**, *258*, 139.

[23] All simulations were carried out with the CPMD package developed by J. Hutter, A. Alavi, T. Deutsch, M. Bernasconi, S. Goedecker, D. Marx, M. Tuckerman, and M. Parrinello at the MPI solid-state research institute in Stuttgart and the IBM Research Laboratory Zurich.

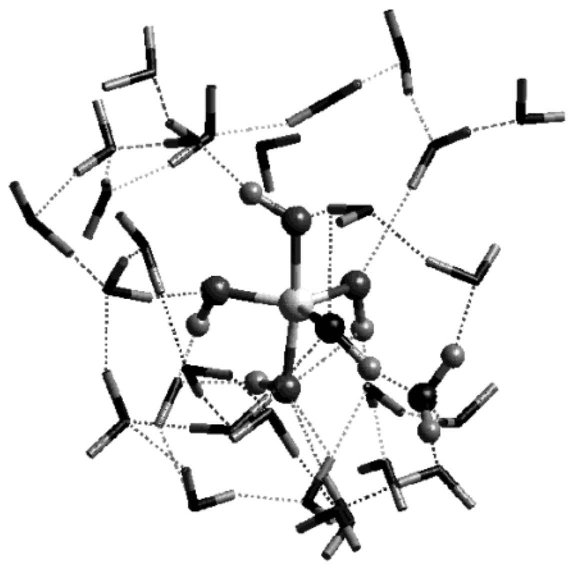

Figure 2. The aqueous $P(OH)_5$ model system used, with a snapshot of a coordination-enforced proton transfer. $P(OH)_5$ and the H_2O involved are drawn as balls and sticks: the OH under coordination control is black. Periodic boundary conditions are applied.

time scale of the simulation (5 ps). The apical monoanion relaxed by a pseudorotation to the equatorial form, consistent with the expected conformational stability. The dianion was found to be strongly basic, converting to a monoanion by deprotonation of a coordinated water molecule.[24]

In two separate series of calculations, the method of deprotonation by coordination control was applied to an apical and an equatorial hydroxyl group. Starting from the equilibrium value of $n_H = 0.98$, which was chosen as the reference state,[25] the proton coordination number n_H was decreased toward zero, thus transferring a proton from the donor hydroxyl group to an acceptor solvent molecule (Figure 2). For each fixed value of n_H a trajectory was computed, roughly 2 to 3 ps in length. In Figure 3a, the "blue-moon" corrected average constraint (i.e. mean) force[22] is plotted as a function of n_H. The steep rise in restoring force for small perturbation of n_H, reaching a maximum at $n_H = 0.925$, is a reflection of the initial stretching of the OH bond. With further reduction of coordination number the mean force is seen to fall off toward zero due to increased binding to the solvent. The P−O bond donating the proton shrinks by 0.1 Å in the process.[26]

At $n_H \approx 0.2$ transfer is complete and a contact ion-pair $OH_3^+|^-OP(OH)_4$ is formed. At this point the proton, now effectively attached to the water, can initiate a Grotthus-type diffusion process. In our small periodic cell this rapidly brings the excess proton back into contact with the newly created phosphorane monoanion. The four remaining, unconstrained OH groups are vulnerable to attack by the acid solvent, converting them to PO^+H_2. Our attempts at enforced deprotonation invariably ended in such solvent-mediated tautomerization, followed by rapid dehydration to phosphoric acid (which being a strong acid, spontaneously releases a further proton within femtoseconds). The resulting potentials of mean force (PMF, see eq ii) for the two deprotonation routes are compared in Figure 3b. The equatorial curve terminates at a free energy difference of 10.2 kcal/mol for $n_H = 0.2$. This is well below the $\Delta w = 14.4$ kcal/mol at the final point of the apical curve.

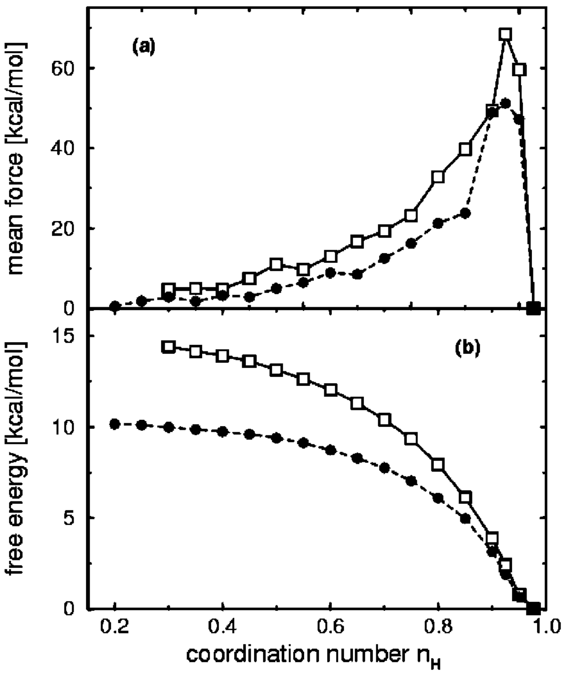

Figure 3. (a) Mean force as a function of proton coordination number for apical (squares) and equatorial (circles) $P(OH)_5$ oxygens and (b) the free energy curves obtained by thermodynamic integration (eq ii), using the equilibrium at $n_H \approx 1$ as the reference point.[25]

Computation of pK_a: Methodology

Computation of pK_a values has been applied in organic chemistry on a number of occasions,[27] and has been implemented in widely available quantum chemistry packages such as Gaussian. These calculations follow a thermodynamic cycle: the acid is taken out of solution and dissociated in a vacuum and the fragments are finally reinserted into solution. Whereas the vacuum proton affinities can be computed with high accuracy by using ab initio electronic structure methods (SCF or DFT), the calculation of the solvation energies is carried out in a reaction field depending on a set of empirical parameters.[27b] (For a very recent example of the application of this approach applied to hydroxyphosphoranes see the Note Added in Proof.) In the approach adopted here, by contrast, the acid remains solvated throughout the dissociation process. The pK_a is then determined from the free energy profiles for deprotonation. The calculation is "in principle" parameter free (but see below).

The basis of our estimation of pK_a is the statistical mechanical method described by Chandler.[28] This purely classical approach is valid for dissociation reactions AB → A + B occurring in

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(24) The ab initio MD approach applied here is similar to previous density functional plane wave based studies of aqueous systems (see refs 19−22). An important difference, however, is that we use the HCTH instead of BLYP gradient-corrected density functional, because of the much improved treatment by HCTH of phosphorus and sulfur compounds (Boese, A. D.; Doltsinis, N. L.; Handy, N. C.; Sprik, M. *J. Chem. Phys.* **2000**, *112*, 1670−1671).

(25) For an explanation of the small deviation from unity see ref 22.

(26) For details see: Doltsinis, N. L.; Sprik, M. To be submitted for publication.

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(28) Chandler, D. *Introduction to Modern Statistical Mechanics*; Oxford University Press: Oxford, 1987.

the gas phase or solution. The key equation is the reversible work theorem relating the AB radial distribution function (RDF) to the PMF according to

$$g(r) = \exp[-w(r)/k_BT] \qquad \text{(iii)}$$

The RDF in eq iii can be interpreted as a probability distribution for distance r between atoms A and B. Equation iii, supplemented by a suitable maximum bonding radius $r = R_c$ distinguishing between reactant AB and product A + B, provides us with all the information needed to determine the reaction quotient at equilibrium and, hence, to derive the classical expression for the (inverse) dissociation constant

$$K_c^{-1} = c_0\int_0^{R_c} dr 4\pi r^2 \exp[-w(r)/k_BT] \qquad \text{(iv)}$$

with c_0 the standard concentration. To apply eq iv to a PMF for proton coordination number, the dependence on n_H must be transformed to a function of r. This was done numerically by inversion of the relationship between the expectation value of AH distance and n_H calculated by averaging over the MD trajectories at fixed proton coordination number. Equation iv holds subject to the condition that $w(r)$ is the total work needed for bringing reactants together from infinite separation. What is available from simulations, however, are relative PMF values (eq ii) referred to a finite maximum separation $r_0 = R_{max} \leq L/2$. This introduces an uncertainty of $w(R_{max})/(2.3\ k_BT)$ in the pK_a that for the small system sizes used in ab initio MD can easily amount to underestimation of several pK units. To reduce this systematic error we have adapted the procedure of Chandler[28] for small systems, exploiting the fact that in controlled dissociation of a weak acid there is only one reactive group AH present, namely the group to which the constraint is applied. This enables us to fix the reference free energy by normalizing the corresponding RDF to unity:

$$\frac{1}{V}\int_V \mathrm{d}\mathbf{r} \exp[-\Delta w(r)/k_BT] = 1 \qquad \text{(v)}$$

where V (=L^3) is the volume of the model cell. By using the normalized RDF of eq v the dissociation fraction α can now be calculated directly from the expectation value of the number of protons within radius R_c from the reactive O atom

$$\alpha(R_c) = 1 - \frac{\int_0^{R_c} \mathrm{d}r\ 4\pi^2 \exp[-\Delta w(r)/k_BT]}{\int_0^{R_{max}} \mathrm{d}r\ 4\pi r^2 \exp[-\Delta w(r)/k_BT]} \qquad \text{(vi)}$$

where the volume integral in eq v has been approximated by the integral over a sphere with radius R_{max}. To obtain our estimate of the equilibrium constant, we express K_a in terms of the dissociation fraction and insert eq vi

$$K_a = \frac{\alpha(R_c)^2}{1 - \alpha(R_c)}\frac{N}{c_0V} \qquad \text{(vii)}$$

setting $N = 1$. A similar approach can be employed for the estimation of the ionization constant of liquid water from free energy profiles for autodissociation.[21,22] Since dissociation is enforced for only one selected H_2O molecule, eq vi remains valid. The equivalence of the water molecules is accounted for by the relationship between K_w and the dissociation fraction α replacing eq vii. The activity of the undissociated reactant (H_2O) is set to unity giving

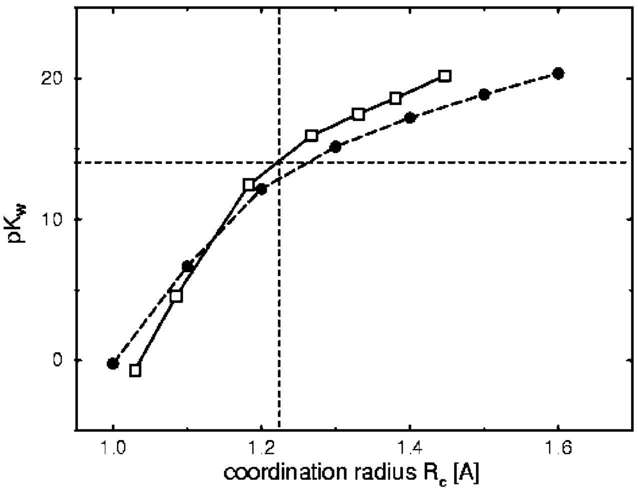

Figure 4. Dependence of the pK for the ionization of liquid water on the bonding criterion R_c. The circles give the result applying eqs vi and viii to the potential of mean force (PMF) of ref 21 generated by using a distance constraint. The squares are the pK values obtained when the PMF for proton coordination from ref 22 is used. The crossing dashed lines locate the value of R_c that reproduces the experimental ionization constant of water.

$$K_w = \left(\frac{\alpha(R_c)N}{c_0V}\right)^2 \qquad \text{(viii)}$$

and instead of $N = 1$ the total number of solvent molecules in the model cell is used ($N = 32$).[21,22]

Computation of pK_a: Results

As a first crucial test, the modified scheme for computing pK_a was applied to the free energy profiles for autodissociation of water obtained previously.[21,22,29] The result is shown in Figure 4, plotted as a function of the bonding radius R_c.

Considering that the two sets of PMF data were generated with different deprotonation constraints, the good agreement can be seen as a validation of our methodology. Moreover, when the parameter R_c is adjusted to reproduce the experimental ionization constant (pK_w = 14), a value of $R_c \approx 1.2$ Å is found, consistent with accepted criteria for maximum extension of OH bond lengths. Repeating the same procedure for the PMF values for acid dissociation of $P(OH)_5$ we find the result displayed in Figure 5. For distances where the OH bond can be considered broken, the curves for the equatorial and apical hydroxyl groups differ by at least 4 pK units.

As is also evident from Figures 4 and 5, the computed equilibrium constants show significant dependence on R_c, making specification of this parameter a critical step in the calculation. This dilemma was resolved by treating R_c as an adjustable parameter. Fitting the pK_w obtained by the coordination constraint method to the experimental value of 14 gives R_c = 1.22 Å. Applying this value to the phosphorane PMF of Figure 3b we obtain pK_a values of 9.8 and 14.2 for the equatorial

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(29) The agreement between the work for deprotonation of a water molecule and the pK_w must be considered fortuitous and the claim made in ref 22 that this number can be used as an estimate of the equilibrium constant is unjustified. for a proper treatment of the kinetics of water autodissociation see: Geissler, P.; Dellago, C.; Chandler, D.; Parrinello, M. *Science* **2001**, *291*, 2121.

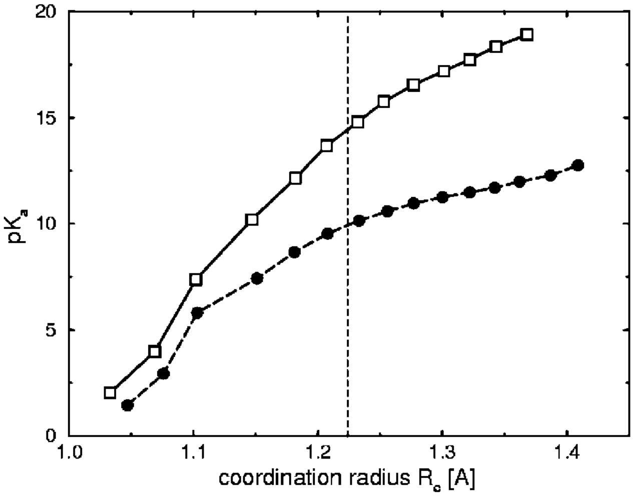

Figure 5. pK_a values for equatorial (circles) and apical (squares) acid dissociations of $P(OH)_5$ as a function of maximum bonding radius R_c, corresponding to the potentials of mean force in Figure 3. The vertical dashed line indicates the optimum value of R_c reproducing the experimental pK_w of liquid water (see Figure 4).

and apical dissociations, respectively, in good agreement with our experimental estimates for a related system.

Discussion

The two methods used in this work allow independent estimates of the pK_a values of both apical and equatorial P−OH groups of phosphoranes: in systems $(CyO)_4P{-}OH$ and $(HO)_4P{-}OH$, respectively. The two systems are different, and not expected to have identical acidities, so small differences in the estimates are to be expected. The relative values of the pK_a estimates also make good sense: the pentahydroxyphosphorane is expected to be the weaker acid because hydrogen-bonding solvation will reduce electron withdrawal by the remaining four OH groups and thus raise the pK_a of a given P−OH.[30] The results confirm, as is well-known, that equatorial P−OH groups are more strongly acidic than apical, and put an order of magnitude on the difference (expected to be more accurate than the absolute values of the estimates) of some 5 pK_a units. They also fall reassuringly near the middle of the range of previous estimates of pK_a(1).[2]

The estimated value of pK_a(1) of ca. 9 for a hydroxyphosphorane bearing only OH or O-alkyl groups provides a firm basis for discussing phosphate transfer mechanisms of phosphate esters. The thermodynamically stable form at pH 7 is clearly identified as the neutral phosphorane, so any anionic intermediate that lives long enough to reach proton transfer equilibrium will be converted to, and thus be present primarily as the neutral, OH form. (Phosphorane dianions, understood, as discussed above, to have at best a borderline existence toward P−O cleavage, also appear from our calculational results to be basic enough to be protonated by solvent water.) Of course the predominant neutral species is unlikely to be the *reactive* form of a hydroxyphosphorane near pH 7, and the familiar problems of kinetic equivalence in systems involving a mobile proton or protons still have to be resolved.

The crystal structure correlation method depends crucially on the quality and quantity of the data available. It offers a simple route to a rough estimate of almost any pK_a of interest that cannot be measured directly. But extensive, high-quality data are needed to allow precise estimates, for example for the cyclic phosphoranes of interest in ribonucleotide reactions; and it seems clear that more such data will be hard won. In this situation theory may turn out to be the more promising way forward. So it is important and encouraging that our first calculations at this level give estimates closely similar to those based on experiment.

Note Added in Proof. In a very recent investigation of acidity constants of phosphoranes with structures related to **1**, using partly empirical continuum dielectric methods, Lopez et al. (*J. Am. Chem. Soc.* **2002**, *124*, 5010−5018) report a value of pK_a = 7.9 for the first ionization of an equatorial OH group of ethylene phosphorane. This value is in good agreement with our experimental estimate of 8.6 for the corresponding OH group of $(CyO)_4POH$, though lower than our calculated value of pK_a = 9.8 for $P(OH)_5$. Applying the statistical correction described by Lopez et al. gives a macroscopic value of 9.3. Thus the two calculations bracket the experimental estimate, and the result of Lopez et al. lends further support to a best estimate for the pK_a of an equatorial OH group of a hydroxyphosphorane close to our experimental value of 8.6.

Acknowledgment. We thank Christoph Dellago for helpful discussions. C.D.R. was a NATO/Royal Society Postdoctoral Fellow, further supported within the TMR Programme of the European Commission by the European Network ENDEVAN. N.L.D. is grateful to EPSRC for financial support. Computational resources were provided by the High Performance Computing Facility of the University of Cambridge.

JA025779M

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(30) Pentahydroxyphosphorane is used here as a model for the sorts of intermediates described in the Introduction. It is not a viable target for direct measurements in aqueous solution, so statistical corrections to the estimated pK_a are not appropriate.