Article

Self-Assembly of Hydrogen-Bonded Cage Tetramers of Phosphonic Acid

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Abstract: The self-association of phosphonic acids with general formula $RP(O)(OH)_2$ in solution state remains largely unexplored. The general understanding is that such molecules form multiple intermolecular hydrogen bonds, but the stoichiometry of self-associates and the bonding motifs are unclear. In this work, we report the results of the study of self-association of *tert*-butylphosphonic acid using low temperature liquid-state 1H and ^{31}P NMR spectroscopy (100 K; CDF_3/CDF_2Cl) and density functional theory (DFT) calculations. For the first time, we demonstrate conclusively that polar aprotic medium *tert*-butylphosphonic acid forms highly symmetric cage-like tetramers held by eight OHO hydrogen bonds, which makes the complex quite stable. In these associates, each phosphonic acid molecule is bonded to three other molecules by forming two hydrogen bonds as proton donor and two hydrogen bonds as proton acceptor. Though the structure of such cage-like tetramers is close to tetrahedral, the formal symmetry of the self-associate is C_2 .

Keywords: hydrogen bond; low-temperature NMR; phosphonic acid; tetramer; self-association

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1. Introduction

Self-association via multiple hydrogen bonds is characteristic for low-molecular weight compounds that exhibit both proton-donating and proton-accepting functional groups in mutual orientations that do not prevent several hydrogen bonds forming at the same time. Examples of such compounds include pyrazoles [1,2], amidines [3–5], and carboxylic acids [6–9]. Linear or cyclic self-associates, such as dimers, trimers, and tetramers, can be formed between the molecules in the gas or condensed phases [10,11]. An interesting case is presented by phosphorus-containing acids (phosphinic, phosphoric, and phosphonic), which have the POH and P=O groups acting as proton donors and acceptors, respectively, thus being able to form hydrogen-bonded self-associates. Previously, we determined the stoichiometry and structure of self-associates of dimethylphosphoric [12], diphenylphosphoric, dimethylphosphinic, phenylphosphinic, and bis(2,4,4-trimethylpentyl)phosphinic acids in polar aprotic solutions using low temperature NMR [13,14] and density functional theory (DFT) calculations [15,16]. We have shown experimentally that R_2POOH and $(RO)_2POOH$ acids predominantly form cyclic trimers in CDF_3/CDF_2Cl mixtures. It should be noted, however, that in the gas phase, several phosphinic and phosphoric acids most probably form cyclic dimers, as it was discussed in [17,18] and supported by numerous quantum-chemical calculations [19–26]. In crystal state, phosphinic and phosphoric acids form either cyclic dimers or infinite chains, see e.g., [27–31]. Anions like $P(O^-)(OH)_2$ are able to form linear oligomers as well [32]. Besides, recently we also studied hetero-complexes formed by molecules of two different POOH-containing acids (namely, diphenylphosphoric, dimethylphosphoric, diphenylphosphinic, and dimethylphosphinic ones), using low-temperature NMR spectroscopy and the partial hydrogen/deuterium (H/D) substitution in the mobile proton sites [33]. For such systems we showed the formation of cyclic hetero-tetramers, in addition to hetero-dimers and hetero-trimers.

There are several papers in which the structure of self-associates of phosphonic acids, RP(O)(OH)_2 , are discussed. In the crystalline state, phosphonic acids form infinite ladder-like “double H-bonded” [34,35] or “triple H-bonded” chains [36], or two-dimensional sheets (see Figure 1a–c, respectively) [37]. Judging from these structural motifs, one could conclude that the presence of two OH groups, their relative orientation in the P(O)(OH)_2 moiety, as well as the strong tendency of the P=O group to form two hydrogen bonds place phosphonic acids as versatile and underexplored synthons for the design of H-bonded molecular crystals [38,39]. In disordered environments, the structure of phosphonic acid self-associates are less known. For example, phenylphosphonic acid encapsulated in mesoporous silica (SBA-15 and aminopropyl-modified SBA-15) forms an amorphous state between liquid and solid with unknown structure, as the crystallinity is broken by the confinement [40]. The ability of phosphonic acids to form extended hydrogen-bonded networks has several industrial applications. For example, in proton conducting polymer membranes, phosphonic acid moieties presumably form H-bonded chains of various lengths and structures, which serve as a path for the long-range proton transfer (Grotthuss mechanism) [41–43]. Phosphonic acid-based organic and organic–inorganic coatings are used as alternative surface treatments for aluminum [44] and titanium [45,46]. Self-assembled monolayers (SAMs) of phosphonic acid-based molecules are commonly used to modify the surface of dielectrics [47–49].

Figure 1. The hydrogen bond motifs in crystalline forms of phosphonic acids: (a) infinite ladder-like “double H-bonded” chains, (b) “triple H-bonded” chains, and (c) two-dimensional sheets.

In this work, we report the results of the study of self-association of *tert*-butylphosphonic acid (see Figure 2) using low temperature liquid-state ^1H and ^{31}P NMR spectroscopy and DFT calculations. For the first time, we demonstrate conclusively that polar aprotic medium *tert*-butylphosphonic acid forms cage-like tetramers held by eight OHO hydrogen bonds.

Figure 2. Structure of *tert*-butylphosphonic acid: (top) schematic, (bottom) calculated for the gas phase (B3LYP/6-311++G(d,p)).

2. Experimental

For sample preparation, *tert*-Butylphosphonic acid was purchased from Sigma-Aldrich and used without further purification. *Tert*-Butylphosphonic acid was weighed and placed into a thick-walled NMR tube with a J. Young valve (Wilma low pressure/vacuum NMR tube 522-LPV-7). Finally, to all the samples, a mixture of liquefied freonic gases ($\text{CDF}_3/\text{CDF}_2\text{Cl}$) was added as a solvent by vacuum transfer. This mixture was synthesized by a modified method of Siegel and Anet [50]. The overall concentration of the samples was in the range 0.001–0.025 M.

For NMR measurements, low-temperature (down to 110 K) liquid-state NMR spectra were recorded at the Center for Magnetic Resonance (St. Petersburg State University Research Park) on a Bruker Avance III 500 MHz NMR spectrometer (11.74 T, 500.03 MHz for ^1H and 202.42 MHz for ^{31}P). The 1D sequence with power-gated decoupling scheme was used for the measurements of $^{31}\text{P}\{^1\text{H}\}$ NMR spectra. 30° -pulses were used with an acquisition time of 2.6 s for ^1H and 0.8 s for ^{31}P , and the relaxation delay was 6.5 s for both nuclei. Spectra were recorded as the sum of 128 and 256 scans for $^1\text{H}/^1\text{H}\{^{31}\text{P}\}$ and $^{31}\text{P}/^{31}\text{P}\{^1\text{H}\}$ spectra, respectively. ^1H and ^{31}P NMR chemical shifts were calibrated using the deuterium signal of CDClF_2 (7.17 ppm) as an internal standard and recalculated to the conventional tetramethylsilane (TMS) and H_3PO_4 (85% in H_2O) scales using the unified Ξ scale, according to IUPAC recommendations [51].

QC calculations were carried out at the Computing Center (St. Petersburg State University Research Park) using the Gaussian 16 package [52]. The optimized geometries and vibrational frequencies were obtained by means of density functional theory (DFT) at the B3LYP/6-311++G(d,p) level under vacuum conditions. This level of theory was chosen for its accessibility and reasonably good performance for the description of hydrogen-bonded systems [53] at a low computational cost. The isotropic ^1H and ^{31}P NMR chemical shieldings were obtained using the gauge-independent atomic orbitals GIAO method at the same level of theory, as were spin-spin coupling constants. The calculated ^1H NMR shieldings were converted into chemical shifts in tetramethylsilane (TMS) scale: $\delta_{\text{H}} = \sigma_{\text{H}}(\text{TMS}) - \sigma_{\text{H}}$. The calculated ^{31}P NMR shieldings were converted to chemical shifts by using the monomeric H_3PO_4 molecule in vacuum as a standard: $\delta_{\text{P}} = \sigma_{\text{P}}(\text{H}_3\text{PO}_4) - \sigma_{\text{P}}$. This approach has inherent imperfections, as outlined in [54], but it seems to be one of the most common approaches used in the literature and it serves the purpose of this work sufficiently well [15]. The visualization of obtained structures was carried out using GaussView 5.0 [55] and Chemcraft. [56] The simulation of the NMR spectra was done using the gNMR software [57]. Analysis of the electron density maps within the framework of Bader's Quantum Theory of Atoms in Molecules (QTAIM) and characterization of bond critical points (BCPs) of the (3, −1) type for OHO bonds was done using AIM2000 2.0 software [58,59].

3. Results and Discussion

Figure 3 shows the low-temperature (180–110 K) ^1H , $^1\text{H}\{^{31}\text{P}\}$, ^{31}P , and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of a sample containing *tert*-butylphosphonic acid dissolved in a $\text{CDF}_3/\text{CDF}_2\text{Cl}$ mixture. For visual clarity, the signals are centered at 0 ppm to compensate for the temperature dependence of chemical shifts (ca. 0.014 ppm per 10 K in ^1H NMR spectra and ca. 0.07 ppm per 10 K in ^{31}P spectra; the non-centered signals are shown in Figure S1 in Supplementary Information). This temperature dependence reflects a slight shortening of hydrogen bonds upon decrease of temperature; in turn, the hydrogen bond shortening is caused by an increase of the dielectric constant of the solvent, which is typical for freonic gases and their mixtures [60].

Figure 3. Temperature dependences of low-field parts of ^1H and $^1\text{H}\{^{31}\text{P}\}$ NMR spectra (**left**) and ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (**right**) of *tert*-Butylphosphonic acid in a mixture of $\text{CDF}_3/\text{CDF}_2\text{Cl}$.

At temperatures below 180 K, two signals are resolved in the proton spectra, which coincide exactly in intensity, from which it can be concluded that the solution contains only one type of self-associates, which exhibits nonequivalent hydrogen bonds that have different chemical shifts of the bridging protons and, thus, different strengths of hydrogen bonds [61–63]. All phosphorus nuclei in these self-associates are equivalent, as evidenced by the single ^{31}P NMR signal. At 130 K, the absolute values of chemical shifts are approximately 11.9 and 11.8 ppm for ^1H and 43.8 ppm for ^{31}P , as shown below in Figure 4. The value of the chemical shifts of OH protons indicates the formation of strong (or medium-strong) OHO hydrogen bonds, while the observation of separate OH signals indicates that the chemical exchange between nonequivalent bridging protons is slow in the NMR time scale.

Figure 4. Fragments of ^1H (top) and ^{31}P (bottom) NMR spectra of *tert*-butylphosphonic acid dissolved in $\text{CDF}_3/\text{CDF}_2\text{Cl}$ at 130 K. Below the experimental spectra, the simulation of the multiplet structure is shown. The values of the spin-spin coupling constants are given above the signals.

The proton signals are split into doublets with 9.9 Hz and 3.7 Hz couplings. Since there was no splitting in the phosphorus-decoupled ^1H NMR spectra ($^1\text{H}\{^{31}\text{P}\}$ spectra), we conclude that both couplings correspond to the spin-spin interaction $^2J(\text{P,H})$ either directly in the POH group or across the hydrogen bond in the $\text{PO}\cdots\text{HO}$ fragment; in the last case, the constants can also be significant (several Hz) [64]. The question which of these two possibilities are correct will be discussed below, while here, looking ahead, we will assume that the observed coupling corresponds to the interaction within the POH group. In proton-decoupled phosphorus spectra ($^{31}\text{P}\{^1\text{H}\}$ spectra), there is one narrow signal which, when the decoupling is turned off, transformed into a multiplet. Line shape analysis of multiplets performed using the gNMR 5.0 software (Adept Scientific) is shown in Figure 4. It could be seen that the ^{31}P NMR signal was split due to the two abovementioned $^2J(\text{P,H})$ couplings as well as an additional spin-spin interaction, $^3J(\text{P,H}) = 17.4$ Hz, with nine chemically equivalent CH protons of the *tert*-butyl group, whose signal is shown in the top right corner of Figure 4.

Thus, considering the obtained solution-state spectral data in its entirety, we can conclude that acid molecules which form self-associates are chemically equivalent, and each one of them forms two hydrogen bonds as a proton donor and, accordingly, two hydrogen bonds as a proton acceptor. In turn, these four hydrogen bonds are divided into two groups, which differ by the proton chemical shift value. Keeping in mind the symmetry of *tert*-butylphosphonic acid molecule, it seems impossible to propose the structure of a cyclic dimer or a cyclic trimer that would explain all of the features of the obtained spectra (for example, in cyclic dimers and trimers, either all OH groups are equivalent, or free OH groups remain that are not involved in the formation of strong hydrogen bonds; this is confirmed by the results of quantum chemical calculations, see below). The search for the simplest structure that satisfies all the spectral requirements led us to conclude that that

the molecules of *tert*-butylphosphonic acid self-assemble into three-dimensional tetramers, which have a cage-like structure. Such tetramer formation can be regarded as the result of interaction of two cyclic dimers, where “free” OH groups form hydrogen bonds with the remaining unoccupied lone pairs of oxygen atoms of the P=O groups of another dimer (see Figure 5a). As a result, a nonplanar structure is stabilized, in which not only all eight OH protons are involved in hydrogen bonds, but also each P=O group is involved in two hydrogen bonds as a proton acceptor. In other words, neither free OH groups nor free electron pairs of the P=O group remain in this structure, which makes it more stable and complicates the rearrangement of hydrogen bonds, which could lead to various proton exchange processes [8]. The protons highlighted in different colors in Figure 5a remain chemically nonequivalent.

Figure 5. (a) The self-assembly of phosphonic acid tetramer: two cyclic dimers approach each other and form four additional hydrogen bonds; $R = -C(CH_3)_3$. (b,c) Unfolded and assembled tetrahedron models showing the layout of hydrogen bonds in phosphonic acid tetramer. (d,e) Unfolded and assembled models of a tetrahedron depicting an alternative arrangement of hydrogen bonds in a phosphonic acid tetramer, which does not correspond to the experimental spectra. Orange dots at the vertices of the tetrahedra represent phosphorus atoms.

The structure of the tetramer could be visualized as an unfolded tetrahedron (see Figure 5b), at the vertices of which there are phosphorus nuclei, and on each face, two hydrogen bonds of OHO are depicted, bridging protons which are color-coded, demonstrating their chemical nonequivalence. A papercut pattern and assembled tetrahedron is shown in Figure 5c. It should be noted that there is another way to construct a non-planar tetramer from four phosphonic acid molecules. The unfolded and assembled models of this tetramer are shown in Figure 5d,e. The larger versions of the papercut patterns can be found in the Supplementary Information, Figure S2. In the alternative layout (Figure 5e), however, the symmetry of the self-associate is higher and the protons in all eight hydro-

gen bonds are chemically equivalent, which does not correspond to the experimental ^1H NMR spectrum, so this option is not considered further. One version of the tetrahedron (Figure 5c) can be converted into another one (Figure 5e) as a result of a double proton transfer in one of the “dimeric” fragments. However, under experimental conditions at temperatures below 180 K, this does not happen; otherwise, two signals of bridging protons in the ^1H NMR spectrum would average out.

Additional and quite convincing evidence for the formation of a tetramer was given by the results of quantum-chemical calculations (DFT at the B3LYP/6-311++G(d,p) level). The optimized tetramer structure is shown in Figure 6a. The calculated values of chemical shifts and spin-spin coupling constants are shown in Figure 6b.

Figure 6. (a) Optimized (B3LYP/6-311++G(d,p)) structure of tetramer of *tert*-butylphosphonic acid in vacuum: (left) the complete structure, and (right) the same structure in which the *tert*-butyl groups have been omitted for clarity. (b) The values of chemical shifts and coupling constants calculated for the tetramer of *tert*-butylphosphonic acid.

Indeed, in such tetramers, all four ^{31}P nuclei are chemically equivalent, and the eight bridging protons are divided into two groups of four, which differ by the chemical shift value. The formal symmetry of the tetramer is C_2 (this is evident upon inspection of the Figure 5a), but the distances between all four phosphorus atoms are rather similar (the $\text{P} \dots \text{P}$ distance is ca. 4.2 Å within the “dimer” and ca. 4.6 Å between the “dimers”), so that the overall structure of the tetramer looks similar to a slightly distorted tetrahedron, as visualized in Figure 6a, right. The calculated values of chemical shifts agree relatively well with experiment. The chemical shift of ^{31}P is higher than the experimental one by 2.5 ppm, and the chemical shifts of the bridging protons are less than the experimental ones by about 2 ppm. The hydrogen bonds connecting two “dimeric” fragments of the tetramer turned out to be shorter, and the bridging protons in them are less shielded than in the hydrogen bonds within the “dimers” themselves. The agreement of the calculated spin-spin coupling constants with the experiment is worse. However, it can be seen that the value of the POH coupling is much larger than the value of the $\text{PO} \cdots \text{HO}$ coupling (10 Hz and 1–3 Hz, respectively). Based on this, we assumed that the experimentally observed signal splittings in ^1H NMR spectra are due to the POH coupling. Nevertheless, caution should be exercised here, since the calculated values of the spin-spin coupling constants are very sensitive, both to the geometry of the hydrogen bonds and to the

level of theory at which the calculation was performed. Additionally, we performed quantum-chemical calculations of self-associates with a different stoichiometry (using the examples of phosphonic, methylphosphonic, phenylphosphonic, and *tert*-butylphosphonic acids). However, in the case of cyclic dimers and trimers, the optimized structures did not correspond to the experimental spectra. Each molecule had one OH group participated in the formation of a ring of hydrogen bonds, and the second remained free (see the case of *tert*-butylphosphonic acid presented in Figures S3 and S4 in Supplementary Information).

The formation of hydrogen-bonded tetramers is a rather rare type of association since, as a rule, it is not favorable in terms of entropy. The entropy loss can be small if the molecules retain high conformational mobility relative to each other within the complex [15], or the entropy loss could be compensated by the high complexation enthalpy. Previously, hydrogen-bound cyclic (ring) tetramers were found in crystals [1,65–67] or in solution [33,68], and tetramers were also considered experimentally (IR) [69] and theoretically [70] for methanol, but in the latter case, the structure with tetrahedral symmetry (with the equivalence of all four molecules) was obtained only dynamically, as a result of successive proton transfers and rearrangements of hydrogen bonds in the cluster. As far as we know, experimental proof of the existence of stable hydrogen-bonded “tetrahedral” tetramers in an aprotic medium is presented here for the first time. It can be assumed that such tetrameric structures are fully or partially retained in the disordered medium of proton-conducting polymers synthesized on the basis of phosphonic acids.

The reasons for the high stability of *tert*-butylphosphonic acid tetramers are not entirely clear. At a first glance, the tetramer lacks high conformational mobility of acid molecules relative to each other, which could reduce the entropy loss. It is also difficult to suggest the presence of a fast (in the NMR timescale) dynamic process associated with proton transitions and switching of hydrogen bonds in a tetramer. Such a process would lead to a different spectral picture, namely, to the averaging of two bridging proton signals or to the changes of their multiplicities into triplets due to spin-spin interaction with two phosphorus nuclei on either side of the hydrogen bridge. However, it is difficult to completely exclude any motion within the tetramer based on the available data. Finally, it could be noted that structures of sufficiently high symmetry and without charge separation, such as the tetramer described above, do not have additional stabilization factors in a polar medium (dielectric constant of a freonic mixture >30 at 110 K) [60]. Summarizing all these arguments, we attribute the high stability of the tetramer primarily to the enthalpy contribution due to the formation of eight strong hydrogen bonds. Indeed, quantum chemical calculations of the enthalpy, entropy, and Gibbs free energy of formation of cyclic dimers, cyclic trimer, and “tetrahedral” tetramers of *tert*-butylphosphonic acid in the gas phase (see Table S1 and the accompanying text) support this conclusion. The high strength of hydrogen bonds in self-associates of phosphorus-containing acids was previously noted in several publications [16,71]. Estimates of the hydrogen bond strengths in the optimized tetramer structure based on the theory of R. Bader (Atoms in Molecules, AIM) [72,73] give average values of about 14 kcal/mol per bond (depending on whether the E_V or E_G value at bond critical point was used to estimate the bond strength) or ca. 110 kcal/mol per tetramer (the total average values of $E_V = -94.4$ kcal/mol and $E_G = -127.2$ kcal/mol); see Figure S5 in Supplementary Information. These values of hydrogen bond strengths are consistent with what one could expect from the changes of ^1H NMR chemical shifts upon complexation (in our case, tetramerization brings about ca. 8 ppm low-field shift of the OH proton signal), for which a very rough conversion factor “1–2 kcal/mol per 1 ppm shift” could be used (it varies for different types of H-bonds and various subsets of complexes) [74–76]. Previously, based on quantum-chemical calculations, the hydrogen bond energies in cyclic self-associates of phosphinic and phosphoric acids were estimated to be within the range 10–14 kcal/mol [16], which matches reasonably well with what we see here for *tert*-butylphosphonic acid. Such hydrogen bonds could be classified as medium-strong or strong ones, depending on one’s frame of reference [10].

4. Conclusions

In this work, we tackled the largely unexplored question of the self-association of phosphonic acids $\text{RP}(\text{O})(\text{OH})_2$ in polar aprotic media, using the example of *tert*-butylphosphonic acid dissolved in $\text{CDF}_3/\text{CDF}_2\text{Cl}$ mixture. Judging from the spectral patterns observed in the low temperature ^1H and ^{31}P NMR spectra, we conclude that only one type of self-associate is formed under such conditions. The following could be stated about this complex: (a) all acid molecules are equivalent; (b) all OH protons form strong hydrogen bonds (besides, half of OH protons are chemically non-equivalent to the other half); (c) both types of OH protons exhibit spin-spin coupling to a single ^{31}P nucleus; and (d) below 150 K, there is no fast chemical exchange between non-equivalent OH protons. Assuming the lowest stoichiometry of the self-associate, we conclude that it is a cage-like tetramer shaped as a distorted tetrahedron, which matches quite well with the results of quantum-chemical modelling. The formation of such tetramers could be envisioned as the result of interaction between “free” OH groups and $\text{P}=\text{O}$ groups of two cyclic dimers approaching each other. In the emerging tetramer, each acid molecule is bonded to three other molecules by strong hydrogen bonds (eight bonds in total), thus making such complexes quite enthalpically stable.

Supplementary Materials: The following are available online at <https://www.mdpi.com/2073-8994/13/2/258/s1>. Figure S1: Temperature dependencies of low-field parts of ^1H , $^1\text{H}\{^{31}\text{P}\}$, ^{31}P and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of *tert*-butylphosphonic acid in $\text{CDF}_3/\text{CDF}_2\text{Cl}$, Figure S2: Papercut patterns for the assembly of the tetrahedron models showing the layout of hydrogen bonds in phosphonic acid tetramer, Figure S3: Two projections of the equilibrium structures of *tert*-butylphosphonic acid cyclic dimer and trimer, Figure S4: The comparison of calculated ^1H NMR spectra of cyclic dimer, cyclic trimer and cage-like tetramer of *tert*-butylphosphonic acid with its experimental low-temperature ^1H NMR spectrum, Figure S5: The QTAIM topological analysis of the electron density at the OHO hydrogen bond critical points (BCP) of *tert*-butylphosphonic acid, Table S1: The thermodynamic parameters of the dimerization, trimerization and tetramerization reaction of *tert*-butylphosphonic acid.

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