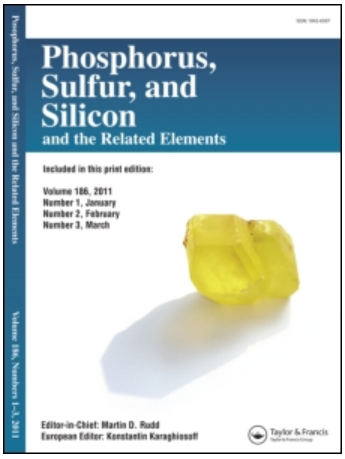

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Weak Hydrogen Bond in $Cl_3CH\cdots OP(n\text{-}Bu)_3$

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The phosphoryl group (P=O) is able to form hydrogen bonds with the relatively low acidic atoms like in C–H···O=P system. In this article, we present experimental and theoretical investigations on the C–H···O=P hydrogen bond for the complex of tributylphosphine oxide and chloroform.

Keywords Chloroform; phosphino oxide; weak hydrogen bond

INTRODUCTION

The organophosphonic compounds reveal diverse and interesting biological and biochemical properties. Phosphorus atoms occur in nucleic acids (DNA, RNA) phosphonolipides and proteins. Phosphoroorganic compounds are inhibitors of many enzymes, for example rennin,[1] EPSP synthase,[2] and HIV protease.[3] They are also used as antibacterial agents and plant growth and calcium metabolism regulators, as well as hypertensive and immunosuppressive agents.[4,5] The phosphoroorganic compounds such as phoshine oxide, phosphinate, phosphonate, and phosphate have a highly polarized phosphoryl oxygen atom P=O facile for the formation of hydrogen bonds via intra- and intermolecular interactions, the strength of which

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

Calculations were performed at the Wrocław Centre for Networking and Supercomputing (WCSS), Poznan Supercomputing Networking Center (PCSS), and Academic Computer Centre in Gdansk (CI TASK). The authors thank Dr. Marek Daszkiewicz (PAN) for help in analyzing crystallographic data, and MSc Agata Malinowska (maiden name Napieracz) for repeat NMR experiments using solvent cycklohexane as solvent.[36] The measured values of K by Malinowska in cyklohexane were in accordance with the presentation date.

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depends on atoms around phosphorus atom. The P=O interaction with H–O and H–N groups usually forms strong hydrogen bonds[6–10] and is the most popular interaction found in many phosphoryl compounds. These hydrogen bonds determine the conformational preferences in hydroxyphosphonates and aminophosphonates in solution and in crystal networks,[10,11] and is important in transferring spin–spin interaction.[13,14] The strong hydrogen bond N–H··O=P is important in some cases, for example in stability and decomposition of α-aminophosphonates.[6,12]

The phosphoryl group is also able to form hydrogen bonds with the relatively low acidic hydrogen atoms such as in C–H···O=P system.[11,15,16] These very weak hydrogen bonds have been observed in some NMR experiments by monitoring the chemical shift changes[17,18] and spin–spin coupling.[19] Such a weak hydrogen bond was found also between chloroform as donor of proton with oxygen acceptors (C=O, –C–O–C–, S=O, etc.) and with free electron pairs (–N: –S:, –P: etc).[17,20–23] The enhancement of the C–H as a proton donor by neighboring electronegative groups has also been observed in $CH(NO_3)_3$. It seems that although this type of interaction C–H···O(P) is weak, it plays an important role in nature.

In this article, we present crystallographic analysis, NMR experimental, and theoretical studies on energy, chemical shifts, and coupling constants in systems with participation of the C–H···O=P hydrogen bond.

RESULTS AND DISCUSSION

The hydrogen bond C–H···O=P is very common in the solid state for organic phosphorus compounds. Analysis of the crystallographic database (Cambridge Structural Database –CSD)[24] for such interactions is presented in Figure 1a,b. There are overall about 6000 entries in the CCDB with close C–H distance to O(P). The smallest distance between carbon and oxygen (l_{CO}) in the range from 2.8 to 2.9 Å was found only for 30 analyzed compounds. Most of them were intramolecular. The angles $\alpha_{C-H\cdots O}$ and distances l_{CO} were typical for hydrogen bonds. The other structures were characterized by the distance l_{CO}between 3.0 to 3.8 Å, indicating very weak hydrogen bonds.

In addition to a typical hydrogen bond where the proton donor is attached to the heteroatom, more interesting interactions are cases when the hydrogen bond is formed with acidic proton attached to carbon atom, C–H. The crystallographic database contains 33 crystal structures with Cl_3C–H···O=P interactions. The first observation of

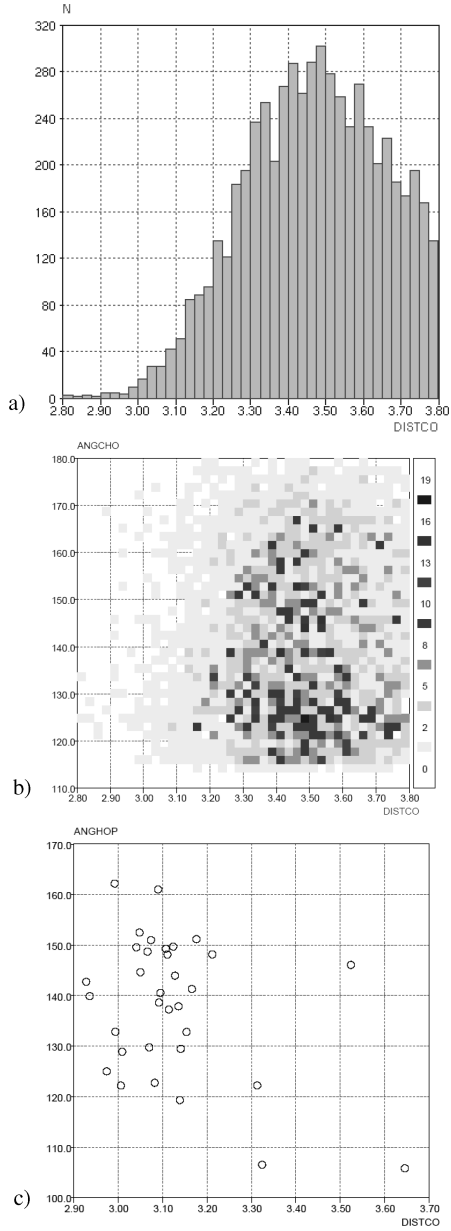


FIGURE 1 a) Distribution of the number of compounds in CSD in relation to the C· · · · ·O distance in C–H· · ·O=P. b) Scatterplot of the dependence of the angle C–H· · ·O and C· · · · ·O distance. c) Scatterplot of the dependence of the C· · · · ·O distance and angle H· · ·O–P in Cl_3C–H· · ·O=P interactions.

such a hydrogen bond between chloroform and compounds having O=P group was noticed in 1972, for $((CH_3)_2N)_3PO$.[17] The authors characterized this hydrogen bond by measuring the change in proton chemical shift, by analysis of the IR spectra, and based on that they calculated equilibrium constants K and ΔH.[17] The calculated K for this system, $Cl_3C{-}H\cdots O{=}P(N(CH_3)_2)_3$, was found to be 15.5 mol^{-1} and ΔH was 4.9 kcal/mol. These data indicate the presence of weak hydrogen bonds.

We have studied the formation of the tributylophosphino oxide (TBPO) complex with chloroform in tetrachloromethane, and we have measured the changes of the chemical shifts for hydrogen, carbon, and phosphorus atoms, and based on that, we have calculated the equilibrium constant K for formation of the complex by the same methods as Slejko.[17] The observed chemical shift changes of chloroform proton in ^1H NMR for various concentrations of TBPO were in the range 0 to 1.7 ppm, and chemical shifts of chloroform carbon in ^{13}C NMR were 0 to –3.7 ppm. (Table I). We attributed those changes as a result of hydrogen bond formation. We have also observed small changes of the chemical shift of the phosphorus atom signal in ^{31}P NMR (0 to 0.8 ppm) and carbon atoms in ^{13}C NMR from methylgroup of TBPO (0 to 0.2 ppm) (Table I). The last changes can also be attributed to the formation of the hydrogen bond between P=O and CH_3 in *n*-butyl fragments of TBPO, or changes in polarizability of the solvent due to higher concentration of TBPO. Based on NMR experiment data, we have calculated equilibrium constants K for formation of the $Cl_3C{-}H\cdots O{=}P(n\text{-but})_3$ complex. The calculated K in chloroform was 1.8 mol^{-1}or 2.8–3.2 mol^{-1} based on changes of the proton chemical shifts or carbon respectively (Figure 2). The difference between the two obtained values is about 1. We believe that the more confident value is the one obtained from the CNMR

TABLE I Concentration of $TBPO^o$, $CHCl_3^o$ [mol/dm^3], and Change of Chemical Shift $\Delta\delta$ [ppm] Chloroforms Proton ($\Delta\delta_H$) and Carbon ($\Delta\delta_C$); and Change of Chemical Shift Methyl Group ($\Delta\delta_{CH3}$) and Phosphorus Atom ($\Delta\delta_P$) of TBPO

Nr	$[CHCl_3^o]$	$[TBPO^o]$	$\Delta\delta_H$	$\Delta\delta_C$	$\Delta\delta_P$	$\Delta\delta_{CH3}$
1MD	0.1000	0.0000	0.000	0.000		
2MD	0.1012	0.5061	0.923	−2.293	0.000	0.000
3MD	0.1004	0.9619	1.284	−2.852	0.035	0.065
4MD	0.1020	1.4543	1.475	−3.271	0.378	0.085
5MD	0.1016	1.9536	1.577	−3.468	0.871	0.113
6MD	0.1008	2.4162	1.523	−3.372	0.699	0.099
7MD	0.1028	3.2727	1.748	−3.695	0.753	0.180

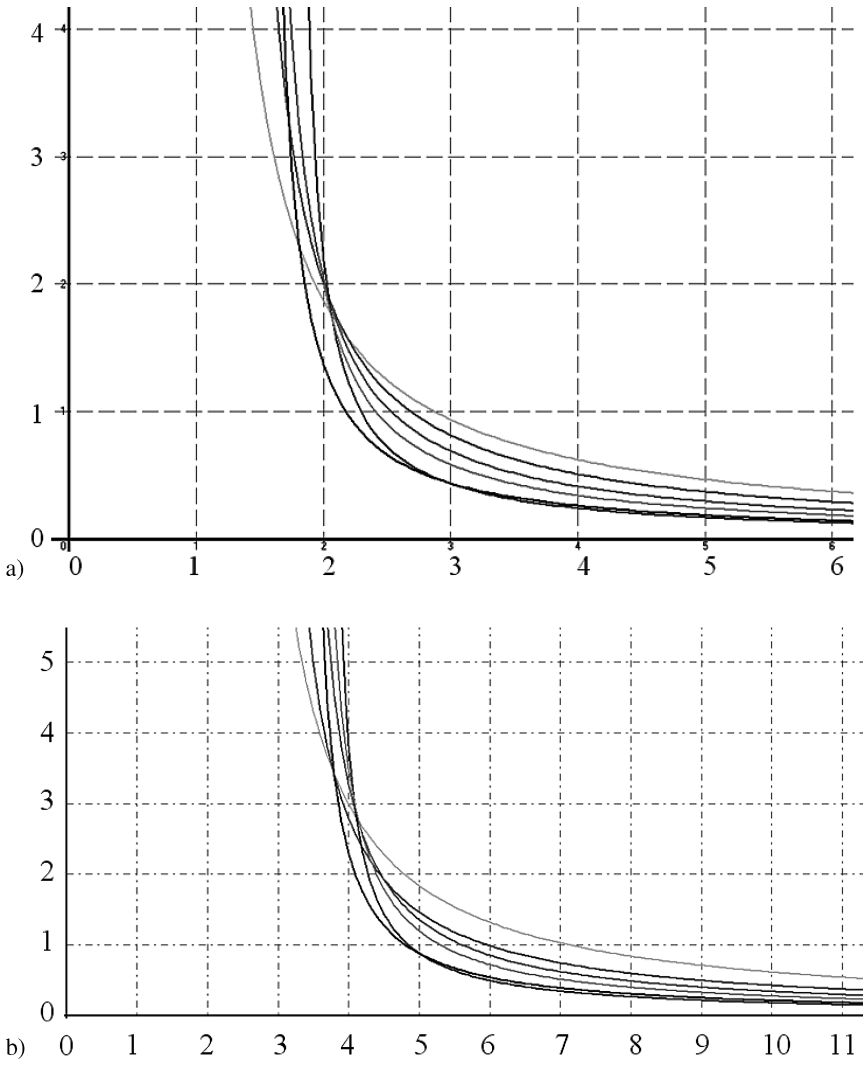


FIGURE 2 The graph K equation as function of $\Delta\delta$. a) Proton chemical shift in C**H**Cl_3, b) carbon chemical shift in **C**HCl_3.

experiment, as in this case the changes in the chemical shifts were larger, so the error was smaller. The obtained K value is smaller than that observed for $((CH_3)_2N)_3PO$. This is understandable, as $((CH_3)_2N)_3P{=}O$ is a stronger base than TBPO.[11] We have also verified our results on theoretical level B3LYP in gas phase. The geometry of

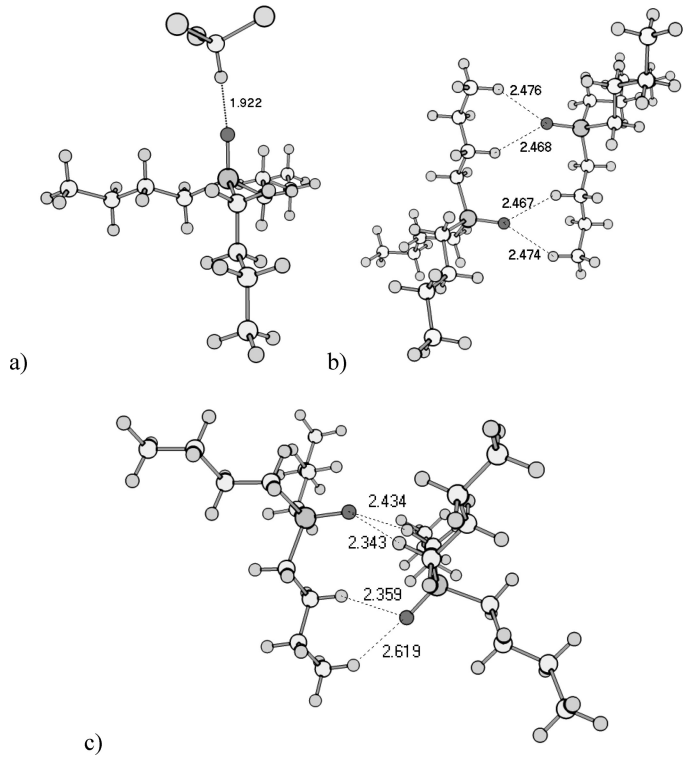


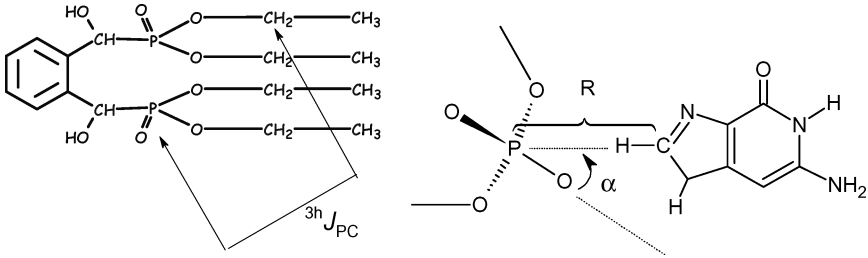
FIGURE 3 Structure of complex TBPO with chloroform and TBPO. On the structure is the selected hydrogen bond and distance between proton and phosphoryl oxygen. B3LYP/6-31G(d,p).

interaction C—H· · ·O=P in TBPO complex ($\alpha_{C—H\cdots O} = 177.4^{\circ}$, l_{CO} =3.01 Å, $l_{HO=}$ 1.92 Å) indicates weak hydrogen bond formation (Figure 3a). The calculations have also shown that two molecules of TBPO can interact with each other and form dimers (Figure 3b,c). The last conclusion is based on some geometrical parameters. The hydrogen bond in the dimer is however much weaker than that in the complex of chloroform with TBPO. The distance between proton and oxygen was 2.30–2.6 Å in the dimer, whereas in chloroform it was 1.92 Å.

The calculated energy showed that interaction of TBPO with chloroform (ΔE = –6.7 kcal/mol, ΔEsol = –4.7 kcal/mol) approaches the energy of interaction in dimers (for the structure in Figure 3b is ΔE = –4.3 kcal/mol, ΔEsol = –2.2 kcal/mol; in Figure 3c is ΔE = –2.3 kcal/mol, ΔEsol = –0.2 kcal/mol). This can be explained by the fact that

in the case of the dimer there are many hydrogen bonds involved in the complex formation.

In 2006, Vladimir Sychrovsky et al. predicted spin–spin coupling across P=O···H—C hydrogen bond in nucleotides (in ribosomal subunit), by the theoretical calculation.[19] Calculations done in the Sychrovsky model system, dimethyl phosphate-guanine, suggested that indirect spin–spin coupling across the linkage is sensitive to the mutual orientation and distance between the nucleotide base and phosphonate group. The conclusion that comes from his investigation is that a short distance between the nucleic acid base and phosphate group and the angles C···P—O and P···C—H smaller than 50° are prerequisites for a measurable spin–spin interaction of either coupling ($|J| > 1$ Hz).[19] There are few examples of such hydrogen bond across hydrogen bonds in the literature (notation is ${}^{nh}J_{XY}$) (Scheme 1). The coupling constants ${}^{3h}J_{PC}$ was observed also by us in 2003 (Scheme 1, figure on the left)[5] and confirmed by our theoretical and experimental work.[25–27] The coupling constants across intermolecular hydrogen bond C—H···O=P was found to be ${}^{2h}J_{PH} \sim 1$ and ${}^{3h}J_{PC} \sim 3$ Hz (Scheme 1).

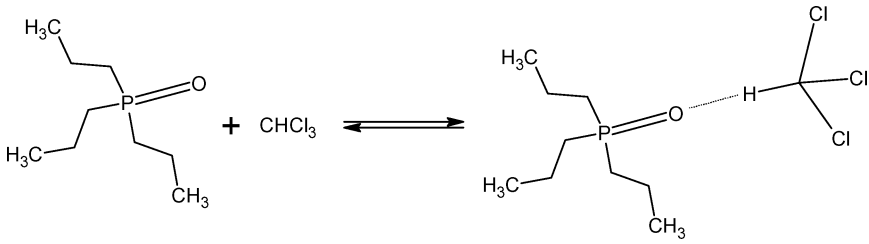


SCHEME 1

We have applied Sychrovsky's approach to calculate the corresponding coupling constant in the case of the interaction of TBPO with chloroform, and we have predicted it to be ${}^{2h}J_{PH} = -3.4$ Hz, ${}^{3h}J_{PC} = -11.9$ Hz. Based on this prediction, it should be observed in the NMR spectrum. We were however unable to observe it experimentally, probably due to the fact that the system is in fast dynamic equilibrium, too fast for the NMR coupling constant time scale. Most of the observed coupling constants across hydrogen bonds in the literature have been measured for relatively rigid systems such as a DNA double strand.

The calculated and measured chemical shift changes are, however, in good agreement and support our hypothesis on the hydrogen bond formation in the system Cl_3C—H···O=P(*n*-but)$_3$ system. The calculated chemical shift change of chloroform carbon atom was –5.0 ppm and

proton was 2.2 ppm and nicely corresponds to experimental values; –3.70 ppm for carbon and 2.05 ppm for proton (see the Experimental section).



SCHEME 2

EXPERIMENTAL

The studies on intermolecular interactions involving P=O· · ·H–C hydrogen bonds between chloroform and tributylophosphinoxid (TBPO) were measured in tetrachloromethane (Scheme 2). The chemical shift of chloroform signal in HNMR and CNMR were measured for various tributylophosphinoxide (0 to 3.3 mol/dm3) concentrations in tetrachloromethane (Table I). The NMR spectra were recorded on a Bruker Avance 300.13 MHz instrument, operating at 300.13 MHz (1H) and 75.46 MHz (13C) at room temperature. Water signal from 80% phosphorus acids and tetrachloromethane was used as external reference for proton and carbon NMR respectively. The complex constant formation as shown in (Scheme 2) was estimated according to the following equation:[17,18]

$$K = \frac{\Delta\delta}{(\Delta\delta_{CA} - \Delta\delta) \cdot \left([TBPO^o] - \frac{[CHCl_3^o]\Delta\delta}{\Delta\delta_{CA}}\right)}$$

Where $\Delta\delta$ is chemical shift of hydrogen or carbon atom of chloroform, $[TBPO^o]$ and $[CHCl_3^o]$ at initial concentration of TBPO and chloroform. $\Delta\delta_{CA} = (\Delta\delta_{AB} - \Delta\delta_A)$, stands for the difference in chemical shift between the completely complexed and uncomplexed molecule.

THEORETICAL METHODS AND COMPUTATIONAL DETAILS

Structures of TBPO, chloroform, dimer of TBPO, and complex TBPO with chloroform were optimized, and their NMR parameters were calculated using the density functional theory (DFT).[29] The DFT approach applied here utilizes Becke's three-parameter functional[30] with the

Vosko et al. local correlation part[31] and the Lee et al.[32] non-local part, abbreviated as B3LYP. The optimization was performed with standard base 6-31G(d,p) and single point calculated with tetrachloromethane solvent model CPCM. No symmetry constraints were imposed during the optimization process, and the structures were verified by frequency calculations. The interaction energy of complex was calculated as a difference of energy between substrate and products using basis set superposition error (BSSE) ($\Delta E_{TBPO.HCCl3} = E_{TBPO.HCCl3} - E_{TBPO} - E_{HCCl3}$). The NMR chemical shift and spin–spin coupling constants were calculated using coupled perturbated DFT method with B3LYP functional by including the diamagnetic spin-orbit, paramagnetic spin-orbit, Fermi-contact, and spin-dipolar terms.[19,33] We have used basis sets IGLO II for spin–spin coupling calculations.[34] We used the same bases and methods as Sychrovsky et al. did in their theoretical studies on spin–spin coupling constants across hydrogen bond P—O$\cdots$H—C.[19] All computations were carried out using the Gaussian 03 revision D01 suite of codes.[35]

CONCLUSIONS

The hydrogen bonds of the type C—H$\cdots$O=C are suggested to influence at least the secondary structure of proteins and peptides.[16] The hydrogen bonds C—H$\cdots$O=P are likely to have influence on the structure of the biomolecules containing phosphonate group. This weak hydrogen bond however can be measured by the NMR technique. We have observed intermolecular complex formation between chloroform and phosphine oxide, and we were able to evaluate the equilibrium based on the chemical shift change. The calculated chemical shift change of chloroform carbon atom was –5.0 ppm and proton was 2.2 ppm, which nicely corresponds to experimental values: –3.70 ppm for carbon and 2.05 ppm for proton. The coupling constant via the hydrogen bond between proton and phosphorus was theoretically predicted; however it can not be measured due to fast dynamic equilibrium. The calculated K in chloroform was 1.8 mol^{-1}or 2.8–3.2 mol^{-1} based on changes of the proton chemical shifts or carbon, respectively.

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