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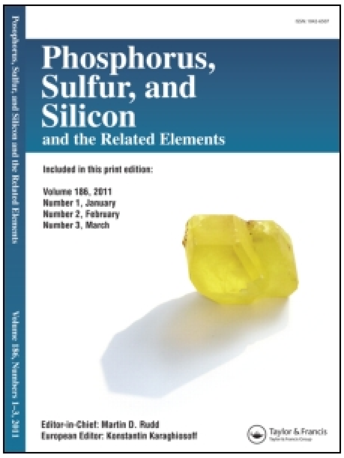

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Hydrogen Bonded Phosphate Rings

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HYDROGEN BONDED PHOSPHATE RINGS

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Abstract Reaction of phosphorus acids with imidazole and 1-methylimidazole leads to the formation of the hydrogen bonded salts, $[(PhO)_2PO_2][C_3H_3NHNMe]$ (**1**), $[(PhO)_2PO_2][C_3N_2H_5]$ (**2**), $[Cl_3CP(OH)O_2][C_3H_3NHNMe]{\bullet}H_2O$ (**3**), $[Cl_3CP(OH)O_2][C_3N_2H_5]{\bullet}H_2O$ (**4**), and $[PhP(OH)O_2][C_3N_2H_5]$ (**5**). X-ray analysis reveals that the structure of **1** consists of a hydrogen bonded ion pair, **2** forms hydrogen bonded chains while **3** and **4**, which exist as monohydrates, form more complex networks, each possessing twelve-membered hydrogen bonded rings involving alternately water molecules and PO_2 units of the phosphonate anion. A correlation is obtained between NH stretching frequency and N-H---X (X = O, N) hydrogen bond lengths defining strong to intermediate hydrogen bonds useful in refining models for enzyme-substrate interactions.

INTRODUCTION

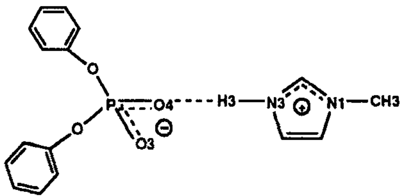
A study of hydrogen bonding possibilities between imidazoles and phosphates should prove useful in interpreting enzyme-substrate interactions occurring between active site residues and phosphoryl groups. X-ray analysis of active sites of phosphoryl transfer enzymes are hampered by the necessarily low resolution crystallographic studies encountered when dealing with large molecular systems, for example, ribonuclease action on uridylyl-(3',5')-adenosine[1] and staphylococcal nuclease action on thymidine 3',5'-bis(phosphate).[2] Recent X-ray work by Loll and Lattman[3] indicates the degree presently reached in structural refinement of the latter enzyme system, down to about 1.65Å.

The uncertainty in bond parameters accompanying protein crystallographic studies, especially for prevalent hydrogen bonds, may be reduced by obtaining a knowledge of the types of hydrogen bonds that form between important active site components and relatively simple phosphate molecules. The accuracy of the hydrogen bond parameters resulting from such studies reduces uncertainty by at least an order of magnitude and thus should prove useful as a basis for increasing refinement in the structural analysis of enzyme systems having these types of components.

Toward this end, we synthesized[4] a number of hydrogen bonded salts from the reaction of phosphorus acids with imidazole and 1-methylimidazole. These are $[(PhO)_2PO_2][C_3H_3NHNMe]$ (**1**), $[(PhO)_2PO_2][C_3N_2H_5]$ (**2**), $[Cl_3CP(OH)O_2][C_3H_3NHNMe]\bullet H_2O$ (**3**), $[Cl_3CP(OH)O_2][C_3N_2H_5]\bullet H_2O$ (**4**), and $[PhP(OH)O_2][C_3N_2H_5]$ (**5**). All were characterized by ^{1}H NMR and infrared spectroscopy and the X-ray structures of **1-4** were obtained.[4] A summary of these studies are presented here. The hydrogen bonds that form are of the types P-O---H-N and P-O---H-O either between the phosphoryl oxygen and imidazole hydrogen or between the phosphoryl oxygen and hydrogen of a water molecule. Other systems whose structures have been obtained by X-ray analysis[5-7] also involve these two types of hydrogen bonds.

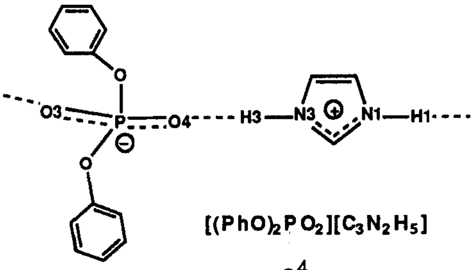
SOLID STATE STRUCTURES

Although **1** was very hygroscopic, it was isolated as an anhydrous substance as was **2**. However, **3** and **4** gave crystals suitable for X-ray studies only as monohydrated salts. The X-ray structures of **1-4** are illustrated schematically.



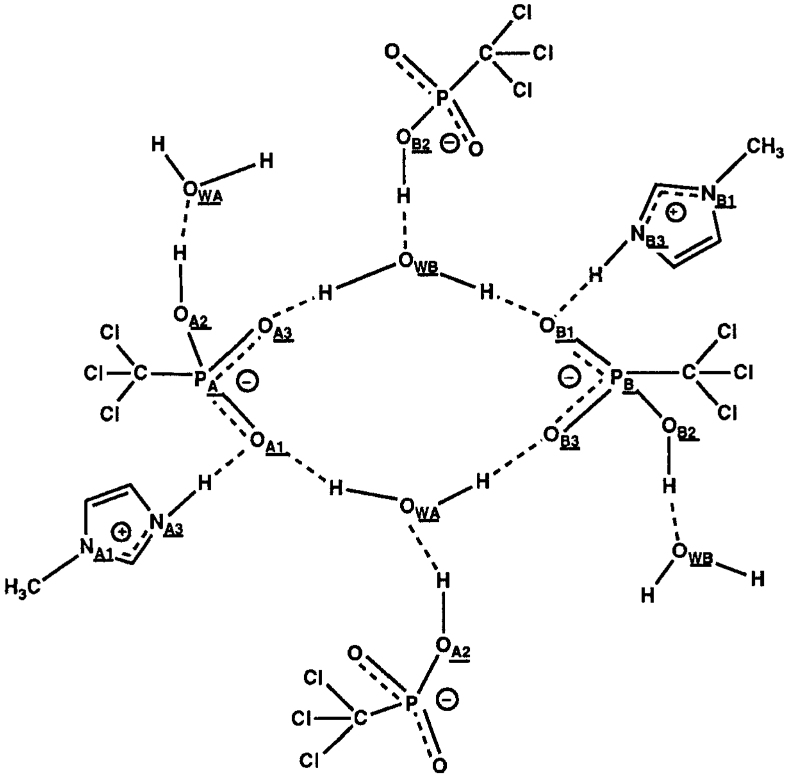
$[(PhO)_2PO_2][C_3H_3NHNMe]$

1[4] Ion pair



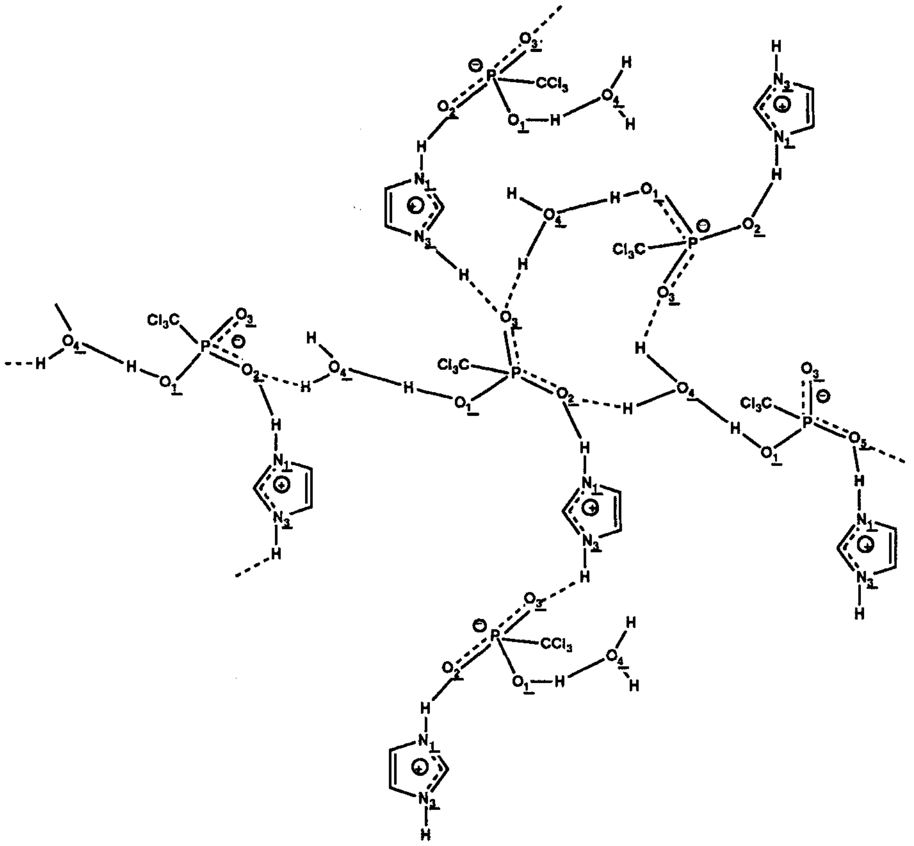
$[(PhO)_2PO_2][C_3N_2H_5]$

2^4 chain



$[Cl_3CP(OH)O_2][C_3H_3NHNMe]\bullet H_2O$

3^4



$[Cl_3CP(OH)O_2][C_3N_2H_5]\cdot H_2O$

4[4]

For **1** and **2**, N-H---O hydrogen bonding links the phosphate anion with the base cation forming a hydrogen bonded ion pair for **1** and hydrogen bonded chains for **2**. The same type of cation-anion interaction is found in **3** and **4** but, in addition, water molecules in these monohydrates provide additional hydrogen bonding possibilities, specifically with the phosphonate anions, that result in the formation of hydrogen bonded twelve-membered rings.

This preference of water molecules to hydrogen bond with phosphoryl oxygen atoms to the exclusion of hydrogen bonding to the imidazole units that are present, suggests that water molecules may specifically associate with phosphate substrates rather than histidine residues at active sites. For example, this observation is in line with enzymatic action in the staphylococcal nuclease-thymidine 3',5'-bis(phosphate)-Ca^{++} ion system where hydrolysis of the phosphate is proposed[2] to be initiated by a nearby water molecule. Its ready availability for such action may be a direct consequence of the strong hydrogen bonding interaction resulting as the substrate assumes its anionic character.

The hydrogen bonding scheme in **3** and **4** leads to polymeric networks that consist of two-dimensional hydrogen bonded networks. Details of these complex networks are given elsewhere.[4]

HYDROGEN BOND PARAMETERS

Table I summarizes hydrogen bond parameters of **1-4** that are useful for comparisons with similar data for related phosphorus compounds.[5-7] Ideally, the hydrogen bond length O---H should be used but accurate O---H values only result from neutron diffraction studies which are not available for the compounds we are discussing. For comparative purposes then, we use the A---O distances. These are more qualitative, especially if the A-H---O angles vary widely. For the data in Table I, the angle variation introduces a corresponding A---O distance variation of approximately 0.05Å, calculated by comparing the sum of the O---H and H-A X-ray lengths (column 2) with the A---O distance (column 3).

The shortest O---N distances reported so far for the O---H-N hydrogen bond system are found in the pyridinium salt of 2-hydroxyphenyl phenylphosphonate **6**[5] between the phosphonate O2 and pyridinium N atom, 2.600(5)Å, and in zwitterionic inosine cyclic 3',5'-monophosphate **7**[6] between the phosphate O2 atom and N7 atom of the base unit, 2.521(3)Å. The O---H hydrogen bonds, however, are equal within experimental uncertainty due to the different angles present. For **6**, the O---H-N system approaches linearity 172(5)° while the one in **7** has an angle of 149(3)°. A short O---N distance of 2.611Å reported for the O---H-N hydrogen bond in **8**[7] is not particularly informative since no angle was given.

TABLE I Bond parameters for hydrogen bonded phosphoryl groups.[4]

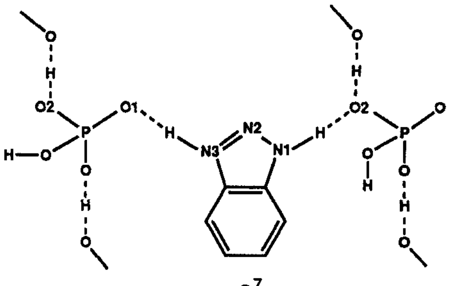
entry[a]	bond distance, Å[b]	A---O,[c] Å	A-H---O angle, deg.
1_1	O3=====P=====O4-------H3———N3 1.465(2) 1.485(2) 1.95(4) 0.71(4)	2.650(3)	169(4)
2_1	O3=====P=====O4--------H3———N3 1.479(2) 1.478(2) 1.78(4) 0.90(4)	2.647(3)	162(4)
2_2	O4=====P=====O3--------H1———N1 1.478(2) 1.479(2) 1.88(4) 0.79(4)	2.669(4)	133(1)
$3A_1$ [d]	OA1=====PA=====OA3--------HWB1———OWB 1.492(7) 1.483(6) 1.662(6) 1.010(7)	2.673	179.9(4)
$3A_2$	OA3=====PA=====OA1--------HW1———OWA 1.483(6) 1.492(7) 1.679(8) 1.058(1)	2.729	171.4(4)
$3A_3$	OA3=====PA=====OA1-------HNA3———NA3 1.483(6) 1.492(7) 1.758(6) 0.993(6)	2.751	177.3(8)
$3B_1$ [d]	OB1=====PB=====OB3-------HWA2———OWA 1.498(7) 1.472(6) 1.651(6) 1.046(7)	2.690	171.9(5)
$3B_2$	OB3=====PB=====OB1-------HWB2———OWB 1.472(6) 1.498(7) 1.839(8) 0.937(7)	2.731	158.3(6)
$3B_3$	OB3=====PB=====OB1-------HNB3———NB3 1.472(6) 1.498(7) 1.713(6) 1.007(7)	2.706	169.6(8)
4_1	O3=====P=====O2-------HN1———N1 1.482(3) 1.490(3) 1.871 0.900	2.737	160.8(3)
4_2	O3=====P=====O2-------HW1———O4 1.482(3) 1.490(3) 1.834 0.931	2.716	157.3
4_3	O2=====P=====O3-------HN3———N3 1.490(3) 1.482(3) 1.919 0.900	2.755	153.7
4_4	O2=====P=====O3-------HW2———O4 1.490(3) 1.482(3) 1.794 0.911	2.688	166.4

a. The subscript numbers are used only to refer to different entries for the same molecule.

b. The PO_2 unit has a negative charge.

c. A is the non-hydrogen atom (O or N) involved in the hydrogen bond interaction.

d. Two independent molecular assemblies per unit cell labeled A and B in the schematic drawing for 3.

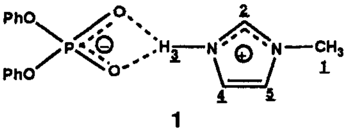


8^7

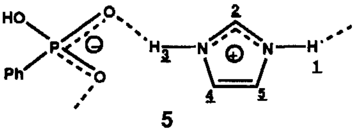
In one study,[8] short O---O lengths in O-H---O hydrogen bonds have been defined as those lying between 2.4-2.6Å. Based on this interpretation, since the Van der Waals' radius of N is 0.1Å greater than that of O, strong N-H---O hydrogen bonds would be expected to reside in the 2.5-2.7Å region which encompasses many of the values in Table I[4] and in earlier work.[5-7]

^{1}H NMR AND INFRARED MULL SPECTRA

Proton NMR dilution studies[4] on **1** and **5**, where the latter compound is assumed to have a polymeric arrangement similar to **4**, confirm the presence of hydrogen bonding in that all imidazole protons shift downfield on formation of the salts with H2 showing a greater downfield shift compared to H4 and H5. This is rationalized by the greater positive charge expected to reside on H2 in the hydrogen bonded imidazolium cation.



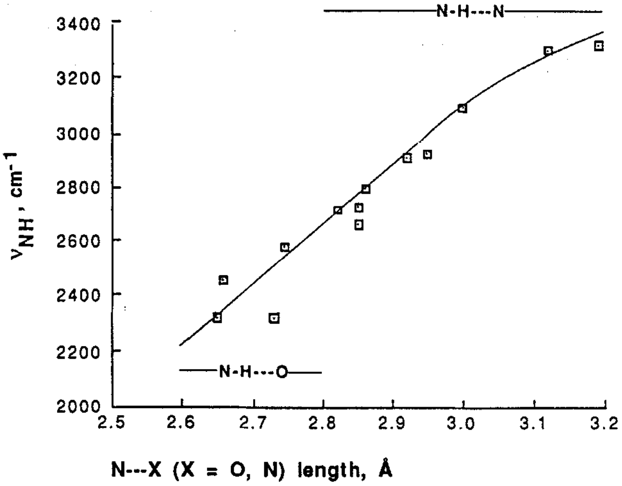
1



5

From this study, it was concluded that the ion pairs for **1** found in the X-ray study remained intact in solution, whereas the one dimensional structure postulated for **5** breaks up on dilution.

Analysis of Halocarbon grease mull and Nujol mull infrared spectra led to assignments of N-H absorptions that are likely associated with hydrogen bonded N-H---X stretching modes.[4] When coupled with bond distance data of Table I[4] and other literature values,[8] a relation is obtained showing a correlation between ν_{NH} stretching frequences and N---X (X = O, N) length for N-H---X hydrogen bonding (Figure).



In summary, the above correlation as well as the availability of accurate hydrogen bond parameters should prove useful in modeling studies of enzyme-substrate active site interactions.

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