
Research Article

Synthesis and spectroscopic study of a new diamidophosphoester, (4-CH₃-C₆H₄O)((CH₃)₂CHNH)₂P(O)

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ARTICLE INFO:Received:
11 July 2023Accepted:
12 September 2023Available online:
18 September 2023✉: F. Sabbaghi
Fahimeh_sabbaghi@yahoo.com**ABSTRACT**

A new diamidophosphoester, (4-CH₃-C₆H₄O)((CH₃)₂CHNH)₂P(O), was synthesized from the reaction of freshly prepared (4-CH₃-C₆H₄O)Cl₂P(O) reagent and isopropylamine (1:4 mole ratio) in dry CH₃CN. The prepared compound was characterized by IR, ¹H-NMR, ¹³C{¹H}-NMR and ³¹P{¹H}-NMR spectroscopies. Two methyl groups of the NHCH(CH₃)₂ moiety are magnetically non-equivalent and are revealed in different chemical shifts in the ¹H- and ¹³C-NMR spectra, but with equal hydrogen-hydrogen coupling constants in ¹H-NMR (³J(H,H) = 6.4 Hz for both) and phosphorus-carbon coupling constants in ¹³C-NMR (³J(P,C) = 5.7 Hz for both). The NH protons reveal a triplet with apparent coupling constant of 10.1 Hz (due to geminal phosphorus-hydrogen and vicinal hydrogen-hydrogen couplings). The *ipso* and *ortho* carbon atoms of the 4-CH₃-C₆H₄O moiety appear as doublets with ²J(P,C) = 6.5 Hz > ³J(P,C) = 4.8 Hz. In the IR spectrum, the NH stretching vibrations appear at 3281 cm⁻¹ and 3194 cm⁻¹. The phosphorus chemical shift of the title compound was compared with some literature compounds to show the electronic and anisotropic effects of substituents attached to phosphorus.

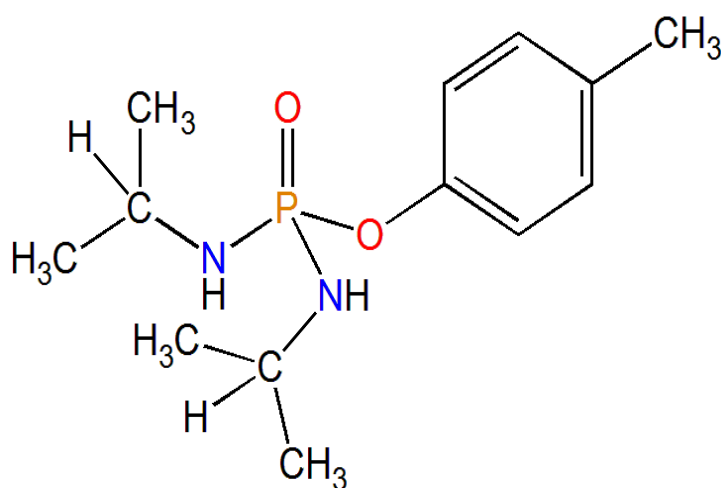
Keywords: Diamidophosphoester; NMR; Phosphorus-carbon coupling constant

1. Introduction

Extensive studies have been conducted on the biochemical properties of phosphoramidate derivatives, especially amidophosphoesters. Some of these compounds act as inhibitors of the acetylcholinesterase enzyme that controls the nervous systems of insects and mammals. Thus, their applications in the preparation of pesticides, insecticides and nerve drugs were investigated [1].

Nuclear magnetic resonance (NMR) is a beneficial technique to study of organophosphorus compounds, due to the existence of NMR-active nuclei (^{31}P , ^1H , ^{13}C). NMR spin-spin coupling constants are used in the assignment of signals, analysis related to conformation/configuration and stereochemistry, and provide knowledge about the nature of chemical bonds [2–4].

In this research, the synthesis and spectroscopic characterization of a new diamidophosphoester, $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})((\text{CH}_3)_2\text{CHNH})_2\text{P}(\text{O})$ (Scheme 1), are investigated. Some topics related to the phosphorus chemical shifts and phosphorus-hydrogen/phosphorus-carbon coupling constants were issued.



Scheme 1. Chemical structure of $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})((\text{CH}_3)_2\text{CHNH})_2\text{P}(\text{O})$.

2. Experimental

2.1. Synthesis and Identification

The liquid phosphorus-chlorine reagent, (4-CH₃-C₆H₄O)Cl₂P(O), was obtained from stirring P(O)Cl₃ and 4-CH₃-C₆H₄OH (3:1 mole ratio) in a reflux condition for 9 hours and then removing the excess P(O)Cl₃ under a reduced pressure distillation. To a solution of (4-CH₃-C₆H₄O)Cl₂P(O) in dry CH₃CN, a solution of isopropylamine in the same solvent (1:4 mole ratio) was added dropwise and stirred for 4 hours. The initial temperature to start the reaction is 0 °C (ice-bath) which warms to room temperature during the reaction time. After removing the solvent (under a vacuum), the resulting solid was washed with distilled water to separate the (CH₃)₂CHNH₃Cl salt. The product was dried in the air, and the solid substance was re-crystallized in a mixture of chloroform and normal hexane. IR (KBr, cm⁻¹): 3281 (NH), 3194 (NH), 2965, 1612, 1512, 1473, 1448, 1420, 1381, 1240 (P=O), 1199, 1169, 1142, 1107, 1071, 1017, 923 (P—N), 819 (P—N), 691, 644, 571, 498, 437; ¹H-NMR (500.13 MHz, DMSO-d₆, 300.0 K, TMS): δ = 1.04 (*d*, ³*J*(H,H) = 6.4 Hz, 6H, CH₃), 1.05 (*d*, ³*J*(H,H) = 6.4 Hz, 6H, CH₃), 2.24 (*s*, 3H, CH₃), 3.26 (*m*, 2H, CH), 4.44 (*t*, ²*J*(P,H) & ³*J*(H,H) = 10.1 Hz, 2H, NH), 7.06 (*d*, ³*J*(H,H) = 8.6 Hz, 2H, Ar-H), 7.09 (*d*, ³*J*(H,H) = 8.6 Hz, 2H, Ar-H); ¹³C{¹H}-NMR (125.76 MHz, DMSO-d₆, 300.0 K, TMS): δ = 20.21 (*s*, *p*-CH₃), 24.95 (*d*, ³*J*(P,C) = 5.7 Hz, CH₃), 25.07 (*d*, ³*J*(P,C) = 5.7 Hz, CH₃), 42.76 (*s*), 120.07 (*d*, ³*J*(P,C) = 4.8 Hz, C_{ortho}), 129.46 (*s*), 132.05 (*s*), 149.72 (*d*, ²*J*(P,C) = 6.5 Hz, C_{ipso}); ³¹P{¹H}-NMR (202.46 MHz, DMSO-d₆, 300.0 K, H₃PO₄ external): δ = 10.39 (*s*).

3. Results and discussion

3.1. NMR spectroscopy

The phosphorus signal (in ³¹P{¹H} NMR spectrum) of the title compound appears as a singlet at 10.39 ppm (Figure 1). For a comparison, the phosphorus chemical shifts of some

analogous compounds are given in Table 1.

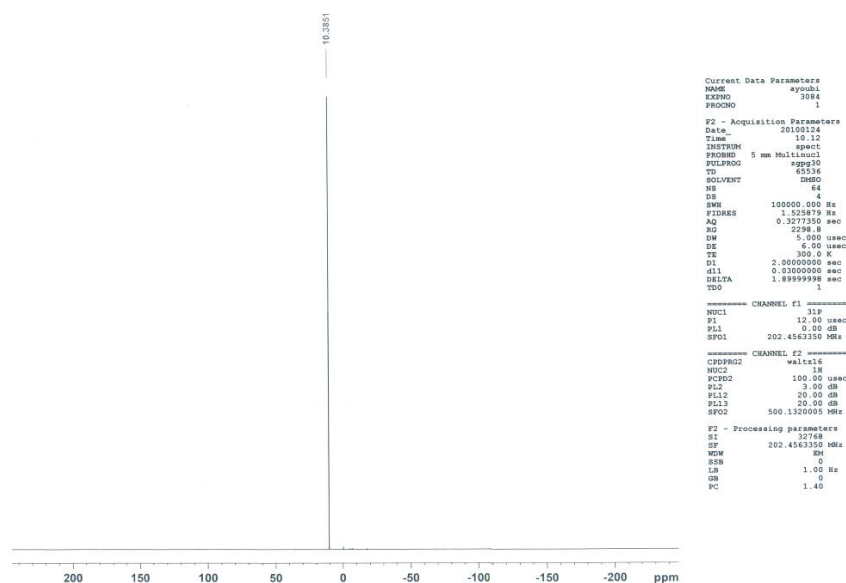


Fig. 1. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})((\text{CH}_3)_2\text{CHNH})_2\text{P}(\text{O})$ in DMSO-d_6 .

The amidophosphoester given as entry 2 (with the $4\text{-Cl-C}_6\text{H}_4\text{O}$ moiety) shows a higher value of phosphorus chemical shift with respect to the title compound. The entries 3 and 4 differ by the $(\text{CH}_3)_2\text{CHNH}/(\text{CH}_3)_3\text{CNH}$ groups, and the amidophosphoester with a $(\text{CH}_3)_3\text{CNH}$ group shows the lower value of chemical shift (10.71 ppm) in comparison to the other (13.70 ppm) (due to a higher electron-donation of $(\text{CH}_3)_3\text{CNH}$). The chemical shift near to zero for entry 5 or negative chemical shift for entry 6 (with three aromatic groups) can be attributed to the magnetic anisotropy effect of the arene rings.

Table 1. Phosphorus-31 chemical shifts of some phosphoryl-based compounds.

Entry	Compound	Chemical shift (ppm)	Ref.
1	(4-CH ₃ -C ₆ H ₄ O)((CH ₃) ₂ CHNH) ₂ P(O)	10.39 (DMSO-d ₆)	Title compound
2	(4-Cl-C ₆ H ₄ O)((C ₆ H ₁₁)(CH ₃)N) ₂ P(O)	15.07 (DMSO-d ₆)	[5]
3	(4-CH ₃ -C ₆ H ₄ O)((CH ₃) ₂ CHNH)((CH ₃) ₂ N)P(O)	13.70 (CDCl ₃)	[6]
4	(4-CH ₃ -C ₆ H ₄ O)((CH ₃) ₃ CNH)((CH ₃) ₂ N)P(O)	10.71 (CDCl ₃)	[6]
5	(4-CH ₃ -C ₆ H ₄ O)(4-CH ₃ -C ₆ H ₄ NH) ₂ P(O)	1.23 (CDCl ₃)	[7]
6	(C ₆ H ₅ O) ₂ (4-CH ₃ -C ₆ H ₄ CH-R-(+)(CH ₃)NH)P(O)	-0.71 (DMSO-d ₆)	[8]
7	(C ₆ H ₅ O) ₂ ((C ₆ H ₅)CH-R-(+)(C ₂ H ₅)NH)P(O)	-2.16 (CDCl ₃)	[9]
8	(C ₆ H ₅) ₂ ((C ₆ H ₅)CH-R-(+)(C ₂ H ₅)NH)P(O)	21.13 (DMSO-d ₆)	[9]

The anisotropic effect of arene rings is explained by the comparison of phosphorus chemical shifts of two typical compounds belonging to the amidophosphodiester and phosphinamide families (entries 7 and 8). In (C₆H₅O)₂((C₆H₅)CH-R-(+)(C₂H₅)NH)P(O) and (C₆H₅)₂((C₆H₅)CH-R-(+)(C₂H₅)NH)P(O) pair, the phosphorus signals appear at -2.16 and 21.13 ppm, respectively. The high difference of phosphorus chemical shifts is related to ring currents and anisotropic effects of two phenyl rings on phosphorus nuclei. In (C₆H₅O)₂((C₆H₅)CH-R-(+)(C₂H₅)NH)P(O), the phosphorus atom is separated by ester oxygen atoms from arene rings which allows displacing it towards the zone where more magnetic field is needed (symbol (+) in Figure 2). In (C₆H₅)₂((C₆H₅)CH-R-(+)(C₂H₅)NH)P(O), the phosphorus is directly bonded to the rings and located in the zone specified with (-) symbols; in this region, a higher chemical shift is expected as observed. In the structure of (C₆H₅O)₂((C₆H₅)CH-R-(+)(C₂H₅)NH)P(O), the two ester oxygen atoms are placed in the region shown with (-) symbols (Figure 2). In the title compound and the

analogous compounds given as entries 2, 3 and 4, one arene ring exists and this effect is lower than the compounds given in entries 5, 6 and 7.

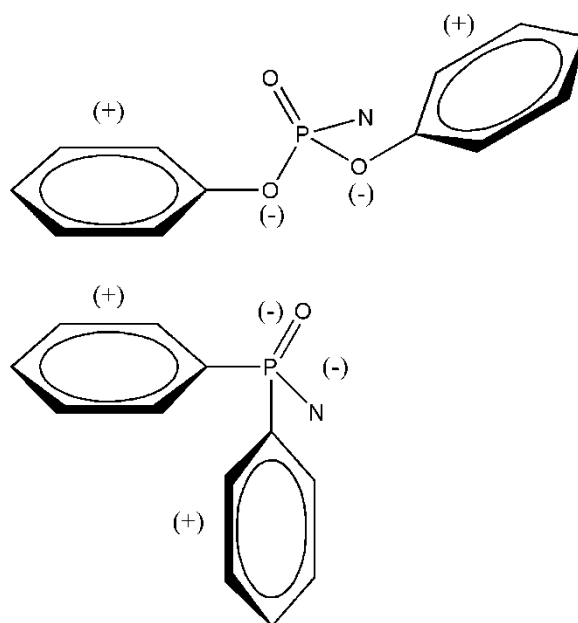


Fig. 2. The symbols (+) and (–) respectively denote to the zones where more and less magnetic fields are needed. Only the N atom of the amine moiety was drawn.

In the $^1\text{H-NMR}$ spectrum of the title compound, two mixed doublet signals are observed for the two methyl groups of the $\text{CH}(\text{CH}_3)_2$ fragment (Figure 3). The evaluation of coupling constants for these two methyl groups is done by considering the lines 1 & 3 for one doublet and 2 & 4 for the other doublet (the chemical shifts of these lines with three integers after points are 1.038/1.051 ppm and 1.042/1.054 ppm, respectively), yielded a $^3J(\text{H,H}) = 6.4$ Hz for both signals. This assignment was done by considering the estimated $^3J(\text{H,H})$ coupling constant of the multiplet at 3.26 ppm which is equal to the coupling constants of these doublets (as they are coupled with each other). The singlet at 2.24 ppm associates to the CH_3 group of the $4\text{-CH}_3\text{-C}_6\text{H}_4\text{O}$ fragment. The $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})\text{Cl}_2\text{P}(\text{O})$ reagent shows a doublet for the CH_3 group, due to the long-range coupling of phosphorus-hydrogen with seven bonds separation [10]. Substitution of chlorine atoms with amines reduces the coupling constant value of $^7J(\text{P,H})$ to 0.0 Hz.

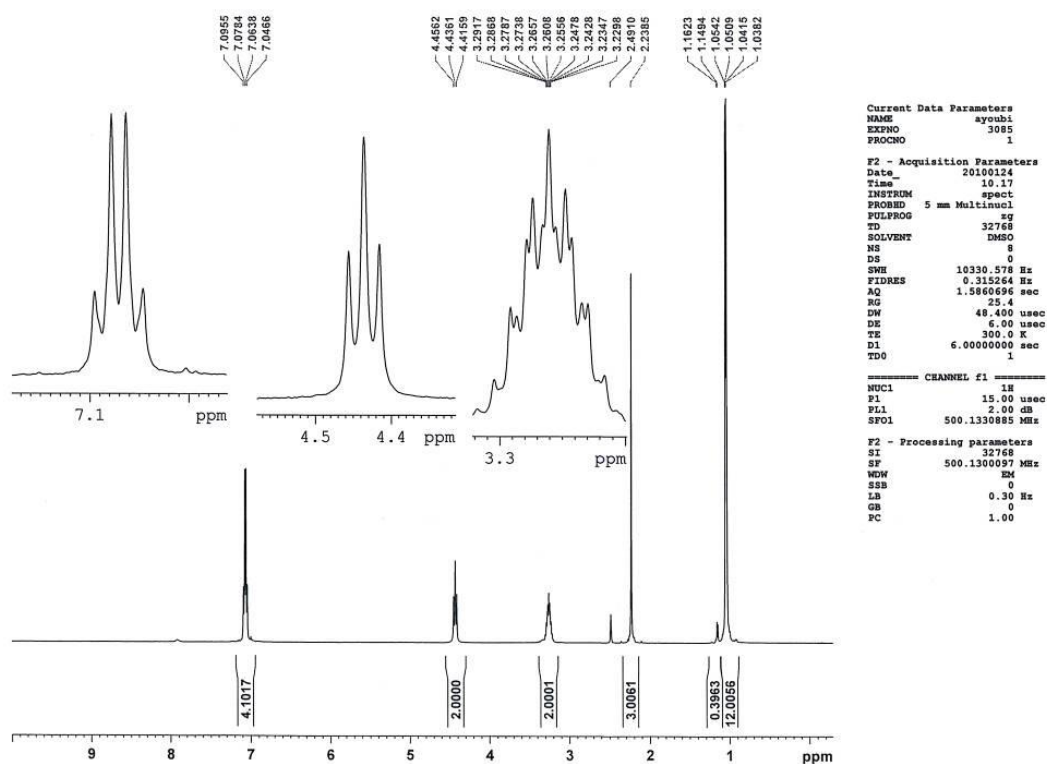


Fig. 3. ^1H -NMR spectrum of $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})((\text{CH}_3)_2\text{CHNH})_2\text{P}(\text{O})$ in DMSO-d_6 .

In the ^{13}C -NMR spectrum, two doublets at 24.95 and 25.07 ppm associate to the methyl carbons of the isopropyl fragment with $^3J(\text{P},\text{C})$ equal to 5.7 Hz for both (Figure 4). The doublets at 149.72 ppm ($^2J(\text{P},\text{C}) = 6.5$ Hz) and at 120.07 ppm ($^3J(\text{P},\text{C}) = 4.8$ Hz) are related to the *ipso* and *ortho* carbon atoms of the $4\text{-CH}_3\text{-C}_6\text{H}_4\text{O}$ moiety. The values are in the region for analogous compounds, typically the doublets at 119.94 ppm and 150.07 ppm in the ^{13}C -NMR of $(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{O})\text{NC}_4\text{H}_8\text{NP}(\text{O})(\text{OC}_6\text{H}_5)_2$ show $^3J = 4.7$ Hz and $^2J = 6.4$ Hz [11].

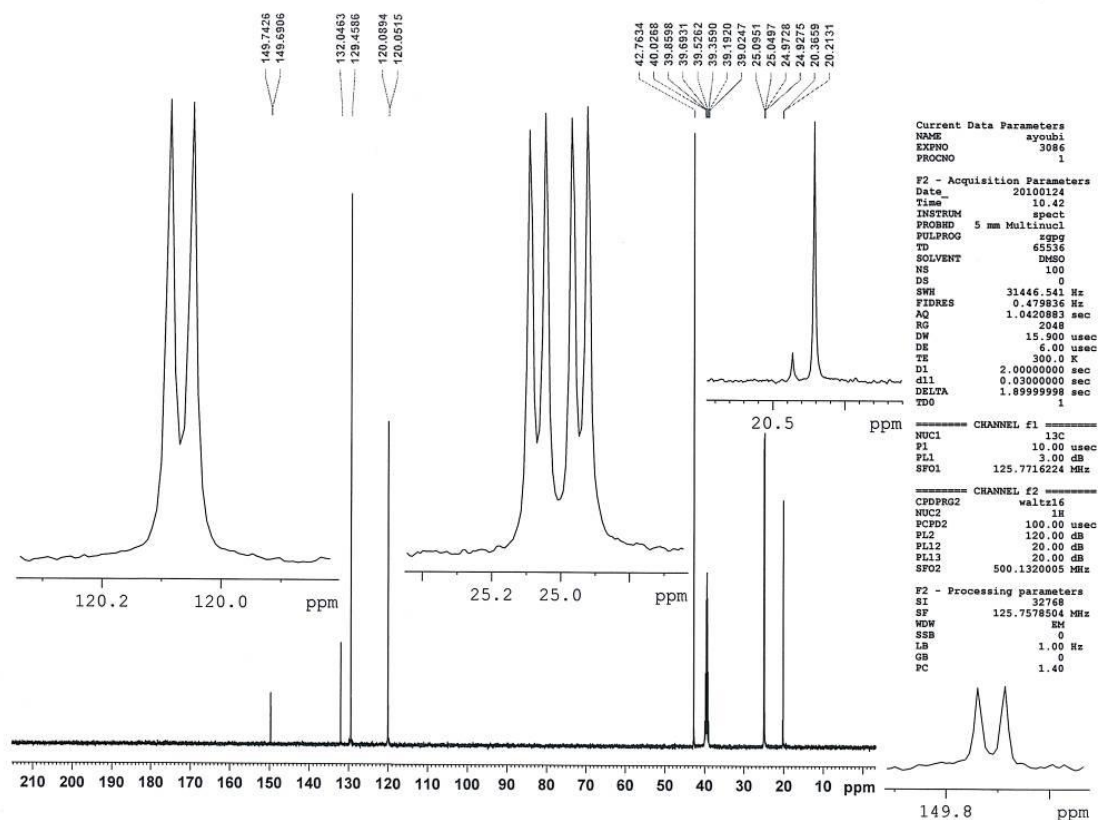


Fig. 4. $^{13}\text{C}\{^1\text{H}\}$ -NMR spectrum of $(4\text{-CH}_3\text{-C}_6\text{H}_4\text{O})((\text{CH}_3)_2\text{CHNH})_2\text{P}(\text{O})$ in DMSO-d_6 .

3.2. Infrared spectroscopy

The band centered at 3281 cm^{-1} and 3194 cm^{-1} associate to the NH stretching vibrations, and the bands at 1240 cm^{-1} and $923/819\text{ cm}^{-1}$ are assigned to the $\text{P}=\text{O}$ and $\text{P}-\text{N}$ vibrations, respectively (Figure 5).

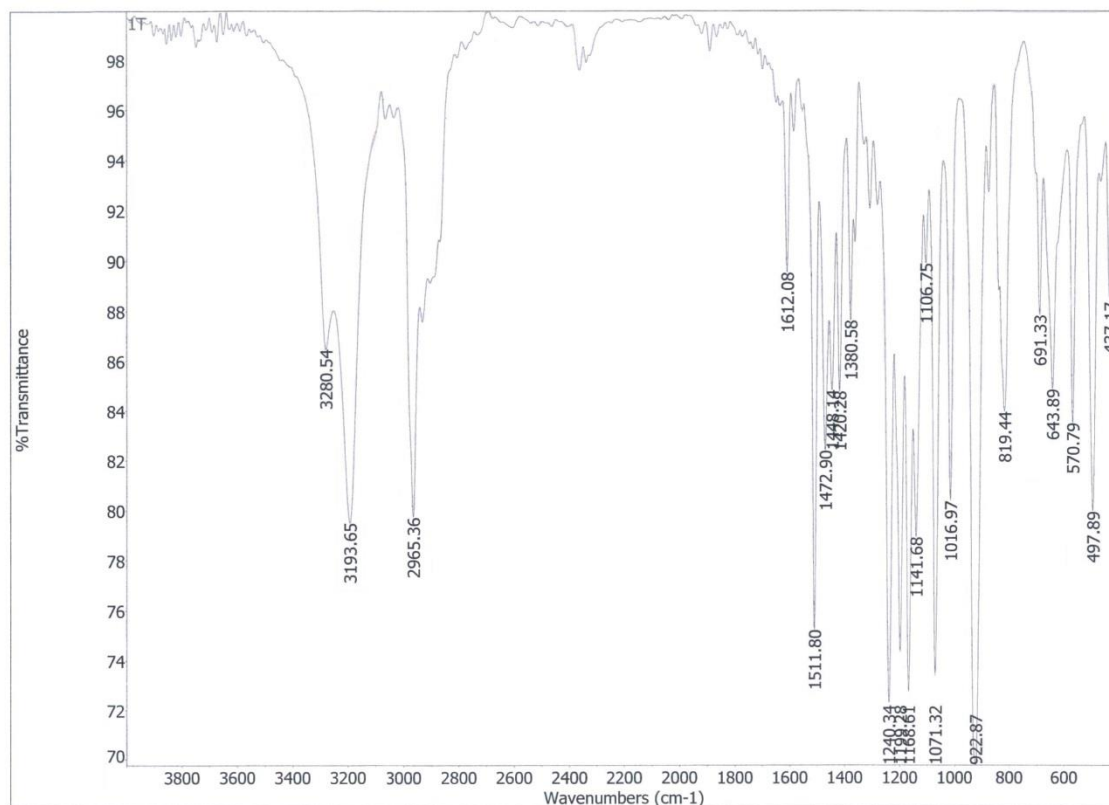


Fig. 5. IR spectrum of (4-CH₃-C₆H₄O)((CH₃)₂CHNH)₂P(O) (KBr).

4. Conclusion

In the (4-CH₃-C₆H₄O)((CH₃)₂CHNH)₂P(O) diamidophosphoester, the CH₃ groups of the NHCH(CH₃)₂ fragment are magnetically non-equivalent but show the equal phosphorus-carbon coupling constant (³*J*) in the ¹³C-NMR spectrum. The carbon atom of the CH unit in this fragment does not show coupling with phosphorus. The (4-CH₃-C₆H₄O)P(O) moiety shows two doublets for *ipso*- and *ortho*-carbon atoms, with ²*J*(P,C) > ³*J*(P,C). The long-range coupling constant (⁷*J*(P,H)) reported for the starting material, (4-CH₃-C₆H₄O)Cl₂P(O), is not seen in the title compound.

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