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1,2-Bis[bis(methoxyethyl)phosphino]ethane, 1,2-bis[bis(methoxypropyl)phosphino]ethane and their quarternary salts. Unexpected hydrolytic susceptibility of the ethanediylbis[bis(methoxyethyl)phosphonium]-PH,P'H' cation

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Abstract

The syntheses, properties and NMR data of ether substituted diphosphines, 1,2-bis[bis(methoxyethyl)phosphino]ethane (**1a**) (tmepe), 1,2-bis[bis(methoxypropyl)phosphino]ethane (**2a**) (tpepe) and their quarternary salts, $[tmepeH_2]$ $(HSO_4)_2$ (**1b**) and $[tpepeH_2]Cl_2$ (**2b**), are described. The unique role of the phosphonium proton in **1b** hydrolytic unstability is discussed.

1. Introduction

Phosphines are excellent ligands for transition metals and their complexes are being widely investigated and used as exceptionally effective homogeneous catalysts in many chemical processes [1]. Recently, some phosphine complexes of ^{99m}Tc have been extensively investigated as very promissive radiopharmaceuticals [2,8]. The effectiveness of these biologically active complexes strongly depends on their lypophilicity and hydrophilicity. For that purpose, we have synthesized and characterized diphosphines substituted with etheral groups, **1a** (tmepe) and **2a** (tpepe) and their quarternary phosphonium salts, **1b** $\{[tmepeH_2](HSO_4)_2\}$ and **2b** $\{[tpepeH_2]Cl_2\}$.

2. Results and discussion

1,2-Bis[bis(methoxypropyl)phosphino]ethane, (tpepe), was prepared in the reaction between 1,2-bis (dichlorophosphino)ethane and an excess of Grignard reagent, 3-methoxypropylmagnesium chloride. The other, 1,2-bis[bis(methoxyethyl)phosphino]ethane, (tmepe), could not be prepared in the same way because the proper Grignard reagent could not be obtained [3]. The diphosphine was synthesized by free radical promoted addition of a carbon–carbon double bond to the P–H moiety [4]. The reaction between 1,2-bis(phosphino)ethane and methyl vinyl ether in the presence of 2,2-azobis(2-methylpropionitrile) (AIBN) gave more than 70% yield of the pure tmepe. Both diphosphines are colorless, malodorous, highly viscous oils which undergo very fast oxidation when exposed to air. Sealed under an inert gas, they decompose after a few weeks. The dihydrochloride of tpepe, obtained by saturation of a benzene or toluene solution of the diphosphine with gaseous HCl, is a colourless, thick oil which crystallizes below 0°C. When saturation is sustained for a longer period, the weight of the product increases to 16% more than expected for two stoichiometric HCl particles per diphosphine molecule, which is equal to another two HCl particles attached to the diphosphine. Whereas **2b** is very stable and well resistant to oxidation, the same salt of tmepe cannot be

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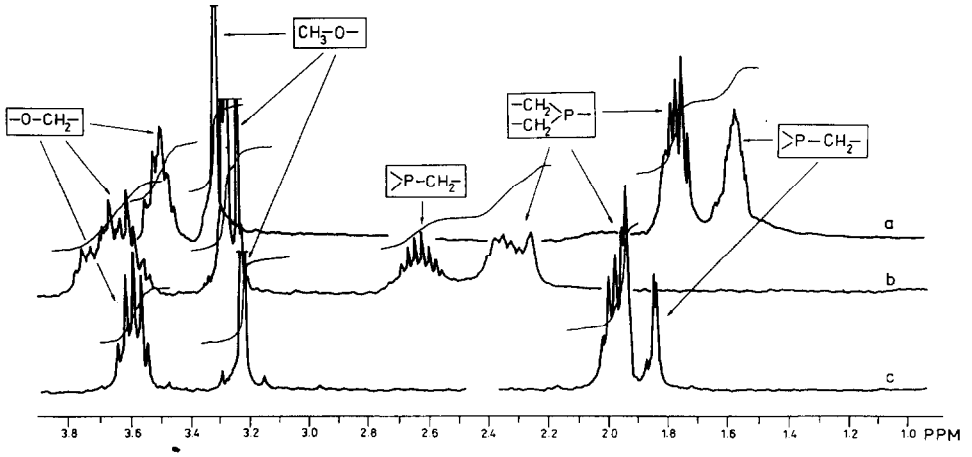

Fig. 1. ^{1}H NMR spectra: (a) tmepe; (b) $[tmepeH_2](HSO_4)_2$; (c) $tmepeO_2$ (a DMSO-d_6 signal is omitted).

isolated. When passing dry HCl through a solution (benzene, toluene or diethyl ether) of tmepe, a gluey, white, polymer-like solid is formed which is unsoluble in any kind of solvent. This polymer treated with a methanolic solution of potassium carbonate resulted in only about 20% of initial diphosphine. The remaining white solid was mainly hydroxyethyl-substituted diphosphine dioxide. Sulphuric acid formed the same type of polymer when used even in a slight excess. However, the desired compound, the dihydrosulphuric salt of tmepe, was finally prepared by treating, in rigorously unaerobic conditions, a cooled solution of **1a** in acetone with a diluted, deaerated acetone solution of a stoichiometrical amount of sulphuric acid. For analytical measurements, **1b** was purified by fast crystallization from methylene chloride. Both salts can be used directly for complex syntheses as they are easily convertible into neutral bases in elevated pH. Whereas free diphosphines, **1a** and **2a**, are extremely sensitive to air and thermodynamically unstable, their salts, **1b** and **2b**, are quite stable, oxygen resistant, well soluble in water, alcohols and moderately soluble in chlorinated alkanes. FAB-MS spectra of free bases are abundant in peaks of fragmentation and except for the molecular ion peaks, contain two other significant peaks relative to mono- and dioxides being formed in the spectrometer's ion beam. Spectra of the salts show only the molecular ion peaks without those of fragmentation and oxides.

Amongst the compounds' properties, one spectacular difference is observed: the totally opposite behaviour of salts **1b** and **2b** in acidic media. The salt $[tpepeH_2]Cl_2$ is very stable in acidic conditions whereas $[tmepeH_2](HSO_4)_2$ undergoes rapid acidic hydrolysis. This was the reason for the failure of the isolation of the tmepe hydrochloride by means of gaseous HCl. The source of this difference in the chemical behaviour of diphosphonium salts seems to be their molecular structure, namely the length of the carbon atom chain in etheral substituents. The substituent of tmepe, $CH_3OCH_2CH_2-$, is known to be very susceptible to β-elimination rearrangement. For example, the Grignard reagent $CH_3OCH_2CH_2MgCl(Br)$ is not observed [3] while CH_3OCH_2MgCl [3,5] and $CH_3OCH_2CH_2CH_2MgCl$ are stable. But in the case in question, this fact does not seem to be the main reason and should be considered together with an influence made by the phosphonium proton. Compounds with the $CH_3OCH_2CH_2-$ fragment, diphosphine dioxide $tmepeO_2$, as well as its transition metal complex $(tmepeO_2)MoO_2Cl_2$ are very resistant to acidic hydrolysis [6].

^{1}H NMR spectra of the diphosphines and their quarternary salts (Figs. 1 and 2) show the strong influence that the phosphonium proton has on molecules of

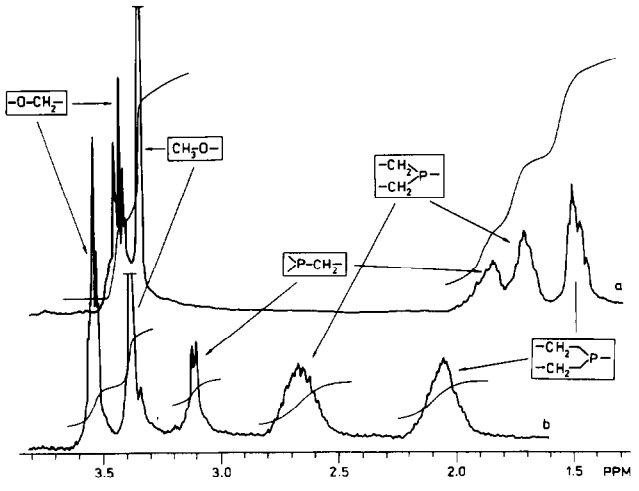

Fig. 2. ^{1}H NMR spectra: (a) tpepe; (b) $[tpepeH_2]Cl_2$.

both diphosphines. Their protonation causes remarkable downfield shifts and hyperfine structure changes in signals belonging to the protons adjacent to the phosphorus atoms. That fact could be assigned to the phosphorus atom hybridization change from p^3 type in diphosphines to sp^3 type in their quarternary salts [7]. But the character of the phosphonium protons is different in each phosphonium salt. In the tmepeH_2^{2+} cation, signals of protons adjacent to the oxygen atoms are strongly affected by the phosphonium proton and show very complicated structures (Fig. 1(b)). In contrast, there are no notable changes in the structures of related proton signals of the tpepeH_2^{2+} cation (Fig. 2(b)) and small differences are a result rather of the imperfect shape of the salt's spectrum than real interactions. Other spectra for related monophosphine and its salt, $(CH_3OCH_2CH_2CH_2)_3P$ and $[(CH_3OCH_2CH_2CH_2)_3PH]Cl$, respectively, show the same range of shifts and identical structure of CH_3–O– and –O–CH_2– proton signals for the free phosphine and the salt [8].

Moreover, ^{31}P NMR spectra (Fig. 3) give further evidence of the difference between the phosphonium protons of each salt. While in the spectrum of **2b** the phosphorus atom signal is split into a doublet with coupling constants $^1J(P-H) = 520.3$ Hz, a range characteristic for protonated tertiary phosphines [7], the spectrum of **1b** shows one unresolved, broad complex signal. On the basis of the structural data obtained for MoO_2Cl_2 (tmepeO_2) [6] and taking a common P–H bond length of 1.41 (2) Å [9], we tried to choose a

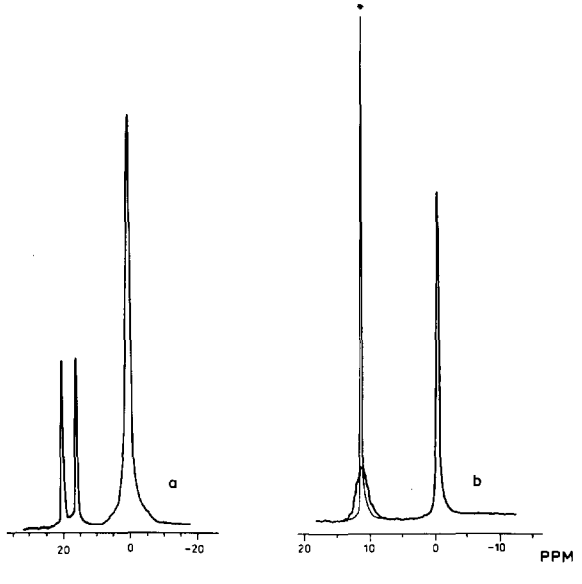

Fig. 3. ^{31}P NMR spectra: (a) [tpepeH_2]Cl_2; (b) [tmepeH_2]$(HSO_4)_2$; the signal marked with an asterix is a decoupled spectrum.

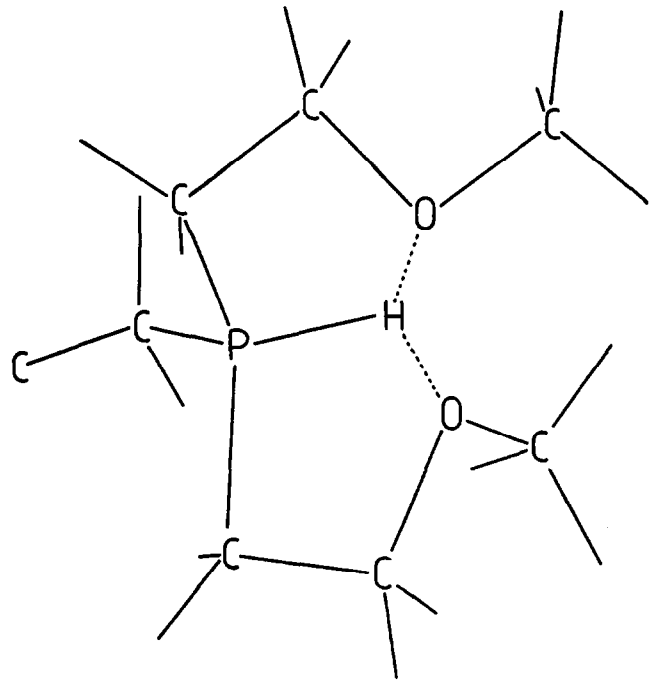

Fig. 4. Phosphonium proton position in [tmepeH_2]$(HSO_4)_2$ (half a cation is presented).

model for the most stable conformation of the **1b** molecule. Such a model has been computed [10] and one projection of the molecule is shown in Fig. 4. As can be seen, the phosphonium proton is suitably oriented to form hydrogen bonds with two acceptor atoms of oxygen. This type of system, called a bifurcated hydrogen bond, has been well investigated and occurs quite frequently [11]. This model is in good agreement with the spectroscopic data for [tmepeH_2] $(HSO_4)_2$. Remarkable changes in the hyperfine structure of CH_3–O– and –O–CH_2– proton signals can be assigned to a direct interaction of the phosphonium proton and oxygen atoms. The phosphonium proton vibrational movement (a proton chemical exchange) between three acceptors, two oxygen and one phosphorus atom, is reflected in a dramatic reduction in the P–H coupling constant, a phenomenon characteristic for hydrogen bond systems [12]. Bifurcated hydrogen bond systems are usually very dynamic and intervibrational interactions have an influence on the nature of the X–H bond [11]; in this case, P–H.

IR measurements show that ν(P–H) stretching vibration in **1b** is about 100 cm^{-1} lower than in **2b** for which the bifurcated hydrogen bond model is not energetically favoured. In fact, no spectroscopic data provide proof for such a system in [tpepeH_2]Cl_2. On the other hand, the phosphonium proton interaction with oxygen atoms activates oxygen–carbon bonds and it

may cause the etheral substituent to be very sensitive to acidic hydrolysis. When the salt is oxidized into dioxide, such activation no longer exists and the substituent becomes inert toward hydrolysis. The hyperfine structure of the ^1H NMR spectrum simplifies and becomes very similar to that of free diphosphine (Fig. 1(c)). As far as **2b** is concerned, there is no interaction between the phosphonium proton and protons of CH_3–O– and –O–CH_2– fragments and oxygen–carbon bonds are not sensitive to cleavage so that the salt is stable in acidic conditions. Moreover, one **2b** molecule can fix another two HCl molecules, most probably because of hydrogen bond formation between those additional HCl protons and etheral oxygen atoms.

3. Experimental section

3-Methoxy-1-chloropropane [13], the relative Grignard reagent [14] and 1,2-bis(phosphino)ethane [15] were obtained according to the literature methods. 1,2-Bis(dichlorophosphino)ethane and methyl vinyl ether were purchased from Aldrich Co. 2,2-Azobis(2-methylpropionitrile) (AIBN) was purchased from Alfa Products (Morton Thiokol). Fast atom bombardment mass spectra (FAB-MS) were recorded using *m*-nitrobenzyl alcohol and glycerol matrixes on a VG 30-250 spectrometer (VG Instrument Inc.) at the probe temperature. ^1H and ^{31}P NMR spectra were run on 300-MHz Nicolet, Varian VRX 300 and Jeol 100FT spectrometers. IR spectra were recorded with Perkin-Elmer 599 and 621 spectrometers. All syntheses were carried in a dry and oxygen-free atmosphere in an argon/nitrogen vacuum line.

3.1. 1,2-Bis[bis(methoxyethyl)phosphino]ethane (tmepe) (1a), $(CH_3OCH_2CH_2)_2PCH_2CH_2P(CH_2CH_2OCH_3)_2$

1,2-Bis(phosphino)ethane, $H_2PCH_2CH_2PH_2$, (1.267 g, 13.48 mmol) dissolved in 20 ml of heptane and 1.363 g (8.18 mmol) of AIBN were placed under nitrogen in a heavy-walled, high pressure reactor. The reactor was cooled in a dry ice/acetone bath and 10 ml (226.6 mmole) of vinyl methyl ether were then condensed into it. The vessel was sealed tightly, put into a bath and heated at 80°C for 2 h, then cooled down over the next 2 h. The solvent was evaporated off and the phosphine, a viscous, colourless liquid, was distilled through a short Vigreaux column at 140–145°C/0.24 mmHg. Yield: 3.120 g (9.57 mmol), 71%. FAB-MS (positive ion mode) spectrum shows a molecular ion at 327 Da (M + 1). ^1H NMR($CDCl_3$, TMS): δ 1.58 (m, 2H, PCH_2CH_2P); 1.73–1.83 (m, 4H, $CH_3OCH_2CH_2P$); 3.33 (s, 6H, $CH_3OCH_2CH_2$); 3.46–3.56 (m, 4H, $CH_3OCH_2CH_2$) ppm. ^{31}P NMR ($CDCl_3$, H_3PO_4): δ −32.33 ppm.

3.2. $[(CH_3OCH_2CH_2)_2P(H)CH_2CH_2P(H)(CH_2CH_2OCH_3)_2]^{2+}2HSO_4^-$ (1b)

The resulting amount of the diphosphine was dissolved in 5 ml of dry and deaerated acetone and cooled in an ice bath. To this solution, a mixture consisting of 1.913 g (98%) of sulphuric acid and 10 ml of acetone was added dropwise with stirring. A white powder of the salt separated, acetone was removed by syringe and the solid was washed twice with 2-ml portions of acetone. The compound was recrystallized from a small amount of methylene chloride and dried in *vacuo* at room temperature. The recovery was 90%. ^1H NMR (D_2O, HMDS): δ 2.20–2.40 (m, 4H, $CH_3OCH_2CH_2$); 2.55–2.80 (m, 2H, PCH_2CH_2P); 3.20–3.35 (m, 6H, $CH_3OCH_2CH_2$); 3.50–3.80 (m, 4H, $CH_3OCH_2CH_2$) ppm. ^{31}P NMR (CH_3OD, H_3PO_4): δ 11.45 ppm (singlet for decoupled, unresolved multiplet for undecoupled spectrum) [16*]. IR: ν(P–H) 2340 cm^{-1} (KBr disc).

3.3. 1,2-Bis[bis(methoxypropyl)phosphino]ethane (tpepe) (2a), $(CH_3OCH_2CH_2CH_2)_2PCH_2CH_2P(CH_2CH_2CH_2OCH_3)_2$

To a cooled (in an ice bath) and vigorously stirred solution of Grignard reagent made from 28.068 g (0.258 mol) of 3-methoxy-1-chloropropane and 6.29 g of magnesium turnings in 130 ml of THF, 5 g (0.021 mmol) of 1,2-bis(dichlorophosphino)ethane in 50 ml of THF was added dropwise over 15 min. The reaction mixture was stirred for an additional 30 min and then boiled for over 1 h. Then 80 ml of a deaerated, saturated solution of NH_4Cl was added slowly to the cooled mixture. The layers separated and the organic layer was dried over anhydrous Na_2SO_4 overnight. THF was distilled off and the phosphine was distilled *in vacuo*. The product was collected at 185–190°C/0.35 mmHg as a colourless, viscous oil. Yield: 5.325 g (0.0319 mol), 65%. FAB-MS (positive ion mode): 383 Da (M + 1). ^1H NMR ($CDCl_3$, TMS): δ 1.40–1.55 (m, 4H, $CH_3OCH_2CH_2CH_2CH_2$); 1.60–1.80 (m, 4H, $CH_3OCH_2CH_2CH_2P$); 1.80–2.05 (m, 2H, PCH_2CH_2P); 3.33 (s, 6H, $CH_3OCH_2CH_2CH_2$); 3.40–3.55 (m, 4H, $CH_3OCH_2CH_2CH_2$) ppm. ^{31}P NMR ($CDCl_3$, H_3PO_4): δ −25.44 ppm.

3.4. $[(CH_3OCH_2CH_2CH_2)_2P(H)CH_2CH_2P(H)(CH_2CH_2CH_2OCH_3)_2]^{2+}$ 2Cl⁻ (2b)

The last diphosphine was converted into the dihydrochloride by saturation of its toluene solution with gaseous HCl. It forms a colourless, thick oil crystalliz-

* Reference number with asterisk indicates a note in the list of references.

ing below 0°C. The recovery was *ca.* 100%. ^{1}H NMR ($CDCl_3$, TMS): δ 1.90–2.23 (m, 4H, $CH_3OCH_2CH_2$-CH_2); 2.50–2.70 (m, 4H, $CH_3OCH_2CH_2CH_2P$); 3.10–3.20 (m, 2H, PCH_2CH_2P); 3.38 (s, 6H, CH_3OCH_2-CH_2CH_2P); 3.50–3.60 (m, 4H, $CH_3OCH_2CH_2CH_2P$) ppm. ^{31}P NMR ($CDCl_3$, H_3PO_4): δ 19.47 (d, J(P–H) = 520.3 Hz) ppm. IR: ν(P–H) 2430–2450 cm^{-1} (thin film).

References and notes

1 B.L. Shaw, in E.C. Alyea and D.W. Meek (eds.), *Catalytic Aspects of Metal Phosphine Complexes, Advances in Chemistry Series*, Vol. 196, Am. Chem. Soc., Washington, 1982, pp. 101–115; L.H. Pignolet (ed.), *Homogeneous Catalysis with Metal Phosphine Complexes*, Plenum Press, New York, 1983.

2 E. Deutsch, J.-L. Vanderheyden, P. Gerundini, K. Libson, W. Hirth, F. Colombo, A. Savi and F. Fazio, *J. Nucl. Med., 28* (1987) 1870; E. Deutsch, P. Gerundini and F. Fazio, in R.P. Spencer (ed.), *New Procedures in Nuclear Medicine, CRC Press*, Boca Raton, FL, 1988; E. Deutsch and W. Hirth, *J. Nucl. Med., 28* (1987) 1491; E. Deutsch, K. Libson and J.-L. Vanderheyden, *Med. Nucl., 3*(6) (1986) 41–46; J.-L. Vanderheyden, M.J. Heeg and E. Deutsch, *Inorg. Chem., 28* (1985) 1666.

3 F. Runge, E. Taeger, C. Fiedler and E. Kahlert, *J. Pract. Chem., 19* (1963) 37.

4 B.D. Dombek, *J. Org. Chem., 43* (1978) 3409; C. Walling and M.S. Pearson, in F.J. Griffith and M. Grayson (eds.), *Topics in Phosphorus Chemisty*, Vol. 3, Interscience, New York, 1966, p. 4; L. Maier, *Prog. Inorg. Chem., 5.* (1963) 179; M.M. Rauhut, H.A. Currier, A.M. Semsel and V.P. Wystrach, *J. Org. Chem., 26* (1961) 5138.

5 B. Castro, *Bull. Soc. Chim. Fr.*, (1967) 1533.

6 A. Herbowski, T. Lis and E. Deutsch, *J. Organomet. Chem., 460* (1993) 25.

7 D.G. Gorenstein, *Phosphorous-31 NMR. Principles and Applications*. Academic Press, New York, 1984.

8 E. Deutsch *et al.*, Chemistry, Animal Biodistribution and Evaluation in Humans of Cationic Technetium-99m Myocardial Perfusion Imaging Agents Derived from Phosphine Ligands, *J. Nucl. Med.*, in preparation.

9 D.E.C. Corbridge, *Phosphorus, Studies in Inorganic Chemistry*, Elsevier, Amsterdam, 1980, Ch. II; D.E.C. Corbridge, *The Structural Chemistry of Phosphorus*, Elsevier, Amsterdam, 1974, Ch. 10.

10 J. Appelyard and M.J.C. Crabbe, *DMM Program*, Oxford University Press, 1989.

11 H.T. Flakus, *J. Mol. Struct. (Theochem), 201* (1989) 319.

12 A. Zschunke, *Kernmagnetische Resonanzspectroscopie in der organischer Chemie*, Akademie-Verlag, Berlin, 1972; G. Glaros and N.H. Cromwell, *J. Chem. Educ., 48* (1971) 202.

13 R.L. Letsinger and A.W. Schnizer, *J. Org. Chem., 16* (1951) 704.

14 W.E. McEwen, A.B. Janes, J.W. Knapczyk, V.L. Kyllingstad, W.-I. Shiau and S. Shore, *J. Am. Chem. Soc., 100* (1978) 7304.

15 R.C. Taylor and D.B. Walters, *Inorg. Synth., 14* (1973) 10.

16 Spectra recorded in CD_2Cl_2, D_2O, and DMSO-d_6 had resonance peaks at 13.65, 12.31 and 12.30 ppm, respectively.