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Biological activity of new amino phospha betaines with C_{10}–C_{18} alkyl groups

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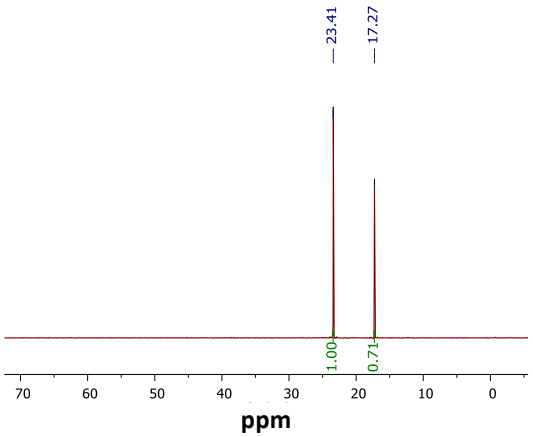


Figure S1 ^{31}P NMR spectra of the reaction mixture of the compound **2**

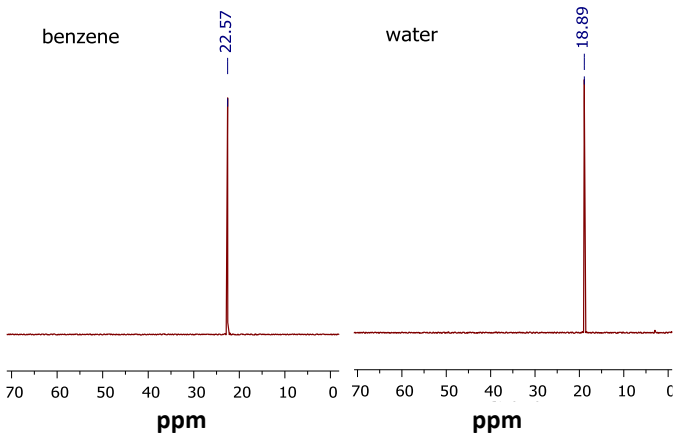


Figure S2 ^{31}P NMR spectra of the compound **2** after extraction in system benzene/water

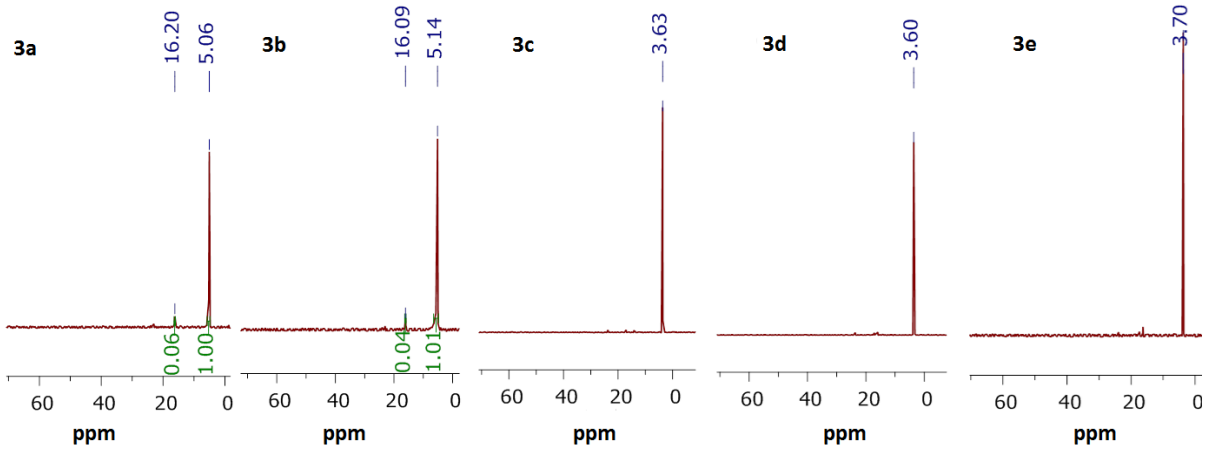


Figure S3 ^{31}P NMR spectrum of the reaction mixture of compounds **3a-e**

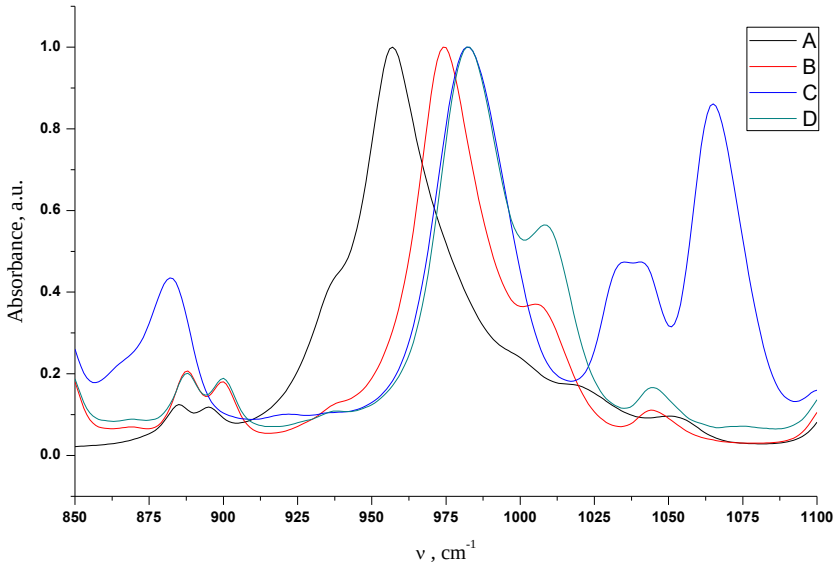


Figure S4 Overlap of FTIR spectra of the compounds: **A** – diisopropyl phosphite **B** – diisopropyl (dimethylaminomethyl)phosphonate **1**, **C** - potassium isopropyl (dimethylaminomethyl)phosphonate **2**, **D** – amino phospha betaine **3a**

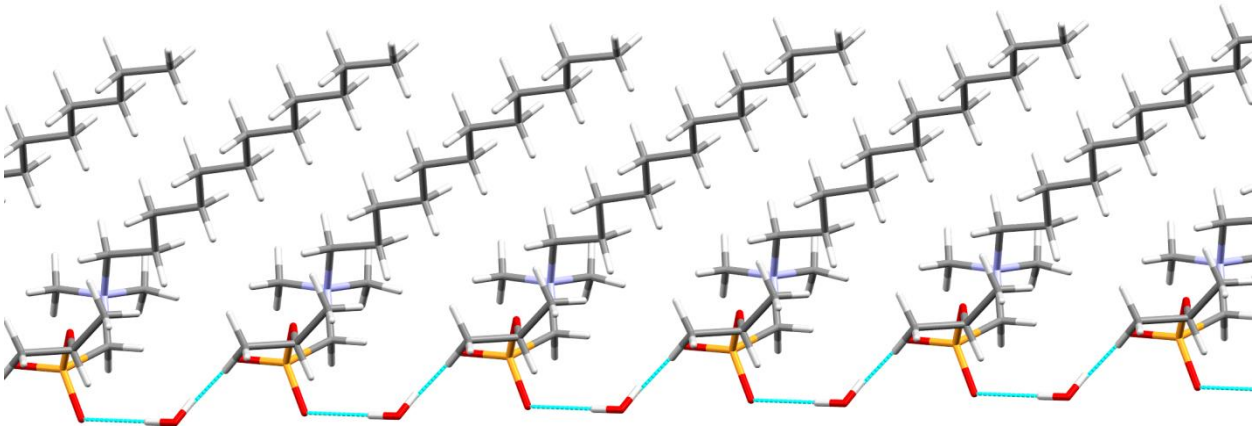


Figure S5 Crystal packing for compound **3b**. Hydrogen bonds are blue lines.

Table S1

Hydrogen bonds for compound **3b**.

D-H···A	Symmetry code	D–H, Å	H···A, Å	D···A, Å	∠DHA, deg
O1W–H1WA···O1	-	0.87(3)	1.99(3)	2.852(2)	174(3)
O1W–H1WB···O2	–1+*x*, *y*, *z*	0.83(3)	1.98(3)	2.806(2)	179(3)

Table S2

Selected geometric parameters (Å, deg) for compound **3b**

N2–C1	1.510(2)	P1–C1	1.834(2)
N2–C3	1.498(2)	P1–O1	1.489(2)
N2–C4	1.500(2)	P1–O2	1.487(2)
N2–C5	1.520(2)	P1–O3	1.601(2)
O1–P1–O2	118.40(9)	O1–P1–C1	103.73(8)
O2–P1–O3	110.58(9)	O2–P1–C1	110.53(9)
O1–P1–O3	110.04(8)	O3–P1–C1	102.15(9)
P1–C1–N2–C3	-58.8(2)	C1–N2–C5-C6	64.2(2)
P1–C1–N2–C4	–176.37(14)	C3–N2–C5–C6	–173.45(18)
P1–C1–N2–C5	61.8(2)	C4–N2–C5–C6	–56.3(2)

Experimental section

Equipment

NMR spectra were recorded on the Bruker Avance III instrument with an operating frequency of 162 MHz for ^{31}P spectra, an operating frequency of 400 MHz for ^{1}H spectra and an operating frequency of 100.6 MHz for ^{13}C spectra in a solution of $CDCl_3$.

The Fourier Transformed InfraRed (FT-IR) spectrum of the sample was recorded using Perkin Elmer UATR Two FT-IR Spectrometer (Spectrum Two) with an ATR (attenuated total reflectance) diamond crystal. Spectra were baseline corrected and normalized.

The mass spectra were obtained on an AB Sciex 5600 Triple TOF mass spectrometer with positive electrospray ionization. The elemental analysis was carried out on a CHNS analyzer EuroEA3028-HTOM.

Melting points were recorded on an Electrothermal, model IA9000 SERIES digital melting point apparatus with an accuracy of ± 0.5 °C, resolution 0.1 °C

The X-ray diffraction data were collected on a Bruker AXS Kappa diffractometer.

Synthesis

Commercially available alkyl bromides (Acros Organics) were used for the preparation of isopropyl (*N*-alkyl-*N*,*N*-dimethylammoniomethyl)phosphonates **3a-e**. Commercially available solvents (C_6H_6, Pr^iOH, petroleum ether) were purified standardly. *p*-Toluenesulfonic acid 97.5% chemical grade were used.

Chemical shifts are reported on the δ (ppm) scale and are relative to the residual ^1H and ^{13}C signal of $CDCl_3$. Coupling constants (J) are reported in Hertz and refer to apparent peak multiplications. The abbreviations s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet in that order.

*Synthesis of the diisopropyl (dimethylaminomethyl)phosphonate **1***

A mixture of dimethylamine 35% water solution, 3.5 mM, paraformaldehyde 3.5 mM and *p*-toluenesulfonic acid 0.2 mM was heated ($t_{bath} \approx 50°C$) under reflux in acetonitrile (10 ml) for 0.5 h. Then benzene (5 ml) and 3.5 mM diisopropyl phosphite were added. The mixture was stirred for 4 h at 50 °C. The benzene phase was separated and evaporated under vacuum to give pure compound **1**

Diisopropyl (dimethylaminomethyl)phosphonate 1

Yield 78%. FTIR spectrum, cm^{-1}: 957 (P-O-C), 1240 (P=O). ^{31}P NMR (C_6H_6): δ_P 22.9 ppm

Synthesis of potassium isopropyl (dimethylaminomethyl)phosphonate **2**

A mixture of 2 mM of diisopropyl (dimethylaminomethyl)phosphonate **1** and 2 mM of KOH (10 wt % excess) in 1,4-dioxane (10 ml) was heated under reflux for 5 h. After removal of the solvents, the resulting salt dried *in vacuo*.

Yield 40%. ^{31}P NMR (H_2O): δ_P 18.9 ppm

Synthesis of alkyl (N-alkyl'-N,N-dialkylammoniomethyl)phosphonates is described previously [A. R. Garifzyanov *et al.*, *Russ. J. Gen. Chem.*, 2018, **88**, 2445 (*Zh. Obshch. Khim.*, 2018, **88**, 1923)].

Isopropyl (*N*-decyl-*N*,*N*-dimethylammoniomethyl)phosphonate 3a

mp 74.0 ± 0.5 °C. Yield 81%. FTIR spectrum, cm^{-1}: 1066 (P-O-C), 1211 (P=O). ^1H NMR ($CDCl_3$), δ_H, ppm.: 0.87 t. (3H, $C\underline{H_3}CH_2$, $^3J_{HH}$ 6.79 Hz), 1.20-1.80 m. (22H $(C\underline{H_2})_8CH_3$, $(C\underline{H_3})_2CH$), 3.35 s. (6H, $C\underline{H_3}N$), 3.44-3.53 m. (4H, $NC\underline{H_2}CH_2$, $PC\underline{H_2}$), 4.59-4.69 m. (1H, $(CH_3)_2C\underline{H}$). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ_C, ppm.: 14.01 s. ($CH_2\underline{C}H_3$), 24.57 d. ($OCH(\underline{C}H_3)_2$ $^3J_{CP}$ 4.12 Hz), 22.55 s., 22.97 s., 26.16 s., 29.13 s., 29.32 s., 31.73 s. ($(\underline{C}H_2)_8CH_3$), 52.72 d. ($N\underline{C}H_3$, $^3J_{CP}$ 2.42 Hz), 61.69 d. ($N\underline{C}H_2P$, $^1J_{CP}$ 129.94 Hz), 67.00 d. ($N\underline{C}H_2CH_2$, $^3J_{CP}$ 3.45 Hz), 67.97 d. ($PO\underline{C}H$, $^2J_{CP}$ 5.80 Hz). $^{31}P\{^1H\}$ NMR (propanol-2): δ_P 4.2 ppm. Found, $[MH]^+$ = 322.2511, Calculated, $[MH]^+$ = 322.2511.

Isopropyl (*N*-dodecyl-*N,N*-dimethylammoniomethyl)phosphonate 3b

mp 77.0 ± 0.5 ºC. Yield 80%. FTIR spectrum, cm^{-1}: 1067 (P-O-C), 1212 (P=O). ^{1}H NMR ($CDCl_3$), δ_H, ppm.: 0.87 t. (3H, C$\underline{H_3}$CH_2, $^{3}J_{HH}$ 6.78 Hz), 1.19-1.80 m. (26H (C$\underline{H_2}$)$_{10}$CH_3, (C$\underline{H_3}$)$_2$CH), 3.37 s. (6H, C$\underline{H_3}$), 3.48-3.53 m. (2H, NC$\underline{H_2}$CH_2), 3.56 d. (2H, PC$\underline{H_2}$, $^{2}J_{PH}$ 12.30 Hz), 4.60-4.70 m. (1H, C$\underline{H}$OP). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ_C, ppm.: 14.03 s. (CH$_2$C$\underline{H_3}$), 24.52 d. (OCH(C$\underline{H_3}$)$_2$ $^{3}J_{CP}$ 4.12 Hz), 22.58 s., 22.98 s., 26.15 s., 29.17 s., 29.22 s., 29.34 s., 29.38 s., 29.49 s., 29.58 s., 31.80 s. ((C$\underline{H_2}$)$_{10}$CH$_3$), 52.77 d. (NC$\underline{H_3}$, $^{3}J_{CP}$ 2.51 Hz), 61.38 d. (NC$\underline{H_2}$P, $^{1}J_{CP}$ 131.66 Hz), 66.93 d. (NC$\underline{H_2}$CH$_2$, $^{3}J_{CP}$ 2.45 Hz), 68.28 d. (POC$\underline{H}$, $^{2}J_{CP}$ 6.04 Hz). $^{31}P\{^{1}H\}$ NMR (propanol-2): δ_P 4.3 ppm. Elemental analysis: Found, %: C 61.65, H 11.47, N 3.96, P 8.81. $C_{18}H_{40}NO_3P$. Calculated, %: C 61.86, H 11.54, N 4.01, P 8.86.

Isopropyl (*N*-tetradecyl-*N,N*-dimethylammoniomethyl)phosphonate 3c

mp = 92.0 ± 0.5 ºC. Yield 80%. FTIR spectrum, cm^{-1}: 1068 (P-O-C), 1211 (P=O). ^{1}H NMR ($CDCl_3$), δ_H, ppm.: 0.87 t. (3H, C$\underline{H_3}$CH_2, $^{3}J_{HH}$ 6.65 Hz), 1.24-1.81 m. (30H (C$\underline{H_2}$)$_{12}$CH_3, (C$\underline{H_3}$)$_2$CH), 3.34 s. (6H, C$\underline{H_3}$), 3.44-3.52 m. (4H, NC$\underline{H_2}$CH_2, PC$\underline{H_2}$), 4.59-4.69 m. (1H, C$\underline{H}$OP). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ_C, ppm.: 14.04 s. (CH$_2$C$\underline{H_3}$), 24.58 d. (OCH(C$\underline{H_3}$)$_2$ $^{3}J_{CP}$ 4.13 Hz), 22.59 s., 22.98 s., 26.16 s., 29.13 s., 29.26 s., 29.31 s., 29.37 s., 29.48 s., 29.54 s., 29.57 s., 31.82 s. ((C$\underline{H_2}$)$_{12}$CH$_3$), 52.68 d. (NC$\underline{H_3}$, $^{3}J_{CP}$ 2.07 Hz), 61.82 d. (NC$\underline{H_2}$P, $^{1}J_{CP}$ 129.93 Hz), 67.05 d. (NC$\underline{H_2}$CH$_2$, $^{3}J_{CP}$ 3.52 Hz), 67.93 d. (POC$\underline{H}$, $^{2}J_{CP}$ 5.93 Hz). $^{31}P\{^{1}H\}$ NMR (propanol-2): δ_P 4.3 ppm. Elemental analysis: Found, %: C 63.55, H 11.68, N 3.68, P 8.16. $C_{20}H_{44}NO_3P$. Calculated, %: C 63.63, H 11.75, N 3.71, P 8.20.

Isopropyl (*N*-hexadecyl-*N,N*-dimethylammoniomethyl)phosphonate 3d

mp = 95.6 ± 0.5 ºC. Yield 82%. FTIR spectrum, cm^{-1}: 1069 (P-O-C), 1208 (P=O). ^{1}H NMR ($CDCl_3$), δ_H, ppm.: 0.87 t. (3H, C$\underline{H_3}$CH_2, $^{3}J_{HH}$ 6.72 Hz), 1.24-1.81 m. (34H (C$\underline{H_2}$)$_{14}$CH_3, (C$\underline{H_3}$)$_2$CH), 3.39 s. (6H, C$\underline{H_3}$), 3.50-3.59 m. (2H, NC$\underline{H_2}$CH_2), 3.64 d. (2H, PC$\underline{H_2}$, $^{2}J_{PH}$ 11.28 Hz), 4.64-4.74 m. (1H, C$\underline{H}$OP). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ_C, ppm.: 14.10 s. (CH$_2$C$\underline{H_3}$), 24.59 d. (OCH(C$\underline{H_3}$)$_2$ $^{3}J_{CP}$ 3.38 Hz), 22.66 s., 23.06 s., 26.19 s., 29.17 s., 29.33 s., 29.35 s., 29.42 s., 29.54 s., 29.63 s., 29.65 s., 31.89 s. ((C$\underline{H_2}$)$_{14}$CH$_3$), 52.81 s. (NC$\underline{H_3}$), 61.83 d. (NC$\underline{H_2}$P, $^{1}J_{CP}$ 130.41 Hz), 67.30 s. (NC$\underline{H_2}$CH$_2$), 68.39 d. (POC$\underline{H}$, $^{2}J_{CP}$ 6.14 Hz). $^{31}P\{^{1}H\}$ NMR (propanol-2): δ_P 4.3 ppm. Elemental analysis: Found, %: C 65.02, H 11.88, N 3.41, P 7.60. $C_{22}H_{48}NO_3P$. Calculated, %: C 65.15, H 11.93, N 3.45, P 7.64.

Isopropyl (*N*-octadecyl-*N,N*-dimethylammoniomethyl)phosphonate 3e

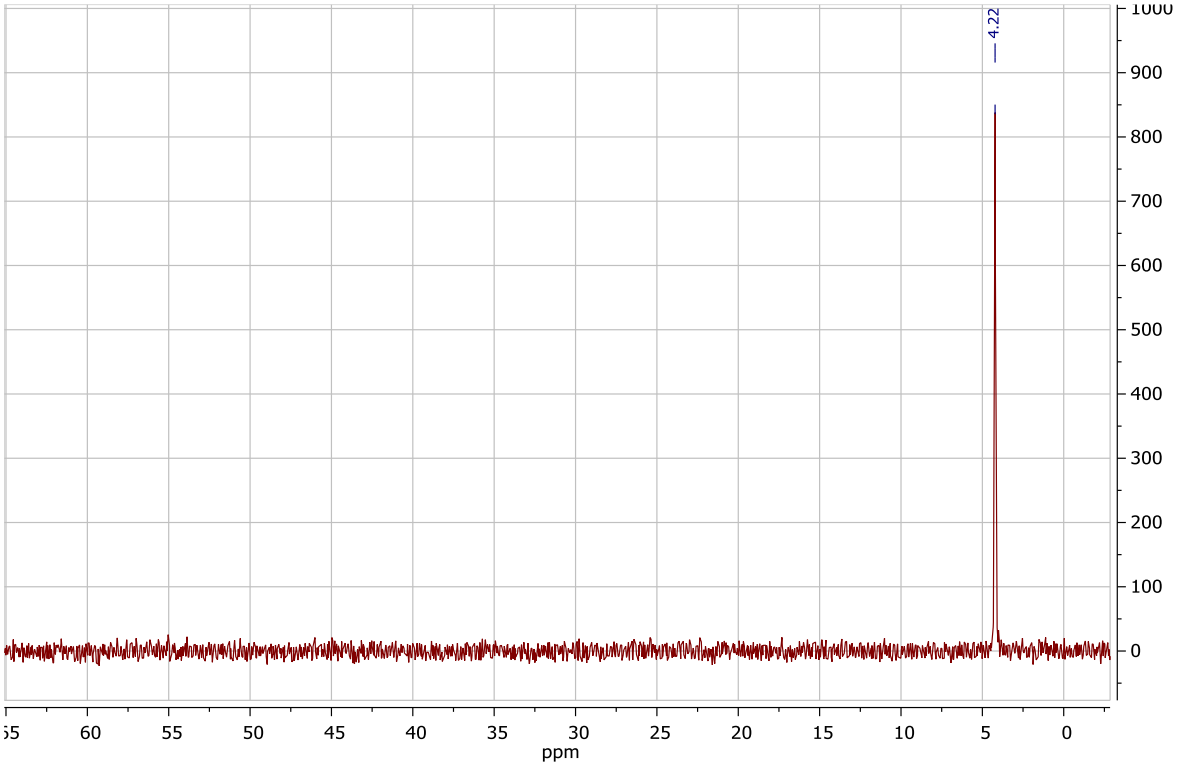
mp = 97.0 ± 0.5 ºC. Yield 80%. FTIR spectrum, cm^{-1}: 1071 (P-O-C), 1208 (P=O). ^{1}H NMR ($CDCl_3$), δ_H, ppm.: 0.86 t. (3H, C$\underline{H_3}$CH_2, $^{3}J_{HH}$ 6.62 Hz), 1.24-1.81 m. (38H (C$\underline{H_2}$)$_{16}$CH_3, (C$\underline{H_3}$)$_2$CH), 3.34 s. (6H, C$\underline{H_3}$), 3.42-3.52 m. (4H, NC$\underline{H_2}$CH_2, PC$\underline{H_2}$), 4.54-4.66 m. (1H, C$\underline{H}$OP). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ_C, ppm.: 14.13 s. (CH$_2$C$\underline{H_3}$), 24.31 d. (OCH(C$\underline{H_3}$)$_2$ $^{3}J_{CP}$ 4.04 Hz), 22.68

s., 23.06 s., 25.31 s., 26.14 s., 29.20 s., 29.38 s., 29.45 s., 29.57 s., 29.69 s., 31.91 s. (($\underline{C}H_2)_{16}CH_3$), 53.01 d. ($N\underline{C}H_3$, $^3J_{CP}$ 2.64 Hz), 60.16 d. ($N\underline{C}H_2P$, $^1J_{CP}$ 139.09 Hz), 67.24 d. ($N\underline{C}H_2CH_2$, $^3J_{CP}$ 3.27 Hz), 70.89 d. ($PO\underline{C}H$, $^2J_{CP}$ 6.42 Hz). $^{31}P\{^1H\}$ NMR (propanol-2): δ_P 4.2 ppm. Elemental analysis: Found, %: C 66.42, H 12.01, N 3.19, P 7.08. $C_{24}H_{52}NO_3P$. Calculated, %: C 66.47, H 12.09, N 3.23, P 7.14

Antibacterial and antifungal activity

The data of antibacterial and antifungicidal activity were defined by the method described previously [R. R. Minnullin *et al*, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2019, **194**, 476]. The testing was performed in water with Gram-positive bacteria: *Staphylococcus aureus* (ATCC 29213), *Bacillus cereus* (ATCC 11778), as well as with Gram-negative cultures: *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), and fungi: *Candida albicans* (ATCC 885-653). Chlorhexidine (Sigma Aldrich) were used as reference drug for bacteria, whereas Griseofulvin (Sigma-Aldrich) was used as reference drug for fungi.

NMR spectra



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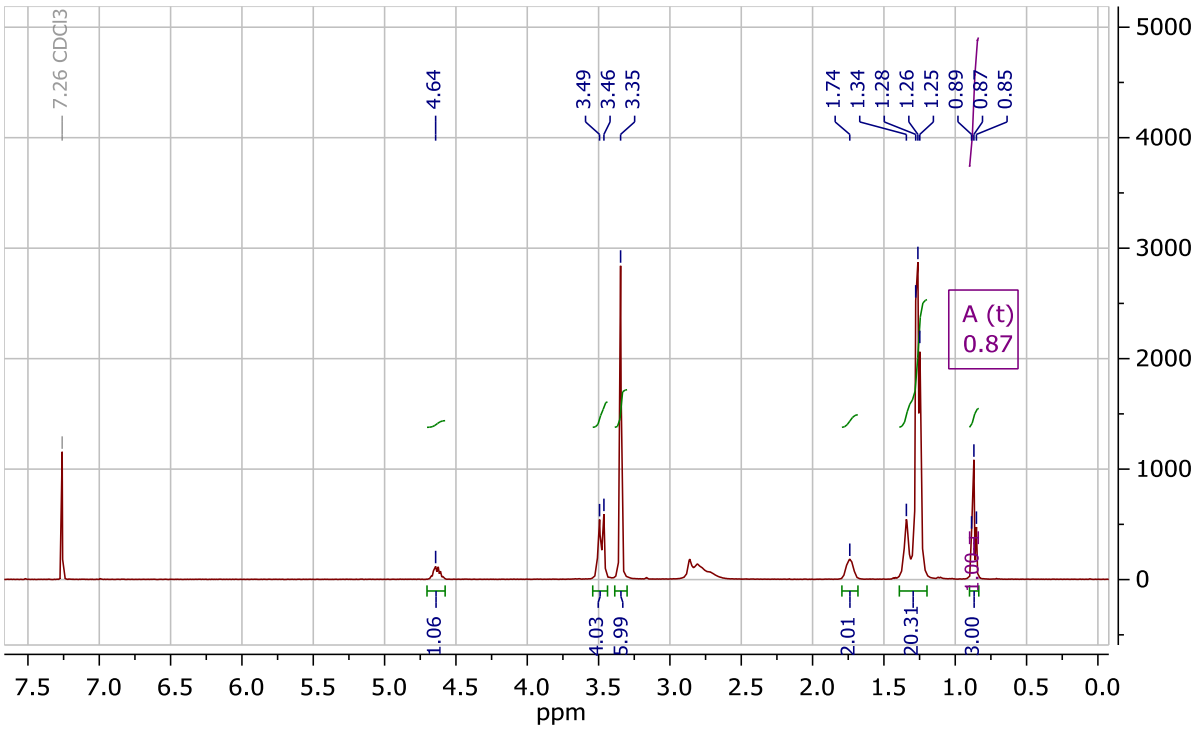
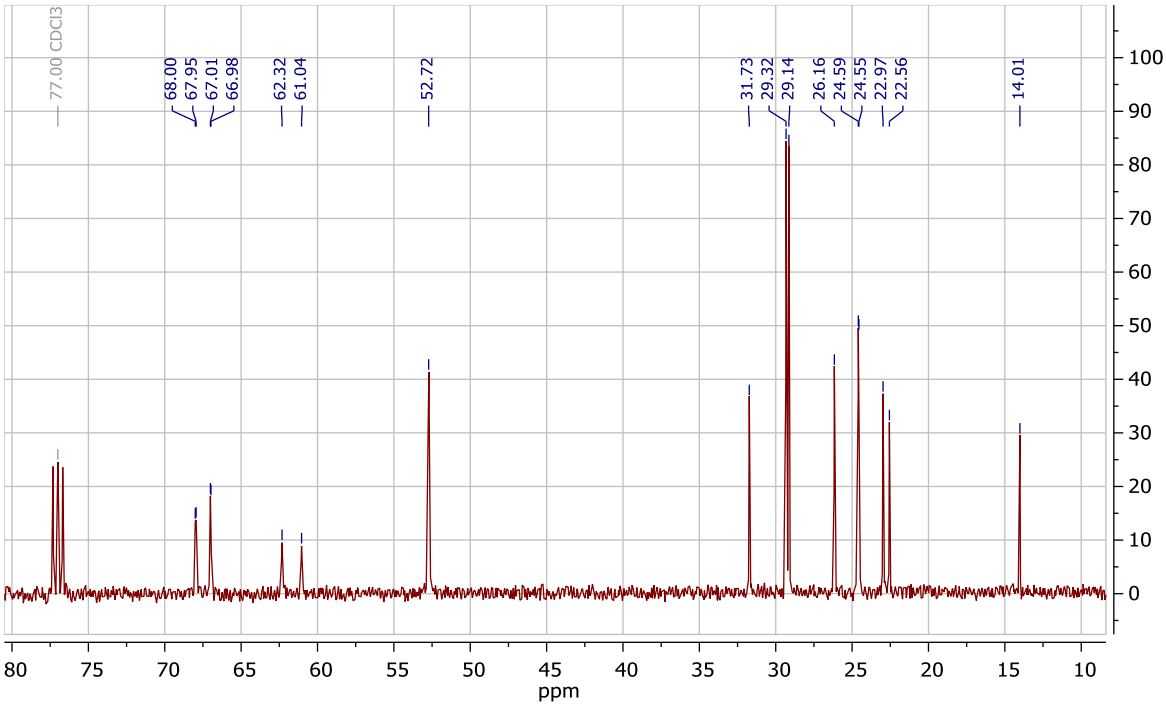
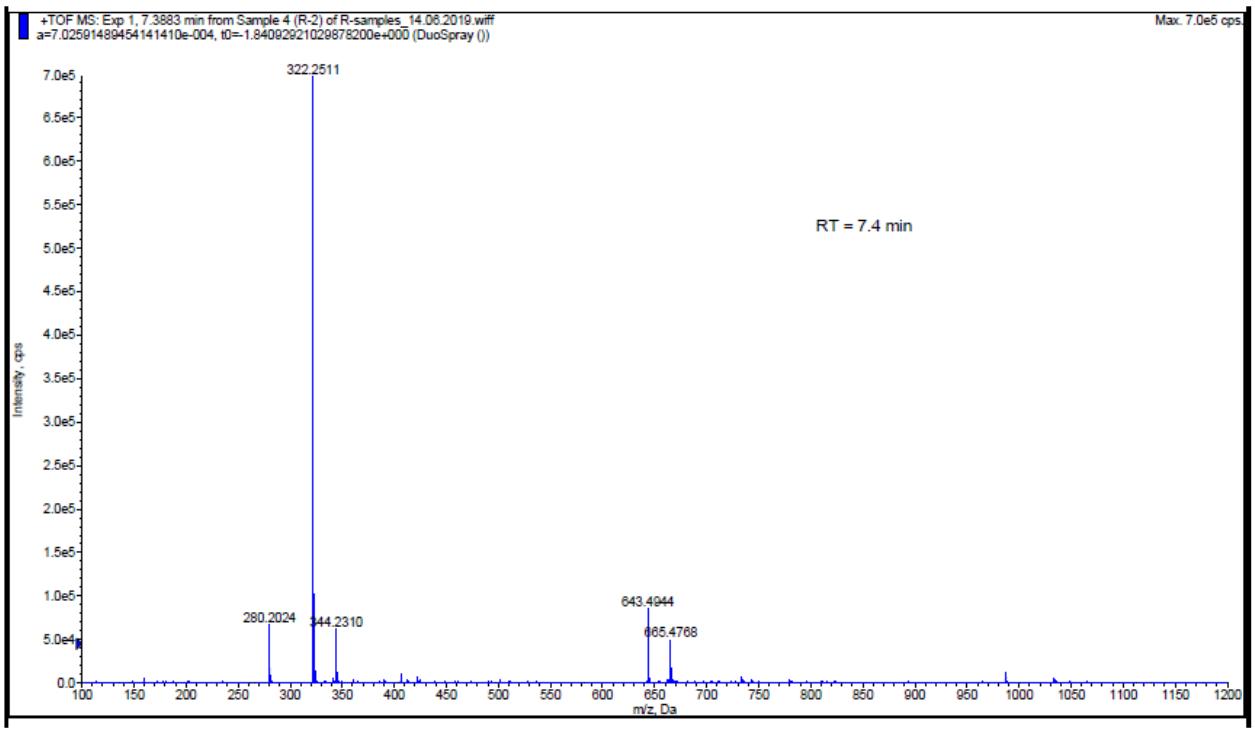
$P\{^1H\}$ NMR (Pr^iOH) of isopropyl (*N*-decyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3a**



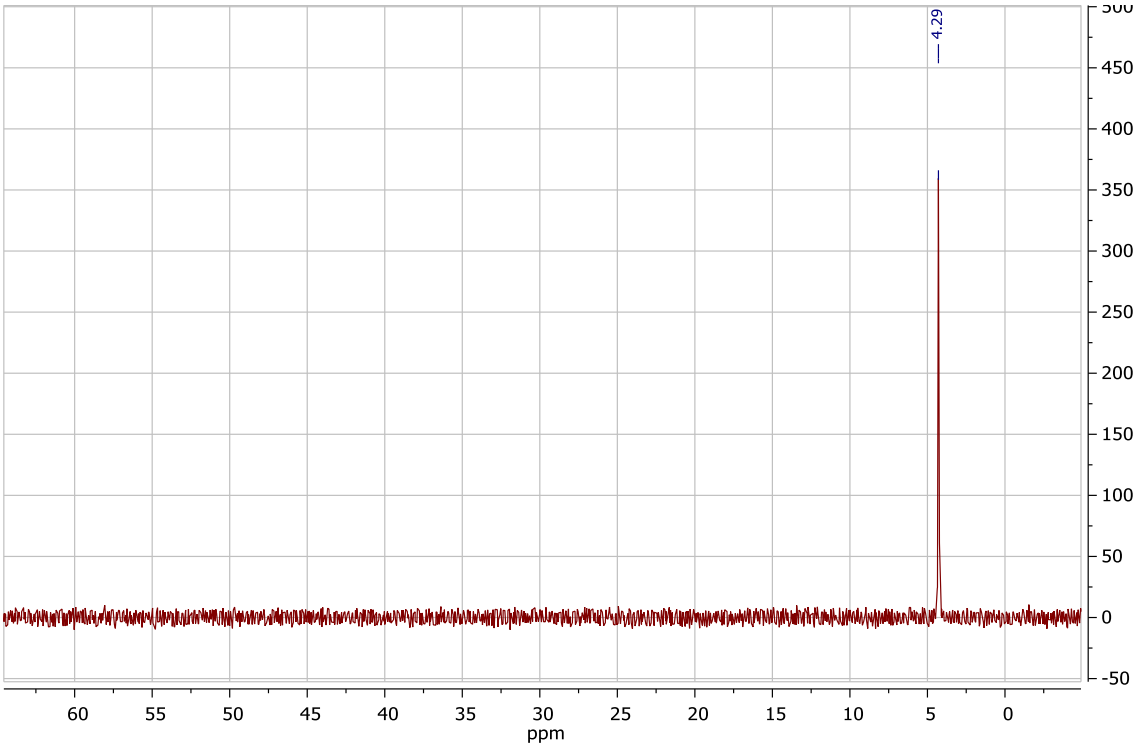
^{1}H NMR ($CDCl_3$) of isopropyl (*N*-decyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3a**



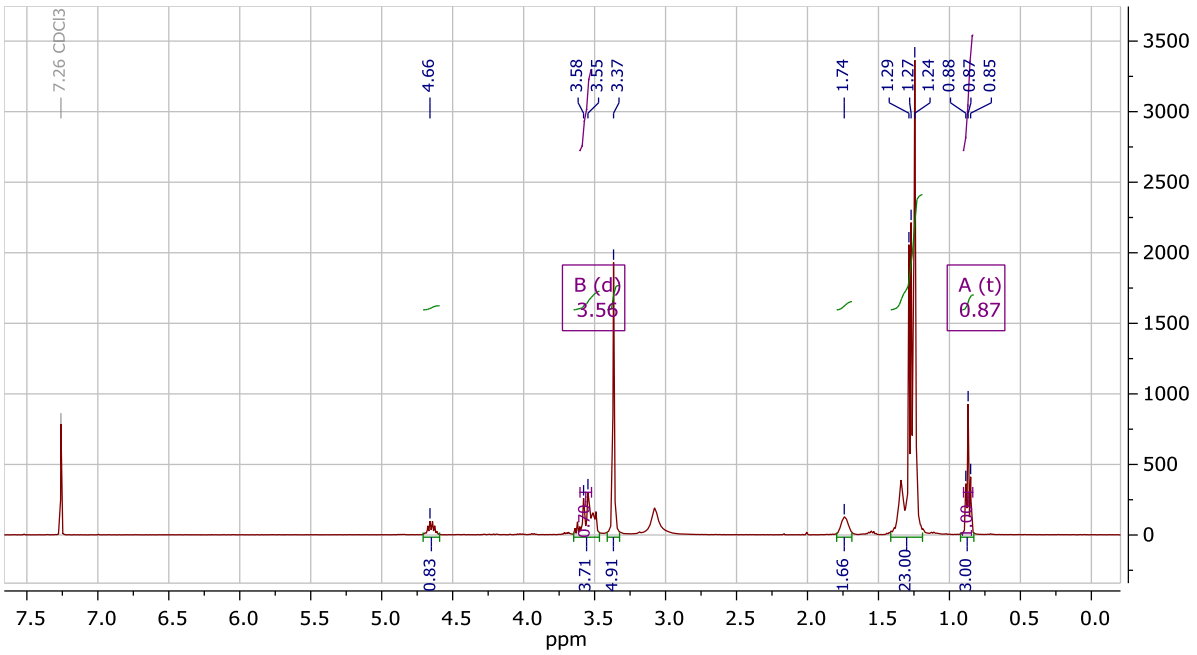
^{13}C{^{1}H} NMR ($CDCl_3$) of isopropyl (*N*-decyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3a**



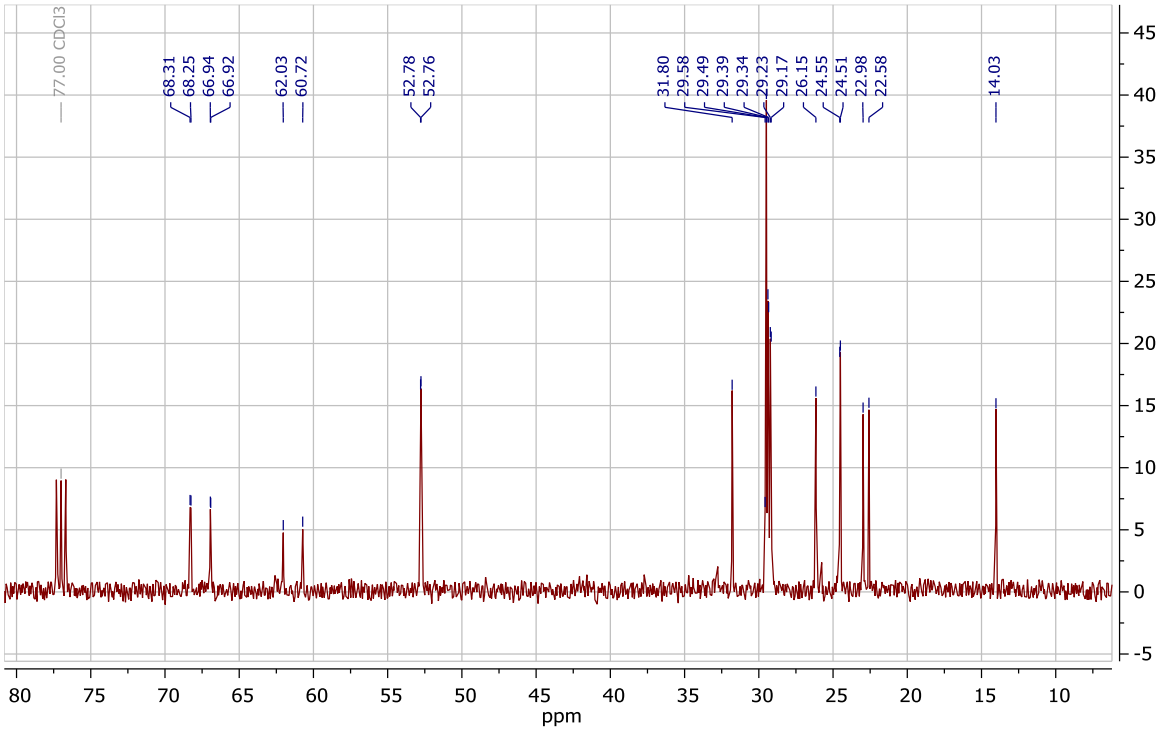
Mass spectrum of isopropyl (*N*-decyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3a**



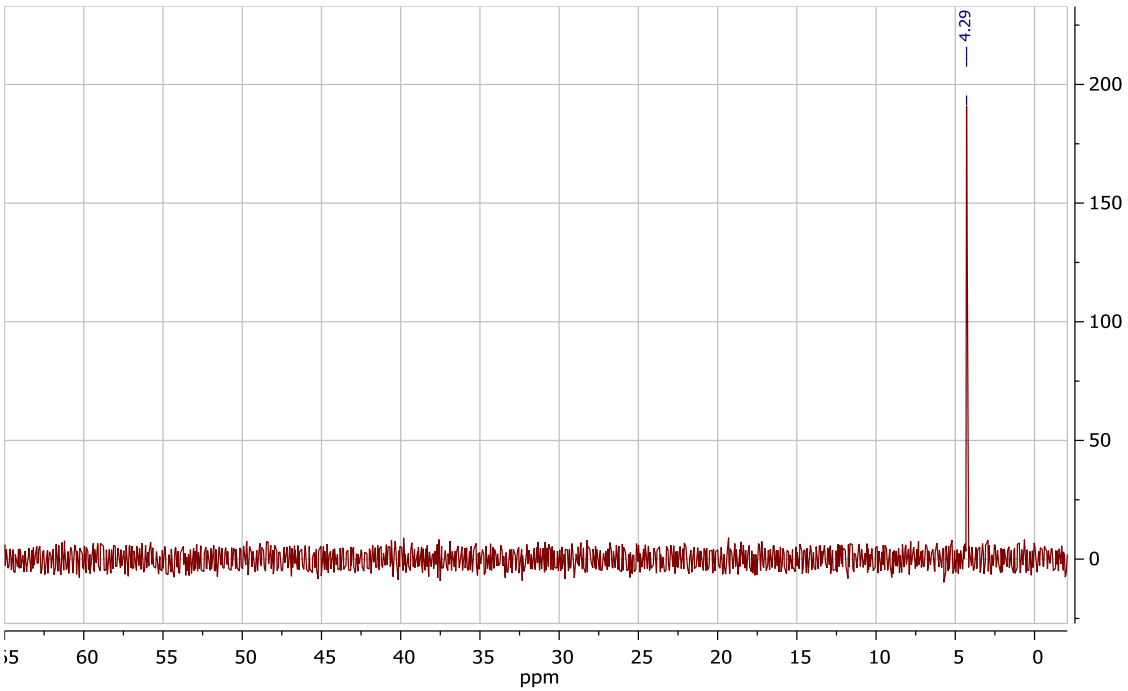
$^{31}P\{^{1}H\}$ NMR (Pr^{i}OH) of isopropyl (*N*-dodecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3b**



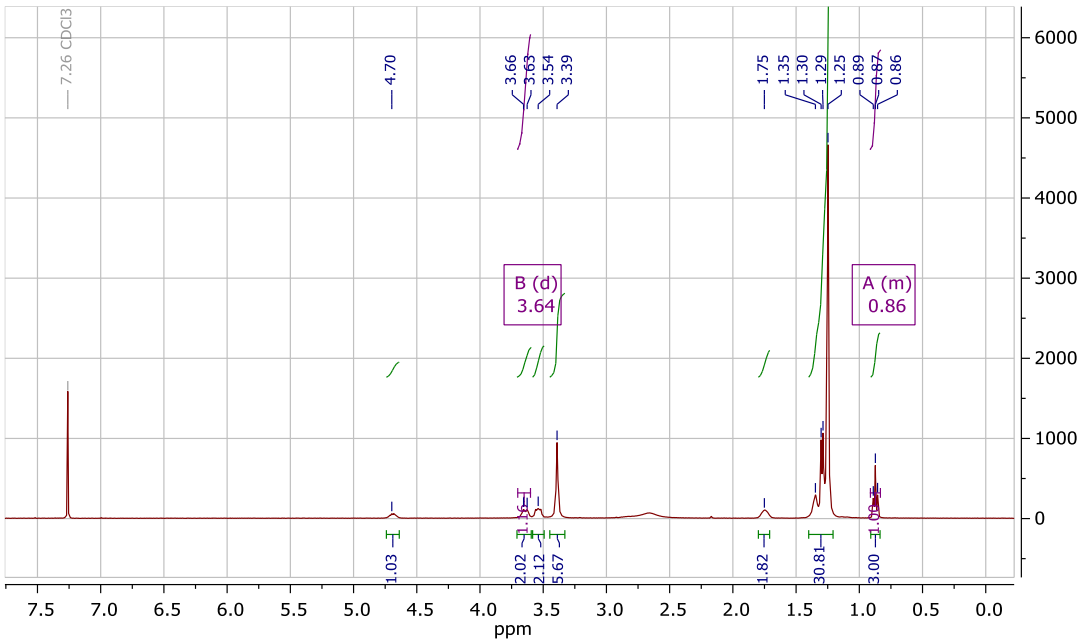
^{1}H NMR ($CDCl_3$) of isopropyl (*N*-dodecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3b**



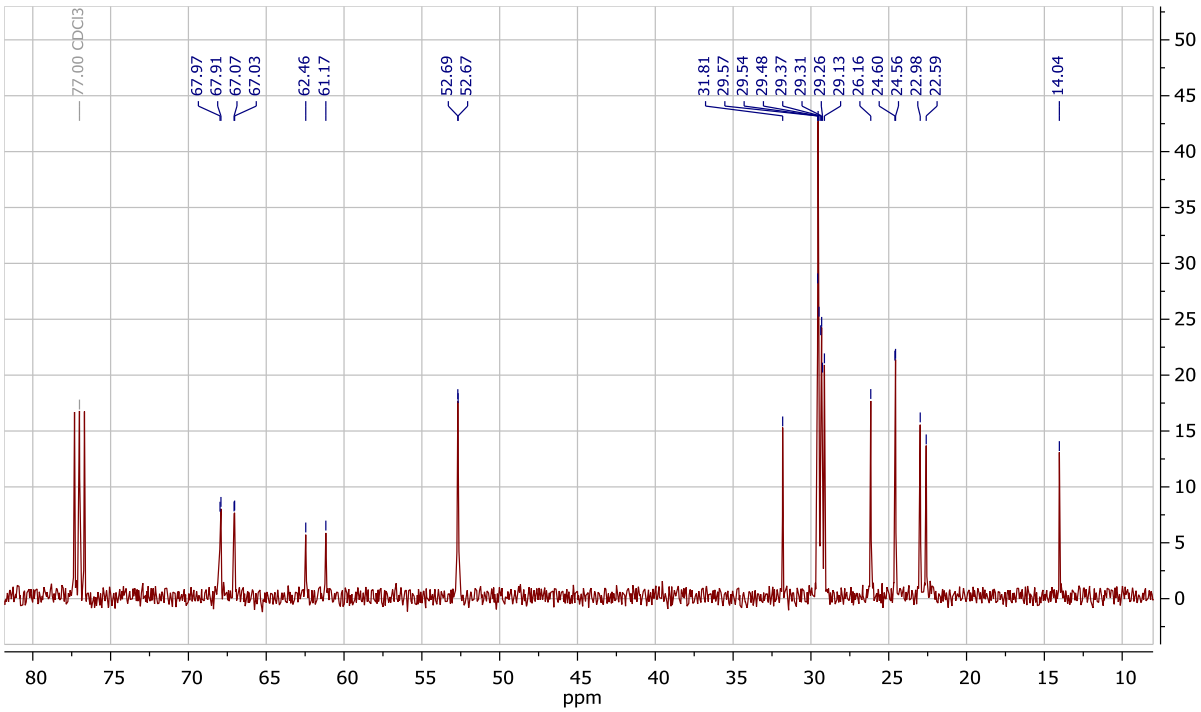
^{13}C{^{1}H} NMR ($CDCl_3$) of isopropyl (*N*-dodecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3b**



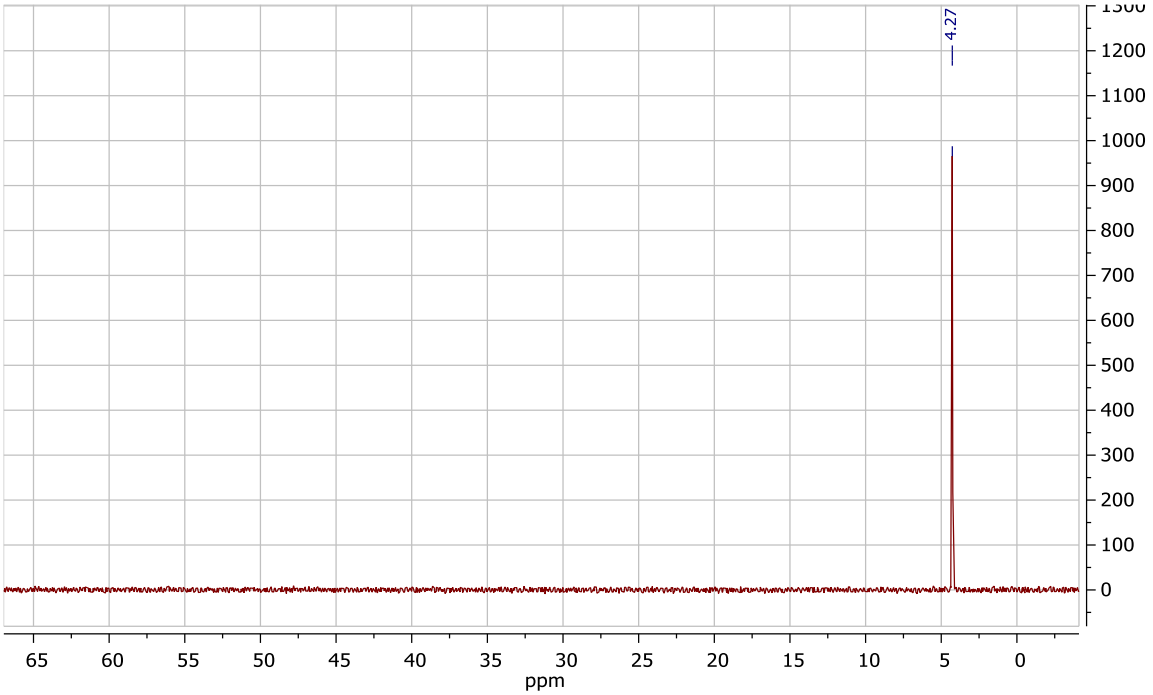
$^{31}P\{^{1}H\}$ NMR ($Pr^{i}OH$) of isopropyl (*N*-tetradecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3c**



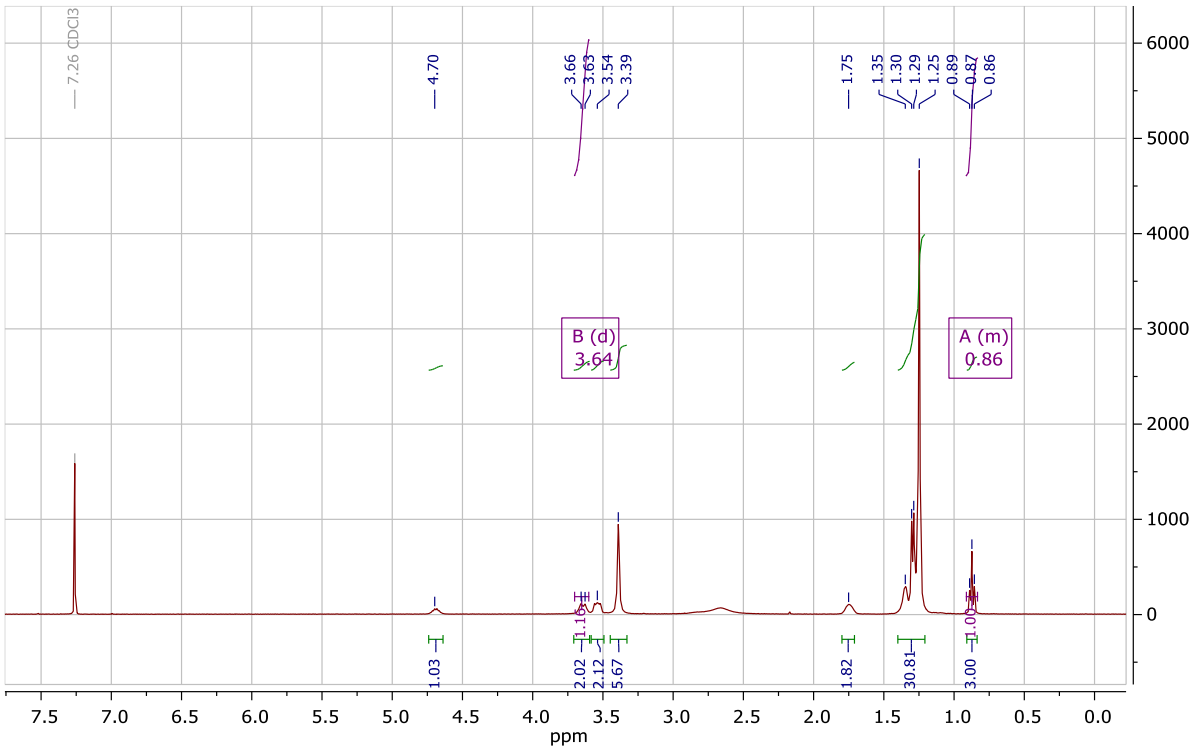
^{1}H NMR ($CDCl_3$) of isopropyl (*N*-tetradecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3c**



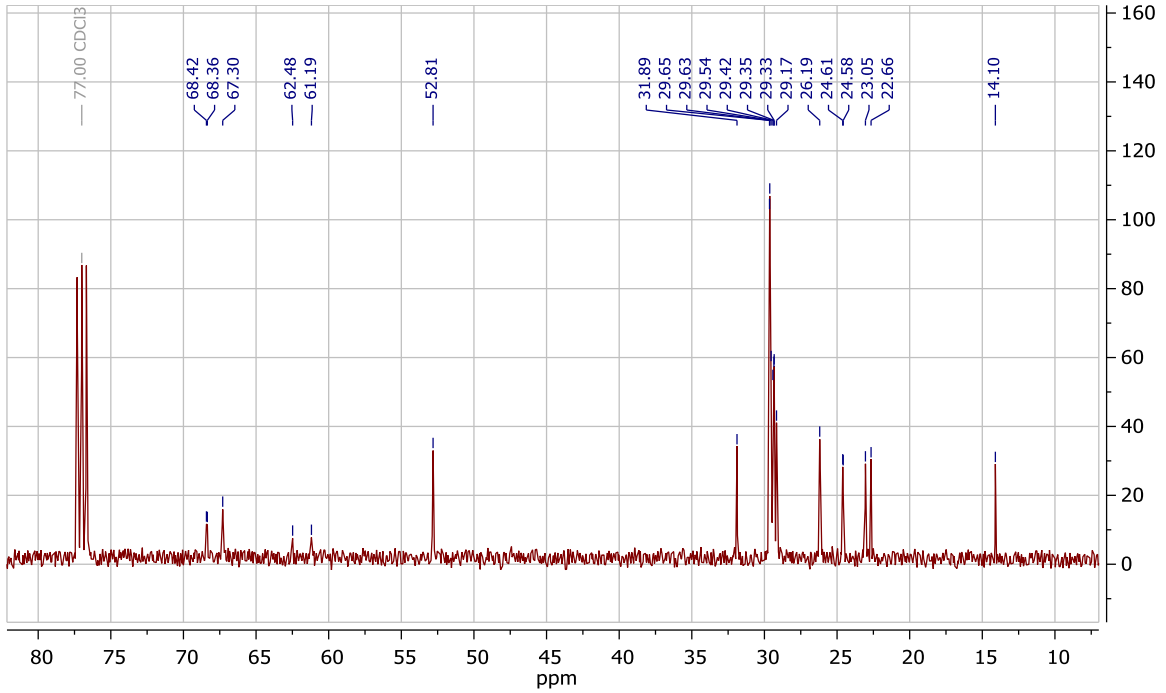
$^{13}C\{^{1}H\}$ NMR ($CDCl_3$) of isopropyl (*N*-tetradecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3c**



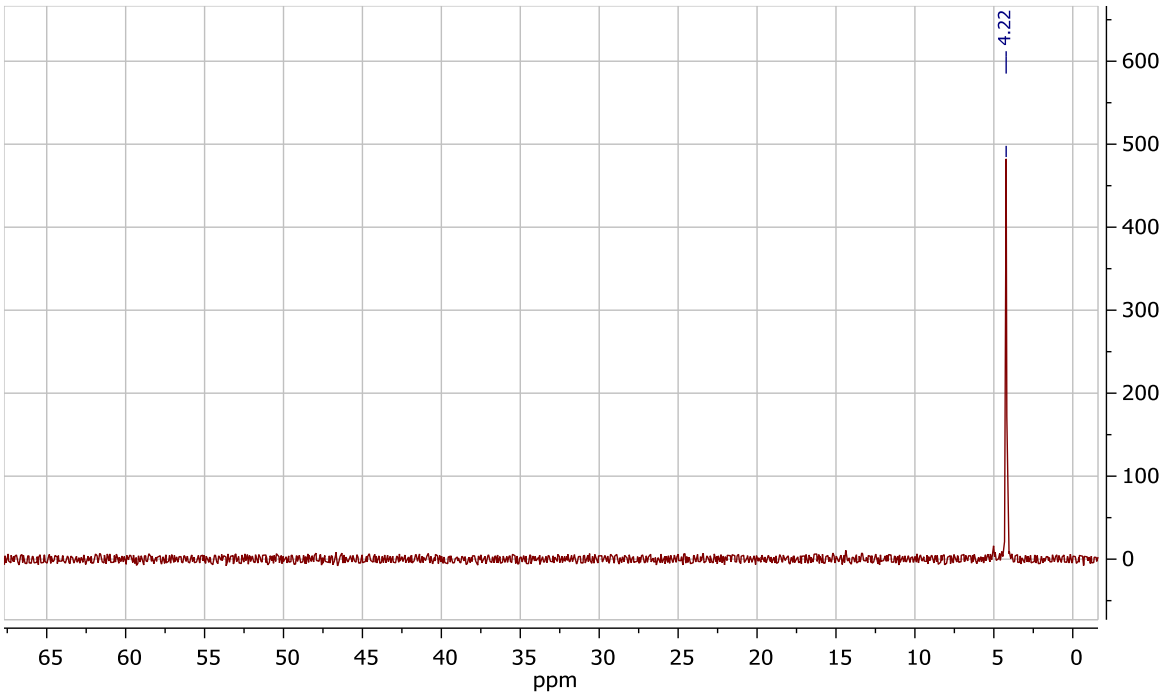
$^{31}P\{^{1}H\}$ NMR ($Pr^{i}OH$) of isopropyl (*N*-hexadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3d**



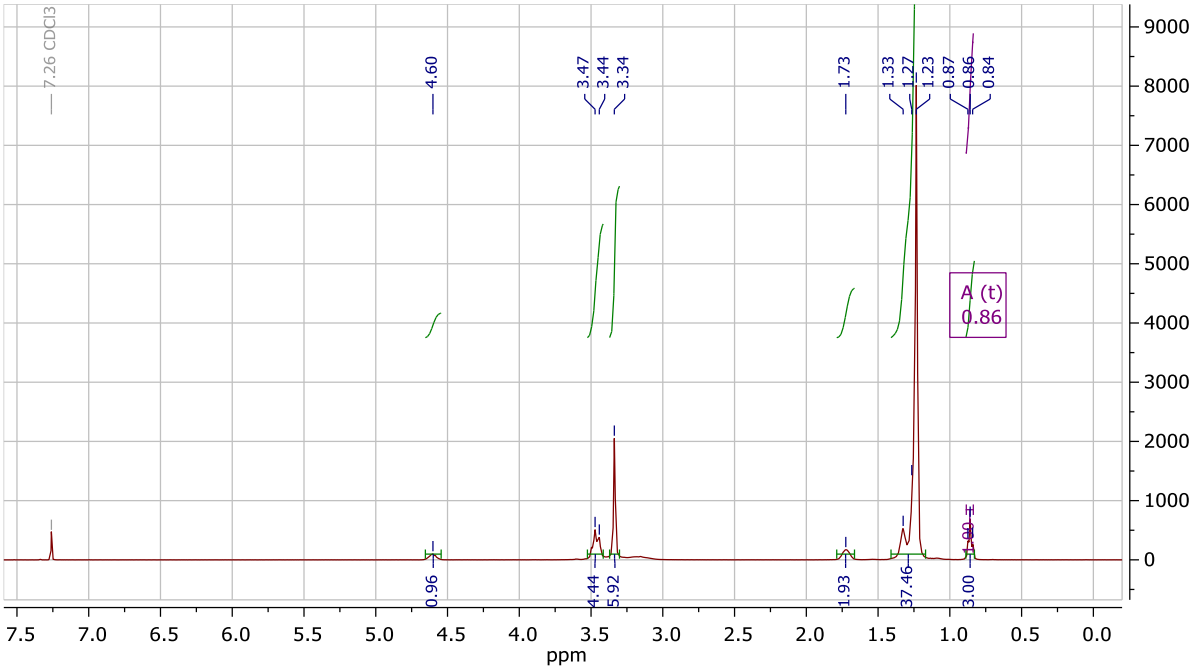
^{1}H NMR (CDCl$_3$) of isopropyl (*N*-hexadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3d**



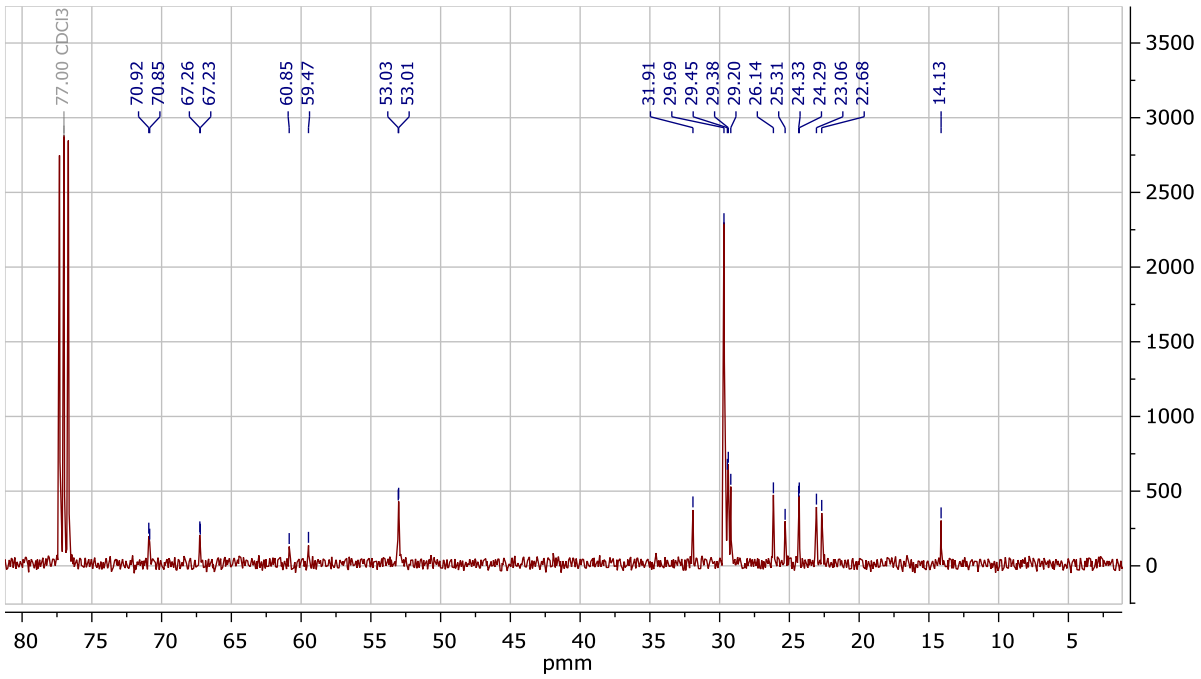
^{13}C{^{1}H} NMR (CDCl$_3$) of isopropyl (*N*-hexadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3d**



$^{31}P\{^{1}H\}$ NMR ($Pr^{i}OH$) of isopropyl (*N*-octadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3e**



^{1}H NMR ($CDCl_3$) of isopropyl (*N*-octadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3e**



$^{13}C\{^{1}H\}$ NMR ($CDCl_3$) of isopropyl (*N*-octadecyl-*N*,*N*-dimethylammoniomethyl)phosphonate **3e**