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SYNTHESIS OF ALIPHATIC SYMMETRIC DIPHOSPHONIUM SALTS AND BACTERICIDAL ACTIVITY OF SELECTED PRODUCTS

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Abstract. Eight new aliphatic symmetrical diphosphonium salts were synthesized by reacting *ω,ω´*-dibromoalkanes with triphenylphosphine or tributylphosphine using N,N-dimethyl acetamide as a solvent at 140-150°C for 17-24 h under a nitrogen atmosphere. Product characterization and bactericidal tests against saprophytic bacteria, sulphate reducing bacteria and iron bacteria were performed. Three compounds presented bactericidal activity, among which 1,12-di(tributylphosphonium bromide)dodecane provided the best results.

Keywords: diphosphonium salts, *ω,ω´*-dibromo alkane, synthesis, bactericidal activity.

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Introduction

Quaternary phosphonium salts are highly efficient and environmentally friendly bactericides of a broad spectrum [1-5]. Quaternary phosphonium salts also have an inhibitory effect on cancer cells [6-9] and show low toxicity and easily degradable in both the environment and aquatic organisms [10]. In recent years, the interest in usage of quaternary phosphonium salts as bactericides has increased [4,11-13], especially in circulated cooling water and oil field water injection systems, because these compounds do not promote the formation of bubbles or exist in the interface or matrix and have little effect on the environment [14]. Up to date, a considerable number of studies on the benefits of quaternary phosphonium salts in material sciences and medicinal chemistry have been published [15-16], thus, research on the synthesis of diphosphonium salts is of significant practical importance [17].

The extension of monophosphonium salts to aliphatic and aromatic compounds has been widely investigated, but studies on the synthesis of diphosphonium salts with aliphatic and aromatic functional groups are relatively rare. Carre, F.H. *et al.* [18] developed a method for the preparation of $[R'R_2P(p\text{-}CH_2C_6H_4CH_2)PR_2R']^{2+}[2Br^-]$, [R' = 8-dimethyl -amino-1-naphthyl, R=Ph], a diphosphonium salt, and Kanazawa synthesized trimethyl(dimethyl) quaternary phosphonium salts with single or double alkyl chains, which showed good antibacterial activity against 11 typical microorganisms [19]. In addition, Villemin, D. *et al.* [20] developed a selective method for the synthesis of phenylene diphosphonium salts based on the reaction of dichloroxylenes with phosphines in dimethylformamide (DMF).

Herein, this paper presents the synthesis method of eight new aliphatic symmetrical diphosphonium salts by the intermolecular nucleophilic additional reaction between the triphenyl or tributyl phosphine and *ω,ω´*-dibromo alkanes as raw materials, using N,N-dimethyl acetamide as solvent. The structural characterization of synthesized compounds was performed using IR, NMR and elemental analysis. Bactericidal activity of selected products was tested against saprophytic bacteria, sulphate reducing bacteria and iron bacteria.

Results and discussion

Eight new aliphatic symmetrical diphosphonium salts were synthesized by the intermolecular nucleophilic addition reaction (Figure 1), and by changing the molar ratio of *ω,ω´*-dibromoalkane/PR_3 or PPh_3 from 1:2.0 to 1:2.2 (Table 1): 1,12-di(triphenylphosphonium bromide) dodecane ($DTPPD_O$), 1,12-di(tributylphosphonium bromide)dodecane ($DTBPD_O$), 1,10-di(triphenylphosphonium bromide)decane (DTPPD), 1,10-di(tributylphosphonium

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bromide)decane (DTBPD), 1,6-di(tributylphosphonium bromide)hexane (DTBPH), 1,6-di(triphenylphosphonium bromide)hexane (DTPPH), 1,3-di(tributylphosphonium bromide)propane (DTBPP), and 1,3-di(triphenylphosphonium bromide)propane (DTPPP). The results from the high performance liquid chromatography proved a good degree of purity of obtained products. The structure of products was characterized using IR, NMR and elemental analysis (IR, ^{1}HNMR and ^{13}CNMR spectra are provided as *Supplementary material* file).

The results of the bactericidal tests of 1,6-di(tributylphosphonium bromide)hexane (DTBPH), 1,12-di(triphenylphosphonium bromide)dodecane ($DTPPD_O$) and 1,12-di(tributylphosphonium bromide)dodecane ($DTBPD_O$) on three strains including saprophytic bacteria (TGB), sulphate reducing bacteria (SRB) and iron bacteria (IB) are presented in Tables 2, 3 and 4.

Tetrakis(hydroxymethyl) phosphonium sulfate (THPS), a bactericide with good efficiency [21,22], was used as a reference in the bactericidal tests on TGB, SRB and IB. From Table 5 we can see that the contact time required by $DTBPD_O$ to achieve a considerable effect is shorter than that of THPS, meaning a significant advantage of $DTBPD_O$ compared to THPS. At a concentration of $DTBPD_O$ of 20 mg/L and contact time of 1 h, the bactericidal rate against TGB, SRB and IB was 98.0%, 96.4% and 99.8%, respectively (Table 5). The obtained results show that, even at a lower concentration (10 mg/L) and a contact time of 0.5 h, $DTBPD_O$ still proved a high bactericidal activity for TGB, SRB and IB.

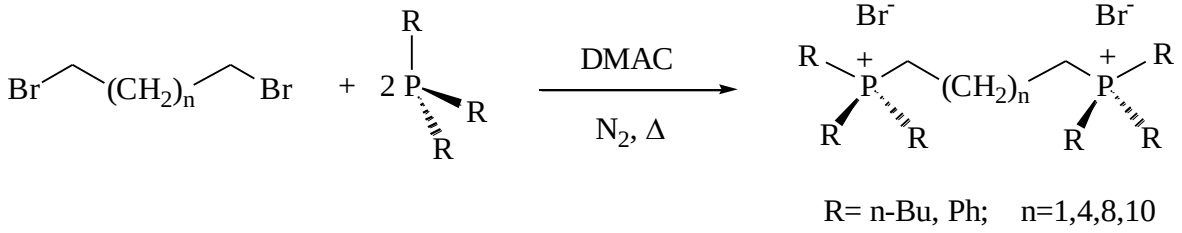

Figure 1. Synthesis route of the products.

Table 1

The reaction conditions and yield of the synthesized diphosphonium salts compounds.

Entry	*Target products*	*Molar ratio of raw materials*	*Reaction time, h*	*Yield, %*
1	$DTPPD_O$	A_1: B_1=1:2.2	20	82.6
2	$DTBPD_O$	A_1: B_2=1:2	24	77.1
3	DTPPD	A_2: B_1=1:2.1	18	82.8
4	DTBPD	A_2: B_2=1:2	18	59.7
5	DTBPH	A_3: B_2=1:2	24	87.6
6	DTPPH	A_3: B_1=1:2.2	18	82.2
7	DTBPP	A_4: B_2=1:2.1	17	75.9
8	DTPPP	A_4: B_1=1:2.1	18	75.7

A_1 indicates 1,12-dibromo dodecane;
A_2 indicates 1,10-dibromo decane;
A_3 indicates 1,6-dibromo hexane;
A_4 indicates 1,3-dibromo propane;
B_1 indicates triphenylphosphine;
B_2 indicates tributyl phosphine.

Table 2

The bactericidal activity against TGB.

Compounds	*Multiple dilutions/ Bacterial growth*					*TGB number per milliliter*	*Bactericidal rate (%)*
	10	10^2	10^3	10^4	10^5		
Blank test	+++	+++	+--	---	---	450	——
DTBPH	++-	+--	++-	---	---	30	93.3
$DTPPD_O$	++-	+--	+--	---	---	20	95.6
$DTBPD_O$	++-	---	---	---	---	9	98.0

"+" indicates that live bacteria were present in parallel samples.
"-" indicates that live bacteria were not present in parallel samples.

Table 3

The bactericidal activity against SRB.

Compounds	*Multiple dilutions/ Bacterial growth*					*SBR number per milliliter*	*Bactericidal rate (%)*
	10	*10^2*	*10^3*	*10^4*	*10^5*		
Blank test	+++	+++	---	---	---	250	——
DTBPH[a]	++-	---	---	---	---	9	96.4
$DTPPD_O$	+++	---	+--	---	---	40	84.0
$DTBPD_O$	++-	---	---	---	---	9	96.4

"+" indicates that live bacteria were present in parallel samples.
"-" indicates that live bacteria were not present in parallel samples.

Table 4

The bactericidal activity against IB.

Compounds	*Multiple dilutions/ Bacterial growth*					*IB number per milliliter*	*Bactericidal rate (%)*
	10	*10^2*	*10^3*	*10^4*	*10^5*		
Blank test	+++	+++	+++	---	---	1400	——
DTBPH	++-	++-	+--	---	---	8	99.4
$DTPPD_O$	+--	+--	+--	---	---	6	99.6
$DTBPD_O$	+--	+--	---	---	---	3	99.8

"+" indicates that live bacteria were present in parallel samples.
"-" indicates that live bacteria were not present in parallel samples.

Table 5

The bactericidal activity of THPS and $DTBPD_O$.

Compounds	*Experimental conditions*	*Bactericidal rate (%)*		
		TGB	*SRB*	*IB*
$DTBPD_O$	20 mg/L, 1.0 h	98.00	96.40	99.79
	20 mg/L, 0.5 h	98.40	96.44	99.73
	10 mg/L, 0.5 h	95.60	96.00	99.36
THPS	20 mg/L, 6 h	98.88	99.47	99.27
	10 mg/L, 6 h	97.40	83.34	97.33
	10 mg/L, 2 h	91.20	68.33	91.76

Conclusions

Eight new compounds of diphosphonium salts were synthesized. The structural characterization of the obtained compounds was performed using IR, NMR and elemental analysis. The bactericidal activity of 1,6-di(tributyl phosphonium bromide)hexane (DTBPH), 1,12-di(triphenylphosphonium bromide)dodecane ($DTPPD_O$) and 1,12-di(tributyl phosphonium bromide)dodecane ($DTBPD_O$) was tested on three strains: saprophytic bacteria (TGB), sulphate reducing bacteria (SRB) and iron bacteria (IB).

The strongest bactericidal activity was observed for 1,12-di(tributylphosphonium bromide)dodecane ($DTBPD_O$) compound. The bactericidal rate of $DTBPD_O$ against TGB, SBR and IB was 98.0%, 96.4% and 99.8%, respectively. $DTBPD_O$ also presented advantages at lower concentrations and shorter contact time, even in comparison to tetrakis(hydroxymethyl) phosphonium sulfate (THPS).

Experimental

General procedure for the synthesis of diphosphonium salts

The aliphatic symmetrical diphosphonium salts were synthesized by reacting *ω,ω´*-dibromoalkanes with triphenylphosphine or tributylphosphine using N,N-dimethyl acetamide (DMAC) as a solvent at 140-150°C for 17-24 h in a nitrogen atmosphere. The reaction time, raw materials and molar ratio are described in Table 1. The mixture of 1,12-dibromo dodecane and triphenyl phosphine was stirred for 20 h, the solvent was then removed under vacuum to give a light yellow liquid. The crude product was dispersed in distilled water (45 mL) and the aqueous solution was extracted twice with petroleum ether (90 mL, *b.p.* 90-120°C). The aqueous solution was removed by a rotary evaporation to acquire a certain amount of the synthesized product (dried sample of $DTPPD_O$).

Analysis of compounds

The structures of products were characterized by using IR, NMR and elements were analyzed by an Elemental analyzer. And as for the calculated results of elements, phosphorus and bromine element analysis was determined by standard methods [23,24].

1,12-di(triphenylphosphonium bromide)dodecane ($DTPPD_O$): white crystalline solid (7.02 g, yield=82.6%). ^{1}HNMR (500 MHz, CD_3OD): δ 7.96 (*ddd*, 18 H, J=1 Hz, 7 Hz, 8.5 Hz), 7.86 (td, 12 H, J=3.5, 8 Hz), 3.65 (m, 4 H, J=8, 13.5 Hz), 1.75 (m, 4 H, J=9 Hz, 15, 22.5 Hz), 1.67 (m, 4 H, J=5.5 Hz, 12.5 Hz, 20 Hz), 1.37 (m, 4 H, J=6.5 Hz), 1.30 (m, 4 H), 1.26 (m, 4 H,). Elemental analysis results: calculated for $C_{48}H_{54}P_2Br_2$: C, 67.75%; H, 6.40%; P, 7.29%; Br, 18.56%. Found: C, 67.57%; H, 6.34%; P, 7.15%; Br, 18.49%. IR (KBr): $V_{\tilde{\nu}max}$=2920, 2853 (for -(CH_2)n-): 1684, 1576 (for ); 735 (for C-P). Mp: 75-80°C.

1,12-di(tributylphosphonium bromide)dodecane ($DTBPD_O$): yellow mucus (5.64 g, yield=77.1%). ^{1}HNMR (500 MHz, CD_3OD): δ 2.26 (m, 16 H), 1.56 (m, 32 H), 1.43 (m, 12 H), 1.03(t, 18 H, J=7Hz). Elemental analysis result: calculated for $C_{36}H_{78}P_2Br_2$: C, 59.15%; H, 10.76%; P, 8.48%; Br, 21.61%. Found: C, 59.07%; H, 10.64%; P, 8.59%; Br, 21.79%. IR (KBr): $V_{\tilde{\nu}max}$ =2928, 2871 (for -(CH_2)n-): 720 (for C-P).

1,10-di(triphenylphosphonium bromide)decane (DTPPD): white crystalline solid (6.82 g, yield=82.8%). ^{1}HNMR (500 MHz, CD_3OD): δ 7.91 (td, 10 H, J=1, 2 Hz), 7.85 (ddd, 10 H, J=1, 6.5, 8.5 Hz), 7.79 (*ddd*, 10 H, J=0.5, 3.5, 8 Hz), 3.46 (t, 4 H, J=5.5 Hz), 1.70 (m, 4 H), 1.57 (5, 4 H, J=7, 14.5 Hz), 1.34 (5, 4 H, J=8, 15 Hz), 1.28 (5, 4 H, J=3, 6 Hz). Elemental analysis result: Calculated for $C_{46}H_{50}P_2Br_2$: C, 67.14%; H, 6.13%; P, 7.53%; Br, 19.20%. Found: C, 66.97%; H, 6.10%; P, 7.59%; Br, 19.34%. IR (KBr): $V_{\tilde{\nu}max}$ =2927, 2855 (for -(CH2)n-); 1635, 1585 (for - ); 748 (for C-P). Mp: 85-95°C.

1,10-di(tributylphosphonium bromide)decane (DTBPD): light yellow mucus (4.21 g, yield=59.7%). ^{1}HNMR (500 MHz, CD_3OD): δ 2.26 (m, 16 H), 1.57 (m, 36 H), 1.03 (t, 18 H, J=7.5 Hz), 0.99 (5, 4 H, J=1, 5 Hz). Elemental analysis results: Calculated for $C_{34}H_{74}P_2Br_2$: C, 58.09%; H, 10.60%; P, 8.82%; Br, 22.47%. Found: C, 57.97%; H, 10.49%; P, 8.89%; Br, 22.58%. IR (KBr): $V_{\tilde{\nu}max}$ =2929, 2871 (for -(CH_2)n-); 719 (for C-P).

1,6-di(tributylphosphonium bromide)hexane (DTBPH): yellow mucus (5.67 g, yield=87.6%. ^{1}HNMR (500 MHz, CD3OD): δ 2.27 (m, 16 H), 1.60 (m, 32 H), 1.04 (t, 18 H, J=7 Hz), 0.99 (5, 4 H, J=7.5, 8.5 Hz). Elemental analysis results: Calculated for $C_{30}H_{66}P_2Br_2$: C, 55.7%; H, 10.29%; P, 9.58%; Br, 24.42%. Found: C, 55.57%; H, 10.34%; P, 9.52%; Br, 24.48%. IR (KBr): $V_{\tilde{\nu}max}$ =2953, 2954 (for -(CH_2)n-); 720 (for C-P).

1,6-di(triphenylphosphonium bromide)hexane (DTPPH): white crystalline solid (6.31 g, yield=82.2%). ^{1}HNMR (500 MHz, CD_3OD): δ 7.92 (td, 10 H, J=1.5, 5.5 Hz), 7.85 (*ddd*, 10 H, J=1.5, 8.0, 11.5 Hz), 7.79 (*ddd*, 10 H, J=2, 4, 6 Hz), 3.48 (q, 4 H, J=7.5, 11.5 Hz), 1.67 (m, 8 H). Elemental analysis results: Calculated for $C_{42}H_{42}P_2Br_2$: C, 65.79%; H, 5.53%; P, 8.09%; Br, 20.60%. Found: C, 65.71%; H, 5.49%; P, 7.99%; Br, 20.98%. IR (KBr): $V_{\tilde{\nu}max}$ =2975, 2987 (for -(CH_2)n-); 1686, 1583 (for ); 735 (for C-P). Mp: 324-326°C.

1,3-di(tributylphosphonium bromide)propane (DTBPP): yellow mucus (4.61 g, yield=75.9%). ^{1}HNMR (500 MHz, CD_3OD): δ 2.35 (m, 16 H), 1.58 (m, 26 H), 1.03 (t, 18 H, J=7 Hz). Elemental analysis results: Calculated for $C_{27}H_{60}P_2Br_2$: C, 53.63%; H, 10.01%; P, 10.25%; Br, 26.12%. Found: C, 53.57%; H, 9.84%; P, 10.20%; Br, 26.22%. IR (KBr): $V_{\tilde{\nu}max}$ =2959, 2932 (for -(CH_2)n-); 718 (for C-P).

1,3-di(triphenylphosphonium bromide)propane (DTBPP): white powder (5.50 g, yield=75.7%). ^{1}HNMR (500 MHz, CD_3OD): δ 7.76 (ddd, 5 H, J=3.5, 5.5, 8.5 Hz), 7.85 (*ddd*, 5 H, J=2.0, 7.0, 8.5 Hz), 7.91 (*ddd*, 5H, J=1.0, 1.5H, 2.5Hz), 3.93 (dt, 4H, J=9.0, 16.5), 1.97 (m, 2 H, J=2.0, 5.0Hz). Elemental analysis results: Calculated for $C_{39}H_{36}P_2Br_2$: C, 64.64%; H, 5.01%; P, 8.56%; Br, 21.80%. Found: C, 64.39%; H, 5.04%; P, 8.51%; Br, 22.14%. IR (KBr): $V_{\tilde{\nu}max}$ =2932, 2865 (for -(CH_2)n-); 1656, 1463 (for ); 725 (for C-P). Mp: 350-352°C.

Bactericidal testing

The bactericidal activity on saprophytic bacteria (TGB), sulphate reducing bacteria (SRB) and iron bacteria (IB) was evaluated using the extinct dilution method [25]. The bactericidal rate was calculated based on the absence of living bacterial cells in three parallel samples after the addition of tested salts:

$$\textit{The number of bacterial cells in 1 mL water samples} = \textit{the number of bacterial cells /Volume (mL)} \times \textit{index of the first digit dilution.}$$

Blank test contained water samples without bactericide but with equal bacteria in phosphate-

buffered saline solution under the same conditions.

The bacterial strains were cultivated as follows: TGB was incubated in a culture medium at 30~37°C for 5~7 days after an inoculation; SRB was grown in a culture medium at 30~37°C for 14~21 days; IB was cultivated in a culture medium at 30~37°C for 7~14 days after an inoculation (Table 6). All procedures were done in a sterile environment.

Table 6

Bacterial growth media.

Medium	*Components (g/L)*[*]
Saprophytic bacteria (TGB) medium	beef extract 3.0; peptone 5.0; NaCl 5.0 (pH 7.4~7.6)
Sulphate reducing bacteria (SRB) medium	K_2HPO_4 0.5; NH_4Cl 1.0; $MgSO_4{\cdot}7H_2O$ 2.0; Na_2SO_4 0.5; $CaCl_2$ 0.1; yeast extract 1.0; sodium lactate 4(mL) (pH 7.4~7.6)
Iron bacteria (IB) medium	$MgSO_4{\cdot}7H_2O$ 0.5; $(NH_4)_2SO_4$ 0.5; KH_2PO_4 0.5; $CaCl_2$ 0.5; $NaNO_3$ 0.5; Ferric ammonium citrate 10 (pH 6.6~6.8)

[*]*All medium components were combined and mixed together; the pH was adjusted to 7.4~7.6 or 6.6~6.8 using 10% of NaOH solution.*

Supplementary information

Supplementary data are available free of charge at http://cjm.asm.md as PDF file.

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