Polymethylene bis(4-dimethylaminopyridinium bromide): synthesis, electrochemical and biological investigation

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A series of bis(4-dimethylaminopyridinium)alkane dibromides (1-7) were prepared from the reaction between 4-dimethylaminopyridine (DMAP) and dibromoalkane(s). Electrochemical studies on 1-7 showed two irreversible reduction potentials, which indicated the presence of two DMAP moieties in a compound. Antibacterial and antifungal activities of these compounds were screened.

Quaternary ammonium salt is usually called as Quat, which is highly reactive and generates nitrogen cation in water. Nitrogen cation is lipophilic and surface active. These two properties made the quat to be useful in the fields of pharmaceuticals, agrochemicals and organic and bioorganic synthesis. Pyridinium salts are served as better medicinal antiseptics, germicides, disinfectants and sanitizing agents. Some diquats and paraquats are found to be good herbicides. For the past two decades, much attention have been given to the quat salt containing DMAP moiety. As a result, DMAP quats are used directly in organic and biochemical reactions such as benzoylation, acetylation, tritylation, tosylation, benzoxylolation, cyanylation and silylation. A few bispyridinium salts obtained from DMAP with anticancer, antiviral, antiparasitic, antifungal and antibacterial activity have been reported. In continuation of our research on the quat salt of DMAP, we made an attempt to prepare title compounds from DAMP with dibromoalkanes. Further it is planned to study their electrochemical properties and antimicrobial activity.

Results and discussion

Reaction between DAMP and dibromoalkanes(s):

The reaction between DAMP and active halide(s) containing electron withdrawing group α- to halogen to give pyridinium salt(s) was reported elsewhere. On the similar way, the reaction between two mole of DAMP and one mole of dibromoalkane(s) has been carried out to give the bispyridinium bromide(s) (1-7) (Scheme 1).

The progress of the reaction was followed by TLC test using methanol as eluent. The physical data of 1-7 and the time required for a reaction to give the isolated yield of the product are presented in the experimental section. The reaction of DAMP with dibromomethane took long time (144 h) to give 1 with the yield of 79%. This is due to serious steric effect felt by bulky DMAP while tends to displace the bromine atoms at the carbon of dibromomethane. Thus the formation of 1 is found to be too slow compared to the formation of 2-7 by the reaction between DMAP and higher dibromoalkane(s). The increase of distance between two bromine atoms in dibromoalkane by increasing the chain length is favored for the formation of 2-7. The reaction time is diminished to about half for each addition of carbon atom into the alkyl chain.

Assignments of the structure of the compounds are based on their spectral data. 1H and 13C NMR spectra of 1-7 show only one type of pyridinium cation. UV-absorption of certain compounds (1-3 and 5) with higher molar extinction coefficient is due to π-π*. The mass spectral data and elemental analysis are consistent with the assigned structure for 1-7. Though the compounds 2 and 3 have been previously described, we have obtained the same with the yield of 83 and 88% against the reported yield of 40 and 54% respectively.

Electrochemistry:

The results of cyclic voltammetric (CV) studies per-
formed on compounds 1-7 as shown in the Experimental section. The reduction potentials are given in experimental section. The cyclic voltammograms exhibit two irreversible reduction peaks. These reductions were found irreversible even when scanning was done just up to the point of reduction. This observation is very similar to reported one18. The two-reduction potentials indicate the presence of two pyridine moieties in a compound and also represent successive reduction of pyridinium ions one after the other.

Antimicrobial screening:

The compounds 1-6 were screened for their antibacterial activity against Staphylococcus aureus, Escherichia coli, Porleus vulgaris and Bacillus pumilis by employing filter paper disc method at 100 and 200 μg/ml in DMF19. At similar conditions, penicillin was used as reference drug. Antifungal activity of these compounds was tested against Aspergillus niger and Aspergillus flavus by standard method19. Nystatin was used as a reference drug. The significant biological results are presented in Table 1. All the compounds are found to be moderately to highly active against test organisms at 200 μg/ml. The activity of 2, 4, 6 against E. coli and 2, 6 against P. vulgaris are significant.

| Compd. | S. aureus (µg) | B. pumilis (µg) | E. coli (µg) | P. vulgaris (µg) | A. niger (µg) | A. flavus (µg) |
|--------|---------------|----------------|--------------|-----------------|--------------|---------------|
| 2      | 16            | 18             | 14           | 100             | 16           | 10            |
| 4      | 14            | 15             | 13           | 14              | 16           | 17            |
| 6      | 17            | 18             | 14           | 15              | 19           | 21            |
| Pencillin | 18          | 20             | 14           | 16              | 18           | 20            |
| Nystatin | -            | -              | -            | -               | -            | -             |

The antimicrobial activity of 2 and 6 is high, whereas, 1, 3, 4, and 5 is moderate.

Experimental

General procedure: A solution of DAMP (0.305 g, 2.5 mmol) in acetone (25 ml) was added into the solution containing required amount of dibromoalkane (2.30 mmol) in acetone (25 ml). The reaction mixture was heated under reflux for the required time (given in the Experimental section). The reaction mixture was allowed to stand to attain room temperature. The white solid that separated was filtered off, washed with acetone, dried in vacuum and recrystallized from aqueous-ethanol (1:3, v/v) to give 1-7.

Melting points determined are uncorrected. IR (KBr) spectra of the compounds 1-7 were recorded on a Perkin-Elmer 1600 FT spectrophotometer, 1H and 13C NMR spectra in DMSO-d6 or D2O on a Bruker, 200 MHz spectrometer using TMS as standard, and mass spectra on a Shimadzu QP 5000 mass spectrometer.

Electrochemistry:

Cyclic voltammetry was performed on EG & G Princeton Applied Research (PAR) Model 273 potentiostat. For all the compounds best results were obtained in aqueous solution. Platinum sphere, platinum plate and Ag/Ag+ were used as a working electrode, counter electrode and reference electrode respectively. Aqueous samples were run at a concentration of 0.001 mol dm⁻³ in 0.1 mol dm⁻³ KCl as supporting electrolyte. Multiple scans were recorded for each compound with little or no variation between scans.

Bis(4-dimethylaminopyridinium)methane dibromide (1):

Reaction time 144 h, yield 79%, m.p. 97-98°; UV λmax (ε) 288 (33500), reduction potential vs Ag/Ag⁺: –456 and –806 mV; IR 1652, 1569, 1403, 1384, 1226, 1151 cm⁻¹; 1H NMR δ 8.10 (4H, d, 2,6- and 2',6'-H), 6.88 (4H, d, 3,5- and 3',5'-H), 3.17 (12H, s, (NMe₂)2). Table 1. (2H, s, N-CH₂-N) ppm;

| Compd. | S. aureus (µg) | B. pumilis (µg) | E. coli (µg) | P. vulgaris (µg) | A. niger (µg) | A. flavus (µg) |
|--------|---------------|----------------|--------------|-----------------|--------------|---------------|
| 2      | 16            | 18             | 14           | 100             | 16           | 10            |
| 4      | 14            | 15             | 13           | 14              | 16           | 17            |
| 6      | 17            | 18             | 14           | 15              | 19           | 21            |
| Pencillin | 18          | 20             | 14           | 16              | 18           | 20            |
| Nystatin | -            | -              | -            | -               | -            | -             |

The antifungal activity of 2 and 6 is high, whereas, 1, 3, 4, and 5 is moderate.
1,3-Bis(4-dimethylaminopyridinium)propane dibromide (3):

Reaction time 30 h, yield 88%, m.p. 52-53°; UV λ_max (e) 285 (2010); IR 1635, 1540, 1420 and 1186 cm^-1; 1^H NMR δ 7.88 (4H, d, 2.6- and 2',6'-H), 6.76 (4H, d, 3.5- and 3',5'-H), 3.12 (12H, s, (NMe_2)_2), 4.19 (4H, t, (N=CH=CH_2)), 1.75 (2H, m, (N=CH=CH_2) ppm; 1^3C NMR δ 159.08, 143.99, 110.80, 42.40, 57 and 32 ppm; MS (EI 70 eV) m/z 442 (M^+-4), 122 (100%, base peak) (Found: C, 39.28; H, 5.62; N, 10.62. Calcd. for C_{17}H_{36}N_4Br_2: C, 39.38; H, 5.79; N, 10.8%).

1,4-Bis(4-dimethylaminopyridinium)butane dibromide (4):

Reaction time 14 h, yield 90%, m.p. 264-266°; reduction potential vs Ag/Ag^+: -462 and -846 mV; IR 1640, 1565, 1430 and 1190 cm^-1; 1^H NMR δ 8.34 (4H, d, 2.6- and 2',6'-H), 7.05 (4H, d, 3.5- and 3',5'-H), 3.21 (12H, s, (NMe_2)_2), 4.24 (4H, t, (N=CH=CH_2)), 1.76 (4H, m, (N=CH=CH_2) ppm; 1^3C NMR δ 159.40, 143.71, 109.48, 41.86, 58.40 and 29 ppm; MS (EI 70 eV) m/z 456 (M^+-4), 122 (100%, base peak) (Found: C, 40.61; H, 6.79; N, 10.34. Calcd. for C_{18}H_{38}N_4Br_2: C, 40.60; H, 6.70; N, 10.52%).

1,5-Bis(4-dimethylaminopyridinium)pentane dibromide (5):

Reaction time 6 h, yield 92%, m.p. 238-240°; UV λ_max (e) 287 (35370), reduction potential vs Ag/Ag^+: -448 and -836 mV; IR 1643, 1560, 1400 and 1178 cm^-1; 1^H NMR δ 8.37 (4H, d, 2.6- and 2',6'-H), 7.08 (4H, d, 3.5- and 3',5'-H), 3.22 (12H, s, (NMe_2)_2), 4.23 (4H, t, (N=CH=CH_2)), 1.83 (4H, m, (N=CH=CH_2)) ppm; 1^3C NMR δ 157.56, 143.78, 109.43, 41.87, 7.89, 31.32 and 24 ppm; MS (EI 70 eV) m/z 474 (M^+-4), 121 (100%, base peak) (Found: C, 39.01; H, 6.98; N, 9.41. Calcd. for C_{19}H_{30}N_4Br_2: C, 39.17; H, 7.21; N, 9.62%).

1,6-Bis(4-dimethylaminopyridinium)hexane dibromide (6):

Reaction time 3 h, yield 93%, m.p. 184-186°; IR 1652, 1569, 1403 and 1180 cm^-1; 1^H NMR δ 8.36 (4H, d, 2.6- and 2',6'-H), 7.09 (4H, d, 3.5- and 3',5'-H), 3.24 (12H, s, (NMe_2)_2), 4.23 (4H, t, (N=CH=CH_2)), 1.76 (4H, m, (N=CH=CH_2)) ppm; 1^3C NMR δ 157.56, 143.75, 109.40, 41.47, 58.17, 3.78 and 26 ppm; MS (EI 70 eV) m/z 488 (M^+), 121 (100%, base peak) (Found: C, 42.81; H, 7.71; N, 9.61. Calcd. for C_{20}H_{32}N_4Br_2: C, 42.85; H, 7.85; N, 10.0%).

1,10-Bis(4-dimethylaminopyridinium)decan dibromide (7):

Reaction time 1 h, yield 95%, m.p. 72-73°, reduction potential vs Ag/Ag^+: -468 and -938 mV; IR 1648, 1560, 1410 and 1176 cm^-1; 1^H NMR δ 7.96 (4H, d, 2.6- and 2',6'-H), 6.8 (4H, d, 3.5- and 3',5'-H), 3.17 (12H, s, (NMe_2)_2), 4.2 (4H, t, (N=CH=CH_2)), 1.78 (4H, m, (N=CH=CH_2)) ppm; 1^3C NMR δ 159.16, 144.22, 110.36, 42.23, 60.53, 32.72, 31.16, 30.89 and 28.04 ppm (Found: C, 46.35; H, 7.76; N, 8.95. Calcd. for C_{32}H_{40}N_4Br_2: 4H_2O: C, 46.75; H, 7.79; N, 9.0%).

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