A Convenient Modified Short Route for the Preparation of [32]ane-N_8 Hydrochloride

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A convenient modified short-cut route for the preparation of a 32-membered octaazamacrocyclic molecule, 1,5,9,13,17,21,25,29-octaazacyclodotriacontane hydrochloride, [32]ane-N_8·8HCl has been described. The proper tetramine has been contemplated to go this new pathway which propagates [32]-N_8·8HCl more effectively.

Keywords: Macrocyclic polyamines; [32]ane-N_8·8HCl; Convenient way.

INTRODUCTION

Macrocyclic polyaza ligands have shown their double roles in coordination chemistry. They afford stable complexes with transition metal ions[1-5] as well as with inorganic or organic anions.[6-14] Anions play important roles in both chemical and biochemical processes[15] and their complexation by synthetic macropolycyclic polyammonium receptor molecules is an area of intense research interest.[6-14] In some instances, these ligands have shown their capability to catalyze biologically significant reactions of the bound substances.[16-19] The protonated forms of polyazamacrocycles having highly positive charges act as anionic receptors in aqueous solution even at neutral pH, and they have an ability to form multisided hydrogen-bonding networks. The result of second sphere interaction between anionic receptors and complex, neutral or charged species provides complexes called 'super-complexes'. Recently, anion receptors have been applied in anion transport in construction of ion selective electrodes and in separation science.[14,20-30] Our laboratory has prepared macrocyclic polyamine bonded phases and applied them in the electrophoretic separation of organic and inorganic anions and metal ion speciation.[12,22-29] The biologically relevant anions neucleotide polyphosphates, in particular adenosine mono-, di- and tri-phosphates are basic components in the bioenergetics of all living organisms[31,32] as well as being the centre for chemical energy storage and transfer being their polyphosphate chains, are selectively and strongly bound with the protonated form of macrocyclic polyamines. The chemical force which exists in between the cationic binding sites (ammonium groups) of the receptors and the negatively charged polyphosphate groups is the electrostatic force of attraction.[8-10,31]

The macrocyclic polyamine 1,5,9,13,17,21,25,29-octaazacyclodotriacontane, [32]ane-N_8 can be octaprotonated in weakly acidic solution to give [32]ane-$N_8H_8^{8+}$ and has acted as a molecular receptor which binds strongly a number of organic and inorganic anions, forming stable complexes especially with the anionic metal hexacyanides.[33-35] Electrochemical modification[35,36] and photochemical[37] properties of the complexed anion has been reported. It has been shown to induce the dimerization of negatively charged porphyrins in micromolar concentrations.[38] Another useful application has been reported where it converted into unimolecular polyamine-polyhydroxy cores for the accommodation of polar guests as a consequence of solubilization of sugars in apolar organic media via flexible intramolecular polar microsolvation.[39] The advent of new methodologies for the synthesis of macrocyclic polyamines is the consequence of their versatility.[40] Due to the potential applications of [32]ane-N_8 in a variety of areas, an efficient and convenient synthetic route towards this compound is in high demand.

The first synthesis of [32]ane-N_8 was reported by Jean-Marie Lehn et al.[33,34] They took proper triamine as the starting material; the triamine was initially functionalized by the tosyl groups (Ts), affording tosylated triamine (3N, where N is amine-N). The obtained tosylated triamine was then divided into two parts. One part was successively converted to

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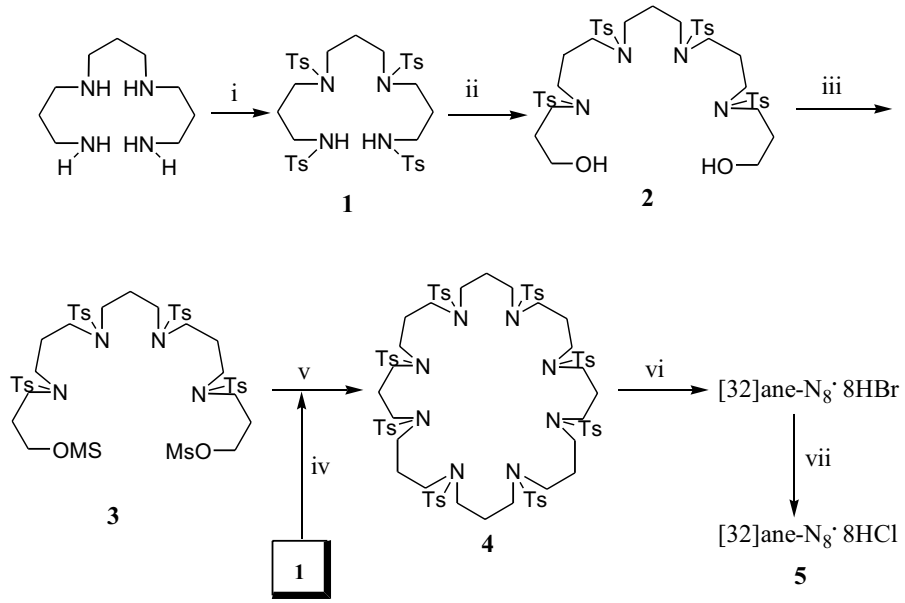
tosylated pentamine (5N) following these steps: (1) Michael addition of acrylnitrile by tritosylated triamine, (2) reduction of the corresponding nitrile groups to amines and (3) further N-tosylation of the newly formed amines. To get the desired [32]ane-N_8, the final cyclization step involved a (3N + 5N) combination where the tosylated triamine (3N) was brought after alkylation with 3-chloropropanol; then converted the hydroxy groups of the resulting diol into good leaving groups by methanesulfonylchloride (MsCl), and further reacted with the dianion of tosylated pentamine. This synthetic pathway is a quite lengthy and time consuming process. In this contribution, we would like to report a new synthetic strategy for the preparation of [32]ane-N_8 under the consideration of a proper tetramine as a starting material. Our new (4N + 4N) pathway will lead to [32]ane-N_8 more efficiently.

RESULTS AND DISCUSSION

The advantages of our innovative route over the previously reported method by Jean-Marie Lehn et al.,[33,34] are simplicity, short length of time and convenience for the preparating of [32]ane-N_8. The way of preparation of [32]ane-N_8 is depicted in Scheme I. The synthesis started with the tosylation[34] of tetramine, N,N′-bis(3-aminopropyl)-1,3-propanediamine which is commercially available at a reasonable price, affording N,N′,4,8-tetra(*p*-toluenesulfonyl)-4,8-diazaundecane-1,11-diamine (**1**) with a yield of 84%. Alkylation of compound (**1**) on the terminal tosylated-N with 3-chloro-1-propanol in DMF at 110 °C gave 4,8,12,16-tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane-1,19-diol (**2**) in 66% yield. The two hydroxyl groups in diol **2** were further converted to be the good leaving groups with methanesulfonylchloride (MsCl) to give 1,19-di(methanesulfonyl)-4,8,12,16-tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane (**3**) with an isolated yield of 97%. Compound **3** was then subjected for the final cyclization with the dianion of compound **1**.

As a consequence tosylated cyclic 32-membered, [32]ane-$N_8(Ts)_8$ was obtained in 45% yield. Detosylation with 33% HBr-AcOH/PhOH at 80 °C provided the bromide salt of 1,5,9,13,17,21,25,29-octaazacyclodotriacontane. Passing through anion exchanger resin Dowex 1X8/Cl^- gave the chloride salt of 32-membered macrocyclicpolyamine, [32]ane-$N_8H_8^{8+}\cdot 8HCl^-$, with a yield of 82%. Our simple and more efficient synthetic pathways took measured with proper tetramine as a starting material. The final cyclization step was guided by a (4N + 4N) combination. Thus, in our attempt, there is no need to endeavor to increase the amine-containing chain length. This minor modification has been signifi-

Scheme I



Reagents: (**i**) TsCl/K_2CO_3/H_2O; (**ii**) 3-chloro-1-propanol/K_2CO_3/DMF; (**iii**) MsCl/Et_3N/dry CH_2Cl_2/-18 °C; (**iv**) NaH/DMF/stir at rt; (**v**) DMF/110 °C; (**vi**) 33% HBr-AcOH/PhOH/80 °C; (**vii**) Dowex 1X8/Cl^-.

cant for the omission of three tedious steps: Michael addition of tritosylated triamines (3N) on acrylnitrile, reduction of corresponding nitrile groups to amines and further N-tosylation; those were compulsory in the previously reported method for the synthesis of [32]ane-N_8.

CONCLUSION

We have established a convenient short-cut route to prepare the 32-membered macrocyclicpolyamine, 1,5,9,13,17,21,25,29-octaazacyclodotriacontane hydrochloride, [32]ane-N_8·8HCl, starting with a proper tetramine instead of a triamine. Our present contribution has made the synthesis of this intriguing macrocyclicpolyamine more convenient and efficient.

EXPERIMENTAL

DMF and triethylamine were distilled from CaH_2 and KOH, respectively, and stored over 4 Å molecular sieves. All other chemicals were analytical reagent grade used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker AC-400 spectrometer. IR spectra were obtained on a Perkin-Elmer Model 983 spectrophotometer. Mass spectra were measured with a JEOL SX-102 mass spectrometer. HRMS were performed in the same spectrometer in FAB mode.

N,N′,4,8-tetra(*p*-toluenesulfonyl)-4,8-diazaundecane-1,11-diamine (1)[34]

N,N′-Bis-(3-aminopropyl)-1,3-propane diamine (5 g, 27 mmol) and K_2CO_3 (14 g, 10 mmol) were taken in 500 mL water and stirred vigorously at 70 °C, then *p*-toluenesulfonyl chloride (35 g, 180 mmol) was added in several portions over a period of 1 h. Stirring was continued at 70 °C for 4 h. The reaction mixture was allowed to cool overnight. The precipitate was filtered off and washed thoroughly with water. The residue was dissolved in 250 mL of CH_2Cl_2 and washed with 1M HCl and H_2O thoroughly. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in EtOAc-MeOH (1:5 v/v) and slow evaporation resulted in a white solid. The solid was filtered off and dried in a vacuum to afford *N,N′*,4,8-tetra(*p*-toluenesulfonyl)-4,8-diazaundecane-1,11-diamine (18 g, 84%). m.p. 130-132 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74-1.85 (m, 6H), 2.41 (s, 12H), 2.97 (t, J = 12.0 Hz, 12H), 7.60 (d, J = 8.0 Hz, 8H), 7.70 (d, J = 8.0 Hz, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.5, 143.2, 136.6, 135.3, 129.7, 129.6, 126.9, 126.8, 47.4, 46.5, 40.2, 29.5, 28.7, 21.6.

4,8,12,16-Tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane-1,19-diol (2)

Compound **1** (10 g, 120 mmol) and K_2CO_3 (9 g, 60 mmol) in DMF (80 mL) were heated and stirred at 100 °C. A solution of 3-chloro-1-propanol (3.4 g, 36 mmol) in 20 mL DMF was added dropwise over a period of ½ h. The reaction mixture continued to be stirred at 110 °C overnight. Thereafter, the mixture was cooled down and filtered; the solid was washed with CH_2Cl_2. The organic solutions evaporated to dryness. The crude material was dissolved in CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. The pure compound was obtained as an oil after column chromatography on alumina and eluted with 1% MeOH in CH_2Cl_2. Yield: 7.5 g, 66%. IR (KBr) ν 3418, 2932, 2875, 1661, 1596, 1493, 1454, 1384, 1330, 1153, 1088, 1019, 968, 926, 840, 817, 761, 719, 655 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70-1.76 (m, 4H), 1.82-1.90 (m, 6H), 2.38 (s, 12H), 3.08-3.18 (m, 16H), 3.63-3.67 (m, 4H), 7.23-7.29 (m, 8H), 7.60-7.67 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.4, 143.3, 135.5, 129.7, 129.6, 126.8, 59.1, 47.4, 47.2, 47.1, 46.2, 31.8, 29.1, 29.0, 21.6; MS (*m/z*) 921.3 (100, M + 1), 863.3 (28), 765.3 (40); HRMS calcd for $C_{43}H_{61}O_{10}N_4S_4$ (M + H) 921.3271, found 921.3267.

1,19-Di(methanesulfonyl)-4,8,12,16-tetra(*p*-toluenesulfonyl)-4,8,12,16-tetraazanonadecane (3)

Compound **2** (7.5 g, 8 mmol) in 200 mL dry CH_2Cl_2 was stirred, cooled down at -18 °C; Et_3N (5 g, 50 mmol) was added. A solution of methanesulfonyl chloride (2 g, 17 mmol) in 10 mL dry CH_2Cl_2 was added dropwise over a period of ½ h. The resulting mixture was stirred for another 2 h at the same temperature, and then allowed to warm up to room temperature for ½ h. The mixture was washed with 1M HCl and with brine. The organic solution was dried over $MgSO_4$ and evaporated to dryness. This gave the desired waxy solid compound. Yield: 8.5 g, 97%. IR (KBr): ν 3029, 2938, 2873, 1596, 1494, 1459, 1336, 1157, 1089, 1018, 973, 925, 815, 717, 696, 655, 549, 528 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.84-1.91 (m, 6H), 1.96-2.03 (m, 4H), 2.40 (s, 12H), 2.99 (s, 6H), 3.01- 3.19 (m, 16H), 4.26 (t, J = 11.6 Hz, 4H), 7.26-7.31 (m, 8H), 7.60-7.64 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 135.5, 135.4, 129.7, 127.0, 67.5, 47.4, 47.2, 45.8, 37.4, 29.1, 28.9, 21.6; MS (*m/z*) 1077.3

(100, M + 1), 941.3 (28), 921.2 (33), 785.3 (15), 730 (10); HRMS calcd for $C_{45}H_{65}O_{14}N_4S_6$ (M + H) 1077.2822, found 1077.2809.

1,5,9,13,17,21,25,29-Octa(*p*-toluenesulfonyl)-1,5,9,13,17,21,25,29-octaazacyclodotriacontane (4)[34]

Compound **1** (8.9 g, 11 mmol) was dissolved in DMF (200 mL) and then NaH (1.5 g, 63 mmol) was added wholly at the same time. After stirring for 2 h at room temperature the excess NaH was discarded by filtration and the filtrate having dianion of compound **1** was stirred at 110 °C. A solution of compound **3** (12 g, 11 mmol) in 30 mL DMF was added dropwise within 10 min. to the solution of dianion. After complete addition, the resulting mixture was maintained under the same conditions for another 3 h. Thereafter the solution was evaporated and the residue was partitioned between 400 mL CH_2Cl_2 and 1M HCl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to dryness thus providing the crude product. The desired compound was purified by column chromatography on silica gel and eluted with 1% MeOH in CH_2Cl_2. Solid crystalline product was obtained from CH_2Cl_2EtOH (1:2 v/v). Yield 8 g, 45%. m.p. 186-188 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.85 (br, 16H), 2.38 (s, 24H), 3.08 (m, 32H), 7.26-7.32 (m, 16H), 7.58-7.65 (m, 16H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.5, 143.2, 135.7, 129.9, 129.6, 127.1, 126.9, 49.1, 47.1, 31.6, 28.9, 21.6; MS (*m/z*) 1090.6 (100, M+1), 1533.6 (84), 1379.5 (40), 845.3 (116), 689.3 (60).

1,5,9,13,17,21,25,29-Octaazacyclodotriacontane hydrochloride (5)[34]

Compound **4** (4 g, 24 mmol), phenol (6 g, 60 mmol), and a 100 mL 33% HBr-AcOH mixture were heated at 80 °C with vigorous stirring for 48 h. Thereafter, the solvent was distilled off under vacuum and the residue was refluxed with 300 mL Et_2O. The pale brown solid was isolated by filtration and washed thoroughly by acetone, CH_2Cl_2 successively. The crude [32]ane-N_8·8HBr was dissolved in a minimum volume of water, filtered and then allowed to pass over a column of Dowex 1X8 resin in chloride form. The pH of the aqueous solution was maintained at 2-3 with 2M HCl. The solution was evaporated to dryness under vacuum and the residue was recrystallised from hot aq. EtOH providing [32]ane-N_8·8HCl as white needles. Yield 1.4 g, 82%. m.p. > 250 °C; ^{1}H-NMR (400 MHz, D_2O) δ 2.09-2.16 (m, 16H), 3.07-3.20 (m, 32H); ^{13}C-NMR (75 MHz, D_2O) δ 45.2, 44.9, 23.4, 23.0; MS (*m/z*) 493.4 (40, M+1), 457.5 (100), 431.5 (36), 369.2 (56).

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