Tetrahedron Vol. 42, No. 1, pp. 137 to 141, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00

THE SYNTHESIS OF ASYMMETRIC MACROCYCLIC POLYETHERS CONTAINING NITRO GROUP ON AROMATIC RING

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(*Received in UK* 11 *October* 1985)

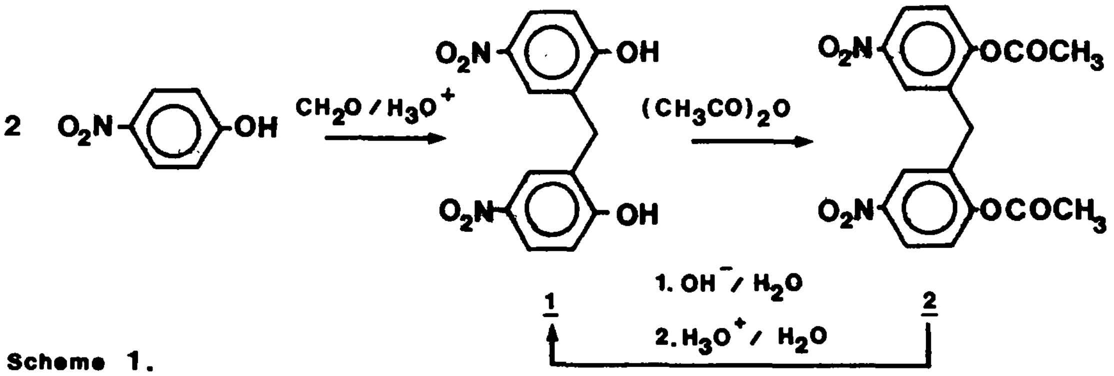
Abstract - The macrocyclic polyether: 12,18-dinitro-2,5,8-trioxatricyclo *(14,4,0,0^{9,14})* eicosa-1(20),9,11,13,16,18-hexaene (6): 15,21-dinitro-2,5,8,11-tetraoxatricyclo *(17,4,0,0^{12,17})* tricosa-1(23),12,14,16,19,21-hexaene (7) and 18,24 dinitro-2,5,8,11,14-pentaoxatricyclo *(20,4,0,0^{15,20})* hexacosa-1(26),15,17,19,22,24-hexaene (8) have been synthesized by reaction of 2,2'-methylenebis (4-nitrophenol) (1) with diethylene glycol ditosylate (3) triethylene glycol ditosylate (4) and tetraethylene glycol ditosylate (5) respectively in the presence of KOBu-t. These compounds did not form stable complexes with alkali and alkaline-earth cations. The macrocyclic polyethers were purified by chromatography and crystallization. The structures of these new compounds have been determined by elemental analysis, molecular weight determination, ^{1}H NMR, IR and UV spectra.

The synthesis and complexing abilities of macrocyclic polyethers with cations have been widely investigated.[1,2,3] So far, catechol, glycols, 2,2'-dihydroxydiphenyl, 2,2'-dihydroxydinaphtyl and their derivatives have been utilised in the synthesis of macrocyclic polyethers.[1,4-11]

In these experiments, macrocyclic polyethers, (6,7 and 8),[12] which carry nitro groups on two different benzene rings, were prepared directly by taking 2,2'-methylenebis(4-nitrophenol)[16,17] as starting material and their properties were studied.

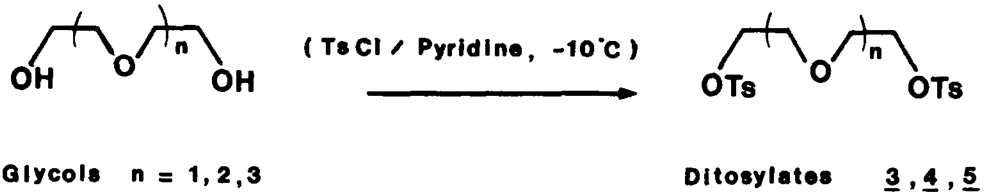
RESULTS AND DISCUSSION

2,2'-Methylenebis(4-nitrophenol) (1) was prepared according to Chattaway and Goep[16] method by reacting p-nitrophenol and formaldehyde (Scheme 1). The crude product obtained from this reaction



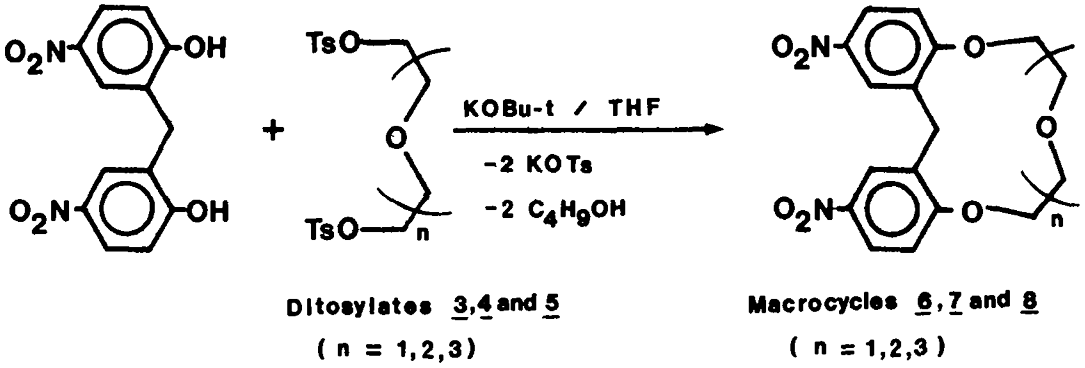
Scheme 1.

was treated with 4% NaOH solution and filtered off. The solution was then acidified with HCl solution and the precipitated compound was filtered off and dried. However, the purity of the compound so obtained was observed to be unsatisfactory and therefore it was purified by the preparation of its diacetyl derivative (2) with acetic anhydride. Then compound (1) was recovered by the saponification of the recrystallized diester (2). The compound (1) obtained in this way was found to be easily crystallizable from glacial acetic acid-water mixture. This method was found to be superior to the method given by Bohmer and Lotz[17] in terms of overall yield (53% yield has been reported by Bohmer and Lotz, compared to our 74.5%). The ditosylates, (3, 4 and 5) were prepared by general esterification process[4,18,19] (Scheme 2).



Scheme 2.

The ditosylates synthesized in this way were treated with (1) in basic solution (experimental section, in procedure-a KOBu-t, procedure-b K_2CO_3). These reactions were carried out in dry tetrahydrofuran (THF)-KOBu-t solution and the following asymmetric macrocyclic polyethers (6, 7 and 8) were isolated (Scheme 3). THF is the preferred solvent for these reactions because the tosylate salts formed during the reactions are insoluble in this solvent and cause no difficulty in their removal.



Scheme 3.

The structures of these crown compounds "coronands" were suggested on the basis of elemental analysis, molecular weight determination, ^1H NMR, IR and UV spectra. Characteristic OH stretching band observed at 3330 cm^{-1} in the IR spectrum of (1) is not observed in the spectra of compounds (2), (6), (7) and (8). The characteristic C=O stretching band for compound (2) is present at 1770 cm^{-1}. In the IR spectra of all the compounds synthesized, characteristic NO_2 bands at 1510 cm^{-1} and 1340 cm^{-1} and also alkylether ($-CH_2-O-$) and arylether ($Ar-O-CH_2-$) bands are observed at 1160-1080 cm^{-1} and at 1265 cm^{-1} respectively. Peaks due to OH, aromatic protons and benzylic protons ($Ar-CH_2-Ar$) of the compound (1) are observed at 10.4 ppm, 7.0-8.3 ppm and 4.18 ppm respectively. OH resonance peaks are not present in the spectra of macrocyclic polyethers (6), (7) and (8). The peak due to benzylic protons ($Ar-CH_2Ar$) seem to be partly superimposed with the one due to $ArO-CH_2-$ protons (at 4.0-4.3 ppm). The multiplets at 4.0-4.3 ppm and 3.6-4.0 ppm intervals are due to Ar-O-CH_2- and -CH_2-O- protons respectively. The values observed for aromatic protons fit well with those given in the literature[20,21] for crown ethers and cryptands. Characteristic IR and ^1H NMR data of the compounds support the proposed structures given in Figure 1.

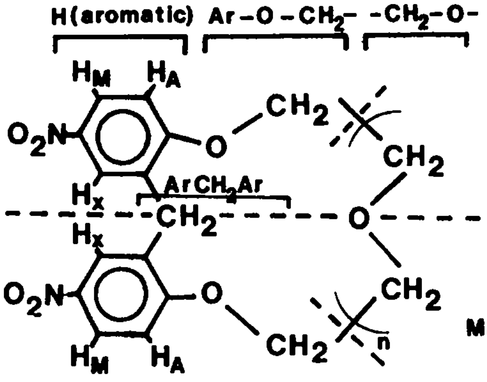


Figure 1

Macrocycles (n = 1,2,3)
6, 7 and 8

Spectral data, melting points, elemental analysis results and molecular weights are given in the relevant parts of the experimental section. Molecular weight determinations show that only the monomeric products have been isolated from Scheme 3. In spite of the expectations from Scheme 3 that the dimeric-products would form, no special effort was made for that purpose. It can also be seen that a significant reduction occurs in the melting points as the macro-ring gets larger.

The general formulae of symmetric-macrocyclic polyethers can be written in the form 3n-c-n whereas the asymmetric-macrocyclic polyethers prepared by us can be written in the slightly different form (3n+3)-c-n where (n) indicates the number of the heteroatoms in the macro-ring. The hole sizes of these synthesized coronands can be predicted from the data obtained from the literature.[22] The predicted values are 1.20 A^o for (6); 1.70-2.20 A^o for (7) and 2.60-3.20 A^o for (8). It was not possible to prepare complexes with alkali and alkaline-earth cations. The picrate test[23] gave negative results with their salts. This can be explained by the reduction of the basicity power of oxygens on the macro-ring by the effect of benzene rings carrying nitro group and the distortion of the macro-ring by the benzylic-CH_2- group which hinders the cations from being surrounded by oxygens and therefore the formation of metal complexes. Also in the literature[24] it is reported that hexabenzo-18C6 and heptabenzo-21C7 are noncomplexing.

EXPERIMENTAL

General

^1H NMR, IR and UV spectra were taken on Varian T60-A (60 MHz), Perkin Elmer 377 and Beckman DB-G instruments respectively. Molecular weights were determined by vapour phase osmometry in $CHCl_3$ using a Hitachi-Perkin Elmer 115 molecular weight apparatus. C and H percentage were determined by "Microanalyticshes Laboratorium-Beller 34 Göttingen-Theaterstrasse 23, Germany". Nitrogen analyses were performed according to the Kjeldahl method. Melting points were determined in air employing a Thomas-Hoover apparatus using a capillary tube and all the values reported are uncorrected.

Starting materials

All starting glycols were purchased from Fluka and were distilled from anhydrous $CuSO_4$ prior to use. Dimethylformamide (DMF) was also distilled from KOH, benzene and THF were distilled from metallic sodium prior to use, respectively. All reactions involving K_2CO_3 and KOBu-t were conducted in an inert atmosphere of N_2. Ditosylates, diethylene glycol ditosylate (3), triethylene glycol ditosylate (4) and tetraethylene glycol ditosylate (5) were prepared as described in the literature.[4,18,19]

2,2'-Methylenebis(4-nitrophenol)(1)

27.8 gr (0.20 mole) of p-nitrophenol and 5 ml of water were put into a three-necked flask of 500 ml capacity. A mechanical stirrer was mounted and the mixture was heated to 75 °C on a water-bath. Then 24.0 ml of conc. H_2SO_4 and 10 ml of 40% aqueous CH_2O (1 mole) was mixed into the mixture and stirred thoroughly. Using an oil bath the temperature was kept between 120-128 °C. After about an hour a greenish semi-solid mass formed, and it was dissolved in 4% NaOH solution and filtered off. The dark-red coloured filtrate was reprecipitated by adding 5M HCl solution; filtered off again and washed with distilled water and the solid product dried at 110 °C. The product could not be recrystallized from glacial acetic acid. The compound decomposed at 268 °C (lit,[16] mp 268 °C). The yield was 26.1 gr (90%).

2,2'-Methylenebis(4-nitrophenylacetate)(2)

40 gr (0.136 mole) of (1) was added to a flask fitted to a reflux-condenser. Then 40 ml (32.64 gr, 0.32 mole) of acetic anhydride and 2-3 drops of H_2SO_4 were added by constant stirring. The system was boiled (for about 2 hours) until all of (1) was dissolved. Then it was cooled down and solid-white product was filtered off. The product was recrystallized from glacial acetic acid. The yield was 47.4 gr (92%), m.p. 156 °C (lit,[16] 153 °C), IR (KBr pellet, cm^{-1}): 3090 (aromatic C-H), 1770 (sharp, C=O), 1520 (sharp, NO_2, asym.) 1350 (sharp, NO_2, sym.). ^1H NMR ($CDCl_3$, TMS, δppm): 4.2 (s, 2H, Ar-CH_2-Ar), 2.2 (s, 6H, $OCOCH_3$), 7.0 (d, J_{AM}=9H_z, 2H), 7.8-8.3 (m, 4H, H_M+H_X). UV[$CHCl_3$ (ε)]: 241 (8.1×10^3), 273 nm (1.9×10^4).

Hydrolysis of 2,2'-methylenebis(4-nitrophenylacetate) (2)

29.2 gr (0.05 mole) of (2) was put into a 500 ml flask and treated with a little excess of 4% NaOH solution. The mixture was boiled for about 1.5-2.0 hours by constant stirring. After (2) was completely saponified it became a clear orange-coloured mixture. After cooling it was filtered off and then the solution was acidified with HCl solution. The regenerated (1) was filtered off and recrystallized from glacial acetic acid. Needle-shaped crystals were formed. The yield was 20.8 gr (90%). The overall yield calculated from p-nitrophenol was found to be 74.5%, m.p. 272 °C (lit,[17] 269-271 °C), IR (KBr pellet, cm^{-1}): 3330 (broad, OH), 3080 (aromatic C-H), 2940 (aliphatic C-H), 1510 (sharp, NO_2 asym.) 1340 (sharp, NO_2 sym.). ^1H NMR ($CDCl_3$, TMS, δppm): 4,2(s, 2H, Ar-CH_2-Ar), 7.0 (d, J_{AM}=9H_z, 2H, H_A), 7.8-8.2 (m, 4H, H_M+H_X), 10.4 (broad, OH). UV[$CHCl_3$(ε)]: 244 (2.0×10^4), 314 nm (3.1×10^4).

General Synthesis

a) A dropping funnel, a thermometer and a reflux-condenser were fixed to a four-necked flask of one litre capacity. Then THF (350 ml) and 2,2'-methylenebis(4-nitrophenol) (0.02 mole) were added to the flask and N_2 gas was bubbled through the mixture. The mixture was thoroughly stirred with a mechanical stirrer and heated to 40 °C. Then 2.24 gr (0.02 mole) of KOBu-t was added to the system and boiled for 20 minutes. After that the ditosylate (0.01 mole) previously dissolved in dry THF (75 ml) was added to this mixture dropwise by a dropping funnel over a period of 1.5 hours. After the completion of this procedure another 2.24 gr (0.02 mole) portion of KOBu-t was added to the mixture and it was boiled for 20 minutes. Then a solution of 0.01 mole of the ditosylate in 75 ml of dry THF was again added dropwise to the flask over a period of 1.5 hours. The reaction was continued for 24 hours before the mixture was cooled down and the precipitate was filtered off. The solvent (THF) was removed under reduced pressure and the remaining yellow-coloured product was washed first with a 4% NaOH aq.-methanol (1:1) and then methanol-water (2:3) mixture. The crude product was filtered off and dried at 120 °C. A preliminary chromatographic separation was carried out on Alumina (Merck, neutral, 70-230 mesh) column using $CHCl_3$ as solvent. Then a second chromatographic separation was done on silicagel 60 (Merck, 70-230 mesh) column using n-hexane, n-propanol, ether (1:1:1) mixture as eluent.

b) The reaction procedure was similar to that described in procedure (a), but here instead of THF and KOBu-t, DMF and K_2CO_3 (dried at 280 °C) were used. The overall reaction time was 25 hours. The crude product was isolated in two ways after the completion of the reaction: i) The mixture was poured into pure water and left for two days and the precipitate was filtered off. Here the compound was dispersed in a colloidal state and did not precipitate for a long time. Furthermore, it takes a long time to filter this precipitate. ii) Two-thirds of DMF was removed from the reaction mixture under reduced pressure. Then 500 ml of methanol was added to the remaining mixture and the resulting mixture was boiled for 10 minutes. The precipitate formed after cooling the system was filtered off. The crude product was first washed with 4% NaOH solution and then water-methanol (1:1) mixture and dried at 120 °C. The compound was purified by chromatography as described in procedure (a). Specific details are given for each crown compound as follows.

12,18-Dinitro-2,5,8-trioxatricyclo (14,4,0,$0^{9,14}$) eicosa-1 (20), 9,11,13,16,18-hexaene (6)

This macrocyclic polyether has been synthesized according to the general procedures described above. 5.80 gr (0.02 mole) of (1), 8.28 gr (0.02 mole) of (3) and 4.48 gr (0.04 mole) of KOBu-t were used for the preparation. The crude product was recrystallized from acetonitrile and glacial acetic acid-water mixture. The reaction yields were calculated for the products prepared according to process (a) and (b) as 1.86 gr (26%) and 1.42 gr (20%) respectively, m.p. 273 °C. The compound is soluble in cold CH_2Cl_2, $CHCl_3$ and ϕ-NO_2; in hot MeCN. IR(KBr pellet, cm^{-1}): 3090 (aromatic C-H), 2930-2870 (aliphatic C-H), 1510 (sharp, NO_2 asym.), 1340 (sharp, NO_2 sym.), 1265 (aromatic C-O-C, asym.), 1160-1090 (aliphatic C-O-C, asym.), 1060 (aromatic C-O-C, sym.). ^1H NMR ($CDCl_3$, TMS, δ ppm): 3.9-4.1 (m, 4H, -CH_2-O-), 4.1-4.3 (m, 6H, Ar-CH_2Ar+Ar-O-CH_2), 7.0 (d, J_{AM}=9H_z, 2H, H_A), 8.0 (dd, J_{AM}=9H_z, J_{MX}=3H_z, 2H, H_M), 8.3 (d, J_{MX}=3H_z, 2H, H_X), [UV $CHCl_3$(ε)]: 245 (9.2×10^3), 313 nm (1.9×10^4). Found: C, 57.02; H, 4.62; N, 7.45; mol. wt., 356. Calc. for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.48; N, 7.77%; mol. wt., 360, 322.

15,21-Dinitro-2,5,8,11-tetraoxatricyclo (17,4,0,0^{12,17}) tricosa-1 (23), 12,14,16,19,21-hexane (7).

This compound has only been prepared according to procedure (a) and 5.80 gr (0.02 mole) of (1), 9.16 gr (0.02 mole) of (4) and 4.48 gr (0.04 mole) of KOBu-t were used during the process. The product was recrystallized from glacial acetic acid-water mixture, the yield was 2.45 gr (30%), m.p. 240 °C. It is soluble in cold CH_2Cl_2, $CHCl_3$, and Ø-NO_2; in hot MeCN and glacial acetic acid. IR (KBr pellet, cm^{-1}): 3080 (aromatic C-H), 2930-2860 (aliphatic C-H), 1510 (sharp, NO_2 asym.) 1340 (sharp, NO_2 sym.) 1265 (aromatic C-O-C, asym.), 1160-1090 (C-O-C, asym.), 1050 (aromatic C-O-C-, sym.). ^{1}H NMR ($CDCl_3$, TMS, δppm): 3.6-4.0 (m, 8H, -CH_2-O-), 4.0-4.3 (m, 6H, Ar-CH_2-AR+Ar-O-CH_2), 6.9 (d, $J_{AM}=9H_z$, 2H, H_A), 8.0 (dd, $J_{AM}=9H_z$, $J_{MX}=3H_z$, 2H, H_M), 8.2 (d, $J_{MX}=3H_z$, 2H, H_X). [UV $CHCl_3$(ε)]: 245 (8.5 x 10^3), 315 nm (2.0 x 10^4). Found: C, 56.61; H, 4.72; N, 7.15; mol. wt., 405. Calc. for $C_{19}H_{20}N_2O_8$: C, 56.46; H, 4.95; N, 6.93 %; mol. wt., 404.375.

18,24-Dinitro-2,5,8,11,14-pentaoxatricyclo(20,4,0,0^{15,20}) hexacosa-1(26), 15,17,19,22,24-hexaene(8)

This macrocyclic polyether was also prepared according to procedure (a), by treating 5.80 gr (0.02 mole) of (1), 10.04 gr (0.02 mole) of (5) and 4.48 gr (0.04 mole) of KOBu-t. The reaction yield of the product recrystallized from glacial acetic acid-water mixture was found to be 3.96 gr (44%), m.p. 214 °C. The solubility behaviour of this compound is the same as those reported for compound (7) above. IR (KBr pellet, cm^{-1}): 3090 (aromatic C-H), 2930-2870 (aliphatic C-H), 1500 (sharp, NO_2 asym.), 1340 (sharp, NO_2 sym.), 1260 (aromatic C-O-C, asym.), 1160-1090 (aliphatic C-O-C, asym.), (aromatic C-O-C, sym.). ^{1}H NMR ($CDCl_3$, TMS, δppm): 3.6-4.0 (m, 12H, -CH_2-O-), 4.0-4.2 (m, 6H, Ar-CH_2-Ar+Ar-O-CH_2-), 7.0 (d, $J_{AM}=9H_z$, 2H, H_A), 7.8 (dd, $J_{AM}=9H_z$, $J_{MX}=3H_z$, 2H, H_M), 8.2 (d, $J_{MX}=3H_z$, 2H, H_X). [UV $CHCl_3$(ε)]: 245 (7.5 x 10^3), 315 nm (2.0 x 10^4). Found: C, 56.04; H, 5.58; N, 6.12; mol. wt., 449. Calc. for $C_{21}H_{24}N_2O_9$: C, 56.27; H, 5.36; N, 6.25 %; mol. wt., 448.428.

Acknowledgements

We would like to thank Mrs Ihsan Onbasioglu for recording ^{1}H NMR spectra.

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12 The nomenclature used herein is that of IUPAC's.[13] Compounds (6), (7) and (8) can be named as (6): 2,3,5,6-bis[5'(5')-nitrobenzo]-12C3 (c:crown); (7) 2,3,5,6-bis[5'(5'-nitrobenzo]-15C4; (8): 2,3,5,6-bis[5'(5')-nitrobenzo]-18C5 according to Pedersen[1] system and as (6): 11,17-dinitro-1,4,7-trioxa [7] (1,2)benzeno [1] (1,2)benzenophane (7): 14,20-dinitro-1,4,7,10-tetraoxa [10] (1,2)benzeno [1] (1,2)benzenophane (8): 17,23-dinitro-1,4,7,10,13-pentaoxa [13] (1,2)benzeno [1] (1,2)benzephane according to -"Phane[14,15] convention".
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