Notes

Synthesis of Multidentate 1,3,4-Oxadiazole-, Imine-, and Phenol-Containing Macrocycles

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Received August 12, 1992

Introduction

Macrocycles containing a salen-type coordination site for a soft cation together with a polyether cavity that binds a hard cation have been reported.[1,2] Such macrocycles have been found to be useful for urea transport.[3] Macrocyclic ligands able to complex two transition-metal cations with charge compensation and one alkali metal or alkaline earth cation have also been reported.[4] There are few examples of cyclic complexes containing both a transition-metal ion and a non-transition-metal ion.[5] The formation of salen-type units, both in the presence and in the absence of template cations, usually takes place in high yield.[6,7] A good yield was obtained even in the formation of a hexaimine ditopic macrobicycle by the multiple nontemplated condensation of an amine and an aldehyde.[8] In this paper, we report the synthesis of multidentate macrocycles with two salen-type coordination sites potentially able to bind divalent transition metal cations with electron neutrality. The macrocyclization step involves the nontemplated formation of the imino phenol subunits.

Results and Discussion

An excess of hydrazine hydrate was added slowly to a solution of acid chloride 1 in dichloromethane by means of a syringe pump. The hydrazine acted both as a nucleophile and as a base to capture the HCl evolved in the reaction. This way of addition of the reagents favored the reaction of acid chloride 1 and hydrazine to produce bis(acyl)hydrazine 2 in high yield and minimized the formation of a mono(acyl)hydrazine. Refluxing bis(acyl)-hydrazine 2 in phosphorus oxychloride afforded cyclization product bis(allyloxy) oxadiazole 3 in high yield. The allyloxy group protects the phenol and prevents it from interfering in the cyclization step and the previous step. After the cyclization, the allyl group was used to functionalize the position ortho to the phenol by means of a Claisen rearrangement.[9] The Claisen rearrangement, which was achieved by heating the bis(allyloxy) oxadiazole 3 at 200 °C, afforded bisallyl oxadiazole 4. The double bond of the allyl group was isomerized into conjugation with the aryl group under basic conditions: a large excess of potassium *tert*-butoxide in warm DMSO. The predominant formation of bis(*trans*-1-propenyl) oxadiazole 5 was observed. Oxadiazole 5 was freed from the cis–trans and cis–cis impurities by recrystallization. These isomers would not have affected the next step, ozonolysis of the double bond, as all of them would have lead to the same dialdehyde (6). The oxidative cleavage of the double bond of 5 could have been carried out with an excess of sodium metaperiodate and a catalytic amount of osmium tetroxide, but the use of ozone proved to be more convenient to prepare dialdehyde 6.

The ^{1}H-NMR spectrum of 6 shows phenol protons at δ 11.2 ppm and aldehyde protons at 10.33 ppm. The aldehyde carbons appear at δ 190.5 ppm in ^{13}C-NMR. In the IR spectrum, the stretching frequency of the phenolic OH appears at 3340 cm^{-1} and that of the carbonyl at 1650 cm^{-1}. Dialdehyde 6 is poorly soluble in most organic solvents, has a high melting point (280–281 °C), and does not give the molecular peak in the electron impact mass spectum, unlike the precursors.

The (2 + 2) macrocyclization of dialdehyde 6 and an equimolar amount of either 1,2-benzenediamine or 1,2-ethanediamine was carried out by heating moderately dilute solutions at reflux in acetonitrile. Macrocycle 7 (74%) or 8 (82%) were obtained as orange or yellow powders, respectively. They do not melt under 350 °C and are insoluble in all common organic solvents. Their ^{1}H-NMR spectra in TFA-d_1 show sharp signals; the imine protons appear at δ 9.34 (7) and δ 9.06 ppm (8). Both macrocycles are stable in air for at least 9 months without change. In TFA-d_1 solution, half of macrocycle 7 was hydrolyzed after 4 h at room temperature, whereas for 8 a half-time of 48 h was determined. The IR spectrum of macrocycle 8 shows a band at 1645 for the imine C=N and one at 1620 cm^{-1} for the oxadiazole C=N, but in 7 both bands appear at 1625 cm^{-1}. In the MS, the molecular peak of macrocycle 8 could be seen in low abundance under electron impact, whereas 7 fragmented under these conditions.

Macrocycles 7 and 8 can potentially coordinate two M(II) cations with electron neutrality after deprotonation of the phenol groups. The macrocycles could coordinate two additional cations with external counterions in an MM'M'M fashion. The synthesis of more soluble macrocycles based on 4-propyl-1,2,4-triazole subunits is in progress. Template cyclizations in the presence of an excess of metal salt to arrive at complexes with metal cations that are more soluble than macrocycles 7 and 8 are planned.

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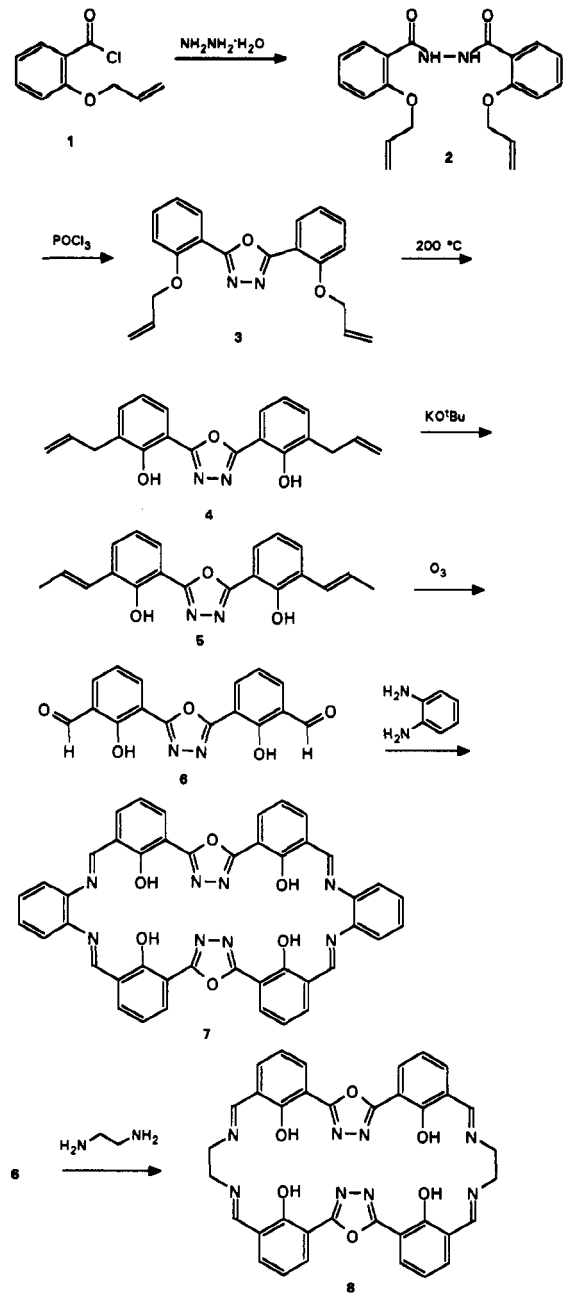

Experimental Section

General. Experimental methods are reported elsewhere.[10] Starting material 2-(allyloxy)benzoic acid was prepared as reported.[11]

Synthesis of 2-(Allyloxy)benzoyl Chloride (1). A mixture of 2-(allyloxy)benzoic acid[11] (0.17 mol, 29.88 g) and thionyl chloride (0.5 mol, 59.85 g) was gently refluxed for 1 h. The thionyl chloride was distilled off at reduced pressure and the acid chloride was distilled in vacuo; bp 80–82 °C (0.15 Torr); yield 32.1 g, 96%.

Synthesis of 1,2-Bis[2-(Allyloxy)benzoyl]hydrazine (2). To a stirred solution of acid chloride 1 (83 mmol, 16.34 g) in CH_2Cl_2 (50 mL) at rt, hydrazine hydrate (250 mmol, 16.65 g) in CH_2Cl_2 (20 mL) was added by means of a syringe pump at a rate of 8 mL/h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), extracted with water (3 × 50 mL), dried ($MgSO_4$), and evaporated; and the residue was recrystallized (methanol): colorless needles, mp 164–165 °C; yield 12.1 g, 82%; ^{1}H-NMR ($CDCl_3$) δ 11.30 (s, 2 H, NH), 8.20 (dd, J_{6-5} = 9.2 Hz, J_{6-4} = 2.5 Hz, 2 H, H_6), 7.40 (m, 2 H, H_4), 7.00 (m, 4 H, H_3, H_5), 6.20 (m, 2 H, H_4), 5.43 (d, J_{trans} = 16.8 Hz, 2 H, =CH_2), 5.37 (d, J_{cis} = 9 Hz, 2 H, =CH_2), 4.85 (d, J = 5.1 Hz, 4 H, OCH_2); ^{13}C-NMR ($CDCl_3$) δ 159.0 (CONH), 156.4 (C-2), 133.2 (C-4), 131.9, 131.8 (C-6, CH=), 121.3 (C-5), 119.3 (=CH_2), 119.0 (C-1), 112.5 (C-3), 70.2 (OCH_2); IR (KBr) 3395 (NH), 1630 (C=O) cm^{-1}; MS m/z 352 (M^+, 9), 161 (100). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.96; H, 5.62; N, 7.89.

Synthesis of 2,5-Bis[2-(Allyloxy)phenyl]-1,3,4-oxadiazole (3). A mixture of hydrazine 2 (102 mmol, 36 g) and phosphorus oxychloride (1.06 mol, 100 mL) was refluxed until the hydrazine completely dissolved (2 h), the excess phosphorus oxychloride was distilled off under reduced pressure, and the residue was washed with water (2 × 100 mL) and purified by flash column chromatography (silica gel, CH_2Cl_2) to give 3 as a pale yellow solid: mp 50–52 °C; yield 32.51 g, 92%; ^{1}H-NMR ($CDCl_3$) δ 8.00 (dd, J_{6-5} = 9.5 Hz, J_{6-4} = 1.9 Hz, 2 H, H_6), 7.40 (m, 2 H, H_4), 7.00 (m, 4 H, H_3, H_5), 6.00 (m, 2 H, CH=), 5.50 (d, J_{trans} = 18 Hz, 2 H, =CH_2), 5.24 (d, J_{cis} = 9 Hz, 2 H, =CH_2), 4.60 (d, J = 4.8 Hz, 4 H, OCH_2); ^{13}C-NMR (DMSO-d_6) δ 162.7 (C=N), 156.3 (C-2), 133.2, 132.9 (CH=, C-4), 130.1 (C-6), 120.9 (=CH_2), 117.0 (C-5), 113.7 (C-3), 112.7 (C-1), 68.7 (OCH_2); MS m/z 334 (M^+, 17), 294 (39), 254 (42), 161 (60), 121 (100). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.54; H, 5.58; N, 8.68.

Synthesis of 2,5-Bis(3-Allyl-2-hydroxyphenyl)-1,3,4-oxadiazole (4). Oxadiazole 3 (13 mmol, 4.30 g) was stirred at 200 °C for 3 h; the reaction was monitored by means of TLC with ethyl acetate as eluent. The product was purified by flash column chromatography (silica gel, CH_2Cl_2) and recrystallized (methanol): needles, mp 162–163 °C; yield 2.57 g, 60%; ^{1}H-NMR ($CDCl_3$) δ 10.12 (s, 2 H, OH), 7.76 (d, J_{6-5} = 7.8 Hz, 2 H, H_6), 7.36 (d, J_{4-5} = 7.8 Hz, 2 H, H_4), 7.00 (t, J_{6-5} = J_{5-4} = 7.8 Hz, 2 H, H_5), 6.05 (m, 2 H, CH=), 5.14 (d, J_{trans} = 17.0 Hz, 2 H, =CH_2), 5.10 (d, J_{cis} = 9.7 Hz, 2 H, =CH_2), 3.52 (d, J = 6.8 Hz, $PhCH_2$); ^{13}C-NMR (DMSO-d_6) δ 162.5 (C=N), 154.1 (C-2), 135.9 (C-4), 133.8 (CH=), 128.1 (C-3), 125.5 (C-6), 119.9 (C-5), 115.8 (=CH_2), 107.8 (C-1), 33.2 ($PhCH_2$); IR (KBr) 3160 (OH), 1610 (C=N) cm^{-1}; MS m/z 334 (M^+, 69), 319 (100), 294 (11), 161 (15). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.72; H, 5.28; N, 8.12.

Synthesis of 2,5-Bis[2-Hydroxy-3-(*trans*-1-propenyl)phenyl]-1,3,4-oxadiazole (5). A suspension of potassium *tert*-butoxide (150 mmol, 16.83 g) in DMSO (75 mL) was heated at 120 °C with stirring until it was completely dissolved. Oxadiazole 4 (15 mmol, 5.01 g) was added, and stirring was continued for 10 min. The DMSO was distilled off at reduced pressure. The residue was treated with 10% HCl (250 mL) and water (500 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layer was dried ($MgSO_4$) and evaporated, and the solid was recrystallized (xylene): mp 208–210 °C; yield 3.35 g, 67%; ^{1}H-NMR ($CDCl_3$) δ 11.56 (s, 2 H, OH), 7.47 (d, J_{6-5} = 7.4 Hz, 2 H, H_6), 7.34 (d, J_{4-5} = 7.6 Hz, 2 H, H_4), 6.77 (t, J_{5-6} = 7.4 Hz, J_{5-4} = 7.6 Hz, 2 H, H_5), 6.67 (d, J_{trans} = 16 Hz, 2 H, PhCH=), 6.28 (dq, J_{trans} = 16 Hz, $J_{(=CH-CH3)}$ = 6.6 Hz, 2 H, =CHMe), 1.81 (d, $J_{(=CH-CH3)}$ = 6.6 Hz, 6 H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 169.8 (C=N), 157.8 (C-2), 131.0 (C-4), 127.0 (C-6), 126.5 (C-3), 125.5 (=CHPh), 124.3 (=CHMe), 118.7 (C-5), 112.5 (C-1), 18.8 (CH_3); IR (KBr) 3270 (OH), 1615 (C=N) cm^{-1}; MS m/z 334 (M^+, 5), 159 (100). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.68; H, 5.31; N, 8.17.

Synthesis of 2,5-Bis(3-Formyl-2-hydroxyphenyl)-1,3,4-oxadiazole (6). Oxadiazole 5 (32 mmol, 10.68 g) dissolved in methanol (150 mL) was cooled to −78 °C, and an excess of ozone was bubbled through. The solution was purged with oxygen, sodium iodide (192 mmol, 28.7 g) was added, and the reaction mixture was allowed to reach rt. The solvent was evaporated; the residue was washed successively with ethyl acetate (50 ml), water (100 mL), and acetone (50 mL) and recrystallized (acetic acid): needles, mp 280–281 °C; yield 3.84 g, 40%; ^{1}H-NMR (DMSO-d_6) δ 11.2 (s, 2 H, OH), 10.33 (s, 2 H, CHO), 8.23 (d, J_{6-5} = 7.9 Hz, 2 H, H_6), 7.95 (d, J_{4-5} = 7.9 Hz, 2 H, H_4), 7.16 (t, J_{5-6} = J_{4-5} = 7.9 Hz, 2 H, H_5); ^{13}C-NMR (DMSO-d_6) δ 190.5 (CHO), 167.3 (C=N), 163.9 (C-2), 134.8 (C-6), 133.8 (C-4), 124.2 (C-3), 118.1 (C-5), 116.4 (C-1); IR (KBr) 3340 (OH), 1650 (C=O) cm^{-1}; MS m/z 149 [(M − $C_8H_5N_2O_2$)$^+$, 100]. Anal. Calcd for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03. Found: C, 61.73; H, 3.47; N, 8.70.

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General Procedure for the Synthesis of Macrocycles 7 and 8. A solution of the dialdehyde **6** (1.5 mmol, 465 mg) in acetonitrile (150 mL) and 1,2-benzenediamine (**7**, 1.5 mmol) or 1,2-ethanediamine (**8**, 1.5 mmol) was refluxed for 30 min. The precipitate formed was filtered, washed with hot acetonitrile (2 × 50 mL), and dried under high vacuum.

7: Orange powder, mp > 350 °C; yield 424 mg, 74%; ^{1}H-NMR (TFA-d_1) δ 9.34 (s, 4 H, HC=N), 8.50 (d, J_{6-5} = 7.5 Hz, 4 H, H_6), 8.27 (d, J_{4-5} = 7.5 Hz, 4 H, H_4), 7.93 (br s, 8 H, *o*-phenylene), 7.45 (t, $J_{5-6} = J_{5-4}$ = 7.5 Hz, 4 H, H_5); ^{13}C-NMR (TFA-d_1) δ 168.4 (N=CH), 167.5 (C=N), 163.4 (C-2), 142.6 (C-6), 137.6 (C-4), 131.7, 130.2, 122.0 (*o*-phenylene), 120.4 (C-5), 114.5, 112.2 (C-3, C-1); IR (KBr) 3420 (OH), 1625 (C=N) cm^{-1}. Anal. Calcd for $C_{44}H_{28}H_8O_6$: C, 69.11; H, 3.69; N, 14.65. Found: C, 68.95; H, 3.76; N, 14.42.

8: Yellow Powder, mp > 350 °C; yield 411 mg, 82%; ^{1}H-NMR (TFA-d_1) δ 9.06 (s, 4 H, HC=N), 8.45 (d, J_{6-5} = 7.2 Hz, 4 H, H_6), 8.10 (d, J_{4-5} = 7.2 Hz, 4 H, H_4), 7.40 (t, $J_{5-6} = J_{5-4}$ = 7.2 Hz, 4 H, H_5), 4.74 (s, 8 H, CH_2); ^{13}C-NMR (TFA-d_1) δ 172.6 (C=NH), 167.4 (C=N), 162.8 (C-2), 140.4 (C-6), 134.9 (C-4), 118.3 (C-5), 113.5, 111.8 (C-3, C-1), 47.6 (CH_2); IR (KBr) 3400 (OH), 1645 (HC=N), 1620 (C=N) cm^{-1}; MS *m*/*z* 668 (M^+, 1). Anal. Calcd for $C_{36}H_{28}N_8O_6$: C, 64.67; H, 4.22; N, 16.76. Found: C, 64.39; H, 4.36; N, 16.57.