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Synthesis of Macrocyclic [*n.n.n*](1,3,5)Cyclophane Polylactones

Masayuki Kanishi, Jun-ichi Kunizaki, Junji Inanaga, and Masaru Yamaguchi*
Department of Chemistry, Faculty of Science, Kyushu University, Higashi-ku, Fukuoka 812

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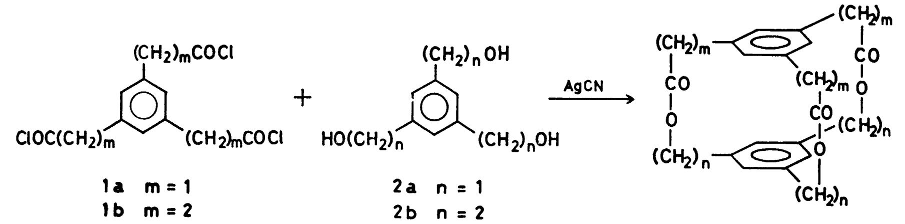
A series of new macrocyclic cyclophane polylactones has been synthesized by one-step condensation of the appropriate tri(acid chloride)s and triols using the silver cyanide-promoted esterification procedure.

A remarkable development of the chemistry of crown ethers and cryptands has promoted the synthesis of various types of macrocyclic diolides or tetraolides.1) However, they have so far been essentially confined to monocyclic compounds in respect to the macrocyclic polyolide rings and no bicyclic analogues2) have been reported, probably because of the lack of powerful lactonization methods suitable for this purpose.3) Most of the hitherto reported polyolides have been prepared by the reaction between di(acid chloride)s and diols4) in varied yields depending on the ease of cyclization of substrates. However, a simple extension of the method to the synthesis of macrobicyclic analogues from tri(acid chloride)s and triols does not seem to be very promising because of the highly unfavorable entropy factors in the dual cyclizations.

Recently, silver cyanide has been found to promote the esterification reaction between acid chlorides and alcohols to a high extent and several strongly hindered esters have been synthesized by this method.5) In this report is demonstrated the applicability of the method to the synthesis of macrocyclic cyclophane polylactones (**3a**—**f** and **5**) which seem to be otherwise difficultly accessible by one-step procedure.

Starting Materials. 1,3,5-Benzenetrimethanol (**2a**) was prepared by lithium aluminum hydride reduction of triethyl 1,3,5-benzenetricarboxylate according to the literature.6) Conversion of **2a** into α,α′,α″-trichloromesitylene by the reported procedure6) followed by the treatment of the latter with potassium cyanide under the presence of phase-transfer catalyst7) gave 1,3,5-benzenetriacetonitrile which was then hydrolyzed to give known 1,3,5-benzenetriacetic acid8) in good overall yield. Conversion of the triacetic acid to the corresponding tri(acid chloride) (**1a**)6) or to 1,3,5-benzenetriethanol (**2b**)6) and transformation of α,α′,α″-trichloromesitylene to 1,3,5-benzenetripropionic acid6) or to 1,3,5-benzenetripropanol (**2c**)9) were carried out by the reported procedures. 1,3,5-Benzenetripropionyl trichloride (**1b**) was prepared from the corresponding triacid in a similar way to **1a**. Treatment of 1,3,5-benzenetricarbonyl trichloride with mono(tetrahydropyranyl) ether10) of 2,2′-oxydiethanol gave **4a** which on hydrolysis with 1 mol dm^{-3} hydrochloric acid gave **4b** in 48% yield from the tri(acid chloride). Treatment of **1a** with a large excess of 2,2′-oxydiethanol in dichloromethane gave **4c** in 61% yield.

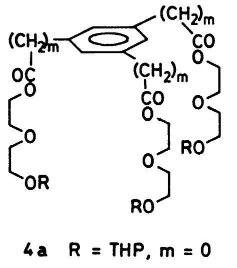
Synthesis of Cyclophanes. Condensations of the tri(acid chlorides)s (**1a** or **1b**) and the triols (**2a**, **2b**, **2c**, or **4c**) were carried out under high-dilution conditions in the presence of silver cyanide in refluxing benzene, xylene, or acetonitrile, giving the cyclophanes (**3a**—**f** and **5**) in 3.6—20.4% yields. They are summarized in Table 1. In an experiment carried out for comparison, reaction of **1b** with **2a** in refluxing pyridine under the similar high-dilution conditions in the absence of silver cyanide gave **3d** in only 3% yield. In experiments with the combination of 1,3,5-benzenetricarbonyl trichloride and **2a** or **4b**, no monomeric products were isolated. Properties of the cyclophanes obtained are listed in



1a m = 1
1b m = 2

2a n = 1
2b n = 2
2c n = 3

3a m = n = 1
3b m = 1, n = 2
3c m = 1, n = 3
3d m = 2, n = 1
3e m = n = 2
3f m = 2, n = 3



4a R = THP, m = 0
4b R = H, m = 0
4c R = H, m = 1

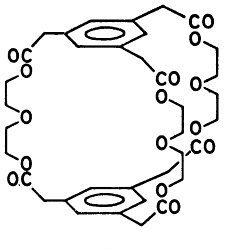


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Table 1. Isolated yield of cyclophanes

Acid chloride	Alcohol	Solvent[a]	Time of addition/h	Product[b]	Mp/°C	Isolated yield/%
1a	**2a**	Benzene	25	**3a**	>305	6.8
1a	**2b**	Benzene	21	**3b**	244	3.9
1a	**2c**	Xylene	26	**3c**	177.5	3.6
1b	**2a**	Benzene	20	**3d**	267	20.4
1b	**2a**	Pyridine	20	**3d**		3.0[c]
1b	**2b**	Benzene	26	**3e**	220	6.0
1b	**2c**	Acetonitrile	9.5	**3f**	190	6.1
1a	**4c**	Xylene	34	**5**	132	13.6

a) Triols were dissolved in a small amount of acetonitrile and then diluted with the solvent given in the Table. b) Each product gave a distinctive molecular ion peak as a monomer in MS spectrum. c) The experiment was carried out in 1 mmol scale without the addition of silver cyanide.

Table 2. Spectral properties of cyclophanes

Compound	UV/nm (ε)	IR[a]/cm^{-1}	^{1}H NMR			
			Aromatic[b]	-CH$_2$-COO-	-CH$_2$-OCO-	Other protons
3a	268(405)	1732	7.04, 6.83	3.32(s)	4.97(s)	
3b	266(767)	1730	6.79, 6.66	3.40(s)	4.42 (t, J=6.0 Hz)	2.82 (t, J=6.0 Hz)
3c	266(533)	1720	7.12, 6.50	3.42(s)	4.16 (t, J=5.9 Hz)	1.65—2.20(m), 2.47(t, J=7.0 Hz)
3d	266(455)	1732	7.24, 6.67	2.73(br. s)[c]	4.94(s)	
3e	263(459)	1724	6.77, 6.71	2.25—2.55(m)	4.03—4.29(m)	2.60—2.93(m)
3f	266(578)	1718	6.73, 6.70	2.10—2.93(m)[d]	4.10(t, J=6.0 Hz)	1.60—2.07(m)
5	265(376)	1720	7.14	3.54(s)	4.08—4.32(m)[e]	

a) ν_{CO}. b) All singlet. c) The signal was overlapped with the neighboring methylene protons α to the benzene ring. d) The signal indistinguishably overlapped with the methylene protons α to the two benzene rings. e) The signal indistinguishably overlapped with other protons of ethylene bridges.

Table 2.

Aromatic protons of these cyclophanes resonated in NMR spectra at the upper field by *ca.* 0.1—0.3 ppm than those of open chain models (the trimethyl esters or triacetates of the corresponding triacids or triols, respectively), as a trend usually observed in cyclophanes. The C=O stretching vibrations of the cyclophanes with shorter bridges (**3a**, **3b**, and **3d**) appeared at the higher wavenumber positions by *ca.* 10 cm^{-1} than those with longer bridges (**3c**, **3e**, **3f**, and **5**) implying the presence of some strain in the former compounds. However, UV absorptions which appeared at almost the same positions as those of open chain models (266 nm) indicated that the strain, if any, is not appreciable. The UV spectra did not change after the addition of tetracyanoethylene.

Recrystallization of the cyclophanes (**3a**—**f**) from benzene, ethyl acetate, or acetonitrile did not give any adducts with the solvent molecule.

Though the open chain triol (**4b**) gave a crystalline 1 : 1 adduct with KSCN, the cyclized **5** did not form the isolable adduct. Further examination of **5** on complexation with metal salts such as KSCN, LiSCN, NaSCN, Cs_2CO_3, $MgSO_4$, $AgNO_3$, $CuSO_4$, and NH_4Cl by 2,4,6-trinitrophenol method[11] also gave negative results.

Experimental

Melting points or boiling points were uncorrected. UV spectra (Hitachi 200-10) were recorded in dichloromethane solutions. IR spectra (Hitachi R-215) were obtained in potassium bromide pellets. ^{1}H NMR spectra (Hitachi R-20B) were taken in deuteriochloroform solutions. Mass spectra (Hitachi RMU-6MG) were recorded with a direct-inlet system operating at 70 eV. Solvents were purified and dried by the standard methods.

1,3,5-Benzenetrimethanol (2a). Mp 77 °C (lit,[6] 77 °C), 95%.[12]

1,3,5-Benzenetriacetonitrile. α,α′,α″-Trichloromesitylene[6] (4 g, 18 mmol) was added dropwise to a mixture of potassium cyanide (6 g, 122 mmol) and 18-crown-6 (690 mg, 2.7 mmol)[7] in acetonitrile at room temperature and the mixture was stirred for 6 days. The reaction was followed by TLC. The mixture was filtered and the precipitate was extracted with dichloromethane. The combined filtrate and extract were concentrated and the residue was chromatographed on a silica-gel column from benzene–ethyl acetate (9 : 1). The early fractions contained the practically pure trinitrile (2.8 g, 80%) which was recrystallized from a mixture of benzene and petroleum ether. Mp 123—125 °C. NMR; δ 3.80 (s, 6H), 7.33 (s, 3H): IR; 2220, 1870, 1600, 1420, 1390 cm^{-1}. Found: C, 73.74; H, 4.74; N, 21.46%. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53%.

1,3,5-Benzenetriacetic Acid. 1,3,5-Benzenetriacetonitrile (1.45 g, 7.46 mmol) was dissolved in a mixture of concentrated sulfuric acid (2.2 ml) and water (2.5 ml) and the solution was refluxed for 5 h. The cooled mixture was diluted with water (5 ml) and extracted with ether. Evaporation of ether gave a colorless solid which was recrystallized from acetic acid to give 1,3,5-benzenetriacetic acid [1.85 g (98%), mp 208—209 °C (lit,[8] 215—216 °C)].

*1,3,5-Benzenetripropionyl Trichloride (**1b**).* It was prepared from 1,3,5-benzenetripropionic acid (294 mg, 1 mmol) by refluxing with excess thionyl chloride (1 ml) in benzene (1 ml) for 4 h. Colorless needles, mp 59—60 °C (from pentane). NMR; δ 6.94 (s, 3H).

*Tris(tetrahydropyranyloxyethoxyethyl) 1,3,5-Benzenetricarboxylate (**4a**).* Pyridine (16 ml) was added to an ice-cooled solution of 1,3,5-benzenetricarbonyl trichloride (5.2 g) and tetrahydropyranyloxyethoxyethanol (11.7 g)[10] in dry benzene under stirring. After stirring overnight at room temperature, the mixture was filtered and concentrated. Hydrochloric acid (0.1 mol dm^{-3}, 140 ml) was added to the residue and the mixture was extracted with ether. The extract was washed with water, aqueous sodium hydrogencarbonate, and water, and dried over sodium sulfate. Evaporation residue was separated by TLC on silica-gel (acetone–benzene, 1 : 4) giving **4a** as a viscous oil, 11.8 g (83%). IR; 2900, 1720, 1240, 740 cm^{-1}: NMR; δ 8.86 (s, 3H), 4.6 (m, 9H), 3.75 (m, 24H), 1.65 (m, 18H). Found: C, 59.18; H, 7.40%. Calcd for $C_{36}H_{54}O_{15}$: C, 59.48; H, 7.49%.

*Tris(hydroxyethoxyethyl) 1,3,5-Benzenetricarboxylate (**4b**).* **4a** (4 g, 5.5 mmol) was stirred in a mixture of hydrochloric acid (1 mol dm^{-3}, 36 ml) and THF (25 ml) at room temperature for 12 h. Sodium hydrogencarbonate (3.4 g) was added and the mixture was extracted with petroleum ether. The aqueous layer was evaporated and the residue was extracted with dioxane. TLC (silica-gel, dioxane–petroleum ether 5 : 2) of the evaporation residue of the extract gave **4b** as a viscous oil[13] (1.51 g, 58%).[9] NMR; δ 8.88 (s, 3H), 4.85 (m, 6H), 3.75 (m, 18H), 3.14 (s, 3H).

Evaporation of a solution of **4b** (32.4 mg, 0.068 mmol) and KSCN (9 mg, 0.093 mmol) in acetone (1 ml) followed by treatment of the residue with ethyl acetate gave an adduct which melted at 85—86 °C (recrystallized from acetone–ethyl acetate). IR; 3500—3200, 2050, 1720, 1240, 740 cm^{-1}. Found: C, 45.96; H, 5.22; N, 2.49%. Calcd for $C_{21}H_{30}O_{12}\cdot KSCN$: C, 46.23; H, 5.29; N, 2.45%.

*Tris(hydroxyethoxyethyl) 1,3,5-Benzenetriacetate (**4c**).* A solution of **1b** (140 mg) in dichloromethane (8 ml) was added dropwise to a stirred solution of 2,2′-oxydiethanol (13.3 ml), pyridine (0.17 ml) and dichloromethane (10 ml) under ice-cooling. After stirring overnight, the mixture was refluxed for 5 h. Solvent and excess 2,2′-oxydiethanol were then removed under vacuum as thoroughly as possible. The residue was separated by TLC (Merck, kieselgel 60HF$_{254}$, silanisiert; water–acetonitrile 2 : 1) giving **4c** as a viscous oil[13] (148 mg, 61.3%). NMR; δ 7.15 (s, 3H), 4.3 (m, 6H), 3.65 (m, 24H), 2.5 (s, 3H). The triol did not give an isolable KSCN adduct.

*Cyclophanes (**3a**—**f**, **5**).* Cyclophanes were prepared by essentially the same procedure as exemplified below for **3a**.

A solution of **2a** (168 mg, 1 mmol) in a mixture of acetonitrile (50 ml) and dry benzene (400 ml), and a solution of **1b** (308 mg, 1 mmol) in dry benzene (450 ml) were added dropwise at the same rate to a stirred suspension of silver cyanide (10 g, 75 mmol) in refluxing benzene (100 ml) over a period of 25 h. The mixture was cooled, filtered, and concentrated. The residue was separated by TLC (silica-gel, benzene–ethyl acetate 4 : 1). The residue of the corresponding zone was recrystallized from ethyl acetate to give **3a** (25 mg, 6.8%) as colorless prisms, mp$>$305 °C. Mass; 366 (M$^+$), 294, 278, 234, 219.

CH-Analyses of these cyclophanes are given in Table 3.

Table 3. CH-analysis of cyclophanes

Compound (Formula)	Found (%)		Calcd (%)	
	C	H	C	H
3a ($C_{21}H_{18}O_6$)	68.62	4.99	68.84	4.98
3b ($C_{24}H_{24}O_6$)	70.33	6.06	70.57	5.92
3c ($C_{27}H_{30}O_6$)	71.73	6.79	71.98	6.71
3d ($C_{24}H_{24}O_6$)	70.32	5.91	70.57	5.92
3e ($C_{27}H_{30}O_6$)	71.90	6.75	71.98	6.71
3f ($C_{30}H_{36}O_6$)	72.95	7.30	73.14	7.37
5 ($C_{36}H_{42}O_{15}$)	60.41	5.97	60.49	5.92

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3) Several mild and fairly rapid esterification methods have recently been developed in connection with the synthesis of natural macrolides [K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977); T. G. Back, *ibid.*, **33**, 3041 (1977); E. Haslam, *ibid.*, **36**, 2409 (1980)]. However, when sensitive functionalities do not exist in the molecule, the use of acyl halides still remains as one of the most effective carboxylic acid-activation.

4) Recently, activation of the hydroxyl group by dibutyltin oxide has been developed and some macrocyclic tetraolide have been synthesized (A. Shanzer and N. Mayer-Shochet, *J. Chem. Soc., Chem. Commun.*, **1980**, 176; A. Shanzer and E. Barman, *ibid.*, **1980**, 259). Reaction of carboxylates and alkyl halides has also been used for the synthesis of this class of compounds (Ref. 1) and the use of caesium carboxylates has recently been recommended [O. Piepers and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, **1978**, 383].

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12) As **2a** was very soluble in water, the isolation procedure

was modified as described below. The ethereal reduction mixture was cooled and after the addition of a calculated amount of water, excess Dry Ice was added to the mixture. The mixture was then filtered and the precipitate was washed well with ethanol. The filtrate and the wash were combined and concentrated to a white solid. Sublimation [140 °C (bath temp), 133 Pa] gave **2a** in 95% yield.

13) The removal of a small amount of contaminating water was difficult and the sample gave a low carbon value by *ca.* 1% in CH-analysis.