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Author's Review

The Preparation of Macrocyclic Diester and Tetraester Ligands by a Transesterification Process

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This short review summarizes the synthesis of macrocyclic diester and tetraester crown ligands by a transesterification process. Compared with the previous method using a diacid chloride, this method is especially effective for the synthesis of macrocyclic diester compounds from secondary glycols. In addition, this method enables the synthesis of some diester compounds, which could not be obtained using other methods.

Although the first synthesis of macrocyclic ester compounds from a diacid was reported in the nineteenth century,[1] there has been a recent interest in these compounds because they are related to the crown ethers first reported by Pedersen.[2] The crown ethers have selective complexing abilities toward a variety of cations.[2,3] Generally speaking, the crown ethers containing ester functions form weaker complexes with cations than do the regular crown ethers. However, several noteworthy properties for the diester crowns have been reported. For example, some synthetic macrocyclic diesters showed a K^+/Ba^{2+} selectivity similar to that observed for certain naturally occurring cyclic antibiotics.[4,5] The diester crowns containing a pyridine subcyclic unit were found to complex strongly with many types of cations.[4,6] New chiral macrocyclic diester crown ligands have been prepared[7–9] and they were found to discriminate enantiomers of amine salts.[9,10] Certain macrocyclic diester compounds were successfully reduced to the corresponding crown ethers directly[11] or *via* the corresponding thiono diester compounds.[12] These latter compounds have also shown interesting complexation properties.[10] In addition, proton-ionizable diester 18-crown-6 compounds containing both triazole and pyridine subcyclic units have been prepared.[13,14] These compounds form stable complexes with water and amine molecules.[13,14]

A detailed description concerning several synthetic methods for the preparation of macrocyclic di- and tetraesters was given in the review published in 1979.[15] Previously, macrocyclic diester crowns used as cation ligands have been prepared by the reaction of diacid chlorides with glycols. Recently, the transesterification process was found to be an excellent method

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for preparing these compounds.[16-18] The transesterification method has the advantages of improving the yields for the cyclization reaction and of allowing the synthesis of some new types of macrocyclic diesters which could not be obtained using the diacid chloride procedure.[19] Thus, the synthesis of new types of ligands (*i. e.*, proton-ionizable diester crowns)[13,14] was possible using this new synthetic method. We here review the synthesis of macrocyclic di- and tetraester crown compounds by means of the transesterification method. Compounds prepared by this method are shown in Figure 1 and Table I.

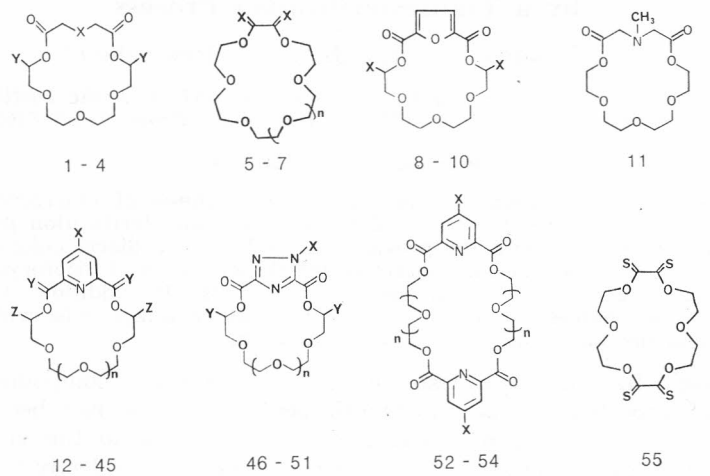


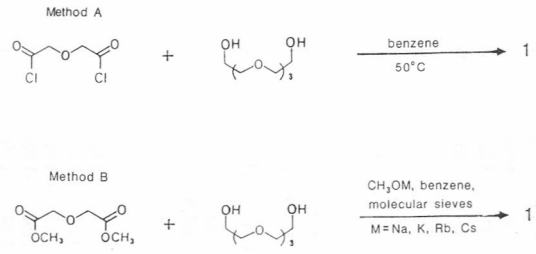
Figure 1. Macrocyclic di- and tetraester compounds prepared by the transesterification process (See Table I for X, Y, and Z designations)

Transesterification was successfully carried out by the reaction of a dimethyl ester with an appropriate oligoethylene glycol in the presence of an alkali metal methoxide catalyst. An acid catalyzed transesterification reaction failed to yield compounds *4* or *13*.[19] Since the base-catalyzed transesterification reaction is an equilibrium process as described below, it is necessary to remove the methanol by-product from the reaction system. We have used molecular sieves for absorption of the methanol generated *in situ*, although azeotropic distillation has also been used successfully.[17,18] Two molecular sieve methods differing in their placement were used. In Method B-1, the sieves were placed in a Soxhlet extractor and the solvent was distilled through the sieves. An excess of molecular sieves was placed directly in the reaction vessel in Method B-2. The latter method has merit in that molecular sieves also catalyze transesterification,[19] although product isolation is much easier in Method B-1. General procedures of the diacid chloride procedure (Method A) and the two transesterification procedures (Methods B-1 and B-2) are summarized as follows (see Scheme 1):

Method A (Diacid Chloride Method)[18]

The glycol (0.03 mol) and acid chloride (0.03 mol), each dissolved in 250 ml of benzene, were added simultaneously to 1 liter of rapidly stirring benzene at 50 °C. After the evolution of hydrogen chloride gas ceased, the solvent was removed

Scheme 1



under reduced pressure. The product was isolated by a hot hexane extraction followed by distillation or recrystallization.

Method B-1 (Transesterification)[19]

A mixture of 0.02 mol of the diester and 0.02 mol of the glycol in 700 ml of benzene was refluxed for 3 h through a Soxhlet apparatus containing 30 g of 4 Å molecular sieves. Three drops of 30% alkali metal methoxide in methanol were added to the solution and the reflux was continued until a TLC analysis showed that all the dimethyl ester had reacted. The spent molecular sieves were replaced by fresh molecular sieves after 18 h. Upon completion of the transesterfication reaction, three drops of glacial acetic acid were added to neutralize the methoxide catalyst and the macrocyclic compound was isolated by a hot hexane extraction followed by distillation or recrystallization.

Method B-2 (Transesterification)[19]

A mixture of 0.02 mol of the diester, 0.02 mol of the glycol and 50 g of 4 Å molecular sieves was stirred in 700 ml of dry benzene for 1 h. Three drops of 30% alkali metal methoxide in methanol were added and the mixture was stirred until a TLC analysis showed that all the dimethyl ester had reacted. Additional methoxide catalyst was added at 24 h intervals. Upon completion of the reaction, three drops of glacial acetic acid were added and the mixture was filtered and worked-up as in Method B-1.

Figure 1 and Table I show structures and some physical data of the compounds prepared by the transesterification reaction along with some examples of compounds prepared by the diacid chloride method. The structures proposed for all macrocyclic compounds are supported by IR, NMR, combustion analyses and molecular weight determinations. A camparison of the yields for macrocyclic compounds prepared from both the diacid chloride (Method A) and transesterification (Method B) processes is shown in Table II. Generally, the transesterification method gave better yields than the diacid chloride method except for the synthesis of compound *8*. No improvement in yields was observed by changing the catalyst (sodium, potassium, rubidium, or cesium methoxide) in the synthesis of compound *13*.[19] This result is probably due to the fact that there was only a catalytic amount of metal cation in the reaction. On the other hand, we observed a distinct template effect in the synthesis of compound *23*.[20] The yield more than doubled (30% to 69%) when the reaction was carried out in the presence of excess potassium thiocyanate. For compounds which form strong complexes such as the pyridino diester crowns, using this type of template effect is expected to improve the cyclization yields dramatically.

TABLE I

A List of Macrocyclic Di- and Tetraester Compounds, The Method of Their Preparation, Yields and Melting Points (See Figure 1 for Structures)

Compound	X	Y	Z	n		Method	Yld %	m. p., °C	ref
1	O	H				B-1	45.6	78.5— 79.5	19
2	O	Ph			(racemic-meso)	B-2	16	128 —129.5	9
3	O	Ph				B-2	48	131 —133	9
4	S	H				B-1	42.7	43.5— 44.5	19
5	O			0		B-2	55.9	45 — 46	19
6	S			0		B-2	4.9	108.5	20
7	S			1		B-1	14.2	136 —137	20
8	H					B-1	37	117 —118	19
9	Ph				(racemic-meso)	B-2	15	169 —170.5	9
10	Ph				(S, S)	B-2	5	168.5—170.5	9
11						B-1	33	184 —185[a]	19
12	H	O	H	0		B-2	25.2	139 —140	19
13	H	O	H	1		B-2	76.6	86.5— 87.5	19
14	H	O	Me	1	(S, S)	A	48.5	94	8
15	H	O	Et	1	(racemic-meso)	A	31	oil	21
16	H	O	C_8H_{17}	1	(racemic-meso)	B-1	9	oil	19
17	H	O	Ph	1	(racemic-meso)	B-2	25.5	124 —142	9, 19
18	H	O	Ph	1	(S, S)	B-1	8.5	171 —173	9
19	H	S	H	0		B-1	71	140 —141	20
20	H	S	H	1		B-1	39	124 —125	20
21	H	S	H	2		B-1	26	124 —125	20
22	H	S	H	3		B-2	—	51	20
23	H	S	Me	1	(S, S)	B-2	30	63.5— 64	20
24	OH	O	H	1			76.2[b]	142 —143.5	14
25	OH	O	H	2			77.8[b]	85 — 89	14
26	OH	O	Me	1	(S, S)		29.8[b]	94.5— 97	14
27	OH	O	Ph	1	(R, R)	B-1	3.1	119 —122	14

Table I (continued)

Compound	X	Y	Z	n		Method	Yld %	m. p., °C	ref
28	MeO	O	H	2		A	18.5	122 —123	22
29	MeO	O	Me	1	(S, S)	A	17	98 — 99	8
30	MeO	O	Ph	1	(racemic-meso)	B-2	4.1	123 —143	9
31	$C_5H_{11}O$	O	H	0		B-2	6.4	99 —101	18
32	$C_5H_{11}O$	O	H	1		B-2	34	54.5— 56.5	18
33	$C_5H_{11}O$	O	H	2		B-2	43	oil	18
34	$C_5H_{11}O$	O	Me	1	(racemic-meso)	B-2	68	oil	18
35	$C_5H_{11}O$	O	Et	1	(racemic-meso)	B-2	68	oil	18
36	$C_8H_{17}O$	O	H	2		A	19	26 — 28	18
37	$C_8H_{17}O$	O	Me	1		A	49	oil	18
38	$C_8H_{17}O$	O	Et	1		A	34	oil	18
39	$PhCH_2O$	O	H	1		B-1	5.4	139 —140	14
40	$PhCH_2O$	O	H	2		B-1	52.7	107 —108.5	14
41	$PhCH_2O$	O	H	3		B-1	21.5	91 — 92	14
42	$PhCH_2O$	O	Me	1	(racemic-meso)	B-1	28.5	111 —113	14
43	$PhCH_2O$	O	Me	1	(S, S)	B-1	34.8	97.5— 99	14
44	$PhCH_2O$	O	Ph	1	(S, S)	B-1	—	88 — 89	14
45	THP	O	H	1		B-1	57	115.5—116.5	14
46	H	H		1			37[b]	134 —135	13, 19
47	H	H		2			19[b]	132.5—134	13
48	H	Me		1	(S, S)		22[b]	114 —116	13
49	$PhCH_2$	H		1		B-1	36	120 —121	13, 19
50	$PhCH_2$	H		2		B-1	12	88.5— 90.5	13
51	$PhCH_2$	Me		1	(S, S)	B-1	—	oil	13
52	H			2		B-2	35.7	163 —164	19
53	$C_5H_{11}O$			2		B-2	24	134.5—135.5	18
54	$C_8H_{17}O$			2		B-2	14	105 —107	18
55						B-2	9.6	169.5—170	20

[a] Isolated as the potassium thiocyanate complex.
[b] From the reduction of the corresponding benzyl-blocked compound.

TABLE II

A Comparison of Yields for Macrocyclic Diester Compounds Prepared from the Diacid Chloride vs Transesterification (See Figure 1 and Table I for Structures)

Type of Compound	Compound	Method A[a]	Method B[b]
Crown-5	*5*	27.7[c]	55.9[d,e]
	12	9.6[f]	25.2[d]
Crown-6	*1*	35[g]	45.6[d]
	4	20[g]	42.7[d]
	8	60[h]	37[d]
	11	0[h]	33[d,i]
	13	78[h,j]	76.6[d,e]
	49	0[d]	36[d]
Crown-7	*28*	18.5[k]	—
	33	—	43[l]
	36	19[l]	—
Crown-10	*52*	0[f]	35.7[d,e]
Dimethyl-crown-6	*14*	48.5[m]	—
	30	17[m]	—
	34	—	68[l]
	37	49[l]	—
Diethyl-crown-6	*15*	31[n]	—
	35	—	68[l]
	38	34[l]	—
Dioctyl-crown-6	*16*	0[n]	9[d]
Diphenyl-crown-6	*17*	0[d]	25.5[d,e]

[a] Diacid chloride, [b] Transesterification, [c] ref. 23, [d] ref. 19, [e] Based on hplc analysis. [f] ref. 24, [g] ref. 25, [h] ref. 26, [i] Isolated as the potassium thiocyanate complex. [j] ref. 27, [k] ref. 22, [l] ref. 8, [m] ref. 18, [n] ref. 21.

Secondary glycols were found to show a lower reactivity toward diacid chlorides than the primary glycols.[21] Transesterification proved to be a superior method for the synthesis of macrocyclic compounds from secondary glycols. Only starting glycols were isolated when the synthesis of compounds *16* and *17* was attempted by the diacid chloride method.[19,21]

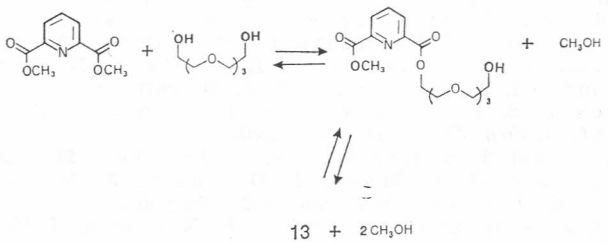
N-Methylamino compound *11*, dithiono esters *19—23* and triazolo compounds *49—51* could not be prepared by the diacid chloride method. The diacid chloride needed for the synthesis of compound *11* cannot be prepared.[19] The acid chlorides needed for the synthesis of compounds *19* and *49* should be unstable. Accordingly, compounds *11*, *19—23* and *49—51* can be synthesized only by the transesterification process using the stable dimethyl esters. Compound *45*, which is blocked by a tetrahydropyranyl group, is important as the precursor for compound *24*. However, the acid chloride method cannot be applied to the synthesis of *45* because THP-blocked compounds are unstable in acidic media.

Compounds *24*, *26*, and *27* are interesting because they complex neutral molecules such as water or primary amines.[14] Compounds *24* and *26* were prepared by reducing the benzyl-blocking groups of compounds *40* and *43*. The corresponding phenyl substituted compound (*27*) could not be obtained by reducing compound *44* because the phenyl-substituted carbons in the macrocyclic ring would also be reduced. This problem was solved by reacting dimethyl 4-(tetrahydro-2-pyranoxy)-2,6-pyridinedicarboxylate (the THP-blo-

cked diester) with the corresponding chiral glycol followed by deblocking the THP group in acid to give compound *27*. Again, compound *27* could not have been prepared by the diacid chloride procedure.

Compound *52* is the 2 : 2 adduct obtained from the reaction of dimethyl 2,6-pyridinedicarboxylate with triethylene glycol.[19] Similarly, compound *53* is obtained from the transesterification reaction of dimethyl 4-pentoxy-2,6--pyridinedicarboxylate with triethylene glycol.[18] In both cases, 1 : 1 adducts were also isolated. Similar 2 : 2 adducts have not been isolated from the reaction of 2,6-pyridinedicarbonyl chloride or the corresponding 4-substituted acid chlorides with triethylene glycol. A study of the transesterification reaction process in the synthesis of compound *13* from dimethyl 2,6-pyridinedicarboxylate and tetraethylene glycol using hplc showed the presence of an intermediate.[19] When compound *13* was allowed to stand in methanol in the presence of a catalytic amount of potassium methoxide, the reverse reaction *via* the same intermediate was observed. Although the intermediate was not isolated, the compound was believed to be the half-transesterified product because it formed both in the formation and the decomposition processes (see Scheme 2).

Scheme 2



13 + 2 CH_3OH

The transesterification process in the reaction of dimethyl 2,6-pyridinedicarboxylate with triethylene glycol to form *12* (and *52*) was also studied using hplc. In this case, a similar intermediate was found.[19] When the 2 : 2 adduct *52* was treated with methanol in benzene in the presence of a catalytic amount of sodium methoxide, a mixture of 28% of the 1 : 1 adduct (*12*) and 32% of the 2 : 2 adduct (*52*) was obtained. It is interesting to note that this ratio of 1 : 1 adduct (*12*) to 2 : 2 adduct (*52*) was about the same as that obtained from the original transesterification reaction of dimethyl 2,6-pyridinedicarboxylate and triethylene glycol. This fact strongly suggests that this cycloaddition transesterification reaction is an equilibrium process.

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POVZETEK

Priprava makrocikličnih diesterskih in tetraesterskih ligandov s pomočjo postopka prestrenja

Yohji Nakatsuji in Jerald S. Bradshaw

Kratek pregled povzema sinteze makrocikličnih diestrov in tetraestrov kot ligandov s pomočjo postopka prestrenja. V primerjavi s prejšnjimi postopki, ki uporabljajo kloride dikarboksilnh kislin, je omenjeni postopek posebno učinkovit za sintezo makrocikličnih diestrov iz sekundarnih glikolov. Poleg tega omogoča ta postopek sintezo diestrov, katere ne moremo pripraviti po drugih postopkih.