

CONVENIENT SYNTHESIS OF MACROCYCLIC COMPOUNDS

CONTAINING TWO OF NITROGEN, OXYGEN OR SULFUR ATOMS

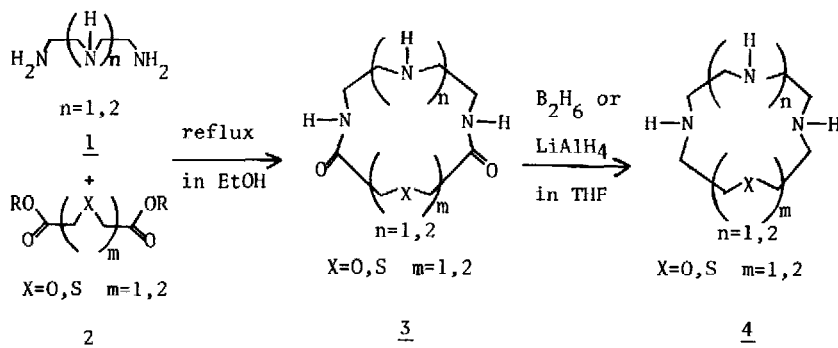
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Macrocyclic compounds containing nitrogen and other hetero atoms as ring components have been prepared by use of transition metal template¹⁾ or high dilution technique²⁾, from polyethylenepolyamines where nitrogen atoms are protected by suitable groups³⁾. We now wish to report a convenient and general synthetic method of a series of macrocyclic amines containing oxygen or sulfur atom(s) as other ring component through the cyclization via aminolysis of readily available dimethyl esters of α,ω -dicarboxylic acids with commercially available polyethylenepolyamines and successive reduction of the macrocyclic amides thus obtained⁴⁾ (see Scheme 1). The present procedure requires neither high dilution technique nor nitrogen protection and is much more convenient than the reported procedures⁴⁾.



Scheme 1

Thus the mixture of polyethylenepolyamines, 1, and α,ω -diesters, 2, was refluxed for 3 to 7 days to yield the corresponding cyclic amides, 3. Structural formulae of cyclic amides ob-

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tained are shown in Figure I. A cyclic amide crystallized out from the reaction mixture on distilling off the solvent was purified by recrystallization and/or chromatography. In the case of 7' or 8', the residue were directly chromatographed on silica gel or alumina column, respectively, and amides obtained were purified by recrystallization. The yields, elemental analyses and physical properties of these macrocyclic amides are summarized in Table I and II.

FIGURE I Structural Formulae and Codes of Cyclic Amides and Cyclic Amines

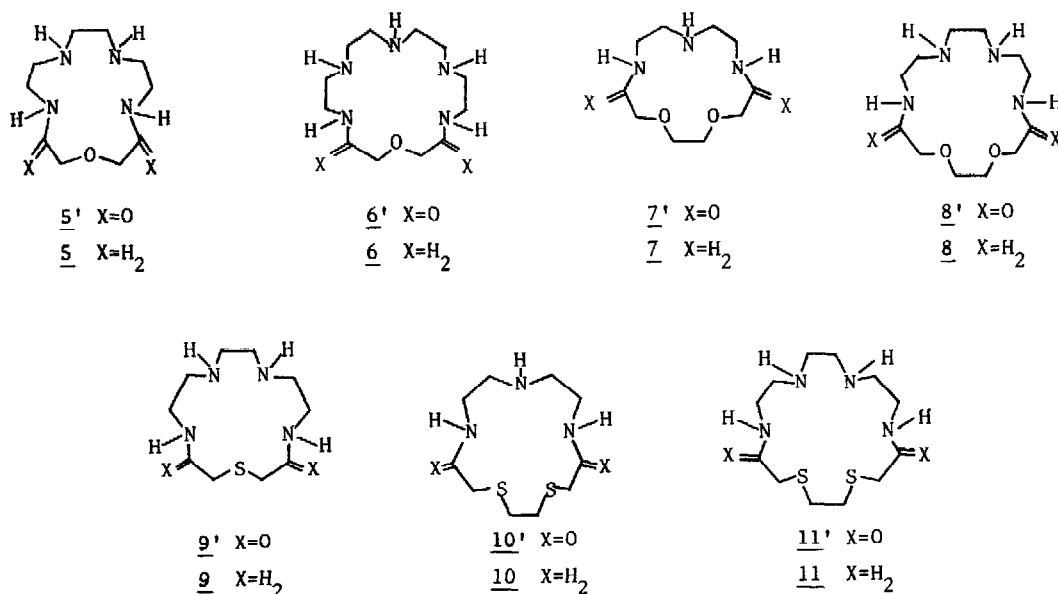


TABLE I Yields and Analyses of Cyclic Amides

Compd	Yield	mp, °C ^a	C		H		N	
			Found	Calcd	Found	Calcd	Found	Calcd
<u>5'</u>	12.1 ^d	159.0-162.0	49.37	49.16	8.20	8.25	22.79	22.94
<u>6'</u>	12.3 ^d	158-164	50.13	50.15	8.83	8.77	24.26	24.37
<u>7'</u>	32.0 ^c	185.0-187.0	45.89	45.62	8.54	8.04	16.10	15.96
<u>8'</u>	67.0 ^b	118.8-120.0	50.59	49.98	8.69	8.39	19.40	19.43
<u>9'</u>	15.4 ^b	174.5-176.5	46.21	46.13	7.84	7.74	21.42	21.52
<u>10'</u>	40.9 ^b	194.0-196.0	43.24	43.29	7.14	6.90	14.96	15.15
<u>11'</u>	28.5 ^b	148.5-151.0	45.00	44.97	7.52	7.55	17.20	17.48

a. uncorrected b. first crop filtered from the reaction mixture

c. separated through silica gel column d. separated through alumina column

TABLE II

NMR spectra and IR spectra of Cyclic Amide

Compd	NMR spectra (60 MHz)	IR spectra
	δ , ppm in CDCl_3	cm^{-1} in KBr
<u>5'</u>	7.20(br. s)* 2H, 4.01(s) 4H, 3.34(m) 4H,	3300, 2940, 2840,
	2.76(m) 8H, 1.30(s)* 2H	1660, 1555, 1275, 1120
<u>6'</u>	7.20(s)* 2H, 4.00(s) 4H, 3.40(m) 4H,	3300, 2925, 2820,
	2.73(m) 2H, 1.88(s)* 3H	1650, 1550, 1340, 1125
<u>7'</u>	7.56(br. s)* 2H, 4.71(s)* 1H, 4.02(s) 4H,	3380, 2925, 2850,
	3.72(s) 4H, 3.40(m) 4H, 2.86(m) 4H	1660, 1550, 1330, 1125
<u>8'</u>	7.18(br. s)* 2H, 4.02(s) 4H, 3.72(s) 4H,	3360, 2910, 2850,
	3.48(m) 4H, 2.80(m) 8H, 1.79(s)* 2H	1660, 1520, 1335, 1110
<u>9'</u>	7.42(br. s)* 2H, 3.56-3.19(m) 8H,	3300, 2925, 2850,
	2.99-2.66(m) 8H, 1.81(s)*	1645, 1550, 1320, 1130
<u>10'</u>	7.2(br. s)* 2H, 3.60-3.20(m) 8H,	3310, 2925, 2825,
	2.98-2.68(m) 8H, 1.22(s)* 1H	1630, 1510, 1310, 1130
<u>11'</u>	7.41(br. s)* 2H, 3.65-3.19(m) 8H,	3310, 2925, 2885,
	2.99-2.71(m) 12H, 1.42(s)* 2H	1655, 1560, 1320, 1105

* Signal disappears on addition of D_2O

The successful cyclization at the terminal amine position seem to be due to the difference in the reactivities between the terminal (primary) and the secondary amine nitrogen in the starting polyethylenepolyamines⁵⁾.

Reduction of the cyclic amides 3 was successfully carried out by lithium aluminium hydride or diborane in tetrahydrofuran, giving the corresponding cyclic amines 4 in 60-80% yield. The macrocyclic amines were purified by sublimation and/or recrystallization. Physical properties of the macrocyclic amines thus obtained are shown in Table III.

Mass spectra of all of these cyclic amines showed corresponding characteristic peaks, P+1. There is a report⁶⁾ that such a peak, P+1, is also observable in 18-crown-6. To the contrary, mass spectra of benzocrowns⁷⁾ showed only molecular ion peak, P, where the peak P+1 was obser-

vable with only weak intensity.

These compounds are of interest since they show very strong binding for transition metal cations and furthermore they are expected to have enhanced selectivity⁸⁾ for metal cations relative to related acyclic compounds or macrocyclic compounds containing only oxygen or only nitrogen atoms.

TABLE III Mass spectra, 100 MHz NMR spectra and IR spectra of Macrocyclic Amines

Compd	mp, °C ^a	Mass spectra m+/e	NMR spectra ppm in CDCl ₃	IR spectra cm ⁻¹ neat
<u>5</u>	54.0-56.0	217(P+1), 186(P-30)	3.63(t)** 4H	3280, 2925,
		172(P-44), 148(P-68)	2.80(m) 16H 2.03(s)* 4H	2875, 1345, 1115
<u>6</u>	paste	260(P+1), 229(P-30)	3.60(m) 4H	3300, 2925,
		215(P-44), 191(P-68)	2.73(m) 20H 1.64(s)* 4H	2850, 1120
<u>7</u>	paste	218(P+1), 187(P-30)	3.64(m) 8H	3375, 2925,
		173(P-44)	2.77(m) 12H 2.25(s)* 3H	2850, 1350, 1120
<u>8</u>	paste	261(P+1), 230(P-30)	3.62(m) 8H	3350, 2925,
		216(P-44), 192(P-68)	2.77(m) 16H 2.52(s)* 4H	1350, 1110
<u>9</u>	paste	233(P+1), 202(P-30)	2.79(m) 20H	3290, 2925
		188(P-44), 164(P-68)	2.15(s)* 4H	2830, 1130
<u>10</u>	62.5-65.0	250(P+1), 219(P-30)	2.85(m) 20H	3275, 2915,
		205(P-44), 181(P-68)	2.04(s)* 3H	2825, 1290, 1115
<u>11</u>	paste	293(P+1), 262(P-30)	2.77(m) 24H	3300, 2920
		248(P-44), 224(P-68)	1.84(s)* 4H	2830, 1120

* The peak disappears on addition of D₂O. ** J=8 cps a Melting points were determined on a Yanagimoto Co. Micro Melting Point Apparatus and are uncorrected.

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