A Convenient Method for the Synthesis of Macrocyclic Tetra-amides by Double Condensation Reaction†

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A facile condensation reaction between bifunctional amines and carboxylic acid derivatives has been found to be very efficient for the formation of macrocyclic tetra-amide rings, and tetralactams with 33- to 37-membered rings were readily synthesized in good yields (60—90%).

Considerable effort has been made recently to prepare macrocyclic compounds bearing amide groups, not only because they show biological activity (*e.g.* anti-tumour,[2] anti-viral,[3] and hypotensive [4,5] properties), but also because they are able to form inclusion complexes with uncharged molecules as neutral hosts.[6,7] In the course of our work on the synthesis of ferredoxin model compounds,[1,8] and the splitting of water by visible light using synthetic iron–sulphur chelates[9] as in photosynthesis, we required a facile method for the preparation of the key intermediates, a series of cyclic tetra-amides containing *ca.* 36-membered rings. However, the preparation of ring compounds through amide bond formation is usually difficult,[10] and there is little precedent for the synthesis of tetralactams with rings larger than 30-membered.[11]

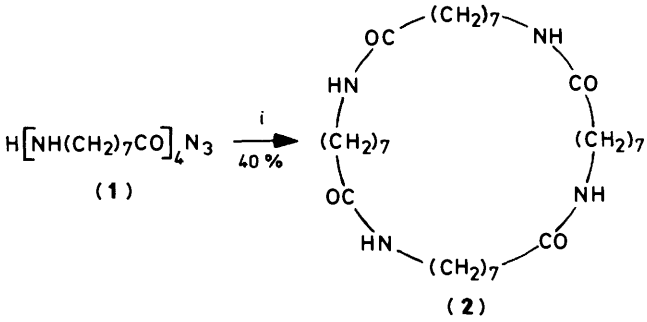
In an earlier paper[8] we described the synthesis of a symmetric 36-membered tetralactam (**2**) from the corresponding linear amide (**1**) *via* an intramolecular azide (Scheme 1), and the possibility of forming both the lipo- and hydro-philic cavities depending on the environment. However, the observed yield was only 40% at best, with a high-dilution technique (0.31×10^{-3}M), and the use of increased concentrations of the substrate led to decreased yields of the desired product (*e.g.*, 14% at 1.8×10^{-3}M concentration, which is insufficient for practical use).

Thus, better syntheses were required, and we present here an alternative preparation of macrocyclic tetra-amides.

Our procedure involves simple double condensation reactions between diamines and dicarboxylic acid derivatives, and the method can be extended for the synthesis of large macrocyclic compounds, as shown below. The sequence of reactions are shown in Scheme 2.

The diamides (**6**) and (**7**) were prepared from 1,8-diaminooctane (**3**) and the benzyloxycarbonylamino acids (**4**) and (**5**), by a mixed anhydride method using isobutyl chloroformate–triethylamine in tetrahydrofuran. Removal of the benzyloxycarbonyl groups of (**6**) and (**7**) with H_2–Pd–C in HCl–MeOH led to the diamines (**8**) and (**9**), which were subjected to cyclization reactions with dicarboxylic acid derivatives (**10**)—(**13**).

When a 2.1×10^{-3}M-solution of the diamine (**9**) in dimethylformamide (DMF) was treated with the acid chloride (**10**), the cyclised product (**14**) was isolated in 30% yield. Since the lability of the acid chloride seemed to depress the product yield, the more stable active ester was employed. Condensation with the *p*-nitrophenyl ester (**11**) with imidazole as catalyst[12] afforded the same product in high yield (68%). The use of increased concentrations of the substrates (by a factor of two or even four) still gave compound (**14**) in over 50% yield.‡



Scheme 1. *Reagents:* i, DMF–MeOH

Table 1. Preparation of the macrocyclic tetralactams (**14**)—(**19**) and (**21**)

Starting compounds		Concentration of (**8**) or (**9**) ($\times 10^{-3}$M)	Product	Yield (%)	[Ring size]
(**9**)	(**10**)	2.1	(**14**)	30	[36]
(**9**)	(**11**)	2.2	(**14**)	68	[36]
(**9**)	(**11**)	4.1	(**14**)	52	[36]
(**9**)	(**11**)	8.2	(**14**)	51	[36]
(**8**)	(**12**)	2.2	(**15**)	59	[33]
(**8**)	(**11**)	2.2	(**16**)	60	[34]
(**8**)	(**13**)	2.2	(**17**)	62	[35]
(**9**)	(**12**)	2.2	(**18**)	60	[35]
(**9**)	(**13**)	2.2	(**19**)	64	[37]
(**9**)	(**20**)	2.1	(**21**)	87	[35]

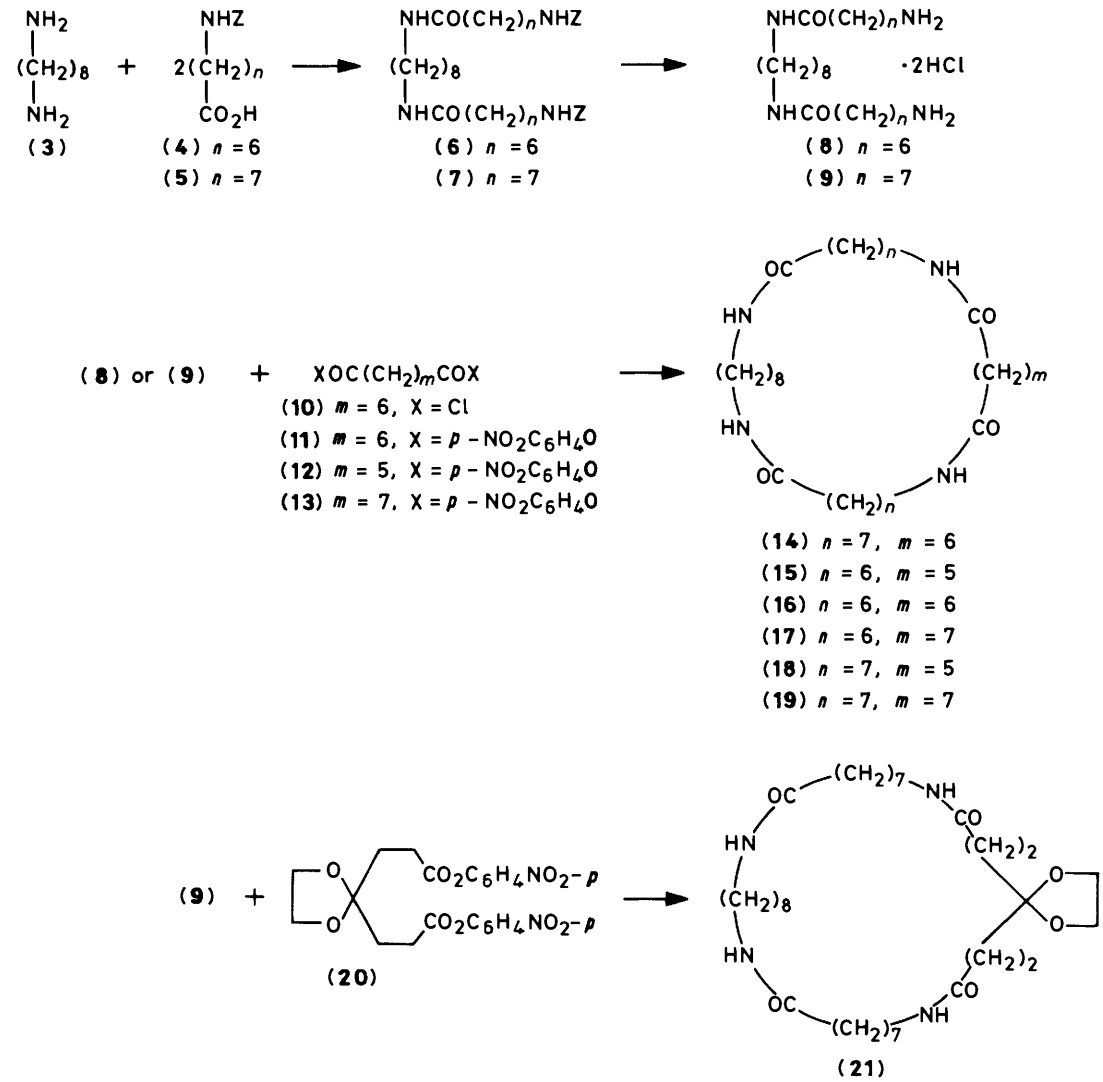
In a similar manner, tetralactams with 33- to 37-membered rings have been successfully prepared in satisfactory yields, and the results are summarized in Table 1.

This very efficient cyclization may, at least in part, be related to the favourable conformation of the substrates. In fact, when an ester containing an acetal group (**20**), *i.e.* with a more rigid conformation, was employed, the cyclization reaction proceeded very smoothly to afford compound (**21**) in 87% yield.

In conclusion, we have introduced an efficient method for the preparation of macrocyclic tetra-amides. This simple amide ring

† A part of this work has been presented at the first Symposium on Roles of Metals in Biological Reactions, Biology and Medicine, Tokyo, 1982.[1]

‡ In these reactions with the active ester, appreciable amounts (10—20% of a 72-membered octalactam) of a less soluble compound, which gives a similar i.r. spectrum (slightly different in the finger print region) to that of (**14**), has been obtained. Further studies are currently in progress.



Scheme 2. Z = $OCOCH_2C_6H_5$

formation may be very useful as a synthetic method not only for ligands of iron–sulphur clusters,[1,8] but also for biologically active macrocyclic lactams,[13] the scope and limitations of the reaction are currently under investigation.

Experimental

M.p.s, determined in capillary tubes, are uncorrected. Microanalyses were performed by the Analytical Centre of Hokkaido University. I.r. spectra were determined with a JASCO IRA-2 spectrophotometer. ^1H N.m.r. spectra were recorded on JEOL JNM-FX 100 and 200 instruments using $SiMe_4$ as an internal standard. Mass spectra were run on a JEOL JMS-D300 spectrometer. Ether refers to diethyl ether.

Preparation of the Diamides (**6**) *and* (**7**).—To a mixture of the amino acid (**4**) or (**5**)* (10 mmol) and triethylamine (10 mmol) in tetrahydrofuran (290 ml), isobutyl chloroformate (1.3 ml) was added dropwise at −20 °C with vigorous stirring. After 7 min, 1,8-diamino-octane (4.8 mmol) in tetrahydrofuran (90 ml) was gradually added so as to keep the temperature below −10 °C, and the solution was stirred for 1 h and then at room temperature overnight under argon. The solvent was then removed under reduced pressure and the residue was washed successively with 2% HCl, sat. $NaHCO_3$, and saline, and purified by recrystallization from MeOH–$CHCl_3$.

7,7′-*Bis*(*benzyloxycarbonylamino*)-N,N′-*octamethylenediheptanamide* (**6**) was obtained as a colourless solid (82%); m.p. 167.5—169.5 °C; $\nu_{max.}$(Nujol) 3 325, 3 290, 1 680, 1 630, and 1 525 cm^{-1}; δ_H($CDCl_3$–CD_3OD) 1.20—1.60 (28 H, m, CH_2), 2.65 (4 H, t, *J* 7.1 Hz, $COCH_2$), 3.02—3.14 (8 H, m, NCH_2), 5.08 (4 H, s, OCH_2Ph), and 7.35 (10 H, s, arom) (Found: C, 68.4; H, 8.8; N, 8.4. $C_{38}H_{58}N_4O_6$ requires C, 68.28; H, 8.83; N, 8.46%).

8,8′-*Bis*(*benzyloxycarbonylamino*)-N,N′-*octamethylenedioctanamide* (**7**) was obtained as a colourless solid (76%); m.p. 152—154 °C; $\nu_{max.}$(Nujol) 3 300, 1 690, 1 630, and 1 530 cm^{-1}; δ_H[$(CD_3)_2SO$, 80 °C] 1.24—1.47 (32 H, m, CH_2), 2.06 (4 H, t, *J* 7.3 Hz, $COCH_2$), 2.94—3.10 (8 H, m, NCH_2), 5.01 (4 H, s, CO_2CH_2), 6.99 (2 H, br, NH), 7.33 (10 H, s, arom), and 7.51 (2 H, br, NH) (Found: C, 69.1; H, 8.9; N, 8.1. $C_{40}H_{62}N_4O_6$ requires C, 69.13; H, 8.99; N. 8.03%); δ_H($CDCl_3$–CD_3OD) 1.32—1.69 (32 H, m, CH_2), 2.08 (4 H, t, *J* 7.3 Hz, $COCH_2$), 3.10—3.28 (8 H, m, NCH_2), 5.08 (4 H, s, CO_2CH_2), and 7.34 (10 H, s, arom).

* Compounds (**4**) and (**5**) were prepared by a similar procedure to that previously described, from the corresponding cyclic ketones,[8] J. C. Eck and C. S. Marvel, *Org. Synth.*, Coll. Vol. II, 1943, 76.

Table 2. Physical constants of the tetralactams (**14**)—(**19**) and (**21**)

Compound	M.p. (°C)	I.r. (Nujol) $\nu_{max.}$ cm^{-1}	Molecular formula	Analysis (%) Required (Found) C	H	N	M^+, m/z (Required)
(**14**)	230—232	3 250, 3 070, 1 640, 1 560	$C_{32}H_{60}N_4O_4$	68.04 (67.9)	10.71 (10.6)	9.92 (9.8)	564.6415 (564.641 76)
(**15**)	208—211	3 280, 3 070, 1 640, 1 550	$C_{29}H_{54}N_4O_4$	66.63 (66.55)	10.41 (10.5)	10.72 (10.6)	522.4146 (522.414 78)
(**16**)	199—202	3 250, 3 070, 1 640, 1 560	$C_{30}H_{56}N_4O_4$	67.12 (67.0)	10.52 (10.9)	10.44 (10.25)	536.4304 (536.4304)
(**17**)	222—224	3 270, 3 080, 1 640, 1 550	$C_{31}H_{58}N_4O_4$	67.59 (67.5)	10.61 (10.7)	10.17 (10.0)	550.4462 (550.4461)
(**18**)	209—211	3 270, 3 080, 1 640, 1 550	$C_{31}H_{58}N_4O_4$	67.59 (67.4)	10.61 (10.6)	10.17 (10.0)	550.4448 (550.4461)
(**19**)	202—204	3 280, 3 070, 1 640, 1 540	$C_{33}H_{62}N_4O_4$	68.47 (68.4)	10.80 (10.7)	9.68 (9.7)	578.4778 (578.477 42)
(**21**)	168	3 270, 3 050, 1 635, 1 540	$C_{33}H_{60}N_4O_6H_2O$	63.22 (63.3)	9.97 (9.6)	8.94 (9.0)	680 (M^+)

Preparation of the Diamines (**8**) *and* (**9**).—Deprotection was carried out by catalytic hydrogenation of the diamide (**6**) or (**7**) (3.0 mmol) in 3.5M-HCl–MeOH (40 ml) overnight in the presence of 10% Pd–C (692 mg), and the residue was purified by recrystallization from MeOH–ether. 7,7′-*Diamino*-N,N′-*octamethylenediheptanamide dihydrochloride* (**8**) was obtained as a colourless solid (89%); m.p. 253—255 °C (decomp); $\nu_{max.}$(Nujol) 3 300, 1 640, and 1 525 cm^{-1}; $\delta_H(CD_3OD)$ 1.35—1.63 (28 H, m, CH_2), 2.20 (4 H, t, *J* 7.2 Hz, $COCH_2$), 2.92 (4 H, t, *J* 7.3 Hz, $CONCH_2$), and 3.15 [4 H, t, *J* 6.5 Hz, N(amino)CH_2] (Found: C, 56.0; H, 10.3; Cl, 15.0; N, 11.9. $C_{22}H_{48}Cl_2N_4O_2$ requires C, 55.82; H, 10.40; Cl, 15.04; N, 11.97%).

8,8′-*Diamino*-N,N′-*octamethylenedioctanamide dihydrochloride* (**9**) was obtained as a colourless solid (97%); m.p. 243—245 °C (decomp.); $\nu_{max.}$(Nujol) 3 275, 1 630, and 1 540 cm^{-1}; $\delta_H(CD_3OD)$ 1.30—1.62 (32 H, m, CH_2), 2.18 (4 H, t, *J* 7.3 Hz, $COCH_2$), 2.91 (4 H, t, *J* 7.6 Hz, $CONCH_2$), and 3.15 [4 H, t, *J* 7.0 Hz, N(amino)CH_2] (Found: C, 57.7; H, 10.5; Cl, 14.2; N, 11.2. $C_{24}H_{52}Cl_2N_4O_2$ requires C, 57.47; H, 10.67; Cl, 14.26; N, 11.09%).

Preparation of the Acid Derivatives (**10**)—(**13**).—The acid chloride (**10**) was obtained by heating suberic acid (4 g, 23 mmol) in thionyl chloride (21 ml) for 8 h, and then distilling the mixture under reduced pressure. Octane-1,8-dioyl dichloride (**10**) was obtained as a colourless oil (3.8 g, 77%); b.p. 112 °C/0.5 mmHg; $\nu_{max.}$(neat) 1 790 cm^{-1}.

The *p*-nitrophenyl esters were prepared from the corresponding acid chloride (5.1 mmol); it was added to a mixture of *p*-nitrophenol (10.4 mmol) and pyridine (822 mg) in $CHCl_3$ (5 ml). After 2.5 h with stirring at room temperature, $CHCl_3$ (20 ml) was added to the solution, and it was then washed with 2M-HCl and sat. $NaHCO_3$. Pale yellow leaflets were obtained after recrystallization from EtOH–$CHCl_3$–ether. *Bis*(p-*nitrophenyl*) *octane*-1,8-*dioate* (**11**) was obtained as leaflets (83%); m.p. 116—117 °C; $\nu_{max.}$(Nujol) 1 750, 1 620, 1 590, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 1.49—1.85 (8 H, m, CH_2), 2.62 (4 H, t, *J* 7.3 Hz, $COCH_2$), and 7.21, 7.30 (4 H, d, *J* 8 Hz, arom), and 8.20, 8.27 (4H, d, *J* 8 Hz, arom) (Found: C, 57.7; H, 4.8; N, 6.7. $C_{20}H_{20}N_2O_8$ requires C, 57.55; H, 4.70; N, 6.80%).

Bis(p-*nitrophenyl*) *heptane*-1,7-*dioate* (**12**) was obtained as leaflets (83%); m.p. 84—85 °C; $\nu_{max.}$(Nujol) 1 750, 1 610, 1 590, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 1.65—1.92 (6 H, m, CH_2), 2.67 (4 H, t, *J* 7 Hz, $COCH_2$), and 7.23, 7.32 (4 H, d, *J* 9.3 Hz, arom), and 8.21, 8.31 (4H, d, *J* 9.3 Hz, arom) (Found: C, 56.8; H, 4.3; N, 6.8. $C_{19}H_{18}N_2O_8$ requires C, 56.71; H, 4.51; N, 6.96%).

Bis(p-*nitrophenyl*) *nonane*-1,9-*dioate* (**13**) was obtained as leaflets (87%); m.p. 80—82 °C; $\nu_{max.}$(Nujol) 1 750, 1 620, 1 590, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 1.45—1.85 (10 H, m, CH_2), 2.62 (4 H, t, *J* 7 Hz, $COCH_2$), 7.23, 7.32 (4 H, d, *J* 9.3 Hz, arom), and 8.22, 8.31 (4H, d, *J* 9.3 Hz, arom) (Found: C, 58.5; H, 5.2; N, 6.6. $C_{21}H_{22}N_2O_8$ requires C, 58.60; H, 5.15; N, 6.51%).

Preparation of the Active Ester (**20**).—To a solution of 4-ethylenedioxyheptane-1,7-dioic acid* (2.47 g, 11.3 mmol) in pyridine–CH_2Cl_2 (10:1) (60 ml), *p*-nitrophenol (3.79 g, 27.1 mmol) and dicyclohexylcarbodi-imide (4.68 g, 24.9 mmol) were added, and the mixture was stirred for 1 h at −5 °C, then at room temperature for 2 h. It was then filtered, the solvent was evaporated off, and the residue was dissolved in CH_2Cl_2 (50 ml) and washed with 4% $NaHCO_3$ and saline. Purification was achieved by column chromatography (silica gel, CH_2Cl_2 MeOH, 60:1), and then recrystallization from EtOH–$CHCl_3$–ether. *Bis*(p-*nitrophenyl*)-4-*ethylenedioxyheptane*-1,7-*dioate* (**20**) was obtained as colourless plates (4.29 g, 82%); m.p. 95—96 °C; $\nu_{max.}$(Nujol) 1 760 cm^{-1}; $\delta_H(CDCl_3)$ 2.19 (4 H, t, *J* 7.4 Hz, CCH_2), 2.70 (4 H, t, *J* 7.4 Hz, $COCH_2$), 4.03 (4 H, s, OCH_2), 7.28 (4 H, d, *J* 8.8 Hz, arom), and 8.27 (4 H, d, *J* 8.8 Hz, arom) (Found: C, 54.95; H, 4.2; N, 6.5. $C_{21}H_{20}N_2O_{10}$ requires C, 54.78; H, 4.38; N, 6.09%).

Preparation of the Macrocyclic Tetra-amides (**14**)—(**19**) *and* (**21**).—To a solution in DMF (109 ml)–MeOH (8 ml) of the diamine (**8**) or (**9**) (0.24 mmol) and triethylamine (0.72 mmol) in the presence of imidazole (0.21 mmol),[12] the corresponding active ester (0.26 mmol) in CH_2Cl_2 (15 ml) was added dropwise during 4 h, and stirred for 48 h at room temperature. After evaporation of the solvent, the residue was extracted with MeOH–$CHCl_3$ (1:3). Recrystallization from MeOH afforded a colourless solid. The physical characteristics of the products are summarized in Tables 2 and 3.

Acknowledgements

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* Synthesized from furfural and malonic acid (S. Rajagopalan, *Org. Synth.*, Coll. Vol. II, 1955, 425; W. Marakwald, *Chem. Ber.*, 1887, 2811; S. Yamada, T. Wakamatsu, and Y. Ban, unpublished results).

Table 3. ^{1}H N.m.r. data of the tetralactams (**14**)—(**19**) and (**21**) in CD_3OD–$CDCl_3$ (200 MHz) (*J* in Hz)

Compound	CH_2	$OCCH_2$	δ/p.p.m. $COCH_2$	NCH_2	OCH_2
(**14**)	1.32—1.78 (m, 40 H)		2.17 (t, *J* 7.0, 8 H)	3.12—3.25 (m, 8 H)	
(**15**)	1.30—1.63 (m, 34 H)		2.14—2.21 (m, 8 H)	3.19 (t, *J* 6.6, 8 H)	
(**16**)	1.30—1.61 (m, 36 H)		2.17 (t, *J* 7.1, 8 H)	3.19 (t, *J* 6.4, 8 H)	
(**17**)	1.30—1.61 (m, 38 H)		2.13—2.20 (m, 8 H)	3.19 (t, *J* 6.6, 8 H)	
(**18**)	1.30—1.67 (m, 38 H)		2.17 (t, *J* 7.1, 8 H)	3.19 (t, *J* 6.6, 8 H)	
(**19**)	1.31—1.69 (m, 42 H)		2.17 (t, *J* 7.1, 8 H)	3.19 (t, *J* 6.8, 8 H)	
(**21**)	1.31—1.63 (m, 32 H)	1.96 (t, *J* 6.8, 4 H)	2.14—2.31 (m, 8 H)	3.23 (m, 8 H)	3.94 (s, 4 H)

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