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Efficient synthesis of macrocycles by oxidation of cysteine-based dithiols

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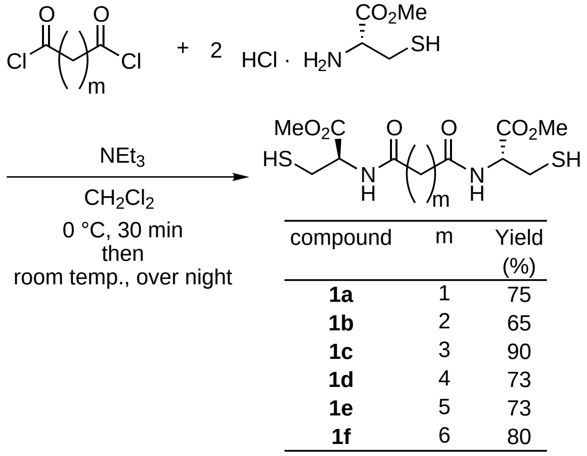
Abstract—The cysteine-bridged macrocycles, 22–32-membered cyclic dimers could be synthesized with a high reagent concentration (1 M) in excellent yields by the oxidation of the cysteine-based compounds having dithiol groups. © 2001 Elsevier Science Ltd. All rights reserved.

Amino acid and peptide-based macrocycles have attracted a great deal of attention in the design of peptidomimetics for studying biological interactions.[1] Ghadiri et al. have synthesized a new class of organic nanotubes based on rationally designed cyclic peptides.[2] Several attempts have been made to conformational flexibility of the macrocycles, such as incorporation of D-amino acids,[2,3] β-amino acid,[4] semirigid aromatic units,[5] and disulfide linkages.[6] They are expected as artificial proteins[7] and peptidomimetic drugs,[8] which would show novel function. However, it is commonly not easy to synthesize the macrocycles because of the difficulty of forming large membered rings. Karle et al. have reported the synthesis of 19–52-memberd cyclic amides consisting of aromatic-bridged cystine (cystinophanes), but the yields were only 4–51%.[9] Furthermore, they have reported that the cyclization of α,ω-acid dichlorides with cystine dimethyl ester hydrochloride was carried out in the presence of triethylamine in CH_2Cl_2 under highly diluted conditions (reagent concentration 0.037 M) to obtain the various membered cyclic oligomers in low yields. Further, those cyclic compounds would have consisted of nanotubes by self-assembly.[10] We have found that those large-membered cyclic amides could be obtained in high selectivity and in high yields by the oxidation of the cysteine-based compounds having dithiols. This article deals with the efficient synthesis of large cyclic amides by oxidation of cysteine-based dithiols.

The cysteine-based dithiols (**1a**–**f**) were synthesized by the reaction of α,ω-acid dichloride $[(CH_2)_m(COCl)_2]$ ($m=1$–6) with L-cysteine methyl ester hydrochloride in CH_2Cl_2 in the presence of triethylamine under a nitrogen atmosphere (Scheme 1). All the dithiols could be isolated as stable solids by recrystallization. The structure of the dithiols was confirmed by ^1H, ^{13}C NMR and IR spectroscopy, besides elemental analysis.[11]

The dithiols were oxidized by atmospheric pressure of oxygen in the presence of 2.2 equiv. of triethylamine in *N*,*N*-dimethylformamide (DMF) and dimethyl sulfox-



compound	m	Yield (%)
1a	1	75
1b	2	65
1c	3	90
1d	4	73
1e	5	73
1f	6	80

Scheme 1.

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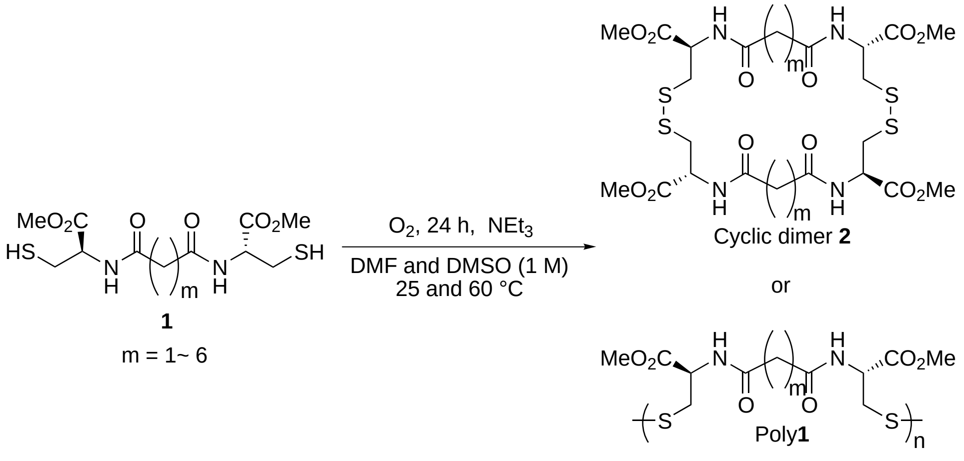
ide (DMSO) (reagent concentration 1 M) at 25 and 60°C for 24 h (Scheme 2). By the oxidation of **1f** in DMF at 60°C, the polymer (poly**1f**) was obtained in 80% yield with a number average molecular weight (M_n) of 4800 and polydispersity (M_w/M_n) of 1.31. Fig. 1(B) illustrates the ^{1}H NMR spectrum of poly**1f**. All the proton signals were observed broadly at the same positions as the monomer (Fig. 1(A)), indicating that poly**1f** was formed by oxidation coupling of the thiol groups. Poly**1f** was similarly obtained in DMSO both at 25 and 60°C in 82 and 85% yields, respectively. In each case, the reaction was observed to be homogeneous, with all starting materials and products remaining in solution. On the other hand, the reaction mixture in DMF (reagent concentration 1 M) at 25°C changed heterogeneously for 6 h after the reaction started, except for **1c**. A colorless solid was obtained by pouring the reaction mixture into a large amount of ethyl ether. Fig. 1(C) illustrates the ^{1}H NMR spectrum of the product from **1f**. No IR absorption assignable to a thiol group was observed around at 2560 cm^{-1}. The FAB mass spectrum showed a parent peak at 813.04 (calcd for $C_{15}H_{27}N_2O_6S_2$: 813.02). Although poly**1f** was soluble in $CHCl_3$, CH_2Cl_2, DMF and DMSO, the obtained product was only soluble in DMSO. The product showed a clear melting point at 207–208°C, and its molar rotation ($[M]_D^{25}$) was −528.5° ($c=0.1$ g/dL, DMSO), which was completely different from **1f** (369.3°). These results might support strongly that it was a cyclic dimer **2f**.

Furthermore, the oxidation of dithiols **1a**–**f** was carried out in the presence of triethylamine in $CHCl_3$, CH_2Cl_2, MeOH and DMF (reagent concentration 1 M) at 25°C under an oxygen atmosphere for 24 h, as summarized in Table 1. The reaction mixture became heterogeneous, expect for **1c**, to afford the corresponding cyclic dimers in 65 to >99% yields.[12] The reaction mixture of **1c** was consistently homogeneous in all the solvents to selectively afford the polymer (poly**1c**) with the M_ns in the range of 3300–6500 (M_w/M_n 1.14–1.53) in 88–95% yields. Interestingly, **1f** afforded the cyclic dimer in



Scheme 2.

Table 1. Oxidation of cysteine-based dithiols **1a**–**f**[a]

Run	Dithiol	Cyclic dimer yield[b] (%)					$[M]_D^{25c}$ (°)
		Solvent					
		$CHCl_3$	CH_2Cl_2	MeOH	DMF	DMSO	
1	**1a**	>99	85	90	70	93	−620.3
2	**1b**	95	90	85	65	92	−547.3
3	**1c**	Poly**1c**[d]	Poly**1c**[d]	Poly**1c**[d]	Poly**1c**[d]	Poly**1c**[d]	–
4	**1d**	>99	95	>99	>99	>99	−146.1
5	**1e**	95	97	>99	>99	>99	580.9
6	**1f**	>99	95	90	>99	Poly**1f**[e]	−528.5

[a] Conditions: dithiols 1.0 mmol, NEt_3 2.2 mmol, solvent 3.0 mL, time 24 h, temperature 25°C, under atmospheric pressure of oxygen.

[b] Ethyl ether-insoluble part.

[c] $[M]_D^{25}=[\alpha]_D^{25}\times MW/100$, where MW represents the molecular weight of the monomer repeating unit, $[\alpha]_D^{25}$ was measured by a polarimeter at 25°C ($c=0.1$ g/dL, DMSO). $[M]_D^{25}$ of the dithiols, **1a**: −83.2°, **1b**: −129.6°, **1c**: −153.2°, **1d**: −104.9°, **1e**: −89.9°, **1f**: 369.3°.

[d] The reaction mixture was homogeneous consistently. The M_n (M_w/M_n) was estimated by GPC based on polystyrene standards; LiBr solution in DMF (5.8 mM). Poly**1c**: yield 90%, M_n 4000 (M_w/M_n 1.23) ($CHCl_3$). Yield 91%, M_n 3700 (M_w/M_n 1.31) (CH_2Cl_2). Yield 88%, M_n 3200 (M_w/M_n 1.35) (MeOH). Yield 92%, M_n 3300 (M_w/M_n 1.14) (DMF). Yield 95%, M_n 6500 (M_w/M_n 1.53) (DMSO).

[e] Yield 82%, M_n 4500 (M_w/M_n 1.27).

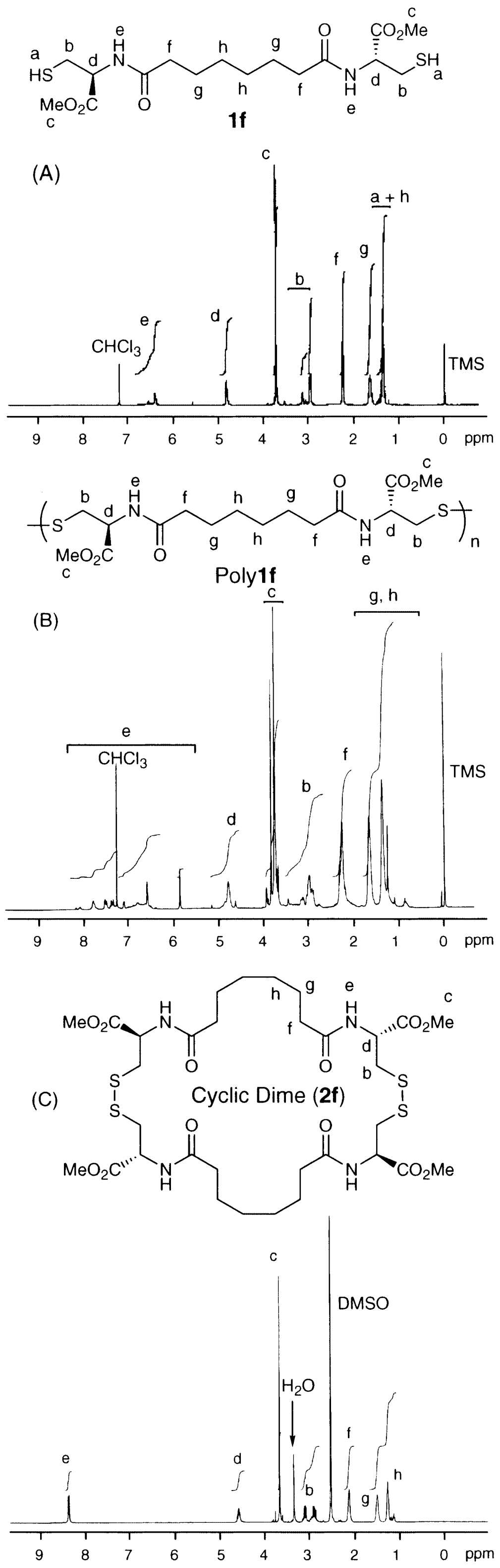


Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of (A) cysteine-based dithiol **1f** and (B) poly**1f** ($M_n = 4800$, $M_w/M_n = 1.31$) obtained by the oxidation of **1f** in DMF (reagent concentration 1 M) at 60°C in the presence of NEt_3 for 24 h. (C) ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of cyclic dimer (**2f**) obtained by the oxidation of **1f** in DMF (1 M) at 25°C in the presence of NEt_3 for 24 h.

$CHCl_3$, CH_2Cl_2, MeOH, and DMF, but the polymer in DMSO. When iodine was used as an oxidant of **1f** in DMF (reagent concentration 1 M) at 25°C under a nitrogen atmosphere, no dimer but the polymer with a M_n of 7600 was formed in 96% yield.

Large membered cyclic compounds are commonly produced under highly diluted conditions in low yields. It is noticeable that 22–32-memberd cyclic dimers could be synthesized with a high reagent concentration (1 M) in excellent yields. The precipitation of the dimers during the reaction should efficiently shift the dimer–polymer equilibrium to the dimer side, that is, highly selective cyclization to form the cyclic dimers was achieved by the oxidation of dithiols. Exquisite balance between the reaction rate and product solubility would result in the satisfactory formation of the cyclic dimers. The molecular conformation might also contribute to the high selectivity, probably restricted by the hydrogen bonding interaction of the amide-ester moieties. It was also surprising that the cyclic dimers and polymers were formed with complete selectivity according to the temperature and solvent, as well as the chain length of the dithiols. In summary, we demonstrated the efficient synthesis of large membered macrocycles by oxidation of cysteine-based dithiols, some of which selectively afforded the corresponding polymers under certain conditions. The formed macrocycles would be promising candidates for self-assembly and molecular-recognizable materials based on the optically active amide–ester–disulfide functionalized structures.

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11. **1a**: Yield 8.46 g (70%). Mp = 80–81°C. $[\alpha]_D^{25} = 66.8°$ (c = 0.1 g/dL $CDCl_3$), −24.6° (c = 0.1 g/dL, DMSO). **1b**: Yield 65%. Mp = 150–151°C. $[\alpha]_D^{25} = 45.2°$ (c = 0.1 g/dL, $CHCl_3$), −36.8° (c = 0.1 g/dL, DMSO). **1c**: Yield 75%. Mp = 96–97°C. $[\alpha]_D^{25} = 43.0°$ (c = 0.1 g/dL, $CHCl_3$), −41.8° (c = 0.1 g/dL, DMSO). **1d**: Yield 80%. Mp = 54–55°C. $[\alpha]_D^{25} = 67.1°$ (c = 0.1 g/dL, $CHCl_3$), −27.6° (c = 0.1 g/dL, DMSO). **1e**: Yield 82%. Mp = 57–58°C. $[\alpha]_D^{25} = 68.1°$ (c = 0.1 g/dL, $CHCl_3$), −22.8° (c = 0.1 g/dL, DMSO). **1f**: Yield 73%. Mp = 60–61°C. $[\alpha]_D^{25} = 85.6°$ (c = 0.1 g/dL, $CHCl_3$), 90.4° (c = 0.1 g/dL, DMSO).
12. **2a**: Yield 235 mg (70%). Mp = 83–84°C. $[\alpha]_D^{25} = -92.2°$ (c = 0.1 g/dL, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.84$–3.08 (m, 8H, -CH_2-S), 3.32 (s, 4H, -C(O)-CH_2-C(O)-), 3.65 (s, 12H, -OCH_3), 4.59–4.70 (m, 4H, >CH-), 7.56 (d, $J = 7.19$ Hz, 4H, >CH-) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): $\delta = 9.33$, 11.04, 45.68, 52.30, 166.75, 170.61 ppm. Anal. calcd for $C_{22}H_{32}N_4O_{12}S_4$: C, 39.28; H, 4.79; N, 8.33; S, 19.06. Found C, 32.22; H, 4.55; N, 8.51; S, 18.89. HRFAB-MS: $(M+H)^+$ calcd for $C_{22}H_{32}N_4O_{12}S_4$: 673.1. Found: 673.1. **2b**: Yield 65%. Mp = 230–233°C (lit.[10] 243–244°C). $[\alpha]_D^{25} = -78.1°$ (c = 0.1 g/dL, DMSO). **2d**: Yield >99%. Mp = 243–244°C. $[\alpha]_D^{25} = -19.32°$ (c = 0.1 g/dL, DMSO). **2e**: Yield >99%. Mp = 220–222°C (lit.[10] 206–207°C). $[\alpha]_D^{25} = 73.9°$ (c = 1 g/dL, DMF). **2f**: Yield >99%. Mp = 207–208°C (lit.[10] 213–214°C). $[\alpha]_D^{25} = -64.6°$ (c = 0.1 g/dL, DMSO). In Ref. 10, **2b**–**2f** have been synthesized by the reaction of α,ω-acid dichloride $[(CH_2)_m(COCl_2)]$ (m = 2–6) with cystine dimethyl ester hydrochloride in the presence of triethylamine in CH_2Cl_2 under highly diluted conditions (reagent concentration 0.037 M) in 1.2–16.0% yields.