

Supporting Information

Aminolysis induced functionalization of (RAFT) polymer-dithioester with thiols and disulfides

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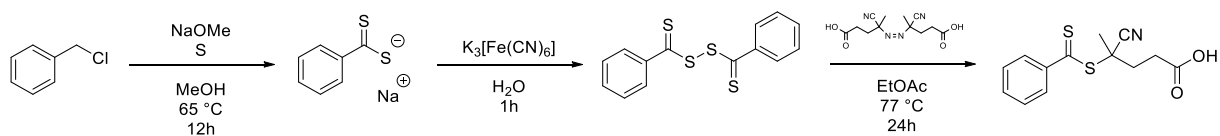
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Chemicals

Sigma Aldrich: 2,2'-Azobisisobutyronitrile (AIBN, 98%), 4,4'-azobis(4-cyanopentanoic acid) ($\geq 98\%$), hexylamine (99%), 2-hydroxyethyl disulfide (technical grade), cystamine dihydrochloride (98%), triphosgene (98%), maleic anhydride (99%), aluminum oxide (activated, basic), sodium (in kerosene, $\geq 99.8\%$), *N,N*-dimethylformamide (DMF, $\geq 99.8\%$, puriss, absolute), 1,4-dioxane (99.8%), poly(ethylene glycol) monomethyl ether (mPEG-OH, average M_n 550). **VWR Chemicals:** Styrene ($\geq 99.5\%$, stabilized), methyl methacrylate (MMA, $\geq 99\%$, stabilized), dichloromethane (DCM, $> 99\%$), diethyl ether (99.5%), magnesium sulfate ($MgSO_4$, $\geq 99.8\%$), ethyl acetate (99%), sodium chloride (NaCl, $\geq 99\%$). **Acros Organics:** Triethylamine (TEA, 99%, pure), benzyl chloride (99%, pure), sulfur (99.5+%, refined), potassium ferricyanide ($\geq 99\%$, for analysis), *p*-toluenesulfonyl chloride (Tos-Cl, 99+%), *N,N'*-dicyclohexylcarbodiimide (DCC, 99%), lithium aluminum hydride ($LiAlH_4$, powder, 95%), tetrahydrofuran (THF, 99.5%, extra dry), methanol (MeOH, 99.8%, extra dry), cyclohexane (99.0+%, pure). **Fischer Scientific:** 1,8-Diazobicyclo(5.4.0)undec-7-en (DBU, 99%), chloroform (99.8%), **Alfa Aesar:** 5,5'-Dithiobis(2-nitrobenzoic acid) (Ellman's Reagent, 99%), potassium thioacetate (98%). **Carl Roth:** Sodium hydroxide ($\geq 99\%$), sodium bicarbonate ($\geq 99\%$), heptanes (99.97%). **Honeywell:** Anisole ($\geq 99\%$). **abcr GmbH:** 2-Mercaptoethanol (98%). **Merck KGaA:** 1M aqueous HCl. **Purac Biochem BV:** L-Lactide. **TCI Deutschland:** γ -Benzyl-D-glutamate (98%). **Macherey-Nagel:** Silica gel (60 M, 0.04–0.063 mm), **Deutero GmbH:** Chloroform-d (99.8% atom D).

All chemicals were used as received, except: AIBN was recrystallized from isopropanol, styrene and MMA were passed through an aluminum oxide filter before use.

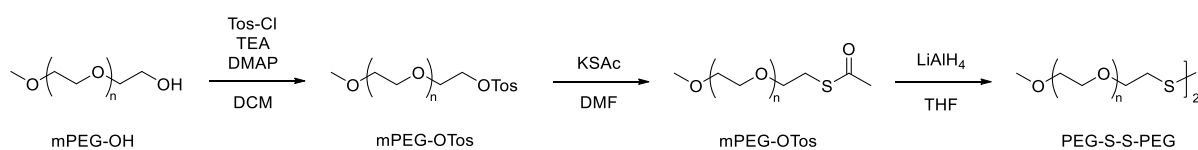
Synthesis of 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPADB)



CPADB was synthesized similar to the published methods by Y. Mitsukami *et al.* (*Macromolecules* **2001**, *34*, 2248-2256) and F. Reyes-Ortega *et al.* (*J. Mater. Chem. B* **2013**, *1*, 850-860).

Elemental sodium (4.6 g, 200 mmol) was added portion wise into 90 mL anhydrous methanol under vigorous stirring. The solution was stirred for 1 h at room temperature and then refluxed until complete dissolution of the sodium. After cooling to room temperature, benzyl chloride (11.5 mL, 100 mmol) and elemental sulfur (6.4 g, 200 mmol) was added and the mixture was refluxed for 12 h. Then, the mixture was cooled to 5 °C with an ice-bath. The mixture was filtered to remove the salt, the methanol was removed in vacuum, 100 mL was added to the residue and filtered again. The crude sodium dithiobenzoate solution was washed with diethyl ether (3 x 40 mL). Then, diethyl ether (40 mL) and 1N HCl (100 mL) were added and the product was extracted into the ethereal layer. Water (60 mL) and 1N NaOH (120 mL) were added and the product was extracted to the aqueous layer. The washing procedure was repeated two times. Potassium ferricyanide (III) (32.93 g, 100 mmol) was dissolved in 500 mL of water and added dropwise over a period of 1 h to the aqueous sodium dithiobenzoate solution under vigorous stirring. The precipitate was filtered and washed with deionized water until the washings became colorless. The residue was dried in vacuum at room temperature overnight. In the last step, di(thiobenzoyl)disulfide (2.13 g, 7 mmol) and 4,4' azobis(4-cyanopentanoic acid) (2.92 g, 11.5 mmol) were dissolved in 40 mL of distilled ethyl acetate. The solution was refluxed for 24 h. The solvent was removed in vacuum and the crude product was purified by column chromatography using ethyl acetate:hexane (2:3 v/v) as eluent. The product was recrystallized from ethyl acetate:hexane (2:3 v/v) and dried under high vacuum overnight. Yield: 70%.

Synthesis of dithiobis[poly(ethylene glycol)], PEG-S-S-PEG



PEG-S-S-PEG is synthesized following procedures described by Lee *et al.* (*Biomacromolecules* **2005**, *6*, 24-26) and Sun *et al.* (*Biomacromolecules* **2006**, *7*, 2871-2877).

Poly(ethylene glycol) monomethyl ether (mPEG-OH) (5 g, 8.92 mmol) was dissolved in 20 mL of dichloromethane (DCM) and cooled to 0 °C with an ice-bath. Then, 4-(dimethylamino)pyridine (DMAP) (0.272 mg, 2.23 mmol), *p*-toluene sulfonyl chloride (Tos-Cl) (2.04 g, 10.70 mmol) and triethylamine (TEA) (6.5 mL) were added and stirred at 0 °C overnight. The solvent was removed by evaporation and the crude product was dissolved in 50 mL of chloroform and washed three times with water and 0.1N HCl. The organic layer was dried with MgSO₄ and the solvent was removed in vacuum to obtain mPEG-OTos.

mPEG-OTos (6.33 g, 8.85 mmol) was dissolved in 44 mL of *N,N*-dimethylformamide (DMF). Potassium thioacetate (1.26 g, 11.07 mmol) was added and the solution was stirred for 7 h at room temperature. The product was extracted with chloroform (3 x 50 mL), dried over MgSO₄, and the solvent was removed in vacuum to obtain mPEG-SAc.

mPEG-SAc (1.71 g, 2.76 mmol) was dissolved in 20 mL of tetrahydrofuran (THF) and cooled to 0 °C. Lithium aluminum hydride (LiAlH₄, 157.33 mg, 4.15 mmol) was added in portions and the mixture was stirred in an open flask overnight. The excess of LiAlH₄ was quenched by the addition of 4 mL of methanol and 4 mL of water. After the salt was removed by filtration, the solvents were evaporated under vacuum. The crude product was dissolved in 20 mL of chloroform, washed three times with water, dried with MgSO₄, and the solvent was removed under vacuum to obtain PEG-S-S-PEG. Yield: 55%. M_n^{app} 1325 g mol⁻¹, \bar{D} 1.12 (SEC).

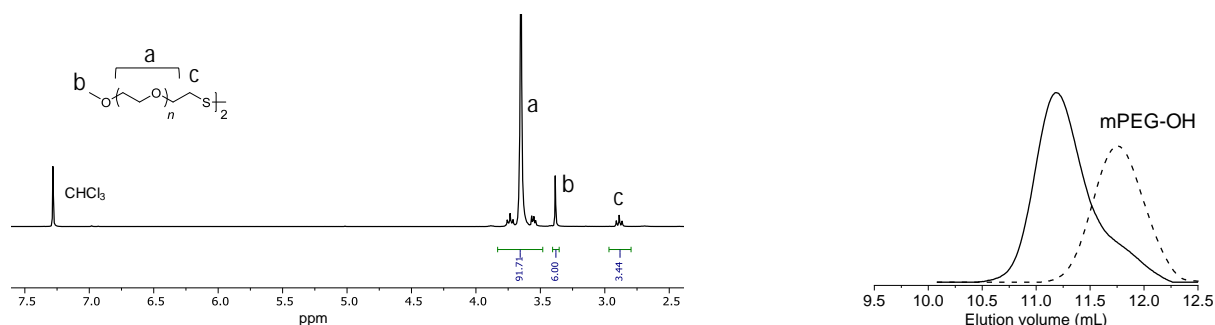
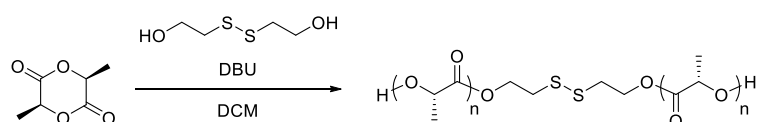


Figure S1. (Left) ¹H NMR spectrum (300 MHz, CDCl₃) and (right) SEC-RI trace (eluent: THF) of PEG-S-S-PEG. Note: the shoulder in the SEC trace at ~12 mL corresponds to non-disulfide coupled PEG chains.

Synthesis of dithiobis[poly(L-lactide)], PLLA-S-S-PLLA



L-Lactide was polymerized similar to the methods described by Pagels *et al.* (*Macromol. Chem. Phys.* **2020**, *221*, 1900396) and Noack *et al.* (*Macromol. Rapid Commun.* **2019**, *40*, 1800639). L-Lactide (34.7 mmol) and 2-hydroxyethyl disulfide (1 mmol) were dissolved in dry DCM (1.2 mL) in a silanized flask. Then, 1,8-diazobicyclo(5.4.0)undec-7-en (DBU) (0.125 mmol) was added to the mixture. After stirring for 1 h at room temperature, the polymerization was quenched by extraction of the DBU with ice-cold 1M aqueous HCl, followed by two times washing with ice-cold water. The polymer was precipitated several times in an excess of cold methanol and freeze-dried from 1,4-dioxane. Yield: 85%. M_n^{app} 4000 g mol⁻¹, \bar{D} 1.12 (SEC).

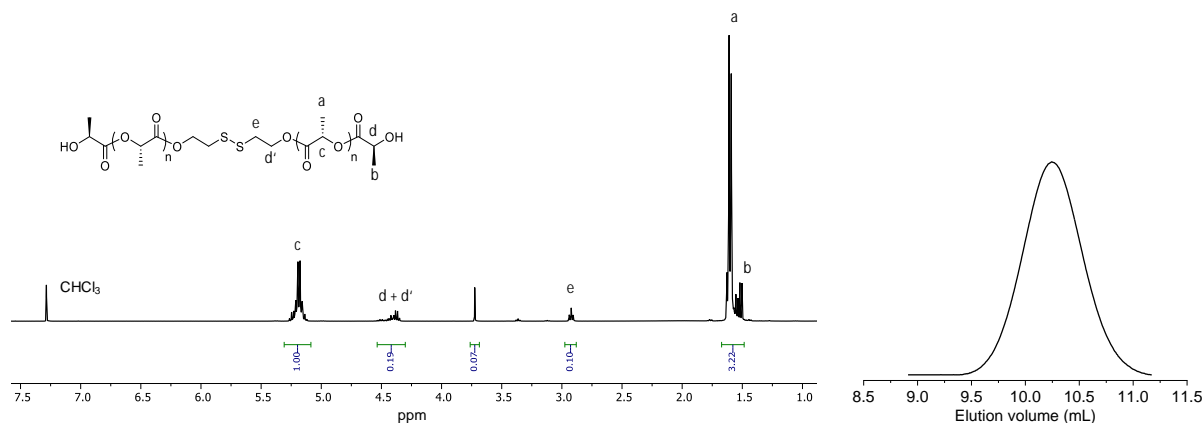
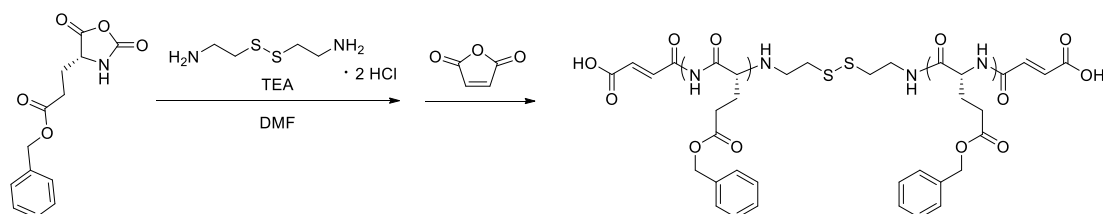


Figure S2. (Left) ¹H NMR spectrum (300 MHz, CDCl₃) and (right) SEC-RI trace (eluent: THF) of PLLA-S-S-PLLA.

Synthesis of dithiobis[poly(γ-benzyl-D-glutamate)], PBDG-S-S-PBDG



γ-Benzyl-D-glutamate *N*-carboxyanhydride (NCA) was synthesized and polymerized as earlier described by Vacogne *et al.* (*Chem. Commun.* **2015**, *51*, 15645-15648; *Polymer* **2017**, *124*, 203-209; *J. Am. Chem. Soc.* **2018**, *140*, 11387-11394).

Synthesis of NCA: To a solution of γ -benzyl-D-glutamate (50 mmol) in dry THF (150 mL) was added triphosgene (20 mmol) and the mixture was heated to 50 °C for 3 h. The mixture was reduced to about 20 mL under reduced pressure and precipitated into 200 mL of heptanes. The precipitate was filtered, washed with heptanes, dried under high vacuum and then re-dissolved in 20 mL of THF, precipitated, filtered and dried under high vacuum overnight.

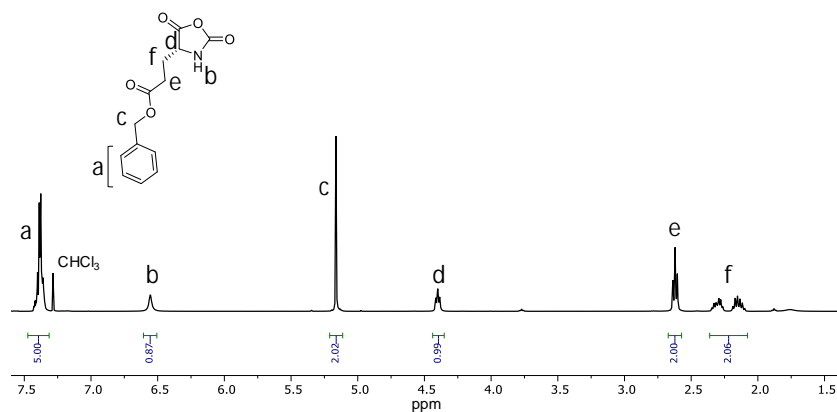


Figure S3. ^1H NMR spectrum (300 MHz, CDCl_3) of γ -benzyl-D-glutamate NCA.

NCA polymerization: To a solution of γ -benzyl-D-glutamate NCA (200 mg) in dry DMF (4 mL) was added a 1:1 mixture of cystamine dihydrochloride (8.63 mg) and TEA (3.84 mg). The mixture was stirred for 16 h at 50 °C and then maleic anhydride (50 equiv) was added to quench the polymerization. The polymer was precipitated into diethyl ether, filtered, and freeze-dried from 1,4-dioxane. Yield: 78%. M_n^{app} 5400 g mol^{-1} , D 1.20 (SEC).

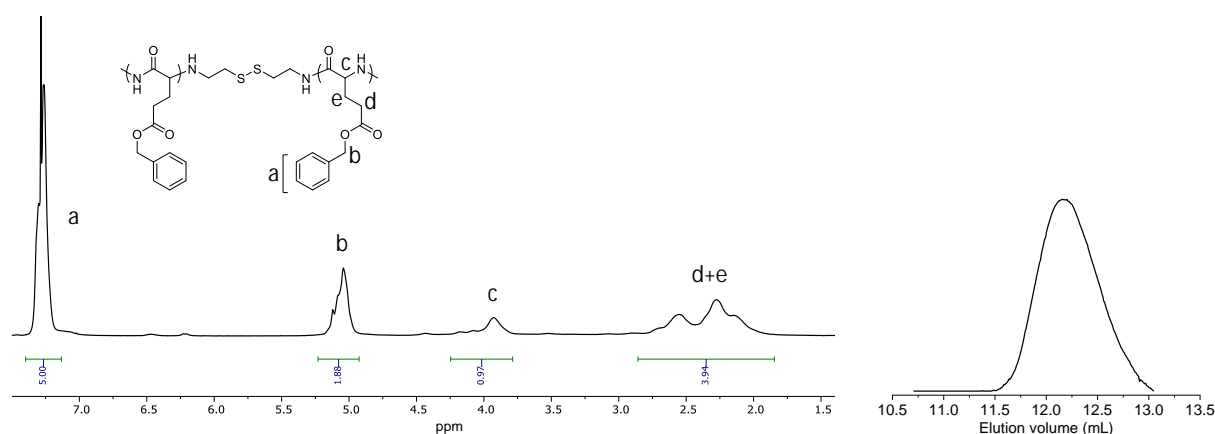


Figure S4. (Left) ^1H NMR spectrum (300 MHz, CDCl_3) and (right) SEC-RI trace (eluent: NMP) of PBDG-S-S-PBDG.

Synthesis of block copolymers by *in situ* aminolysis/functionalization

PS-S-S-PEG

To a solution of PS-dithioester (PS-2) (100 mg, 0.024 mmol) and PEG-S-S-PEG (100 mg, 0.08 mmol) in THF (2 mL) was added a 1:1 mixture of hexylamine/TEA (0.045 mL). The mixture was stirred for 30 min at room temperature and then precipitated into methanol. The polymer was isolated and dried in vacuum. M_n^{app} 6400 g mol⁻¹, D 1.07 (SEC).

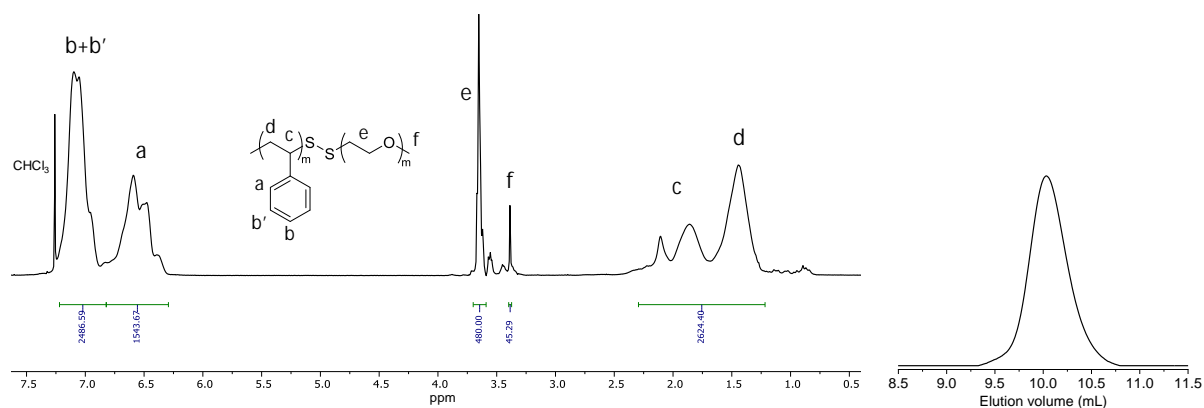


Figure S5. (Left) ¹H NMR spectrum (300 MHz, CDCl₃) and (right) SEC-RI trace (eluent: THF) of PS-S-S-PEG.

PS-S-S-PLLA

To a solution of PS-dithioester (PS-3') (100 mg, 0.015 mmol) and PLLA-S-S-PLLA (440 mg, 0.11 mmol) in THF (2 mL) was added a 1:1 mixture of hexylamine/TEA (0.045 mL). The mixture was stirred for 30 min at room temperature and then precipitated into methanol. The polymer was isolated and dried in vacuum. M_n^{app} 7400 g mol⁻¹, D 1.09 (SEC).

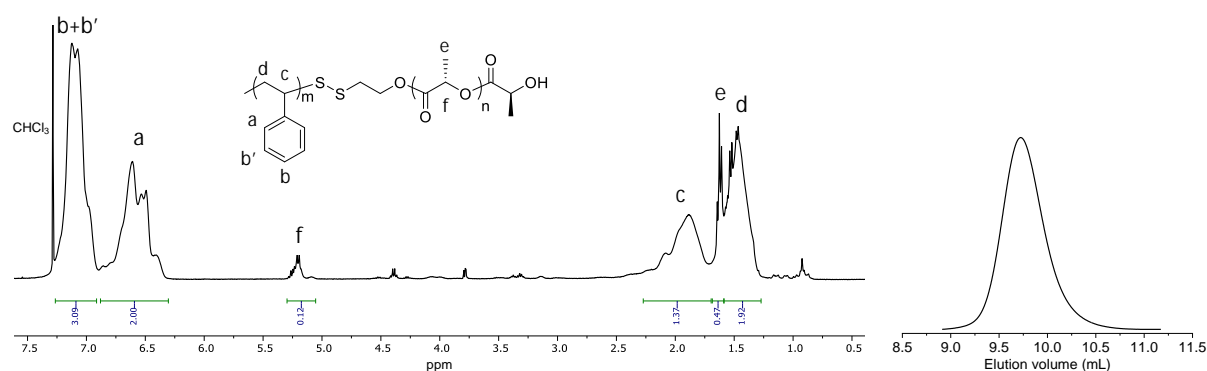


Figure S6. (Left) ¹H NMR spectrum (300 MHz, CDCl₃) and (right) SEC-RI trace (eluent: THF) of PS-S-S-PLLA.

PS-S-S-PBDG

To a solution of PS-dithioester (PS-3') (100 mg, 0.015 mmol) and PBDG-S-S-PBDG (385 mg, 0.07 mmol) in DMF (2 mL) was added a 1:1 mixture of hexylamine/TEA (0.045 mL). The mixture was stirred for 30 min at room temperature and then precipitated into methanol. The polymer was isolated and dried in vacuum. M_n^{app} 7700 g mol⁻¹, D 1.19 (SEC).

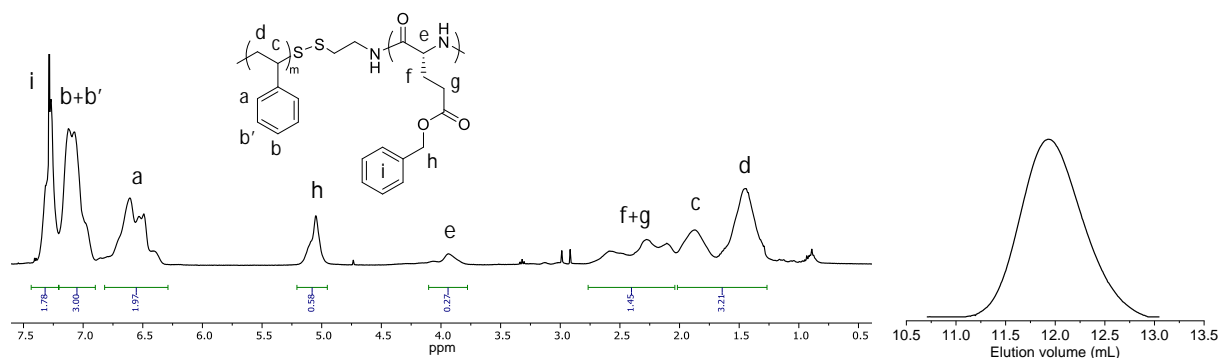


Figure S7. (Left) ¹H NMR spectrum (300 MHz, CDCl₃) and (right) SEC-RI trace (eluent: NMP) of PS-S-S-PBDG.

Table S1. Aminolysis/functionalization of (RAFT) polymer-dithioester with thiols and disulfides; all reactions were performed at room temperature under ambient atmosphere.

