A Convenient Method for Preparing Some New Macrocyclic Diamides

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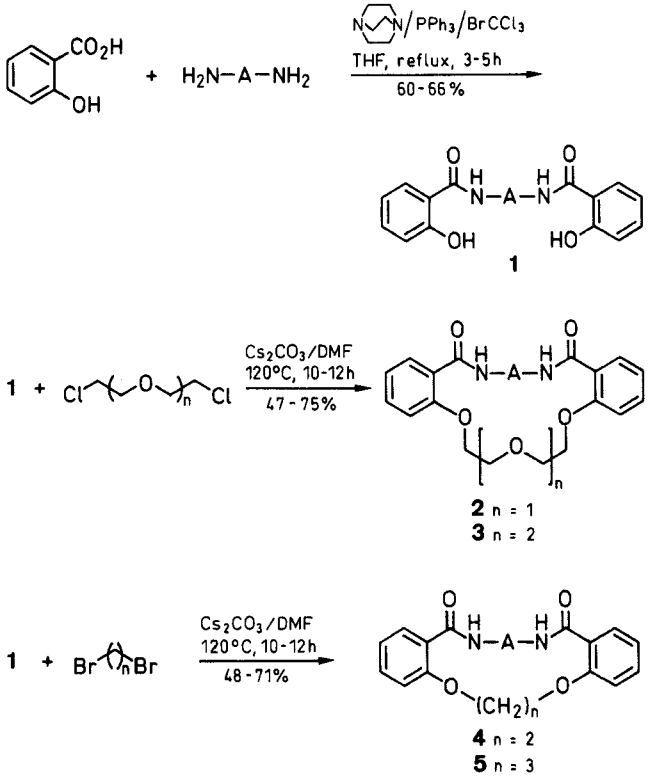
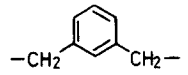
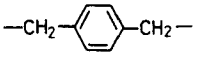
A simple and convenient method for preparing macrocyclic diamides containing two sulfur atoms or two to four oxygen atoms of various ring sizes was developed. This two-step procedure is simply composed of reacting salicyclic acid or 2-mercaptobenzoic acid with various diamines, followed by a Williamson synthesis.

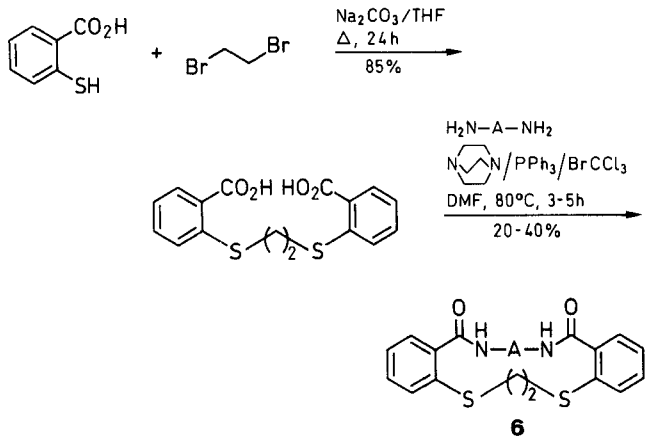
The selectivity of macrocyclic diamides toward noble metals has drawn great attention in recent years; among these the preference of 14-crown-4-diamide toward platinum(II) and palladium(II) over copper(II), nickel(II) and cobalt(II) was reported recently.[1-6] The fact that the reduced form of this diamide does not have such a selectivity[4] reveals that the amino group plays an important role in the complexing process. Although macrocyclic amides were originally regarded as intermediates to azacrowns, only a few procedures have been developed for their preparations. Among these, carboxylic acid derivatives, such as malonic and α,ω-dicarboxylic acid esters,[7,8] labile diacid dichlorides,[9-11] and bis(α-chloroamide) compounds,[12-15] were allowed to react with various diamines under high dilution or for long reaction periods. Controlled and specific conditions such as simultaneous addition of two reactants through syringe pumps at reflux were used to avoid undesired side reactions.[12] With regard to the procedures for the synthesis of macrocyclic amides, Shanzer[16] used silicon as a covalent template to prepare macrocyclic amides in 12–40% yields. Fujita and co-workers[17] monitored the amide ring formation by aminolysis of 3-acylthiazolidine-2-thione. This method generally gave satisfactory yields, yet was handicapped by the use of toxic thallium salts and labile acid dichlorides. Moreover, besides the desired one-to-one adduct, two-to-two cyclization products were sometimes obtained,[14,17] which increased the torment of purification. Therefore, the development of a preparative method using relatively stable and non-toxic starting materials under ordinary conditions was of interest. Since the method used by Hruby[18] and Stork[19] allows a direct preparation of simple amides and peptides from carboxylic acids and various primary or secondary amines in high yields, it may be extended to the preparation of macrocyclic diamides. Indeed, we modified their procedures to obtain bissalicyclic diamides **1** in good yields (60–66%) in a one-pot procedure by heating salicyclic acid, an appropriate diamine of various chain length, triphenylphosphine, bromotrichloromethane and 1,4-diazabicyclo-[2.2.2]octane (DABCO) for 3–5 hours. Cyclization to the desired macrocyclic compounds **2–5** was accomplished by heating **1** and cesium carbonate with the corresponding α,ω-dichloro or dibromo compounds in dimethylformamide at 120 °C for 10–12 hours without high dilution (Scheme 1).

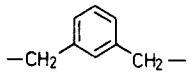


1–5	A
a	$-(CH_2)_2-$
b	$-(CH_2)_3-$
c	$-(CH_2)_4-$
d	$-(CH_2)_5-$
e	
f	

Scheme 1

Replacement of salicylic acid with 2-mercaptobenzoic acid or 2-aminobenzoic acid under similar conditions did not give satisfactory results; the desired products were contaminated with byproducts. These byproducts were a cyclic dimer or even tetramer of the 2-mercaptobenzoic acid, or 2-aminobenzoic acid. The same products were obtained by the reaction of 2-mercaptobenzoic acid or 2-aminobenzoic acid with triphenylphosphine, bromotrichloromethane and DABCO in the absence of diamine under identical conditions. Mass and ^1H NMR spectra suggested that 2-mercaptobenzoic acid led mainly to a dimeric product, while 2-aminobenzoic acid gave dimer, trimer and even tetramer. To overcome this difficulty, we alternated the reaction sequence by coupling 2-mercaptobenzoic acid with 1,2-dibromoethane first, and then reacting the resulting 1,2-bis(2-carboxyphenylthio)ethane with triphenylphosphine, bromotrichloromethane and a variety of diamines. By this procedure a series of desired macrocyclic compounds with two sulfur atoms were obtained (Scheme 2).



6	A
a	$-(CH_2)_2-$
b	$-(CH_2)_3-$
c	$-(CH_2)_4-$
d	$-(CH_2)_5-$
e	

Scheme 2

The structural elucidations of these new compounds were accomplished by satisfactory elemental analyses, and IR, mass and ^{1}H NMR spectra. Decoupling technique was used to solve ambiguity in NMR assignment. Characteristic IR for these macrocyclic diamides included $\nu_{C=O}$ at 1632–1651 cm^{-1} and ν_{NH} at 3304–3412 cm^{-1}. The molecular ions were all prominent peaks ($\geq$ 30%) or even base peaks in EI spectra.

The present procedure is not only simpler and more convenient than the previous methods, but also has many advantages. First, it is composed of two isolation steps using easily handled starting materials. Secondly, macrocyclic diamides, even those containing one hydrogen on the amide nitrogen can be obtained. Thirdly, no high dilution technique or prolonged reaction time is needed. Fourthly, no two-to-two condensation products were found. It is worthwhile mentioning that these macrocyclic diamides containing two to four oxygen atoms showed special selectivity for copper(II) in the presence of zinc(II), nickel(II) and cobalt(II) ions. The details and other analytical applications will be reported elsewhere.

IR spectra (KBr pellet) were run on a JASCO IR-700 spectrometer. The ^{1}H NMR spectra were recorded on either a Bruker AM-300 or a JEOL JNM-EX-400 spectrometer; chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra (EI) were recorded on a JEOL-MSD-300 spectrometer, operating at an ionizing voltage of 70 eV. Elemental analyses were performed with a Perkin-Elmer model 2400 instrument. Melting points were recorded on a Mel-temp instrument and were uncorrected. For all new compounds satisfactory microanalyses were obtained: C $\pm$ 0.4, H $\pm$ 0.33, N $\pm$ 0.16, S $\pm$ 0.2.

Starting materials were commercial chemicals from E. Merck, Aldrich or Fluka Chemical Co. and were used without further purification.

Bissalicyclic Diamides 1a–1f; General Procedure:
A mixture of salicyclic acid (1.38 g, 10 mmol), PPh_3 (3.41 g, 13 mmol), $BrCCl_3$ (2.57 g, 13 mmol), the appropriate diamine (5 mmol) and DABCO (0.56 g, 5 mmol) was dissolved in THF (50 mL). The mixture was heated and stirred magnetically under reflux for 3–5 h, and the progress of the reaction monitored by TLC (silica gel, EtOAc as eluent). After cooling and filtering off the solid, the solvent was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), and washed with 1 N HCl (50 mL). The residual solid obtained by evaporation of CH_2Cl_2 was redissolved in benzene (50 mL) and stirred with 0.25 N NaOH (50 mL) until no product **1** was detected in benzene solution (monitored with TLC). Then the aqueous solution was separated and reextracted with benzene (2 × 50 mL) to remove the residual triphenylphosphine oxide. The aqueous solution was acidified with 6 N HCl until about pH 2, and then extracted with $CHCl_3$ (3 × 50 mL). After drying ($MgSO_4$), the $CHCl_3$ solution was passed through a column of silica gel (15 cm × 4 cm, E. Merck 70–230 mesh), eluting with EtOAc/$CHCl_3$ (1:1) to obtain products **1a–1f** in 60–66% yields. These products gave satisfactory spectroscopic properties (^{1}H NMR and MS), and were used without further purification for the following step.

Macrocyclic Diamides Containing 2 to 4 Oxygen Atoms 2, 3, 4, 5; General Procedure:
A mixture of **1** (5 mmol), Cs_2CO_3 (3.26 g, 10 mmol) and DMF (80 mL) was stirred and heated to 120 °C. To this, a solution of α,ω-dihalo compound (7.5 mmol) in DMF (20 mL) was added dropwise. Stirring was continued for 10–12 h at 120 °C. After evaporation, H_2O was added to the residue; this led to precipitation of crude product as a white solid. After filtration and washing with H_2O the solid was dissolved in $CHCl_3$ (100 mL), dried ($MgSO_4$), and passed through a column of silica gel (10 cm × 4 cm, E. Merck 70–230 mesh) eluting with $CHCl_3$ (150 mL) and then EtOAc. Evaporation of EtOAc under reduced pressure gave products **2, 3, 4** and **5**, respectively.

2a; yield: 1.30 g (70%); mp 265–266 °C.

MS: *m/z* (%) = 370 (M^+, 32).

^{1}H NMR ($CDCl_3$): δ = 3.75 (t, 4H, J = 2.4 Hz, $NHCH_2CH_3NH$), 3.99 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 4.29 (dd, 4H, J = 4.4 Hz, 3.9 Hz $ArOCH_2CH_2O$), 6.91 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.08 (t, 2H, J = 7.2 Hz, aromatic H *ortho* to ArO), 7.39–7.43 (m, 2H, aromatic H meta to ArO), 8.17–8.20 (dd, 4H, J = 7.8 Hz, 2.0 Hz, aromatic H *ortho* to CO and CONH).

IR (KBr): ν = 3390 (m, NH), 1646 cm^{-1} (s, C=O).

2b; yield: 1.40 g (73%); mp 192–193 °C.

MS: *m/z* (%) = 384 (M^+, 100).

^{1}H NMR ($CDCl_3$): δ = 2.03 (quint, 2H, J = 2.8 Hz, $NHCH_2CH_2CH_2NH$), 3.51 (q, 4H, J = 5.8 Hz, 2 × $CONHCH_2$), 3.96 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 4.29 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 6.94 (d, 2H, J = 8.0 Hz, aromatic H *meta* to C=O), 7.06 (t, 2H, J = 5.3 Hz, aromatic H *ortho* to ArO), 7.41–7.46 (m, 2H, aromatic H *meta* to ArO), 8.16 (dd, 2H, J = 7.8 Hz, 2.0 Hz, aromatic H *ortho* to C=O), 8.21 (br, 2H, CONH).

IR (KBr): ν = 3318 (m, NH), 1639 cm^{-1} (s, C=O).

2c yield: 1.49 g (75%); mp 200–201 °C.

MS: *m/z* = 398 (M^+, 88).

^{1}H NMR ($CDCl_3$): δ = 1.76 [m, 4H, $NHCH_2(CH_2)_2CH_2NH$], 3.50 (q, 4H, J = 4.8 Hz, $CONHCH_2$), 3.94 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 4.24 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 6.92 (d, 2H, J = 8.0 Hz, aromatic H *meta* to C=O), 7.08 (t, 2H, J = 7.2 Hz, aromatic H ortho to ArO), 7.42 (t, 2H, J = 7.8 Hz, aromatic H *meta* to ArO), 8.12 (br, 2H, CONH), 8.21 (dd, 2H, J = 7.8 Hz, 1.9 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3330 (m, NH), 1633 cm^{-1} (s, C=O).

2d; yield: 1.40 g (68%); mp 162–163 °C.

MS: *m/z* (%) = 412 (M^+, 79).

^{1}H NMR ($CDCl_3$): δ = 1.58–1.71 [m, 6H, $NHCH_2(CH_2)_3CH_2NH$], 3.53 (q, 4H, J = 5.4 Hz, 2 × $CONHCH_2$), 3.98 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 4.28 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2CH_2O$), 6.95 (d, 2H, J = 8.4 Hz, aromatic H *meta*

to C=O), 7.10 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.40–7.44 (m, 2H aromatic H *meta* to ArO), 8.22 (dd, 4H, J = 7.8 Hz, 1.4 Hz, aromatic H *ortho* to C=O and CONH).

IR (KBr): ν = 3326 (m, NH), 1637 cm^{-1} (s, C=O).

2e; yield: 1.67 g (75%); mp 201–202 °C.

MS: m/z (%) = 446 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 3.61 (dd, 4H, J = 4.4 Hz, 3.4 Hz, $ArOCH_2C\underline{H}_2O$), 4.15 (dd, 4H, J = 4.4 Hz, 3.4 Hz, $ArOC\underline{H}_2CH_2O$), 4.64 (d, 4H, J = 5.1 Hz, 2 × $CONHC\underline{H}_2$), 6.88 (d, 2H, J = 7.6 Hz, aromatic H *meta* to C=O), 7.10 (t, 2H, J = 8.0 Hz, aromatic H *ortho* to ArO), 7.31–7.45 (m, 6 H_{arom}), 8.21 (dd, 2H, J = 7.8 Hz, 1.8 Hz, aromatic H *ortho* to C=O), 8.34 (br, 2H, CONH).

IR (KBr): ν = 3370 (m, NH), 1629 cm^{-1} (s, C=O).

2f; yield: 1.40 g (63%); mp 279–280 °C.

MS: m/z (%) = 446 (m^+, 73).

^1H NMR ($CDCl_3$): δ = 3.43 (dd, 4H, J = 4.4 Hz, 4.4 Hz, $ArOCH_2C\underline{H}_2O$), 4.09 (dd, 4H, J = 4.9 Hz, 4.4 Hz, $ArOC\underline{H}_2CH_2O$), 4.63 (d, 4H, J = 4.4 Hz, 2 × $CONHC\underline{H}_2$), 6.90 (d, 2H, J = 8.0 Hz, aromatic H *meta* to C=O), 7.13 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.42 (m, 6 H_{arom}), 7.95 (br, 2H, CONH), 8.24 (d, 2H, J = 7.4 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3304 (m, NH), 1635 cm^{-1} (s, C=O).

3a; yield: 1.14 g (55%); mp 185–186 °C.

MS: m/z (%) = 414 (m^+, 30%).

^1H NMR ($CDCl_3$): δ = 3.62 (s, 4H, OCH_2CH_2O), 3.74 (q, 4H, J = 1.8 Hz, $NHC\underline{H}_2C\underline{H}_2NH$), 3.84 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2O$), 4.18 (dd, 4H, J = 4.4 Hz, 4.4 Hz, $ArOC\underline{H}_2CH_2O$), 6.89 (d, 2H, J = 8.3 Hz, aromatic H *meta* to C=O), 7.05 (t, 2H, J = 8.0 Hz, aromatic H *ortho* to ArO), 7.36–7.40 (m, 2H, aromatic H *meta* to ArO), 8.10 (dd, 2H, J = 7.7 Hz, 1.9 Hz, aromatic H *ortho* to C=O), 8.16 (br, 2H, CONH).

IR (KBr): ν = 3314 (m, NH), 1642 (s, C=O).

3b; yield: 1.07 g (50%); mp 175–176 °C.

MS: m/z (%) = 428 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 1.95 (quint, 2H, J = 6.8 Hz, $NHCH_2C\underline{H}_2CH_2NH$), 3.56 (q, 4H, J = 6.8 Hz, 2 × $CONHC\underline{H}_2$), 3.70 (s, 4H, OCH_2CH_2O), 3.88 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2O$), 4.24 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOC\underline{H}_2CH_2O$), 6.87 (d, 2H, J = 8.2 Hz, aromatic H *meta* to C=O), 7.06 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.38–7.42 (m, 2H, aromatic H *meta* to ArO), 8.16–8.21 (dd, 4H, J = 7.8 Hz, 2.0 Hz, aromatic H *meta* to C=O and CONH).

IR (KBr): ν = 3360 (m, NH), 1644 (s, C=O).

3c; yield: 1.04 g (47%); mp 185–186 °C.

MS: m/z (%) = 442 (M^+, 68).

^1H NMR ($CDCl_3$): δ = 1.76 [m, 4H, $CONHCH_2(C\underline{H}_2)_2CH_2$], 3.50 (q, 4H, J = 5.4 Hz, 2 × $CONHC\underline{H}_2$), 3.70 (s, 4H, OCH_2CH_2O), 3.88 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2O$), 4.24 (dd, 4H, J = 4.4 Hz, 4.4 Hz, $ArOC\underline{H}_2CH_2O$), 6.89 (d, 2H, J = 8.0 Hz, aromatic H *meta* to C=O), 7.06 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.39–7.43 (m, 2H, aromatic H *meta* to ArO), 8.17–8.21 (dd, 4H, J = 7.8 Hz, 1.9 Hz, aromatic H *ortho* to C=O and CONH).

IR (KBr): ν = 3390 (m, NH), 1641 cm^{-1} (s, C=O).

3d; yield: 1.14 g (50%); mp 180–181 °C.

MS: m/z (%) = 456 (M^+, 79%).

^1H NMR ($CDCl_3$): δ = 1.58–1.73 [m, 6H, $NHCH_2(C\underline{H}_2)_3CH_2NH$], 3.46 (q, 4H, J = 6.2 Hz, 2 × $CONHCH_2$), 3.71 (s, 4H, OCH_2CH_2O), 3.90 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2$), 4.23 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOC\underline{H}_2CH_2O$), 6.89 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.06 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.39–7.43 (m, 2H, aromatic H *meta* to ArO), 8.16–8.21 (dd, 4H, J = 7.4 Hz, 1.9 Hz, aromatic H *meta* to C=O and CONH).

IR (KBr): ν = 3376 (m, NH str); 1646 (s, C=O).

3e; yield: 1.29 g (53%); mp 202–203 °C.

MS: m/z (%) = 490 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 3.09 (s, 4H, OCH_2CH_2O), 3.66 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2O$), 4.16 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOC\underline{H}_2CH_2O$), 4.68 (d, 4H, J = 5.4 Hz, 2 × $CONHC\underline{H}_2$), 6.88 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.08 (t, 2H, J = 7.2 Hz, aromatic H *ortho* to ArO), 7.24–7.41 (m, 6H, aromatic H), 8.23 (dd, 2H, J = 7.8 Hz, 1.9 Hz, aromatic H *meta* to C=O), 8.38 (br, 2H, CONH).

IR (KBr): ν = 3372 (m, NH), 1650 cm^{-1} (s, C=O).

3f; yield: 1.37 g (56%); mp 225–226 °C.

MS: m/z (%) = 490 (M^+, 74).

^1H NMR ($CDCl_3$): δ = 2.98 (s, 4H, OCH_2CH_2O), 3.68 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOCH_2C\underline{H}_2O$), 4.18 (dd, 4H, J = 4.4 Hz, 3.9 Hz, $ArOC\underline{H}_2CH_2O$), 4.72 (d, 4H, J = 4.9 Hz, 2 × $CONHC\underline{H}_2$), 6.88 (d, 2H, J = 7.6 Hz, aromatic H *meta* to C=O), 7.09 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.37–7.45 (m, 6 H_{arom}), 8.25 (dd, 2H, J = 7.8 Hz, 1.9 Hz, aromatic H *ortho* to C=O), 8.29 (br, 2H, CONH).

IR (KBr): ν = 3326 (m, NH), 1635 cm^{-1} (s, C=O).

4b; yield: 1.11 g (65%); mp 223–224 °C.

MS: m/z (%) = 340 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 2.1 (quint, 2H, J = 6.2 Hz, $NHCH_2CH_2CH_2NH$), 3.58 (q, 4H, J = 6.0 Hz, 2 × $CONHC\underline{H}_2$), 4.57 (s, 4H, $ArOC\underline{H}_2$), 7.00 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.12 (t, 2H, J = 7.2 Hz, aromatic H *ortho* to ArO), 7.42–7.44 (m, 2H, aromatic H *meta* to ArO), 8.07 (br, 2H, CONH), 8.21 (dd, 2H, J = 7.8 Hz, 2.0 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3408 (m, NH), 1641 cm^{-1} (s, C=O).

4c; yield: 1.10 g (61%); mp 230–231 °C.

MS: m/z (%) = 354 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 1.79 [m, 4H, $NHCH_2(CH_2)_2CH_2NH$], 3.56 (s, 4H, $CONHCH_2$), 4.61 (s, 4H, $ArOCH_2$), 6.97 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.11 (t, 2H, J = 8.0 Hz, aromatic H *ortho* to ArO), 7.41–7.46 (m, 2H, aromatic H *meta* to ArO), 7.68 (br, 2H, CONH), 8.17 (dd, 2H, J = 7.8 Hz, 1.5 Hz, aromatic H *meta* to C=O).

IR (KBr): ν = 3404 (m, NH), 1632 (s, C=O).

4e; yield = 0.96 g (48%); mp 266–267 °C.

MS: m/z (%) = 402 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 4.57 (s, 4H, $ArOC\underline{H}_2$), 4.73 (d, 4H, J = 4.8 Hz, 2 × $CONHC\underline{H}_2$), 6.90 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.12 (t, 2H, J = 7.6 Hz, aromatic H *ortho* to ArO), 7.25–7.60 (m, 6H, aromatic H), 7.95 (br, 2H, CONH), 8.22 (dd, 2H, J = 7.8 Hz, 1.5 Hz, aromatic H *meta* to C=O).

IR (KBr): ν = 3306 (m, NH str), 1641 cm^{-1} (s, C=O).

5a; yield: 1.20 g (71%); mp 232–233 °C

MS: m/z = 340 (M^+, 58%).

^1H NMR ($CDCl_3$): δ = 2.44 (quint, 2H, J = 5.4 Hz, $OCH_2C\underline{H}_2CH_2O$), 3.75 (t, 4H, J = 2.5 Hz, $NHC\underline{H}_2C\underline{H}_2NH$), 4.35 (t, 4H, J = 5.2 Hz, $ArOC\underline{H}_2$), 6.98 (d, 2H, J = 7.6 Hz, aromatic H *meta* to C=O), 7.11 (t, 2H, J = 7.2 Hz, aromatic H *ortho* to ArO), 7.41–7.45 (m, 2H, aromatic H *meta* to ArO), 7.95 (br, 2H, CONH), 8.10 (dd, 2H, J = 7.8 Hz, 2.0 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3386 (m, NH), 1651 cm^{-1} (s, C=O).

5b; yield: 1.24 g (70%); mp 205–206 °C.

MS: m/z (%) = 354 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 2.13 (quint, 2H, J = 6.0 Hz, $NHCH_2C\underline{H}_2CH_2NH$), 2.40 (quint, 2H, J = 5.2 Hz, $OCH_2C\underline{H}_2CH_2O$), 3.64 (q, 4H, J = 6.0 Hz, 2 × $CONHC\underline{H}_2$), 4.43 (t, 4H, J = 5.6 Hz, $ArOC\underline{H}_2$), 7.03 (d, 2H, J = 8.0 Hz, aromatic H *meta* to C=O),

2H, aromatic H *meta* to ArO), 8.01 (br, 2H, CONH), 8.20 (dd, 2H, J = 7.8 Hz, 1.5 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3400 (m, NH), 1640 cm^{-1} (s, C=O).

5c; yield: 1.14 g (62%); mp 184–185 °C.

MS: m/z (%) = 368 (M^+, 71).

^1H NMR ($CDCl_3$): δ = 1.81 [quint, 4H, J = 2.5 Hz, $NHCH_2(CH_2)_2CH_2NH$], 2.38 (quint, 2H, J = 5.8 Hz, $OCH_2CH_2CH_2O$), 3.59 (d, 4H, J = 5.2 Hz, $2 \times CONHCH_2$), 4.36 (t, 4H, J = 6.4 Hz, $ArOCH_2$), 7.00 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.12 (t, 2H, J = 7.2 Hz, aromatic H *ortho* to ArO), 7.41–7.45 (m, 2H, aromatic H *meta* to ArO), 7.76 (br, 2H, CONH), 8.15 (dd, 2H, J = 7.8 Hz, 1.9 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3356 (m, NH), 1633 cm^{-1} (s, C=O).

5e; yield: 0.99 g (48%); mp 231–232 °C.

MS: m/z (%) = 416 (M^+, 98).

^1H NMR ($CDCl_3$): δ = 2.06 (quint, 2H, J = 6.8 Hz, $OCH_2CH_2CH_2O$), 4.16 (t, 4H, J = 6.4 Hz, $ArOCH_2$), 4.65 (d, 4H, J = 4.8 Hz, $2 \times CONHCH_2$), 6.92 (d, 2H, J = 8.4 Hz, aromatic H *meta* to C=O), 7.11–7.45 (m, 8 H_{arom}), 8.08 (br, 2H, CONH), 8.24 (dd, 2H, J = 7.8 Hz, 1.9 Hz, aromatic H ortho to C=O).

IR (KBr): ν = 3398 (m, NH), 1651 cm^{-1} (s, C=O).

1,2-Bis-(2-carboxyphenylthio)ethane:

A stirred mixture of 2-mercaptobenzoic acid (15.4 g, 0.1 mol), 1,2-dibromoethane (11.3 g, 0.06 mol) and Na_2CO_3 (10.6 g, 0.1 mol) was refluxed in THF (300 mL) for 24 h. After cooling, the mixture was acidified with 6 N HCl and the resulting precipitate was collected, washed with H_2O (3 × 50 mL) and THF (3 × 50 mL), and dried under vacuum overnight; yield: 14.2 g (85%).

Macrocyclic Diamides Containing two Sulfur Atoms 6a–6e; General Procedure:

1,2-Bis(2-carboxyphenylthio)ethane (1.67 g, 5 mmol), PPh_3 (3.41 g, 13 mmol), $BrCCl_3$ (2.57 g, 13 mmol), the appropriate diamine (5 mmol) and DABCO (0.56 g, 5 mmol) were dissolved in DMF (80 mL). The mixture was heated and stirred magnetically at 80 °C for 3–5 h. The progress of the reaction was monitored by TLC (silica gel, EtOAc as eluent). After cooling, the mixture was almost completely evaporated to dryness under reduced pressure. 1 N HCl (100 mL) was added to remove the basic materials, and the precipitate was collected and washed with H_2O and then with benzene (3 × 50 mL) to give the crude product. The benzene solution was dried ($MgSO_4$) and was allowed to stand to obtain more of the product. The combined crude products were dissolved in $CHCl_3$, and passed through a column of silica gel (25 cm × 2.54 cm, E. Merck 70–230 mesh) using $CHCl_3$ as eluent to remove triphenylphosphine oxide, and EtOAc/$CHCl_3$ (1:1) by volume to elute the desired products **6a–6e**.

6a; yield: 0.67 g (38%); mp 226–227 °C.

MS: m/z (%) = 358 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 3.22 (s, 4H, SCH_2CH_2S), 3.78 (t, 4H, J = 2.8 Hz, $2 \times CONHCH_2$), 7.14 (br, 2H, CONH), 7.29–7.58 (m, 8 H_{arom}).

IR (KBr): ν = 3280 (m, NH), 1640 cm^{-1} (s, C=O).

6b; yield: 0.74 g (40%); mp 207–208 °C.

MS: m/z (%) = 372 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 1.98 (quint, 2H, J = 2.9 Hz, $NHCH_2CH_2CH_2NH$), 3.20 (s, 4H, SCH_2CH_2S), 3.70 (q, 4H, J = 5.8 Hz, $2 \times CONHCH_2$), 7.12 (br, 2H, CONH), 7.24–7.58 (m, 8 H_{arom}).

IR (KBr): ν = 3314 (m, NH), 1648 cm^{-1} (s, C=O).

6c; yield: 0.48 g (25%); mp 273–274 °C.

MS: m/z (%) = 386 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 1.92 [m, 4H, $NHCH_2(CH_2)_2CH_2NH$], 3.23 (s, 4H, SCH_2CH_2S), 3.59 (q, 4H, J = 3.2 Hz, $2 \times CONHCH_2$), 6.78 (br, 2H, CONH), 7.31–7.67 (m, 8 H_{arom}).

IR (KBr): ν = 3286 (m, NH), 1634 cm^{-1} (s, C=O).

6d; yield: 0.40 g (20%); mp 279–280 °C.

MS: m/z (%) = 400 (M^+, 32).

^1H NMR ($CDCl_3$): δ = 1.71 [m, 6H, $NHCH_2(CH_2)_3CH_2NH$], 3.16 (s, 4H, SCH_2CH_2S), 3.55 (s, 4H, $2 \times CONHCH_2$), 6.75 (br, 2H, CONH), 7.23–7.58 (m, 8 H_{arom}).

IR (KBr): ν = 3288 (m, NH), 1643 cm^{-1} (s, C=O).

6e; yield: 0.71 g (33%); mp 275–276 °C.

MS: m/z (%) = 434 (M^+, 100).

^1H NMR ($CDCl_3$): δ = 3.03 (s, 4H, SCH_2CH_2S), 4.66 (d, 4H, J = 5.6 Hz, $2 \times CONHCH_2$), 7.29–7.43 (m, 10 H_{arom}), 7.72 (br, 2H, CONH), 7.81 (d, 2H, J = 7.6 Hz, aromatic H *ortho* to C=O).

IR (KBr): ν = 3290 (m, NH), 1643 (s, C=O).

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