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Evidence for Intermolecular Interaction between Sulfonium and Sulfide Sulfur Atoms and Its Application to Synthesis of Cyclic Bis(disulfide) Dimer

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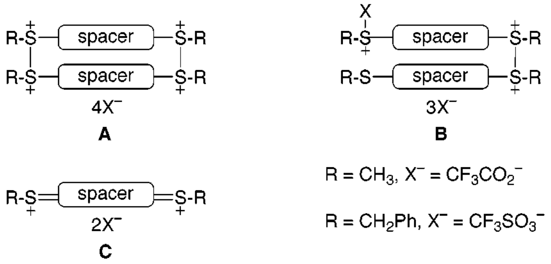
On the basis of the remote Pummerer reaction of *p*-bis(alkylthio)-aromatic *S*-oxides, the intermolecular interaction between the sulfonium and sulfide sulfur atoms is described. (1) In marked contrast to the Pummerer reaction of **1b-*d*$_3$** with $(CF_3CO)_2O$ (*J. Org. Chem.* **1999**, *64*, 3190−3195), the reaction of 3,3′,5,5′-tetramesityl-4-(trideuteriomethylsulfinyl)-4′-(methylthio)biphenyl (**1a-*d*$_3$**) as a sterically hindered analogue of **1b** gave only **2a-*d*$_2$**. (2) Both reactions of the two unsymmetrical regioisomers of 1-(ethylthio)-4-(methylthio)benzene *S*-oxide (**5a** and **5b**) with $(CF_3CO)_2O$ afforded a mixture of the mono-Pummerer products **6a** and **6b**, the bis-Pummerer product **7**, and the bis-sulfide **8** in a similar ratio. The quenching at the initial stage of both reactions produced **5a**, **5b**, **8**, and the bis-sulfoxide **10** in a similar ratio. These results indicate the equilibrium in the intermolecular interaction between the sulfur atoms. (3) The reaction of the *p*-bis(benzylthio)-aromatic *S*-oxide **16** with $(CF_3SO_2)_2O$ gave the cyclic bis(disulfide) dimer **17** for the diphenyl sulfide and diphenylmethane spacers or the cyclic tetrakis(disulfide) tetramer **19** for the benzene and biphenyl spacers via the debenzylation of an intermolecular dithia dication. The cyclic bis(dithia dication) dimer **A** resulting from the intermolecular interaction between the sulfonium and sulfide sulfur atoms is proposed as an intermediate throughout the present reactions.

Introduction

Despite the accumulation of a large body of information about dithia dications formed by intramolecular through-space interactions between sulfur atoms,[1] dithia dications formed by intermolecular interactions have not been studied intensively because a transannular effect is not available.[2] Such formation of dithia dications by intermolecular interactions is worth pursuing from the viewpoint of molecular assembly,[3] as well as from the perspective of organosulfur conducting materials.[4] Recently, we have reported a remote Pummerer reaction of *p*-bis(methylthio)-aromatic *S*-oxides with $(CF_3CO)_2O$ and have proposed a cyclic bis(dithia dication) dimer **A** and/or a linear dithia dication dimer **B** as intermediates (Chart 1, $R = CH_3$, $X^- = CF_3CO_2^-$), arising via intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms.[5−7] To elucidate the intermolecular interaction between sulfur atoms more clearly, and to show its generality, other approaches and molecular designs are required.

Chart 1



$R = CH_3$, $X^- = CF_3CO_2^-$

$R = CH_2Ph$, $X^- = CF_3SO_3^-$

Intramolecular dithia dications with flexible or strained conformations, which are generated from bis-sulfide *S*-oxides and 1 equiv of $(CF_3SO_2)_2O$ in CH_3CN, cause a facile dealkylation to form the corresponding thiasulfonium salt and alkyl cation.[7,8] In particular, a dithia dication with benzyl groups causes a double-debenzylation to form the corresponding disulfide.[7,9] In the remote Pummerer reaction of *p*-bis(methylthio)-aromatic *S*-oxides with $(CF_3CO)_2O$, if a cyclic bis(dithia dication) dimer **A** is truly an intermediate, it should be possible to form

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a cyclic bis(disulfide) dimer or corresponding cyclic disulfide oligomers[10−14] via the debenzylation of **A** (Chart 1, R = CH_2Ph, $X^- = CF_3SO_3^-$) by using a combination of a benzyl group and $(CF_3SO_2)_2O$ in place of the methyl group and $(CF_3CO)_2O$. Herein, we report an essential role for the intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms in the remote Pummerer reaction[5−7] by using substrates with bulky and unsymmetrical substituents. We also describe the syntheses of a cyclic bis(disulfide) dimer and a cyclic tetrakis-(disulfide) tetramer as the result of the debenzylation of the cyclic bis(dithia dication) dimer **A** (R = CH_2Ph, $X^- = CF_3SO_3^-$).

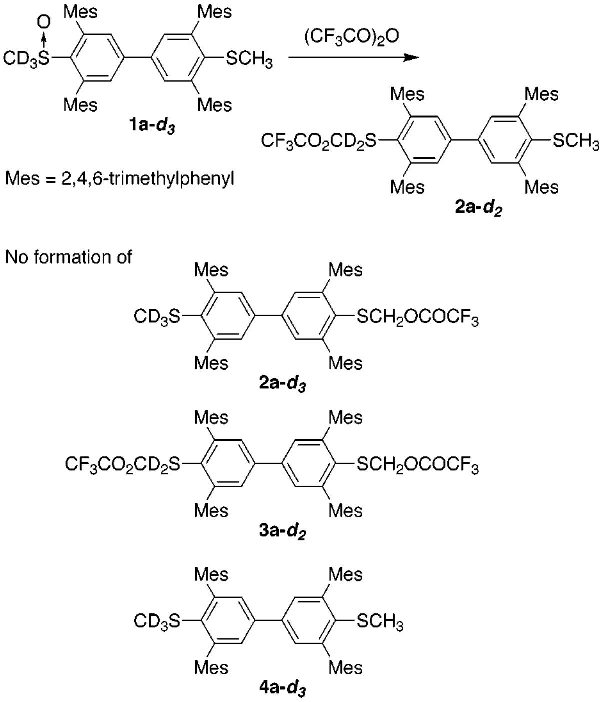
Results and Discussion

Evidence for Intermolecular Interaction between Sulfonium and Sulfide Sulfur Atoms: Reaction between *p*-Bis(methylthio)-Aromatic *S*-Oxide with a Bulky Substituent and $(CF_3CO)_2O$. To elucidate the intermolecular through-space interaction between the sulfur atoms more clearly, we have designed 3,3′,5,5′-tetramesityl-4-(methylsulfinyl)-4′-(methylthio)biphenyl (**1a**)[15] as a sterically hindered analogue of 4-(methylsulfinyl)-4′-(methylthio)biphenyl (**1b**).[5,7] From consideration of the model of **1a**, we infer that the mesityl groups at the 3,5-positions of the biphenyl spacer could completely inhibit the intermolecular interaction between the sulfur atoms.

The reaction of **1a** with 5 equiv of $(CF_3CO)_2O$ in CH_2Cl_2, at −20 °C to room temperature, produced the mono-Pummerer product **2a** exclusively in 88% yield. The reaction of trideuterium-labeled **1a-*d*$_3$** with $(CF_3CO)_2O$ quantitatively produced only **2a-*d*$_2$** (Scheme 1), in marked contrast to **1b-*d*$_3$**, wherein the mono-Pummerer products **2b-*d*$_3$** and **2b-*d*$_2$**, the bis-Pummerer product **3b-*d*$_2$**, and the bis-sulfide **4b-*d*$_3$** occur in a 5.0:0.5:1.0:0.8 ratio.[5] This shows that a normal Pummerer reaction at the methylsulfinyl group dominates exclusively in **1a**. These results clearly indicate that neither the intermolecular through-space nor the intramolecular through-bond interactions between the sulfur atoms are available for the reaction of **1a**. Therefore, in the remote Pummerer reaction of *p*-bis(methylthio)-aromatic *S*-oxide with $(CF_3CO)_2O$,[5] the intermolecular through-space interaction between the sulfur atoms, which forms the intermediates **A** and/or **B**, is essentially a much more favorable process than the intramolecular through-bond interaction between the sulfur atoms leading to the intermediate **C** (Chart 1).

Equilibrium in Intermolecular Interaction between Sulfur Atoms: Reaction of Unsymmetrical *p*-Bis(sulfide)-Aromatic *S*-Oxide with $(CF_3CO)_2O$. To identify an equilibrium in the intermolecular through-space interaction between the sulfur atoms, we have chosen the two unsymmetrical regioisomers of 1-(ethylthio)-4-(methylthio)benzene *S*-oxide (**5**) as a model substrate for the remote Pummerer reaction.

Scheme 1



The reaction of 1-(ethylsulfinyl)-4-(methylthio)benzene (**5a**) with 5 equiv of $(CF_3CO)_2O$ in $CDCl_3$, at −20 °C to room temperature, produced a mixture of the mono-Pummerer products **6a** and **6b**, the bis-Pummerer product **7**, and the bis-sulfide **8**, in a quantitative ratio of 1.0:2.2:0.2:0.1 (Scheme 2). The formation of **6a** results from the reaction at the ethyl group, whereas **6b** results from the reaction at the methyl group. Treatment of 1-(ethylthio)-4-(methylsulfinyl)benzene (**5b**) with $(CF_3CO)_2O$ under the same conditions also exclusively produced a mixture of **6a**, **6b**, **7**, and **8**, in a ratio of 1.0:2.5:0.6:0.4. In general, the Pummerer reaction occurs at the alkylsulfinyl group, but not at the alkylthio group. However, both Pummerer reactions of **5a** and **5b** take place at both groups, and give approximately similar product ratios. Both reactions were monitored by ^1H NMR spectroscopy in $CDCl_3$ at −20 °C, as shown in Figure 1. Upon addition of $(CF_3CO)_2O$, **5a** and **5b** disappeared immediately. In reactions both of **5a** after 1 h (Figure 1b), and **5b** after 40 min (Figure 1d), both trifluoroacetoxysulfonium salts **9a** and **9b** were observed as intermediates, together with the products. In Figures 1b and 1d, it is noted that the ratio of the intermediates is **9a** > **9b**, whereas the product ratio is **6a** < **6b**. These results strongly suggest that the equilibrium between **9a** and **9b** occurs via the same intermediates, such as **A** and/or **B**, as a result of the intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms (Scheme 2).

Further evidence that the equilibrium between **9a** and **9b** occurs via the same intermediates, such as **A** and/or **B**, is drawn from the quenching experiment at the initial stage of the Pummerer reaction, which acts as a snapshot of the reaction.[5] When the reaction of **5a** with 5 equiv of $(CF_3CO)_2O$ in CH_2Cl_2 at −20 °C was quenched quickly, in ∼10 s, with aqueous $NaHCO_3$, a mixture of **5a**, **5b**, **8**, and the bis-sulfoxide **10** was obtained exclusively in 47%,

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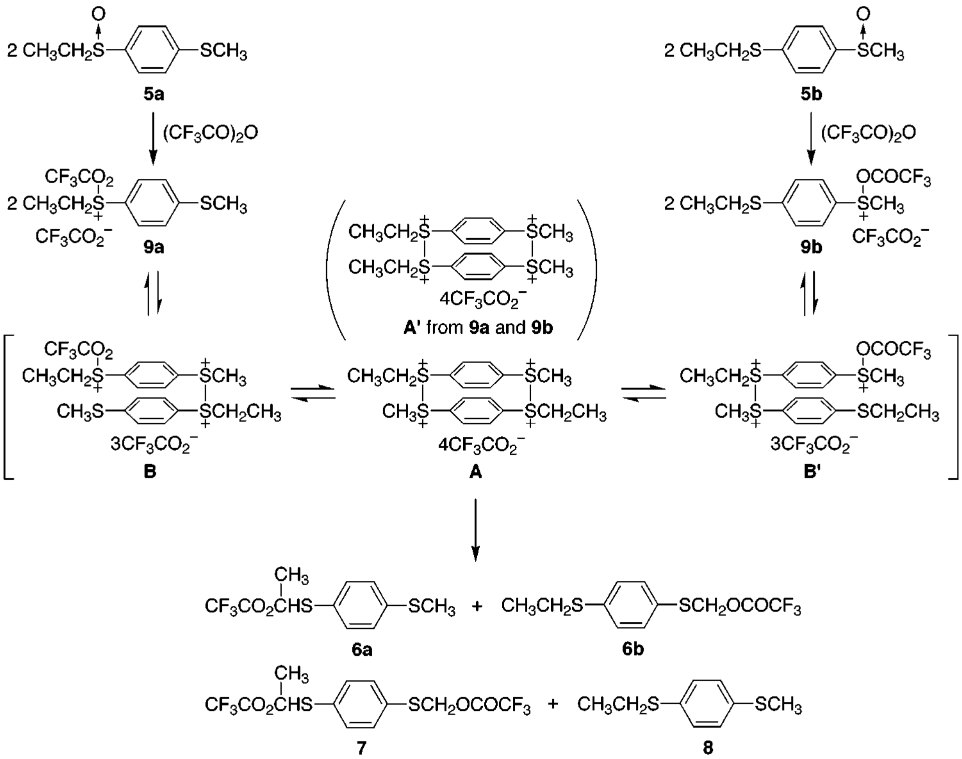
Scheme 2



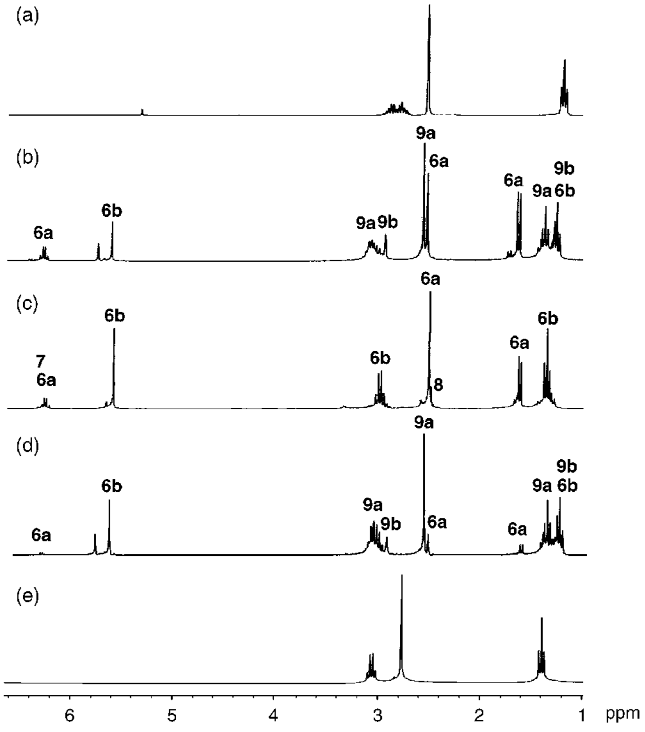


Figure 1. ^{1}H NMR spectra for the reaction mixture of **5** (68 mM) with $(CF_3CO)_2O$ (5 equiv) in $CDCl_3$ at −20 °C. (a) **5a**, (b) **5a** + $(CF_3CO)_2O$ after 1 h, (c) **5a** (or **5b**) + $(CF_3CO)_2O$ after 4 h, (d) **5b** + $(CF_3CO)_2O$ after 40 min, and (e) **5b**.

29%, 8%, and 4% yields, respectively, instead of Pummerer products. The quenching of the reaction of **5b** under the same conditions gave a mixture of **5a**, **5b**, **8**, and **10** in 49%, 28%, 2%, and 6% yields, respectively. In both cases, the product ratio of **5a**/**5b** is almost the same (approximately 1.7:1). The formation of **8** and **10** should result from intermediates **A** and/or **B**. The fact of a similar product ratio in both cases indicates that the equilibrium between **9a** and **9b** occurs via the same intermediates, such as **A** and/or **B**. No formation of Pummerer products at the initial stage indicates that this intermolecular interaction between the sulfur atoms is a much more favorable process than the abstraction of an α-proton from the sulfonium group that leads to the Pummerer products.

Evidence for Cyclic Bis(dithia dication) Dimer A: Syntheses of Cyclic Bis(disulfide) Dimer and Cyclic Tetrakis(disulfide) Tetramer via Debenzylation of Intermolecular Dithia Dication. We have extended the debenzylation of intramolecular dithia dications$^{7-9}$ to that of intermolecular dithia dications to prove that a cyclic bis(dithia dication) dimer **A** is an intermediate ($R = CH_2Ph$, $X^- = CF_3SO_3^-$). The reaction of a 1:1 mixture of 4-methylbenzyl-4′-methylphenyl sulfide (**11**) and its sulfoxide (**12**) with 1 equiv of $(CF_3SO_2)_2O$ in $CH_2Cl_2-CH_3CN$ (v/v 4:1), at −20 °C to room temperature for 2 h, quantitatively produced bis(4-methylphenyl) disulfide (**13**) and *N*-(4-methylbenzyl)acetamide (**14b**) in a 1:2 ratio after quenching with H_2O. This result shows that double-debenzylation is also applicable to intermolecular dithia dications.

Based on this result, the reaction of the *p*-bis(benzylthio)-aromatic *S*-oxide (**16**) (aromatic spacer = benzene (**a**), biphenyl (**b**), diphenyl sulfide (**c**), and diphenylmethane (**d**)) with $(CF_3SO_2)_2O$ was carried out. The mono-sulfoxide **16a** (50 mM) in $CH_2Cl_2-CH_3CN$ (v/v 4:1) was treated with 1 equiv of $(CF_3SO_2)_2O$ at −40 °C, and the resulting mixture was allowed to warm to room temperature (Scheme 3). The reaction was also monitored by ^{1}H NMR spectroscopy in $CDCl_3-CD_3CN$ (v/v 2:1) (Figure 2). Upon addition of $(CF_3SO_2)_2O$ at −40 °C, **16a** immediately disappeared and the corresponding sulfonium salt was observed. At −20 °C, the ^{1}H NMR spectrum of the yellow homogeneous solution showed

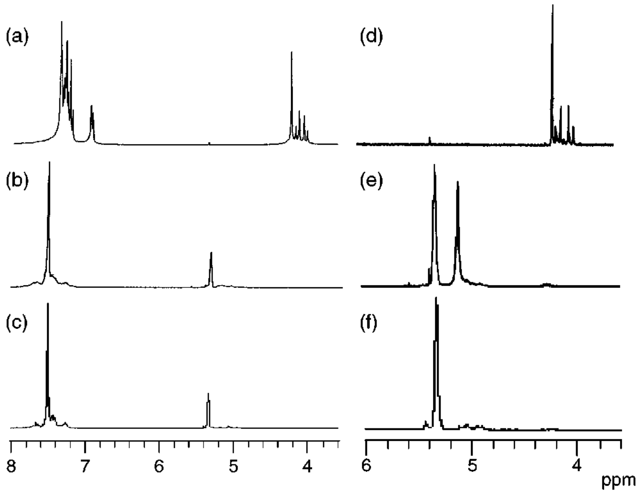


Figure 2. ^{1}H NMR spectra for the reaction mixture of **16** (50 mM) with $(CF_3SO_2)_2O$ (1 equiv) in $CDCl_3-CD_3CN$ (v/v 2:1). (a) **16a** at −20 °C, (b) **16a** + $(CF_3SO_2)_2O$ at −20 °C for 40 min, (c) **16a** + $(CF_3SO_2)_2O$ at 0 °C for 20 min, (d) **16c** at 0 °C, (e) **16c** + $(CF_3SO_2)_2O$ at 0 °C for 30 min, and (f) **16c** + $(CF_3SO_2)_2O$ at room temperature for 40 min.

Scheme 3

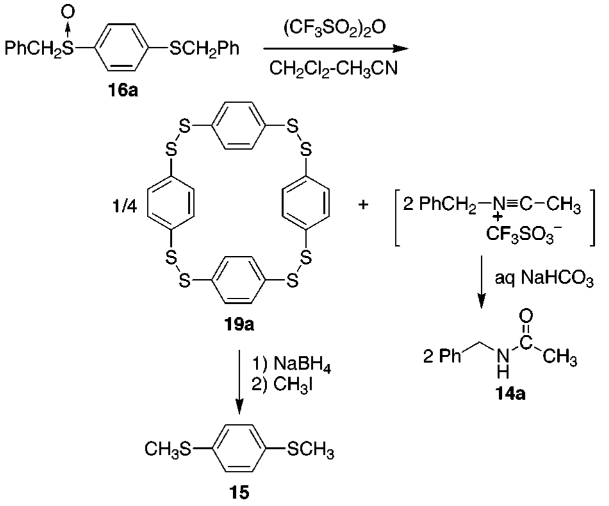
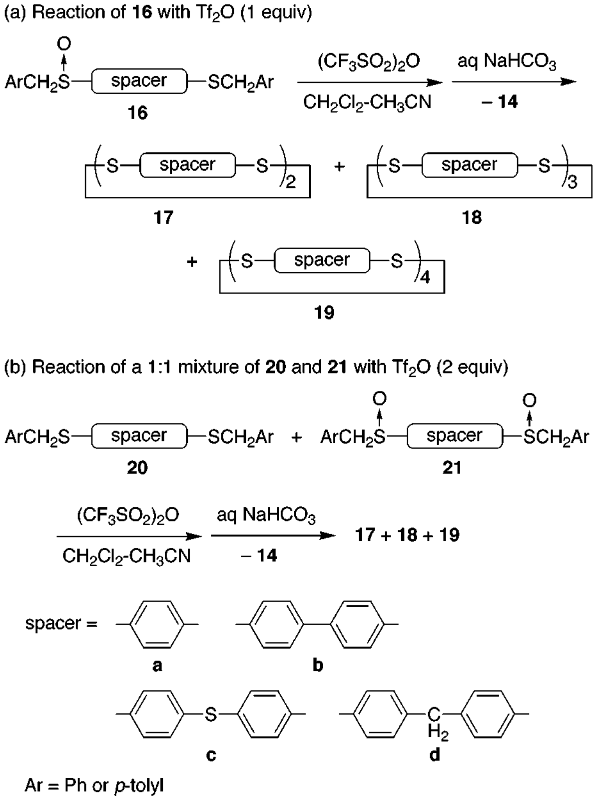


Table 1. Reactions of 16 with $(CF_3SO_2)_2O$ and of a 1:1 Mixture of 20 and 21 with $(CF_3SO_2)_2O$[a]

entry	substrate[b]	spacer	Ar	yield, % 17	18	19	14
1	**16a**	benzene	Ph	0	0	81	93
2	**16b**	biphenyl	Ph	0	0	45	61
3	**16c**	diphenyl sulfide	Ph	51	0	0	64
4	**16c′**	diphenyl sulfide	*p*-tolyl	34	0	0	67
5	**16d**	diphenylmethane	Ph	63	0	0	50
6	**20a** + **21a**	benzene	Ph	0	0	71	76
7	**20c′** + **21c′**	diphenyl sulfide	*p*-tolyl	27	0	0	39

[a] Carried out in a ratio of **16**:$(CF_3SO_2)_2O$ = 1:1 or in a ratio of **20**:**21**:$(CF_3SO_2)_2O$ = 1:1:2 in $CH_2Cl_2-CH_3CN$ (v/v 4:1) at −40 °C to room temperature for 4 h. [b] [**16**] = 50 mM and [**20**] = [**21**] = 25 mM.

Scheme 4



complete debenzylation, wherein the only *N*-benzylacetonitrile adduct was observed at δ 5.38 in the region of the benzyl groups (Figure 2b). At 0 °C, a pale yellow solid precipitated while the solution color faded. Treatment of the supernatant with aqueous $NaHCO_3$ produced *N*-benzylacetamide (**14a**) in 93% yield. The pale yellow solid (81% yield) was found to be the cyclic tetrakis(disulfide) tetramer **19a**, which was characterized by ^{1}H and ^{13}C NMR spectra and FAB-MS and MALDI-TOF-MS spectra. Treatment of **19a** with $NaBH_4$ in THF, followed by the addition of iodomethane, produced 1,4-bis(methylthio)benzene (**15**) in 56% yield.

Several representative results obtained under the same conditions are summarized in Table 1 and Scheme 4.[16] The following features are noteworthy. (1) The reaction of the mono-sulfoxides **16**, bearing the benzene (**a**) and biphenyl (**b**) spacers, with $(CF_3SO_2)_2O$ gave the cyclic tetrakis(disulfide) tetramers **19a** and **19b**, respectively (entries 1 and 2). The corresponding cyclic bis(disulfide) dimer **17** and the cyclic tris(disulfide) trimer **18** were not observed. (2) On the other hand, the reaction of **16**, bearing the diphenyl sulfide (**c**) and diphenylmethane (**d**) spacers, with $(CF_3SO_2)_2O$ produced the cyclic bis(disulfide) dimers **17c** and **17d**, respectively (entries 3 and 5). The corresponding cyclic trimer **18** and the cyclic tetramer **19** were not observed. In the ^{1}H NMR spectra, the debenzylation of **16c** proceeded in approximately 55% of molecules, at 0 °C over 30 min (Figure 2e), and to completion at room temperature over 40 min (Figure 2f) to give **17c** (51% yield) and **14a** (64% yield). Thus, the debenzylation of **16c** is slower than that of **16a**. The reaction mixture remained homogeneous during the course of the reaction of **16c**. (3) The reaction of a 1:1 mixture of the bis-sulfide **20** and the bis-sulfoxide **21** with 2 equiv of $(CF_3SO_2)_2O$ was also observed. The reaction of **20a** and **21a** (spacer = benzene, Ar = phenyl) produced **19a** (entry 6), whereas the reaction of **20c′** and **21c′** (spacer = diphenyl sulfide, Ar = *p*-tolyl) gave **17c** (entry 7).

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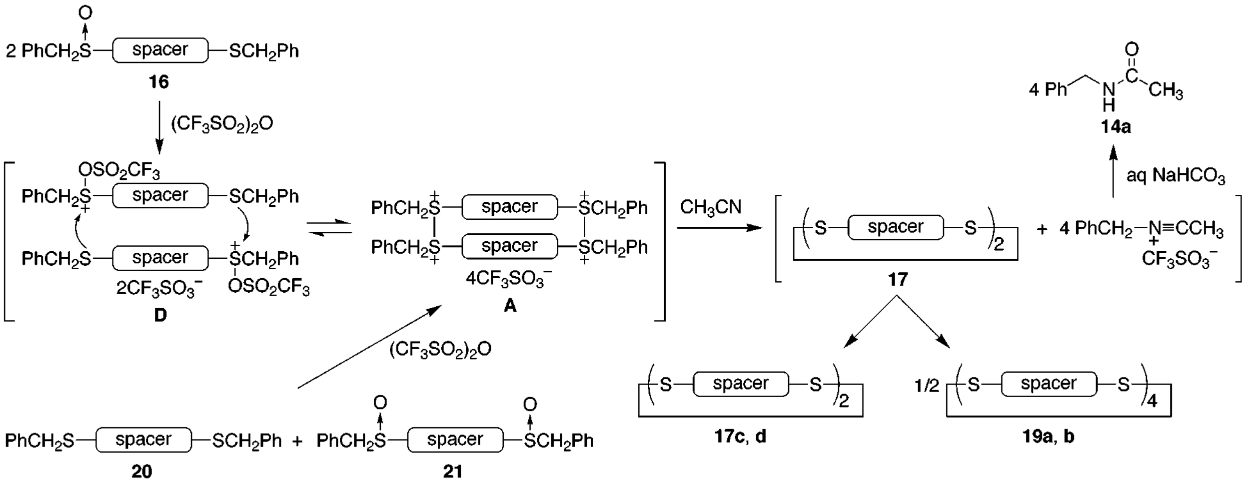
(16) The other products except for the cyclic dimer **17** and cyclic tetramer **19** were unidentified linear oligomers.

Scheme 5



The oxidation of 1,4-benzenedithiol with iodine[10,12b] or Cu(I)$-$O$_2-$TMEDA[13] gives the corresponding cyclic tris(disulfide) trimer **18a** as a main product, but does not produce the cyclic tetramer **19a**.[17] The oxidation of 4,4′-biphenyldithiol also produces the cyclic trimer **18b** without formation of **19b**.[13] The oxidation of 4,4′-thiobis(benzenethiol) gives an approximately 1:1 mixture of the cyclic dimer **17c** and the cyclic trimer **18c**.[13] The oxidation of 2,2-bis(4-mercaptophenyl)propane also gives a similar result.[13] These results are in marked contrast to those for the present reaction of **16** with $(CF_3SO_2)_2O$. It is noted that the reaction of **16a**,**b** with $(CF_3SO_2)_2O$ gives the cyclic tetramers **19a**,**b**, respectively, whereas the reaction of **16c**,**d** with $(CF_3SO_2)_2O$ produces the cyclic dimers **17c**,**d**, respectively. In none of the present reactions are cyclic trimers **18** formed.

These results undoubtedly indicate that the present reaction of **16** with $(CF_3SO_2)_2O$ does not involve the oxidative coupling of the corresponding aromatic dithiols or dithiyl radicals during the course of the reaction.[10−14] The debenzylation of **16** with $(CF_3SO_2)_2O$ should require the formation of a dithia dication.[7−9] On the basis of these results, the following mechanism is plausible, as shown in Scheme 5. At first, the reaction of the *p*-bis(benzylthio)-aromatic *S*-oxide **16** with $(CF_3SO_2)_2O$ gives the trifluoromethanesulfonyloxysulfonium salt **D**. Subsequently, the intermolecular interaction between the sulfonium sulfur atom of one **D** molecule and the sulfide sulfur atom of another **D** could produce the cyclic bis(dithia dication) dimer **A** as an intermediate. Finally, the debenzylation of **A** could produce the cyclic bis(disulfide) dimer **17**. This could explain why no detectable cyclic tris(disulfide) trimer **18** was formed in the present reaction. The cyclic bis(disulfide) dimers **17a**,**b**, bearing the benzene and biphenyl spacers, would be highly strained due to aromatic−aromatic repulsion and hence would be easily expanded to produce the cyclic tetrakis(disulfide) tetramers **19a**,**b**. Thus, the formation of the cyclic tetrakis(disulfide) tetramers **19a**,**b** from **16a**,**b**, and of the cyclic bis(disulfide) dimers **17c**,**d** from **16c**,**d**, strongly supports the role of cyclic bis(dithia dication) dimer **A** as an intermediate in the intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms. Further evidence for this intermediate comes from the reaction of bis-sulfide **20** and bis-sulfoxide **21**. In fact, the reaction of a 1:1 mixture of **20a** and **21a** gave the same cyclic tetramer **19a** as the reaction of the monosulfoxide **16a**, and the reaction of a 1:1 mixture of **20c′** and **21c′** gave the same cyclic dimer **17c** as the reaction of **16c′**.

Conclusion

By using substrates bearing bulky and unsymmetrical substituents, we have demonstrated that the intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms plays an essential role in the remote Pummerer reaction of the *p*-bis(alkylthio)-aromatic *S*-oxides with $(CF_3CO)_2O$. There is an equilibrium in the intermolecular interaction between the sulfonium and sulfide sulfur atoms. This intermolecular through-space interaction is a much more favorable process than the intramolecular through-bond interaction between sulfur atoms and the abstraction of an α-proton from the sulfonium group that leads to the Pummerer products. We have proposed the cyclic bis(dithia dication) dimer **A** as an intermediate in the remote Pummerer reaction, resulting from the intermolecular through-space interaction between the sulfonium and sulfide sulfur atoms. On the basis of these results, we have demonstrated the syntheses of the cyclic bis(disulfide) dimer and the cyclic tetrakis(disulfide) tetramer via the debenzylation of the cyclic bis(dithia dication) dimer **A** that arises from the reaction of *p*-bis(benzylthio)-aromatic *S*-oxides and $(CF_3SO_2)_2O$. The results presented here may provide a basis for the use of the intermolecular sulfur−sulfur interaction as a supramolecular synthon[3,18] and for a greater understanding of the electric conductivity mechanisms of materials bearing sulfur functionalities.[4,19]

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Experimental Section

General. ^{1}H NMR spectra were recorded at 270 or 400 MHz, and ^{13}C NMR spectra were taken at 67.5 or 100 MHz. Mass spectra were obtained by EI, FAB (*m*-nitrobenzyl alcohol as a matrix), or MALDI-TOF (dithranol as a matrix) methods. Preparative HPLC was performed on a Japan Analytical Industry Co., Ltd., model LC-908. CH_2Cl_2 and CH_3CN were distilled from CaH_2 under N_2, and THF was distilled from sodium−benzophenone ketyl under N_2. NMR solvents for monitoring reactions were dried over molecular sieves 4A. $(CF_3CO)_2O$ and $(CF_3SO_2)_2O$ were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.

Pummerer Reaction of 1a with $(CF_3CO)_2O$. To a solution of **1a** (30.0 mg, 0.0408 mmol) in CH_2Cl_2 (5 mL) at −20 °C under an Ar atmosphere was added $(CF_3CO)_2O$ (29 μL, 0.21 mmol). The reaction mixture was allowed to warm to room temperature for 2 h, and saturated aqueous $NaHCO_3$ was added to the mixture. The aqueous layer was quickly extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvent, an analytically pure sample of **2a** was obtained (29.7 mg, 88%) as a pale yellow solid.

3,3′,5,5′-Tetramesityl-4-[(trifluoroacetoxy)methylthio)]-4′-(methylthio)biphenyl (2a): mp 216−218 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3H), 1.98 (s, 12H), 2.00 (s, 12H), 2.25 (s, 12H), 4.79 (s, 2H), 6.86 (s, 4H), 6.87 (s, 4H), 7.24 (s, 2H), 7.31 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 17.4, 20.4, 20.6, 20.8, 21.2, 71.0, 114.1 ($^1J_{CF}$ = 283.8 Hz), 127.5, 127.9, 128.1, 128.4, 129.0, 135.0, 135.5, 135.7, 136.9, 137.2, 137.4, 138.2, 138.5, 140.5, 145.5, 145.7, 156.8 ($^2J_{CF}$ = 42.5 Hz); FAB-MS *m/z* 830 (M^+). Anal. Calcd for $C_{52}H_{53}F_3O_2S_2$: C, 75.15; H, 6.43. Found: C, 74.94; H, 6.75.

Pummerer Reaction of 5a with $(CF_3CO)_2O$. To a solution of **5a** (5.37 mg, 0.027 mmol) in $CDCl_3$ (0.40 mL) at −40 °C under an Ar atmosphere in a NMR tube was added $(CF_3CO)_2O$ (19 μL, 0.13 mmol). The resulting mixture was monitored by ^{1}H NMR spectroscopy at −20 °C. The product ratio of **6a**, **6b**, **7**, and **8** was determined by the integration of the ^{1}H NMR spectrum as shown in Figure 1. Pummerer products **6a**, **6b**, and **7** were unstable and could not be isolated.

Quench at the Initial Stage of Pummerer Reaction of 5a with $(CF_3CO)_2O$. To a solution of **5a** (100 mg, 0.499 mmol) in CH_2Cl_2 (8 mL) at −20 °C under an Ar atmosphere was added $(CF_3CO)_2O$ (350 μL, 2.48 mmol). After 10 s, saturated aqueous $NaHCO_3$ was added to the reaction mixture for quenching the reaction. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the residual mixture was separated with preparative HPLC eluted by $CHCl_3$ to give **5a** (47.0 mg, 47%), **5b** (29.0 mg, 29%), **8** (7.4 mg, 8%), and **10** (4.3 mg, 4%).

Reaction of a 1:1 Mixture of 11 and 12 with $(CF_3SO_2)_2O$. To a solution of **11** (114 mg, 0.499 mmol) and **12** (122 mg, 0.499 mmol) in CH_2Cl_2−CH_3CN (v/v 4:1, 10 mL) at −20 °C under an Ar atmosphere was added $(CF_3SO_2)_2O$ (93 μL, 0.55 mmol). The reaction mixture was allowed to warm to room temperature for 2 h, and saturated aqueous $NaHCO_3$ was added to the mixture. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvents, the residue was subjected to column chromatography on silica gel to give **13** (109 mg, 89%) and **14b** (153 mg, 94%).

Bis(4-methylphenyl) disulfide (13): ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6H), 7.10 (d, *J* = 7.8 Hz, 4H), 7.38 (d, *J* = 7.8 Hz, 4H); EI-MS *m/z* 246 (M^+).

***N*-(4-Methylbenzyl)acetamide (14b):** ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.33 (s, 3H), 4.37 (d, *J* = 5.7 Hz, 2H), 5.83 (brs, 1H), 7.15 (s, 4H); EI-MS *m/z* 163 (M^+).

Reaction of 16 with $(CF_3SO_2)_2O$. Typical Procedure (Scheme 4, Table 1, Entry 1). To a solution of **16a** (100 mg, 0.295 mmol) in CH_2Cl_2−CH_3CN (v/v 4:1, 6.0 mL) at −40 °C under an Ar atmosphere was added $(CF_3SO_2)_2O$ (56 μL, 0.33 mmol). The reaction mixture was allowed to warm to room temperature for 4 h, and a pale yellow solid precipitated. The resulting heterogeneous mixture was filtered and washed with saturated aqueous $NaHCO_3$, H_2O, MeOH, Et_2O, and CH_2Cl_2 to give **19a** (33.4 mg, 81%) as a pale yellow solid. The filtrate was extracted with CH_2Cl_2, and the organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvents, the residual mixture was purified with preparative HPLC eluted by $CHCl_3$ to give **14a** (81.6 mg, 93%).

Cyclic Tetrakis(disulfide) Tetramer (19a), benzene spacer: yield 81%; mp 251−253 °C; ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 16H); ^{13}C NMR ($CDCl_3$) δ 127.6, 135.1; FAB-MS *m/z* 560 (M^+); TOF-MS *m/z* 560 (M^+). Anal. Calcd for $C_{24}H_{16}S_8{\cdot}H_2O$: C, 49.79; H, 3.13. Found: C, 49.84; H, 3.09.

Cyclic Tetrakis(disulfide) Tetramer (19b), biphenyl spacer: yield 45%; mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 16H), 7.52 (d, *J* = 8.6 Hz, 16H); ^{13}C NMR ($CDCl_3$) δ 127.5, 128.5, 131.0, 136.4; TOF-MS *m/z* 865 (M^+). Anal. Calcd for $C_{48}H_{32}S_8{\cdot}3H_2O$: C, 62.71; H, 4.17. Found: C, 63.01; H, 3.95.

Cyclic Bis(disulfide) Dimer (17c), diphenyl sulfide spacer: yield 51%; mp 266−268 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (d, *J* = 8.2 Hz, 8H), 7.26 (d, *J* = 8.2 Hz, 8H); ^{13}C NMR ($CDCl_3$) δ 128.2, 129.0, 130.3, 132.1; FAB-MS *m/z* 496 (M^+). Anal. Calcd for $C_{24}H_{16}S_6{\cdot}0.5H_2O$: C, 56.99; H, 3.39. Found: C, 57.04; H, 3.38.

Cyclic Bis(disulfide) Dimer (17d), diphenylmethane spacer: yield 63%; mp 204−206 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 4H), 6.91 (d, *J* = 8.1 Hz, 8H), 7.22 (d, *J* = 8.1 Hz, 8H); ^{13}C NMR ($CDCl_3$) δ 41.0, 127.0, 128.1, 132.4, 134.0; TOF-MS *m/z* 460 (M^+). Anal. Calcd for $C_{26}H_{20}S_4{\cdot}0.5H_2O$: C, 66.48; H, 4.51. Found: C, 66.54; H, 4.45.

***N*-Benzylacetamide (14a):** ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 4.43 (d, *J* = 5.7 Hz, 2H), 5.85 (brs, 1H), 7.22−7.37 (m, 5H); EI-MS *m/z* 149 (M^+).

Reaction of a 1:1 Mixture of 20 and 21 with $(CF_3SO_2)_2O$. Typical Procedure (Scheme 4, Table 1, Entry 7). To a solution of **20c′** (101 mg, 0.220 mmol) and **21c′** (108 mg, 0.220 mmol) in CH_2Cl_2−CH_3CN (v/v 4:1, 8.8 mL) at −40 °C under an Ar atmosphere was added $(CF_3SO_2)_2O$ (80 μL, 0.48 mmol). The reaction mixture was allowed to warm to room temperature for 4 h, and saturated aqueous $NaHCO_3$ was added to the mixture. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of solvents, the residual mixture was purified with preparative HPLC eluted by $CHCl_3$ to give **17c** (29.4 mg, 27%) as a pale yellow solid and **14b** (56.1 mg, 39%).

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Supporting Information Available: Spectral dada of starting materials **1a**, **5**, **8**, **10**, **16**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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