Comparative Sulfhydryl Reaction Pathways of Chlorooxirane and Chloroacetaldehyde

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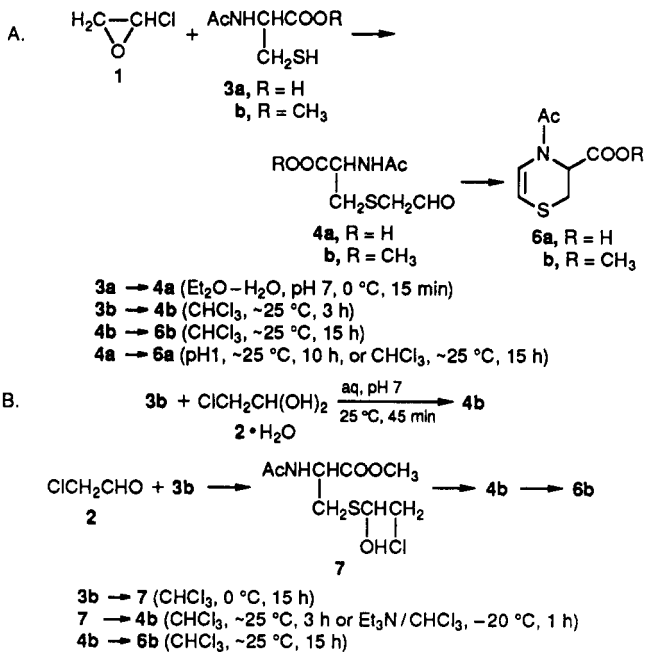
Two bifunctional alkylating agents, chlorooxirane (1) and chloroacetaldehyde (2), which are putative metabolites of vinyl chloride (VC), are expected to be detoxified via *S*-(formylmethyl)glutathione as the common intermediate. This paper compares the behavior of 1 and 2 in their reactions with two model thiols in aqueous and chloroform media to evaluate the above hypothesis. In aqueous media, 1 and 2 reacted with *N*-acetylcysteine (**3a**) or its methyl ester **3b** to form the same *S*-acetaldehyde **4a** or **4b**, which, upon standing, cyclized to the dihydro-1,4-2*H*-thiazine derivatives **6a** and **6b**. In chloroform, the above products were obtained for both 1 and 2 via different pathways: the reaction of **3b** and 2 formed initially the thiohemiacetal 7 at 0 °C, which rearranged to the aldehyde **4b** after warming or treatment with triethylamine. Another thiol, 3,4-dichlorobenzenethiol (8), used for trapping alkylating metabolites from VC as the *S*-acetaldehyde **9**, was found to react with 1 but not 2 in aqueous solution to produce **9**, whose identity was verified by an independently synthesized sample. The reaction of the thiol 8 and 1 in chloroform yielded **9** sluggishly; the reaction of 8 and 2 gave the thiohemiacetal 11, which rearranged to the aldehyde **9** when heated at 50 °C or treated with pyridine.

The bifunctional alkylating agents chlorooxirane (1) and chloroacetaldehyde (2) are metabolites of vinyl chloride (VC),[1] an established human carcinogen that poses occupational hazards. 1 is unstable, and it undergoes chlorine rearrangement to **2**, although the latter may also be a direct cytochrome oxidation product of VC.[1] Both are expected to be detoxified to *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and thiodiglycolic acid, as urinary metabolites,[2a] via a common glutathione conjugate, the *S*-formylmethyl derivative.[2] However, in the case of vinylidine chloride, it has been shown[3] that its intermediary metabolites, 1,1-dichlorooxirane and dichloroacetaldehyde, react differently with glutathione, yielding *S*-(2-glutathionyl)acetylglutathione and *S*-(2,2-dichloro-1-hydroxyethyl)glutathione, respectively. The former is a sulfhydryl β-attack, ring-opened product, while the latter is a thiohemiacetal. Whether 1 and 2 are detoxified via the same glutathione intermediate and how similar or dissimilar they react with a sulfhydryl group are not clear. We report herein the comparative behavior of 1 and 2 in their reactions with two model thiols in both aqueous and chloroform media for the purpose of bridging this gap.

Results and Discussion

***N*-Acetylcysteine Reaction.** Glutathione (GSH) is known to be the primary hepatic nonprotein sulfhydryl compound that shows dose-related depression in rats when exposed to vinyl chloride.[4] In elucidation of its sulfhydryl reactivity, there may arise a complication due to Schiff base formation by the α-amino group of the GSH γ-glutamyl residue. For our purpose, *N*-acetylcysteine (**3a**) or its methyl ester **3b** was used as a model for GSH. Furthermore, the spontaneous oxidation rate of **3a** is very slow, remaining in the reduced form in plasma, and has been used to counteract the urotoxicity of acrolein derived from the cyclophosphamide cancer drug.[5] Thus, the reactivity

Scheme I



of *N*-acetylcysteine reported below may also be relevant to prevention studies of vinyl chloride carcinogenesis. The reaction products of 1 and 2 are anticipated on the basis of reported nucleophilic reactions of similar compounds. Chlorooxiranes have been found to react with a number of oxy anions by several mechanisms to yield either chlorine substitution products[6,7] or ring-opened products by α- and β-attacks.[8] There is no apparent pattern in these reactions. With a mercapto compound, a sulfhydryl attack of the β-carbon is preferred even though the latter may already be substituted by a bulky *tert*-butyl group.[9] In the presence of α-chlorocarbonyl compounds, sulfhydryl groups react to form thiohemiacetals[4] and chlorine displacement products,[10,11] the latter of which are indistin-

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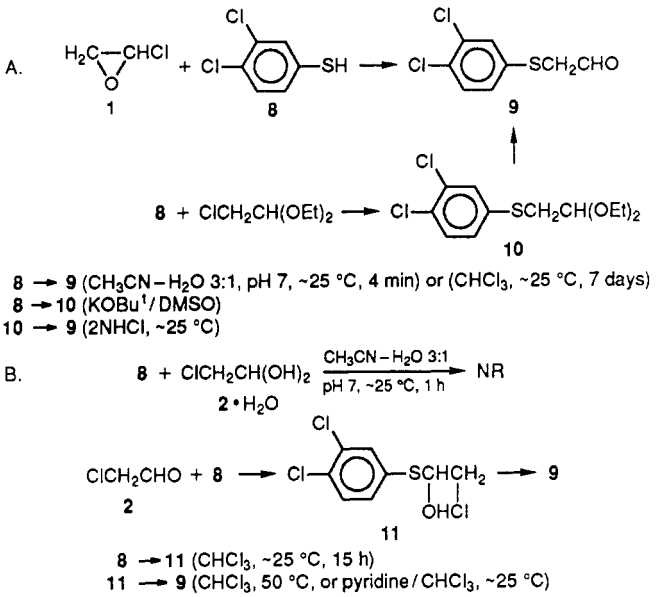
guishable from the ring-opened products of the corresponding chlorooxirane.

To select the solvents for studying the chlorooxirane sulfhydryl reaction, one must take into account the propensity of oxirane **1** rearranging via an α-carbonylcarbenium ion to chloroacetaldehyde (**2**), with **2** being the major product even in aqueous media.[12] ^{1}H NMR was used to follow the disappearance of **1** (δ 2.92 (m, CH_2), 5.05 (m, CH)) in several solvent systems at room temperature: **1** was most unstable in dimethyl sulfoxide ($t_{1/2}$ < 1 min) and quite stable in chloroform and ether ($t_{1/2}$ > 2 days), and in acetonitrile–water (3:1) or ether–water mixture, the half-life of **1** was about 15 min. When the reaction of **1** and *N*-acetylcysteine (**3a**) was conducted in a vigorously stirred ether–water medium at 0 °C, the consumption of 1 equiv of sodium hydroxide as monitored by a pH stat was completed in 15 min. Since the rate of reaction of **1** with **3a** is considerably faster than the rate of isomerization of **1** to **2**, most or all of the product **4a** must arise from the reaction of **3a** with the oxirane **1**. Only one product, viz., the *S*-acetaldehyde derivative **4a** of Scheme I, was detected when the reaction mixture was examined by ^{1}H NMR and HPLC; hence **4a** is either an exclusive product of **1** or a common product of **1** and **2** if the latter was also formed from **1** during the reaction.

To further assess the validity of the direct **1** → **4a** pathway, the reaction was run in chloroform, where **1** was much more stable, using the chloroform-soluble cysteine methyl ester **3b** as the thiol. The reaction took 3 h, slower than the aqueous reaction. This suggests that the thiolate anion (RS^-), being more abundant in an aqueous pH 7 solution than in chloroform, was the reactive nucleophilic species in water. This was also shown in an earlier study[13] of the nucleophilic character of mercaptans toward ethylene oxide in aqueous buffers. Initially, the chloroform reaction yielded **4b** as the only product, consistent with the direct oxirane–thiol reaction in the aqueous mixture. However, it was surprising to find that the *S*-acetaldehyde **4a** or **4b** underwent cyclization–dehydration to yield the new dihydro-1,4-2*H*-thiazine **6a** or **6b** upon standing. For an aqueous solution of **4a** at pH 7 and ~25 °C, the ratio of **4a** to **6a** was 1:8 after 13 days by NMR integration of the two *N*-acetylmethyl groups, which were separated by 0.2 ppm. In the pH range 2–7, there was negligible conversion after 2 days at room temperature. At pH 1, the above ratio was 1:1 after 10 h at ~25 °C. In chloroform, the cyclization of **4b** to **6b** was virtually complete overnight at ~25 °C. Thus, the cysteine acetamido nitrogen is nucleophilic toward the aldehyde group in **4a** and **4b**. This lone pair also took part in the H/D exchange of the vinyl 6-hydrogen of the thiazine products **6a** and **6b** in the presence of D_2O–DCl, indicating enamine–imine tautomerization. The latter probably accounts for the hydrolytic ring opening of the dihydrothiazine when **6a** or **6b** was heated in aqueous acid.

For comparison with the chlorooxirane reactions, chloroacetaldehyde (**2**) was allowed to react with the cysteine compounds **3a** and **3b**. In aqueous solution at pH 7 and ~25 °C, the reaction of **2** and **3b** yielded the aldehyde **4b** after consuming 1 equiv of sodium hydroxide in 45 min, but part of it cyclized to the thiazine **6b** during workup. When the reaction was run in chloroform, only the thiohemiacetal **7** was formed first. At 0 °C, **7** was stable and identified by NMR. Upon warming to room temperature or by adding triethylamine at −20 °C, the thiohemiacetal **7** rearranged to the *S*-acetaldehyde **4b**. In this regard, **7** is less stable than the thiohemiacetal of dichloroacetaldehyde obtained from its reaction with either *N*-acetylcysteine (**3a**) or glutathione, which was also isolated as a vinylidene chloride microsomal metabolite.[3] The cysteine thiol reactions with chlorooxirane (**1**) and chloroacetaldehyde (**2**) are summarized in Scheme I, showing similar behavior in aqueous media but dissimilar behavior in chloroform. Since both **1** and **2** yield the same *S*-acetaldehyde conjugate under a variety of conditions, these model reactions support the hypothesis that *S*-(formylmethyl)glutathione could be an intermediary metabolite common to both **1** and **2**.[2]

Scheme II



It should be noted that the thiazine derivative **6** has not been identified or speculated as a vinyl chloride metabolite. On the other hand, an analogue of **6**, 4-acetyl-3-carboxy-5-cyanotetrahydro-1,4-2*H*-thiazine, was tentatively identified by GC-MS analysis of rat urine after acrylonitrile administration.[14] Whether this cyanothiazine is a true acrylonitrile metabolite or not, there is room for speculation that the present thiazine **6** may be a VC metabolite. In an in vivo metabolic study of ^{14}C-labeled VC,[15] the following distribution of ^{14}C label was found in the urine: *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, 30.4%; thiodiglycolic acid, 25.6%; unidentified materials, 38.6%. The latter group may contain the thiazine **6** derived from the intermediary *S*-(formylmethyl)glutathione.

3,4-Dichlorobenzenethiol Reaction. Two trapping agents have been used to trap alkylating metabolites from vinyl chloride. In a microsomal oxidation of VC,[15] an excess of 4-(4-nitrobenzyl)pyridine (NBP) was added to give an absorption spectrum, λ_{max} 560 nm, identical with that obtained by the reaction of **1** with NBP. There was no increase of the 560-nm peak in reacting NBP with **2** under the same conditions. However, this colorimetric method is based on adducts of unknown structure. Therefore, no meaningful comparison can be made with the present study of the sulfhydryl reaction of **1** and **2**.

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The other trapping agent used was 3,4-dichlorobenzenethiol (8). It formed [(3,4-dichlorophenyl)thio]acetaldehyde (9) from a microsomal preparation of VC, and it was concluded that "the results are consistent with the formation of 1 as a reactive metabolite of VC, but can also be interpreted as indicating the formation of 2".[16] On the basis of the reactions of 1 and 2 with cysteine derivatives described above, a similar study was carried out using the benzenethiol 8 instead of **3a** or **3b**. These results are shown in Scheme II. In neutral aqueous solutions, 8 reacted with 1 to form the *S*-acetaldehyde 9 in 4 min, which remained unchanged upon standing. An authentic sample of 9 was prepared independently by reacting the thiol 8 with chloroacetaldehyde diethylacetal in the presence of potassium *tert*-butoxide to yield the sulfur conjugate 10, which was hydrolyzed in 2 N HCl to 9. The formation of 9 is reminiscent of the *N*-acetylcysteine reaction generating the *S*-acetaldehyde **4a** or **4b**, except the latter undergoes secondary reaction cyclizing to the thiazine derivative **6a** or **6b**. When the reaction of 1 and 8 was run at pH 7 and pH 4, the ratio of 9 produced was 3.45:1, suggesting that the thiolate anion was the reactive species. This is reflected also in the reaction of 1 and 8 conducted in chloroform, where the thiol alkylation was very slow, requiring 7 days at room temperature. Interestingly enough, the thiol 8 and chloroacetaldehyde (2) in aqueous solution showed no reaction, but in chloroform the thiohemiacetal 11 was formed. It reversed to the thiol 8 partially upon heating or during silica gel chromatography but rearranged to yield the stable *S*-acetaldehyde 9 when heated at 50 °C or 1 equiv of pyridine was added to the chloroform solution at ~25 °C. The rearrangement of the thiohemiacetals 11 and 7 to the corresponding aldehydes may proceed intramolecularly via a thiooxirane (neighboring OH displacing Cl) or an episulfonium ion (sulfur displacing Cl). They may also dissociate to the thiolate anion and 2 followed by *S*-alkylation. When the thermal rearrangement of 11 to 9 was followed by ^{1}H NMR, two new multiplets were observed at δ 3.47 and 2.96 in a ratio of 1:2, which are indicative of an intermediate other than 2. However, attempts to isolate this intermediate were not successful. Thus, our present data are inconclusive on this point. Otherwise, the reactions in Scheme II have made it clear how the *S*-acetaldehyde 9 can arise from the thiol 8. Therefore, concerning the trapping of 9 from a microsomal preparation of VC, 9 is most likely a specific product of chlorooxirane (1), the latter being the only alkylating metabolite of vinyl chloride since chloroacetaldehyde (2) was found to give no reaction with the thiol 8 in aqueous solution. Thus, the statement[16] that the trapping of 9 can also be interpreted as indicating the formation of 2 is unfounded.

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained at 90 MHz, and ^{13}C NMR spectra were obtained at either 22.5 or 75 MHz (with Me_3SiX as an internal standard, δ = 0, X = CH_3 for $CHCl_3$ and X = $(CH_2)_3SO_3Na$ for D_2O). Coupling constants (J) are in hertz. Gas chromatography (GC) analyses were performed on a stainless steel column 3.5 ft × 0.125 in packed with 5% OV-17 on Chromasorb W-HP 80/100 mesh. Nitrogen carrier gas flows were approximately 33 mL/min at a column temperature of 200 °C or as specified. GC-MS analysis was carried out in chemical ionization mode. High-pressure liquid chromatography (HPLC) was done using a variable-wavelength detector at either 254 or 210 nm: normal phase made use of a Lichrosorb Si60 column with 1:1 hexane–chloroform as the eluent at 1 mL/min, and reverse phase on a partisil ODS column eluted with 15:85 acetonitrile–H_2O (pH 2.6) at 1 mL/min. All melting points are uncorrected. Organic chemicals including chloroacetaldehyde (2) aqueous solution were purchased from Aldrich Chemical Co. Chlorooxirane (1) was prepared according to the method reported by Rannug et al.[17] by chlorination of ethylene oxide. Since both 1 and 2 tend to polymerize when highly concentrated, they were quantitated by ^{1}H NMR spectroscopy using toluene as the quantitative reference. The same method was used to monitor the stability of 1 in several solvent systems by integrating the multiplet at δ 5.05 (CH–Cl) at various times at room temperature. In the case of heterogeneous ether–water mixture, the presence of 1 in the ether layer was followed since 1 decomposed rapidly in water. The content of the thiol group in sulfhydryl compounds was titrated with Ellman's reagent,[18] with use of 2-mercaptoethanol as a calibration standard.

***N*-Acetylcysteine Reaction with Chlorooxirane (1). Aqueous Medium.** To 5 mL of distilled water was added *N*-acetylcysteine (**3a**, 0.425 g, 2.6 mmol, >95% SH), and the solution was kept under nitrogen at 0 °C and its pH maintained at 7 by a pH stat using 1 N NaOH; the pH range observed was 6.7–7.1. A 1-mL solution of 1 (2.61 mmol) in diethyl ether was added dropwise with vigorous stirring, and 1 equiv of 1 N NaOH was administered by the pH stat in 15 min, thereafter the pH remained unchanged without adding any more base. The solution was evaporated to *S*-(formylmethyl)-*N*-acetylcysteine (**4a**) hydrate as a gummy solid: ^{1}H NMR (D_2O) δ 5.14 (m, $CH(OH)_2$), 4.40 (dd, J = 6.7, 2, CH), 3.03 (m, CH_2, CH_2), 2.05 (s, $COCH_3$); ^{13}C NMR δ 23.9 (CH_3CO), 36.3 ($CHCH_2S$), 40.9 (SCH_2), 56.3 (CH), 57.3 ($CH(OH)_2$), 178.0 (CON), 180.8 (COO). The 2,4-nitrophenylhydrazone derivative **5a** was formed by adding a solution of 2,4-dinitrophenylhydrazine in 50% H_2SO_4 to the solid residue, recrystallized from aqueous dimethyl sulfoxide, mp 119–120 °C; ^{13}C NMR (Me_2SO-d_6) δ 23.5 (CH_3CO), 33.2 ($CHCH_2S$), 33.5 (SCH_2), 52.7 (CH), 117.8–150.4 (CH=N, phenyl), 170.7 (CON), 173.2 (COO).

Anal. Calcd for $C_{13}H_{15}O_7N_5S\cdot{}^1/_2H_2O$: C, 39.59; H, 4.09; N, 17.76; S, 8.13. Found: C, 39.74; H, 3.94; N, 17.48; S, 8.30.

Chloroform Medium. *N*-Acetylcysteine methyl ester (**3b**) was obtained by refluxing **3a** in 10-fold excess of methanol containing a catalytic amount of concentrated HCl, mp 79.5–80.5 °C; ^{13}C NMR ($CDCl_3$) δ 170.7 (COO), 170 (CON), 53.7 (OCH_3), 52.8 (CH), 26.9 (CH_2), and 23.0 (CH_3). A 2-mL deuteriochloroform solution containing 0.225 g (1.27 mmol) of **3b** and 1.27 mmol of 1 was allowed to stand at room temperature, and the reaction was complete after 3 h as monitored by NMR. The product formed was the *S*-formylmethyl derivative **4b** [^{1}H NMR ($CDCl_3$) δ 9.53 (t, J = 3.2, CHO), 4.80 (m, CH), 3.82 (s, CH_3O), 3.29 (d, J = 3.2, CH_2S), 2.92 (m, CH_2), 2.39 (s, $COCH_3$)], trapped as the 2,4-dinitrophenylhydrazone **5b** and recrystallized from methanol, mp 166–167 °C. After standing in solution overnight, **4b** was converted to a new compound as shown by a new GC peak. The solution was concentrated and chromatographed on silica gel; the methylene chloride eluent was evaporated and molecularly distilled (0.25 mmHg, 85 °C) to yield 3-(methoxycarbonyl)-4-acetyl-dihydro-1,4-2*H*-thiazine (**6b**): UV (95% EtOH) λ_{max} 265 nm (ϵ 8580); ^{1}H NMR ($CDCl_3$) δ 6.85 (d, J = 8.7, =CHN), 5.85 (t, J = 3.5, CH), 5.4 (dd, J = 8.7, 2, =CHS, exchanged in D_2O–DCl), 3.80 (s, OCH_3), 3.05 (dd, J = 3.5, 2, CH_2), 2.25 (s, $COCH_3$).

Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.74; H, 5.51; N, 6.96. Found: C, 47.50; H, 5.51; N, 7.07.

***N*-Acetylcysteine Reaction with Chloroacetaldehyde (2). Aqueous Medium.** Both cysteine derivatives **3a** and **3b** reacted with 2 in a similar manner, but **3b** was easier to follow by NMR and is described below. A 5-mL aqueous solution containing 0.177 g (1 mmol) of **3b** and 1 mmol of 2 was maintained at pH 7 by a pH stat using 0.5 N NaOH at room temperature under nitrogen. The pH range observed was 6.9–7.1, and the pH did not change after consuming 1 equiv of base in 45 min. A 1-mL aliquot was evaporated to dryness, dissolved in D_2O, and ^{1}H NMR [D_2O, δ 5.04 (m, $CH(OH)_2$), 4.58 (m, CH), 3.7 (s, OCH_3), 3.06 (m, CH_2, CH_2), 2.0 (s, $COCH_3$)] and HPLC indicated the presence of *S*-

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formylmethyl derivative **4b** (as hydrate).

Chloroform Medium. Chloroacetaldehyde (**2**) monomer was prepared from the commercial aqueous solution by extraction with ethanol-free chloroform. The extracts were dried over $MgSO_4$ and filtered, and the filtrate evaporated by a slow stream of dry nitrogen into a dry ice trap. The condensate was stored over 3A molecular sieves at -20 °C and quantitated by ^1H NMR using a known weight of toluene as internal standard. A 2-mL deuteriochloroform solution containing 1 mmol each of **3b** and **2** monomer was left standing at 0 °C overnight: ^1H NMR ($CDCl_3$) δ 7.35 (s, NH), 5.0 (m, CH, CH), 3.78 (s, CH_3O), 3.75 (d, J = 4.5, CH_2Cl), 3.15 (d, J = 5.6, CH_2S), 2.10 (s, $COCH_3$). This is consistent with the assignment as the $SCH(OH)CH_2Cl$ derivative (**7**). Upon further standing at room temperature and monitoring by ^1H NMR, **7** was gradually replaced by S-CH_2CHO **4b** (its spectrum is described above for **4b** derived from **3b** and **1**). This conversion was also effected with 1 equiv of triethylamine at -20 °C in 15 min. The thiazine **6b** was the final product when a chloroform solution of **4b** was kept overnight at room temperature.

Reaction of 3,4-Dichlorobenzenethiol with Chlorooxirane (1). Aqueous Medium. A solution containing 274 mg (1.53 mmol) of 3,4-dichlorobenzenethiol (**8**) in 5 mL of 3:1 acetonitrile–water was adjusted to pH 7 by adding 0.5 N sodium hydroxide solution. To this solution was added **1** (1.53 mmol) in 1.0 mL of acetonitrile, and the solution was stirred under nitrogen at room temperature. The pH was maintained at 7 by a pH stat using 3 mL of 0.5 N sodium hydroxide in 4 min. The reaction mixture was analyzed by normal-phase HPLC: retention volume (mL) of **8**, 3.9; **8** as disulfide, 3.45; **9**, 7.25 The third peak was identified as [(3,4-dichlorophenyl)thio]acetaldehyde (**9**), and the ratio of **8** to **9** was 1:4.3, 81% yield.

An authentic sample of **9** was prepared as follows. To a solution of potassium *tert*-butoxide (3 mmol) in 20 mL of dry dimethyl sulfoxide was added 179 mg (1 mmol) of **8**. This was followed by the addition of 152 mg (1 mmol) of chloroacetaldehyde diethylacetal, and the solution was stirred for 48 h at room temperature. Water (40 mL) was added, and the reaction mixture was extracted with 3 × 10 mL of methylene chloride. The combined extracts were dried, concentrated, and applied to a silica gel column. Elution with hexane–methylene chloride yielded [(3,4-dichlorophenyl)thio]acetaldehyde diethylacetal (**10**) in 50% yield: ^1H NMR ($CDCl_3$) δ 1.1 (t, J = 6.7, 2 CH_3), 2.96 (d, J = 5.3, CH_2), 3.49 (m, 2 CH_2), 4.5 (t, J = 5.3, CH), 7.37 (m, phenyl 3 H). The diethylacetal was hydrolyzed in 2 N hydrochloric acid at 25 °C for 12 h to the known[16] aldehyde **9**, which was purified by silica gel chromatography as above: ^1H NMR ($CDCl_3$) δ 9.54 (t, J = 3.4, CHO), 7.39 (m, phenyl 3 H), 3.63 (d, J = 3.4, CH_2); ^{13}C NMR ($CDCl_3$) δ 193.8 (CHO), 133–129.6 (phenyl), 43.8 (CH_2).

Chloroform Medium. A solution containing 0.84 mmol each of the thiol **8** and **1** in 2 mL of chloroform was kept under static nitrogen at room temperature. The reaction was monitored by GC on 5% OV-17, T_c 235 °C (programmed at 50 °C for 8 min followed by 5 °C/min increase), and 24 h later the chromatogram showed the following peaks: 3,4-dichlorobenzenethiol, R_T = 16.2 min; the corresponding disulfide, R_T = 33.5 min; and an emerging peak for [(3,4-dichlorophenyl)thio]acetaldehyde (**9**), R_T = 20.2 min, as identified by co-injection with authentic samples; GC-MS (chemical ionization mode) of **9**, m/e 219 ($^{35}Cl_2C_6H_3SCH_2CO^+$), 193 ($^{35}Cl_2C_6H_3SCH_2^+$). The reaction was less than 30% complete, by integration of GC peaks and ^1H NMR [δ 3.48 (s, SH), 2.92 (m, CH_2 of **1**)] after 2 days and was about complete after 7 days.

Reaction of 3,4-Dichlorobenzenethiol with Chloroacetaldehyde (2). Aqueous Medium. The thiol **8**, 0.179 g (1 mmol), was dissolved in 3 mL of acetonitrile. To it was added a solution of 3 mL of acetonitrile and 2 mL of water containing 1 mmol of **2** at room temperature. The initial pH of the mixture was adjusted to 7.0 by adding 0.1 N NaOH, which did not change after 1 h. Analysis of the reaction mixture by ^1H NMR and HPLC (ODS column) showed no sign of **9**, although some disulfide of **8** was detected.

Chloroform Medium. A solution of **2** monomer in ethanol-free, dry chloroform, 1 mmol in 7 mL, was prepared as above. To it was added 0.179 g (1 mmol) of the thiol **8** in 2 mL of chloroform at room temperature under nitrogen. After 15 h and evaporation of the solvent, 0.26 g (100%) of the thiohemiacetal **11** was obtained as a viscous oil: ^1H NMR ($CDCl_3$) δ 7.65 (m, benzene H-2), 7.39 (m, benzene H-5,6), 5.26 (t, J = 5.5, CH), 3.80 (dd, J = 5.5, 2, CH_2), and 2.70 (S, OH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 47.5 (CH_2), 79.1 (CH), 126.4–132.3 (phenyl); IR ($CDCl_3$) 3580 cm^{-1} (OH) and no carbonyl absorption. GC analysis showed reversion to **2** and **8** due to decomposition of **11** at the injection port. Upon heating the chloroform solution at 50 °C, as monitored by ^1H NMR, the starting materials **2** and **8** as well as the aldehyde **9** were produced, the latter increasing with time. An attempt to chromatograph an aliquot of the reaction mixture (before heating) on silica gel with hexane–chloroform resulted in isolation of the thiol **8** only. When 1 equiv of pyridine was added to the chloroform solution containing **11** and this allowed to stand at room temperature overnight, the S-acetaldehyde **9** was formed as evidenced by the above ^1H NMR.

Registry No. 1, 7763-77-1; **2**, 107-20-0; **3a**, 616-91-1; **3b**, 7652-46-2; **4a**, 123751-48-4; **4b**, 123751-54-2; **5a**, 123751-49-5; **5b**, 123751-55-3; **6a**, 123751-50-8; **6b**, 123751-56-4; **7**, 123751-51-9; **8**, 5858-17-3; **8** disulfide, 4235-78-3; **9**, 55251-69-9; **10**, 123751-52-0; **11**, 123751-53-1; $ClCH_2CH(OEt)_2$, 621-62-5.

Template-Controlled Oligomerization Support Studies. Template Synthesis and Functionalization

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The rigid organic template **8** can be rapidly assembled via double Diels–Alder cycloaddition of methyl 9-anthracenecarboxylate (**7**) and *trans-anti-trans*-norbornadiene trimer **5**. Subsequent manipulation leads to differentially functionalized templates capable of mediating the oligoselective polymerization of acrylate monomers. Lactonization studies with template diol **10** provide a useful measure of the "effective molecular size" of the template.

The utilization of rigid organic molecules as templates for imparting selectivity into chemical transformations has led to impressive accomplishments in the areas of regio-, diastereo-, and enantiochemical control of bond forma-

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