Sulfur Compounds, 174[1]

Preparation of Long-Chain Polysulfanes from Dialkoxysulfanes: Synthesis of Bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)tetrasulfane and -undecasulfane

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Received February 4, 1994

Key Words: Tetrasulfane, bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)- / Undecasulfane, bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)- / Polysulfanes, bisorganyl / Sulfanes, dialkoxy- / 1-Thio-β-D-glucopyranose, tetra-*O*-acetyl-

Dialkoxysulfanes $(RO)_2S_n$ ($n \geq 2$) react with thiols R'SH as sulfur transfer reagents to form long-chain diorganylpolysulfanes R'_2S_{n+2} under mild conditions. Condensation of tetra-*O*-acetyl-1-thio-β-D-glucopyranose (^{ac}GlcSH) with diisopropoxydisulfane $(i\text{PrO})_2S_2$ and diisopropoxynonasulfane $(i\text{PrO})_2S_9$ at 40°C yields bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)tetrasulfane (**1**) $(^{ac}\text{Glc})_2S_4$ and bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)undecasulfane (**2**) $(^{ac}\text{Glc})_2S_{11}$, respectively. The analogous reaction using diisopropoxymonosulfane does not yield the corresponding trisulfane.

There are numerous methods to prepare diorganylpolysulfanes R_2S_n ($n \geq 2$)[2] but only the recently developed sulfur transfer reactions provide access to long-chain polysulfanes under mild conditions. Suitable transfer reagents for S_n units are titanocene polychalcogenide complexes like Cp_2TiS_5[3], $Cp_4Ti_2S_4$[4], and $Cp_4Ti_2S_6$[5] (Cp = η^5-C_5H_5) which react with sulfenyl chlorides to give chain-like or cyclic organic polysulfanes, eqs. (1) and (2).

$$2\,\text{RSCl} + Cp_2TiS_5 \rightarrow R_2S_7 + Cp_2TiCl_2 \quad (1)$$

$$R'(SCl)_2 + Cp_2TiS_5 \rightarrow \textit{cyclo}\text{-}R'S_7 + Cp_2TiCl_2 \quad (2)$$

However, if functional groups like OH or CO_2H are parts of the organic substituent R the reaction via an SCl group is difficult or impossible and other sulfur transfer reagents are needed. Thiols react with dialkoxydisulfanes in tetrachloromethane to give tetrasulfanes on heating[6], eq. (3).

$$2\,\text{RHS} + (R'O)_2S_2 \rightarrow R_2S_4 + 2\,R'OH \quad (3)$$

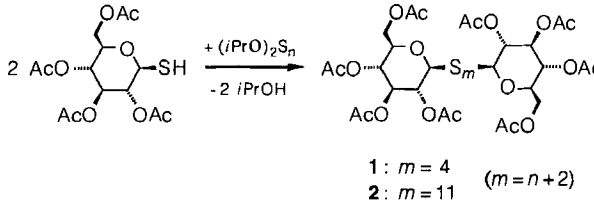
This reaction proceeds under mild conditions, and isolated yields are high. Therefore, we have initiated a program to explore the applicability of this method using a variety of thiols and dialkoxypolysulfanes of different chain length. The aim of the present study has been to synthesize sulfanes with glucosyl substituents which may be water-soluble, amphiphilic, and mesogenic. Tetra-*O*-acetyl-1-thio-β-D-glucose has been chosen as a model thiol to avoid complications arising from the hydroxyl groups of the sugar (note that it is a thio semiacetal). This thiol has been treated with diisopropoxymonosulfane, the -disulfane, and with the corresponding -nonasulfane, the latter being available from the disulfane by chlorination with SCl_2 and subsequent sulfur transfer using Cp_2TiS_5[7], eqs. (4) and (5).

$$(i\text{PrO})_2S_2 + SCl_2 \rightarrow i\text{PrOS}_2\text{Cl} + \tfrac{1}{3}\{i\text{PrCl} + (i\text{PrO})_2\text{SO} + S_2Cl_2\} \quad (4)$$

$$2\,i\text{PrOS}_2\text{Cl} + Cp_2TiS_5 \rightarrow (i\text{PrO})_2S_9 + Cp_2TiCl_2 \quad (5)$$

Results and Discussion

2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucose (^{ac}GlcSH) reacts with diisopropoxydisulfane $(i\text{PrO})_2S_2$ in concentrated dichloromethane solution at 40°C to yield bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)tetrasulfane (**1**) which has been isolated as colorless needles, m.p. 187°C (dec.). The condensation with diisopropoxynonasulfane $(i\text{PrO})_2S_9$ yielded under the same experimental conditions the novel bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)undecasulfane (**2**) as a yellow solid, m.p. 94–96°C (dec.), eq. (6).



(6)

1: $m = 4$
2: $m = 11$ $(m = n + 2)$

The reaction proceeds by nucleophilic displacement of the alkoxy group by the thiol and may be understood as a smooth oxidation of the thiol sulfur by the dialkoxydisulfane[8]. In contrast, the analogous reaction using diisopropoxymonosulfane $(i\text{PrO})_2S$ does not yield the corresponding trisulfane ($m = 3$), since the monosulfanes are readily oxidized[9] and act themselves as reducing agents[10].

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Characterization

400-MHz ^{1}H-NMR spectroscopy reveals the glucopyranose ring in both **1** and **2** to occur as β anomer since all H-H coupling constants within the pyranose ring amount to 10 Hz (Karplus curve). As indicated in Table 1, the signal of the proton at C-1 shows a slight, but characteristic downfield shift which augments with increasing chain length n corresponding to the acidity of the sulfanes H_2S_n[11].

Table 1. Chemical shift of 1-H in bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)sulfanes and 2,3,4,6-tetra-*O*-acetyl-β-D-thioglucose

	^{ac}GlcSH	$^{ac}Glc_2S_2$	$^{ac}Glc_2S_4$	$^{ac}Glc_2S_{11}$
δ	4.55 (dd)	4.63 (d)	4.75 (d)	4.81 (d)

The length of the sulfur chain has been monitored by RP-HPLC analysis. There is a linear relationship between the number of sulfur atoms in the chain (n_S) and the logarithm of the capacity factor (lnk') which is related to the retention time. This has been proven for polysulfanes R_2S_n with various substituents R, e.g. alkyl[3,4], alkoxy[12]. The plot lnk' versus the number of sulfur atoms for the bis(tetraacetylglucosyl)polysulfanes is depicted in Figure 1.

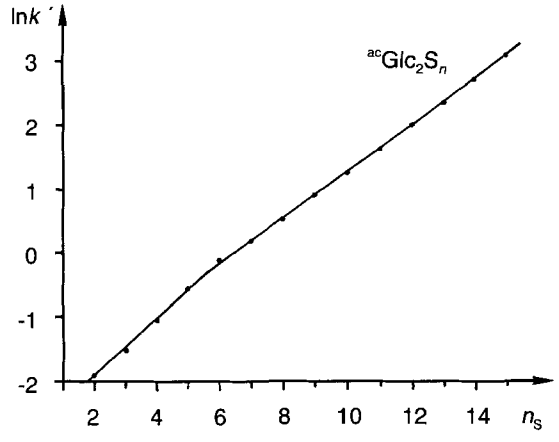

Figure 1. Dependence of lnk' on the number of sulfur atoms n_S in bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)sulfanes; lnk' = 0.46 n_S − 2.85 (r = 0.9993) for 2 ≤ n_S ≤ 6, lnk' = 0.36 n_S − 2.31 (r = 0.9998) for 5 ≤ n_S ≤ 15

Homologues with up to 15 sulfur atoms have been detected in the crude undecasulfane. Their chromatographic data are given in Table 2. The RP-HPLC analysis of the recrystallized product shows only traces of other homologues. The undecasulfane **2** is so far the longest selectively accessible diorganylpolysulfane. In principle, there is no limit to the length of the sulfur chain in compounds of type R−S_n−R. Until now, polysulfanes with up to 18 sulfur atoms have been detected by direct HPLC analysis[12] and chlorosulfanes with up to 30 sulfur atoms by indirect HPLC analysis (after derivatization)[13]. Nevertheless, such polysulfanes become more and more unstable as the chain length increases, and they tend to disproportionate into lower and higher homologues and to split off S_8 or other small sulfur rings.

Table 2. Retention times lnk' values and retention indices RS[14] of bis(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)sulfanes

n_S	t_r [min]	ln k'	RS	n_S	t_r [min]	ln k'	RS
2	1.63	-1.911	-24	9	5.04	0.936	470
3	1.73	-1.522	44	10	6.52	1.279	530
4	1.94	-1.005	133	11	8.66	1.629	591
5	2.24	-0.549	212	12	11.82	1.991	654
6	2.69	-0.112	288	13	16.36	2.353	716
7	3.14	0.192	341	14	22.78	2.711	779
8	3.87	0.545	402	15	32.05	3.071	841

The infrared spectra of **1** and **2** show essentially the absorptions of the organic substituent. Strong absorptions at 1740 cm^{-1} in the ranges 1260−1230 and 1000−1030 cm^{-1} are due to the acetate groups[15]. The Raman spectra exhibit medium to strong lines between 440 and 510 cm^{-1} which are characteristic of the sulfur chain. Signals at 506, 485, and 458 cm^{-1} are detected for the S−S stretching modes of the tetrasulfane **1** which agree with those of the S_4^{2-} anion (483, 469, and 455 cm^{-1})[16]. The Raman spectrum of **2** is dominated by lines originating from the S−S stretching modes, as could be expected for a long-chain polysulfane. A very strong signal at 461 with a shoulder at 470 cm^{-1} is accompanied by two strong lines at 493 and 444 cm^{-1} and a medium one at 515 cm^{-1}. Obviously, incidental degeneracy causes the ten SS bonds to give rise to only five Raman lines.

Since cleavage of the acetate function in the polysulfane has seemed unlikely to occur without destruction of the sulfur chain we have treated thioglucose (without acetyl groups) with diisopropoxydisulfane. A deep-yellow sticky product has been obtained which dissolves completely in water. However, from the solution crystalline S_8 precipitates during the attempts to crystallize the product indicating that the unprotected bis(glucosyl)polysulfanes are unstable under these conditions.

Conclusion

Tetraacetylthioglucose reacts with diisopropoxydi- and -nonasulfane to give the corresponding peracetylated bis(glucosyl)polysulfanes **1** and **2** which are stable at 20°C. This reaction is a model for the built-up of other diorganylsulfanes under mild conditions and especially suitable for functionalized substituents which are sensitive to chemicals used in classical polysulfane syntheses[2]. Since more and more tri- and tetrasulfanes with complex organic substituents are isolated from organisms and turn out to be biologically active (e.g. antitumor activity in very low concentrations)[2], there is clearly a need for new synthetic procedures in this field.

This work was supported by the *Deutsche Forschungsgemeinschaft*, the *Verband der Chemischen Industrie*, and the *Graduiertenkolleg Chemie of the Free University and the Technical University of Berlin*.

Experimental

NMR: Bruker WH 400 spectrometer. – IR: Perkin-Elmer 580 B. – Raman (25°C): Jobin Yvon U 1000 double monochromator, Spectra Physics krypton ion laser model 2020 (647 nm). – MS (70 eV): Varian MAT 311 A double-focussing spectrometer. – HPLC: Gynkotek model 300 C high-precision pump, Negretti and Zamba 190 injector, 10-µl sample loop, Knauer europrep RP-C18 column (20 cm, 10 µm), Waters 440 absorbance detector (254 nm). – Melting points (uncorrected): Büchi 510 capillary melting point apparatus. – Elemental analyses: Hewlett-Packard CHN analyzer 185; sulfur was analyzed after oxidation with bromine/water and titration of the sulfate with barium perchlorate against thorine. – 2,3,4,6-Tetra-*O*-acetyl-β-D-thioglucose was prepared from D-(+)-glucose in a four-step reaction sequence according to the published procedure[17]. Since it was readily oxidized to the disulfane all reactions were carried out with the exclusion of moisture and air. The disulfane $(^{ac}Glc)_2S_2$ was prepared as a reference material by oxidation of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose with hydrogen peroxide[17c]. – Diisopropoxydisulfane was synthesized according to the method of Thompson et al.[18]. To synthesize diisopropoxynonasulfane, diisopropoxydisulfane was chlorinated with dichlorosulfane and the isopropoxychlorodisulfane was allowed to react with titanocene pentasulfide as described in ref.[7].

Bis(2,3,4,6-tetra-O-acetyl-1-deoxy-β-D-glucopyranosyl)tetrasulfane (**1**): To 3.64 g (10 mmol) of 2,3,4,6-tetra-*O*-acetyl-β-D-thioglucose dissolved in 5 ml of dichloromethane was added 0.91 g (5.0 mmol) of diisopropoxydisulfane. The mixture was heated to 40°C for 4 h. The solvent was completely removed under reduced pressure, and the pale yellow residue (4 g) was dissolved in 5 ml of methanol. When the product began to precipitate the mixture was cooled to −5°C for several hours. After filtration and washing with *n*-pentane 1.57 g (40%) of a white powder was obtained. A second recrystallization from dichloromethane yielded 0.45 g (11%) of colorles needles which were washed with diethyl ether; m.p. 187°C (dec.). – ^{1}H NMR ($CDCl_3$): δ = 2.02, 2.04, 2.05, 2.11 (s, 3H, acetyl), 3.80 (ddd, *J* = 2.5, 4.5, 10 Hz, 1H, 5-H), 4.20 (dd, *J* = 2.5, 12 Hz, 1H, 6-H), 4.29 (dd, *J* = 4.5, 12 Hz, 1H, 6'-H), 4.75 (d, *J* = 10 Hz, 1H, 1-H), 5.15 (dd, *J* = 10 Hz, 1H, 4-H), 5.19 (dd, *J* = 10 Hz, 1H, 2-H), 5.27 (dd, *J* = 10 Hz, 1H, 3-H). – MS (70 eV), *m/z* (%): no M^+, 331 (29) $[C_6H_7O(Ac)_4^+]$, 271 (9) $[C_6H_6O(Ac)_3^+]$, 229 (3) $[C_4H_4(OAc)_3^+]$, 211 (5) $[C_6H_5O(Ac)_2^+]$, 169 (100) $[C_4H_3(OAc)_2^+]$, 109 (37) $[C_4H_2OAc^+]$. – IR (KBr): $\tilde{\nu}$ = 1744 cm^{-1} s (C=O), 1375 s (CH_3), 1250 s, 1224 s, 1090 s, 1061 s, 1047 s, 1033 s (acetate). – Raman (solid): $\tilde{\nu}$ = 2938 cm^{-1} s (C−H), 1742 m (C=O), 1360 m (CH_3), 653 m (C−S), 506 m, 485 s, 458 s (S−S), 363 m, 268 m, 223 m, 216 m (SS). – $C_{28}H_{38}O_{18}S_4$ (790.9): calcd. C 42.52, H 4.84, S 16.22; found C 42.13, H 4.89, S 16.78.

Bis(2,3,4,6-tetra-O-acetyl-1-deoxy-β-D-glucopyranosyl)undecasulfane (**2**): To 3.64 g (10 mmol) of 2,3,4,6-tetra-*O*-acetyl-β-D-thioglucose dissolved in 5 ml of dichloromethane was added 2.03 g (5.0 mmol) of diisopropoxynonasulfane. After heating to 40°C for 2 h, the mixture was allowed to react at room temp. for further 12 h. The product began to precipitate, and the solvent was completely removed under reduced pressure to yield 5.0 g of a yellow solid (100%). 570 mg of the crude undecasulfane was dissolved in 40 ml dichloromethane/diethyl ether (1:1). The solution was filtered and the filtrate concentrated until the product began to precipitate (ca. 10 ml). After addition of further 10 ml of diethyl ether, the mixture was cooled to −20°C for 2 d. The pale yellow product (300 mg; 53%) was filtered off and washed with small portions of diethyl ether; m.p. 94−96°C (cloudiness). – ^{1}H NMR ($CDCl_3$): δ = 2.02, 2.04, 2.06, 2.11 (each s, 3H, acetyl), 3.82 (ddd, *J* = 2, 4.5, 10 Hz, 1H, 5-H), 4.18 (dd, *J* = 2, 12 Hz, 1H, 6-H), 4.30 (dd, *J* = 4.5, 12 Hz, 1H, 6'-H), 4.81 (d, *J* = 10 Hz, 1H, 1-H), 5.15 (dd, *J* = 10 Hz, 1H, 4-H), 5.21 (dd, *J* = 10 Hz, 1H, 2-H), 5.28 (dd, *J* = 10 Hz, 1H, 3-H). – IR (KBr): $\tilde{\nu}$ = 1757 cm^{-1} s, 1749 s (C=O), 1378 s, 1369 s (CH_3), 1253 s, 1224 s, 1094 m, 1058 s, 1041 s (acetate). – Raman (solid): $\tilde{\nu}$ = 2940 cm^{-1} s (C−H), 1740 m (C=O), 653 w (C−S), 493 s, 486 sh, 470 sh, 461 vs, 444 sh, 429 m (S−S), 272 m, 150 m, 117 m (SS). – $C_{28}H_{38}O_{18}S_{11}$ (1015.3): calcd. C 33.12, H 3.89, S 34.74; found C 32.61, H 3.68, S 35.52.

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