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Note

Synthesis of *p*-toluenesulfinic esters of cellulose and β-cyclodextrin

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Derivatisation of cellulose as organic esters has been used to study the influence of cellulose morphology on the reactivity of hydroxyl groups [1]; to improve cotton fibre properties [2] or for the preparation of membrane materials or adsorbents [3]. The chiral properties of carbohydrates as well as their ready availability favoured such compounds to be used among the first adsorbents for optical resolution by liquid chromatography [4]. Nowadays, esters of cellulose such as triacetate, tri-*p*-methylbenzoate, tricinnamate, are commercially available chiral stationary phases with excellent performances [5].

We now report on the synthesis of esters of cellulose and cyclomaltoheptaose (β-cyclodextrin) which contain the very polar sulfinate functional group. In comparison to analogous benzoic esters, the sulfinates command interest because of the presence of an additional chirality source on the tetrahedral sulfur atom, as well as of a particular dipole, S–O (Scheme 1). Optically active sulfinic esters of simple alcohols are useful in the synthesis of chiral sulfoxides. The Grignard reaction on diastereomerically pure sulfinate esters of menthol [S-(−)menthyl and R-(+)menthyl *p*-toluenesulfinate are commercially available] is a very convenient technique for the preparation of enantiomerically pure sulfoxides [6].

Esterification of an alcohol with a sulfinyl chloride is the most commonly used method for the preparation of both aliphatic and aromatic sulfinic esters, mainly because of the availability of starting materials [7]. The methodology is now extended to cellulose and β-cyclodextrin using *p*-toluenesulfinyl chloride.

p-Toluenesulfinyl chloride was obtained as previously reported [8] and its purity was checked by ^{1}H NMR. Special care must be taken during its preparation (see Experimen-

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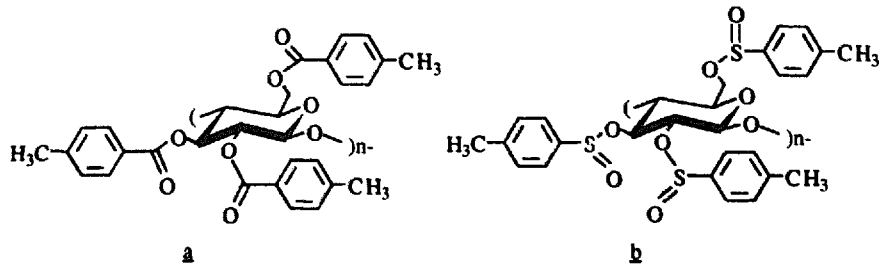


a b

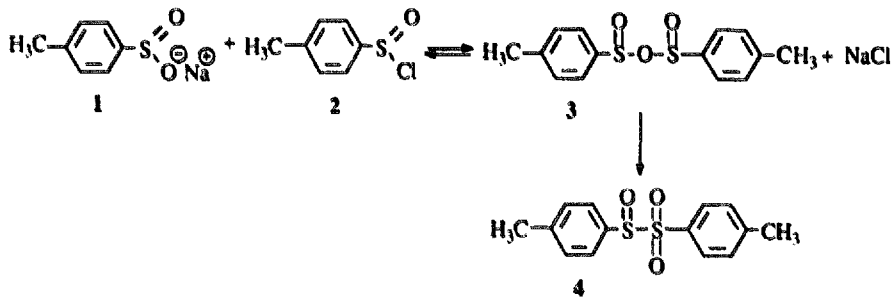
Scheme 1. Comparative structure of cellulose tris(*p*-methylbenzoate) (a) and cellulose tris(*p*-toluenesulfinate) (b).

tal section) since formation of by-products such as sulfinic anhydride (**3**) or sulfinyl sulfone (**4**) was observed under certain conditions, which may result from a reaction between sodium sulfinate (**1**) and sulfinyl chloride (**2**, Scheme 2).

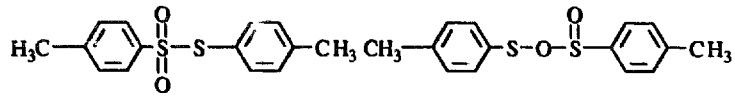
The reaction between *p*-toluenesulfinyl chloride and either cellulose or β-cyclodextrin was performed in pyridine at ambient temperature. Unexpectedly, the isolation and purification of products proved to be very critical with regard to the stability of the final esters. The oligomeric or polymeric structure of the final product presumably facilitated the trapping of impurities which were not easily removed. Isolation by precipitation of the reaction mixture in methanol and further purification by dissolution in dichloromethane and reprecipitation in methanol [1] led to products which decomposed, more or less rapidly, to the parent carbohydrate and a by-product whose IR, ^{1}H, ^{13}C NMR and mass spectra, and elemental analysis were consistent either with structure **5** or **6** (Scheme 3). Final identification of this by-product as **5** resulted from a comparison with an authentic sample [10].

Hypotheses of decomposition leading to **5** are depicted in Scheme 4 taking cellulose as an example. The first hypothesis (a) involves the attack of sulfinyl chloride on the sulfinic ester, with cellulose behaving as a leaving group like chloride in the decomposition of methanesulfinyl chloride [11]. Transformation of a disulfoxide **7** to a thiolsulfonate **5** is reported for dimethyl disulfoxide as intermediate in the methanesulfinyl chloride–*N*,*N*-dimethylformamide reaction [9]. The second hypothesis (b) would involve hydrolysis of a sulfinic ester and further disproportionation of the resulting sulfinic acid **8** to give **5**, as reported in ref. [12].

These considerations suggest a determinant role of the catalysis by an acid or base



Scheme 2.



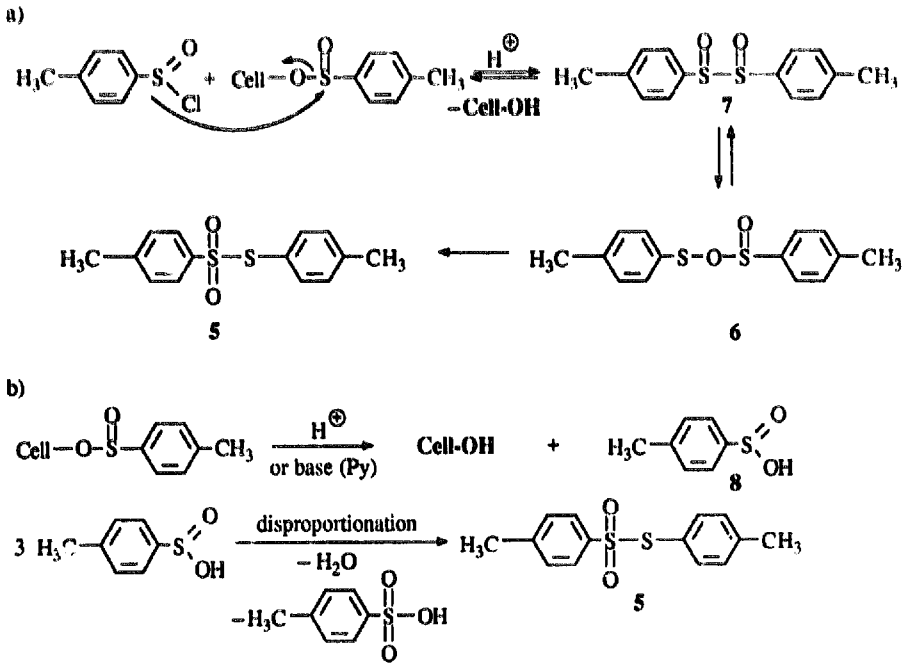
5 6

Scheme 3. Structures of possible decomposition products of cellulose and β-cyclodextrin *p*-toluenesulfinate.

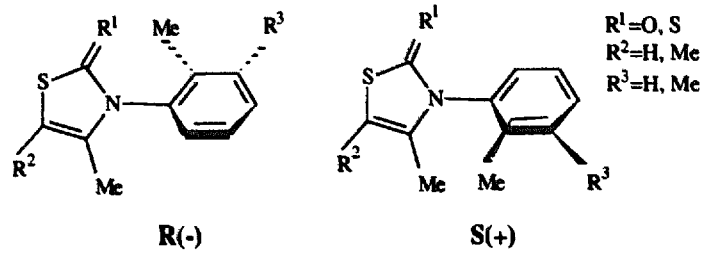
which led us to modify the experimental protocol by pouring the reaction mixture into water and washing the organic phase, in order to eliminate any trace of the reagent or by-product.

The method resulted in stable tris(*p*-toluenesulfinates) of cellulose or β-cyclodextrin which were fully characterised. The ^{1}H NMR spectrum of cellulose tris(*p*-toluenesulfinate) was compared with that of cellulose tris(*p*-methylbenzoate) prepared earlier in our laboratory [13]. The latter gives sharp signals, clearly differentiated for the three types of substitution of the hydroxyl group, whereas the sulfinate gives very broad signals, undifferentiated for the substitution. The presence in sulfinates of strong intermolecular or intramolecular associations and/or of different configurations on chiral sulfur centres might account for the observed spectrum.

Both cellulose and β-cyclodextrin tris(*p*-toluenesulfinates) were used as chiral selectors in liquid chromatography, after coating on silica [14]. The coating technique involves dissolution of the ester in a solvent, suspending silica in it and allowing the solvent to slowly evaporate. An ^{1}H NMR study of the stability of cellulose tris(*p*-toluenesulfinate) in different coating solvents was performed. Two solvents promoted decomposition of the ester: trifluoroacetic acid alone or mixed in dichloromethane and



Scheme 4.



Scheme 5. Structure of *N*-arylthiazolinone and *N*-arylthiazolinethione atropisomers (**1–8**) used in chromatographic studies.

pyridine. Stable products were obtained in dichloromethane, tetrahydrofuran and 5:1 tetrahydrofuran–*N*,*N*-dimethylformamide. Two commercially available silica (aminopropyl or end-capped with diphenyl groups) were tested and diphenyl end-capped silica kept the product stable, at least after six months of use in chromatographic tests.

The separation properties of tris(*p*-toluenesulfinates) of cellulose and β-cyclodextrin are applicable to positional isomers but not to enantiomers [14]. For instance, in a series of *N*-arylthiazolin(ethi)one atropisomers (Scheme 5), the results obtained on two HPLC columns of cellulose tris(*p*-toluenesulfinate) (SC) and β-cyclodextrin tris(*p*-toluenesulfinate) (SD) are reported in Table 1. In this table, the lipophilicity parameter of the analytes, log *k*'w, was determined by reverse phase chromatography as reported in ref. [13b].

Plots of capacity factors for **1–5** (Fig. 1) on SC (a) and SD (b) columns versus the lipophilicity parameter points out that retention on both stationary phases is linearly correlated with lipophilicity, provided the data are treated separately for thiazolinones (R^1 = O, Scheme 5) and for thiazolinethiones (R^1 = S, Scheme 5). Thiazolinethiones are

Table 1
Capacity factors for *N*-arylthiazolinone and *N*-arylthiazolinethione atropisomers (**1–8**) obtained on cellulose tris(*p*-toluenesulfinate) (SC) and β-cyclodextrin tris(*p*-toluenesulfinate) (SD)

Compound	Substitution factor			Lipophilicity parameter	Capacity factor *k*' [a]	
	R^1	R^2	R^3	log *k*'w	SC [b]	SD [c]
1	O	H	H	2.62	2.88	3.09
2	S	H	H	2.69	7.98	4.14
3	O	Me	H	3.18	1.96	1.78
4	S	Me	H	3.18	5.07	1.92
5	O	H	Me	3.12	2.43	2.23
6	S	H	Me	3.12	5.92	2.44
7	O	Me	Me	3.65	1.56	0.94
8	S	Me	Me	3.59	3.44	1.11

[a] *k*' is defined as the ratio $(t_R - t_0)/t_0$, where t_R is the retention time of the analyte and t_0 is the breakthrough time of the column determined by injection of a non-retained compound such as 1,3,5 tris(*tert*-butyl)benzene.
[b] Eluent 97.5:2.5 hexane–2-propanol, 1 mL/min.
[c] Eluent hexane, 1 mL/min.

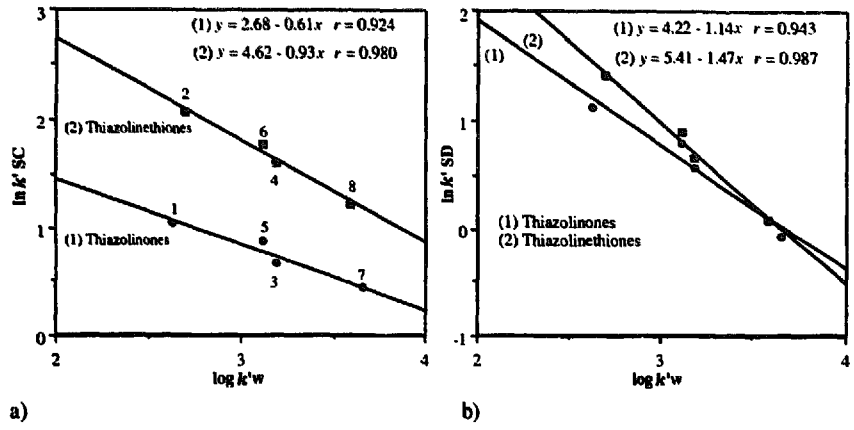


Fig. 1. Plots of capacity factors of compounds **1**–**8**, ln k', on cellulose tris(*p*-toluenesulfinate) (SC) (a) and β-cyclodextrin tris(*p*-toluenesulfinate) (SD) (b) versus the lipophilicity parameter, log k' w.

more retained than the thiazolinones on cellulose tris(*p*-toluenesulfinate), as observed on cellulose tris(*p*-methylbenzoate) [13], whereas β-cyclodextrin tris(*p*-toluenesulfinate) do not systematically retain sulfur compounds more than oxygen compounds.

1. Experimental

Materials and methods.—Sodium *p*-toluenesulfinate and thionyl chloride were obtained from Fluka. Sodium sulfinate was dried under vacuum for 12 h at 120 °C. Pyridine was distilled over KOH and stored 2 days over KOH before use. Anhydrous ethyl ether was kept over molecular sieves. Cellulose microcrystalline Avicel (E. Merck 2331) and β-cyclodextrin (Société Roquette, Lestrem, France) were dried under vacuum for 12 h at 120 °C. IR spectra were recorded with a Perkin–Elmer FT-IR 1720X instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument. Elemental analyses were performed by the Service de Microanalyse de l'Université d'Aix-Marseille III.

The degree of substitution of *p*-toluenesulfinic esters of cellulose and β-cyclodextrin was calculated from the percentage of carbon in elemental analysis taking into account the formula

$$DS = \frac{72 \times 100 - 162 \times \%C}{138 \times \%C - 84 \times 100},$$

deduced from a unit of substituted glucose: for glucose $[C_6H_{10}O_5]_n$ and for sulfinate $[C_{6+7DS}H_{10+6DS}O_{5+DS}S_{DS}]_n$.

HPLC experiments were performed at a controlled temperature of 25 °C with a Merck–Hitachi LiChrograph model L-6000 HPLC pump, a Merck–Hitachi LiChrograph L-4000 UV detector (detection at $\lambda = 254$ nm) and a Merck D-2500 recorder.

p-*Toluenesulfinyl chloride.*—To a stirred suspension of dried sodium *p*-toluenesulfinate (46.46 g, 0.261 mol) in dry ethyl ether (240 mL) was added dropwise freshly distilled thionyl chloride (19.2 mL, 0.263 mol), under nitrogen and at −3 to 0 °C, over

1.5 h. The suspension was stirred 2 h at ambient temperature. The mixture was filtered and the filtrate was evaporated under vacuum, at 35 °C, affording 31 g of residue (70%) with 95% purity [^{1}H NMR, 200 MHz, $CDCl_3$: δ 2.42 (s, 3 H), 7.35 (d, J 8 Hz, A of AB); 7.73 (d, J 8 Hz, B of AB)]. During the filtration step, formation of a white solid, which disappeared on heating at 35 °C after evaporation of the ether, was observed. This solid did not react with cellulose but reacted with ethanol to give ethyl *p*-toluenesulfinate [^{1}H NMR, 200 MHz, $CDCl_3$: δ 1.25 (*t*, 3 H), 2.40 (*s*, 3 H), 3.6–4.2, (*m*, 2 H, CH_2 non-equivalent because of the chiral sulfur); 7.26 (d, J 8 Hz, part A of AB), 7.58 (d, J 8 Hz, part B of AB), 4 H-phenyl]. The ^{1}H NMR spectrum of the white solid indicated the presence of two products, in almost equal proportions, which might correspond to **3** and **4** (Scheme 2). In the case of an attempted reaction with a less reactive alcohol, such as cellulose, the sulfinic anhydride **3** rearranged to the thermodynamically more stable sulfinyl sulfone **4** [9].

Cellulose p-*toluenesulfinate*.—Dried cellulose (1.90 g, 0.012 mol) was suspended in dried pyridine (80 mL) and heated at 80 °C for 2 h, under nitrogen, to allow swelling of the cellulose. Previously prepared *p*-toluenesulfinyl chloride (31 g, 0.185 mol) was added dropwise at ambient temperature, under nitrogen, and the mixture stirred for 14 h. The reaction mixture was then poured into 400 mL of distilled water and stirred for 30 min. Dichloromethane (250 mL) was added in order to dissolve the precipitate formed and the organic phase was washed successively with 2 × 200 mL of $NaHCO_3$ 10%, HCl 0.5% (100 mL), satd NaCl solution (200 mL) and water (200 mL), and dried over $MgSO_4$. This treatment slowed down considerably the decomposition of the title compound to **5**. After complete evaporation of CH_2Cl_2, the yellow oil was dissolved in CH_2Cl_2 (30 mL), divided into two fractions and each fraction slowly poured in MeOH (250 mL), under stirring. After filtration and drying for 1 h in an oven under vacuum at 40 °C, 2 h in a vacuum line at 1 mbar and 50 °C, the title compound (2.5 g, 36%) was obtained as a white amorphous powder. IR(ν^{KBr}): 3300–3500 cm^{-1} (OH unsubstituted), 3055 cm^{-1} (C–H stretch aromatic), 2925 cm^{-1} (CH_3 bonded to aromatic), 1590 cm^{-1} (C–C stretch aromatic), 1136 cm^{-1} (O–S=O), 810 cm^{-1}, 750 cm^{-1} (C–H aromatic). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, large, 9 H, CH_3-phenyl); 4.00 (s, very large, 7 H, H-Glc); 7.20, 7.50 (2 s large, 12 H, H-phenyl). ^{13}C NMR ($CDCl_3$): δ 21.62 (CH_3-phenyl); 72.50 (weak and large massif, CH-Glc); 125.57 (massif, C-4 of phenyl); 129.86 (massif, CH of phenyl), 143.30 (massif, C-1 phenyl–O–S=O). Anal. Calcd for DS 3 $(C_{27}H_{28}O_8S_3)_n$: C, 56.25; H, 4.90; S, 16.5. Found: C, 55.42; H, 4.85; S, 15.5 corresponding to a DS of 2.3.

β-Cyclodextrin p-*toluenesulfinate*.—Dried β cyclodextrin (1.20 g, 0.007 mol) was dissolved in anhydrous pyridine (40 mL). Previously prepared *p*-toluenesulfinyl chloride (19 g, 0.12 mol) was added as for cellulose. Further treatment was the same as for cellulose but the quantities of solvents were changed, i.e. respectively: water (200 mL), CH_2Cl_2 (150 mL), $NaHCO_3$ 10% (2 × 100 mL), HCl 0.5% (100 mL), satd NaCl solution (200 mL), water (100 mL), CH_2Cl_2 (10 mL), MeOH (2 × 50 mL). This treatment slowed down considerably the decomposition of the title compound to **5**. The title compound was obtained as a white amorphous powder (0.857 g, 20%). IR(ν^{KBr}): 3300–3500 cm^{-1} (OH unsubstituted), 3030 cm^{-1} (C–H stretch aromatic), 2925 cm^{-1} (CH_3 bonded to aromatic), 1130 cm^{-1} (O–S=O), 800 cm^{-1}, 650 cm^{-1} (C–H

aromatic). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, large, 9 H, CH_3-phenyl); 3.00–5.50 (s, very large, 7 H, H Glc); 6.50–8.00 (2 s, large, 12 H, H-phenyl). Anal. Calcd for DS 3 $(C_{27}H_{28}O_8S_3)_n$: C, 56.25; H, 4.90; S, 16.5. Found: C, 56.22; H, 4.86; S, 16.0 corresponding to a DS of 2.97.

Identification of the decomposition product **5**.—IR(ν^{KBr}): 2925 cm^{-1} (CH_3 bonded to aromatic), 1591 cm^{-1} (C–C aromatic), 1323 cm^{-1} (O=S=O), 1138 cm^{-1} (O–S=O), 807 cm^{-1}, 654 cm^{-1} (C–H aromatic). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39, 2.43 (2 s, 3 H); 7.13–7.49 (m, 4 H, two AB superposed spectra). ^{13}C NMR ($CDCl_3$): δ 22.04, 22.24 (CH_3-phenyl); 125.16 (C–S); 128.17, 129.93, 130.77, 137.06 (CH-phenyl); 141.04 (C–S=O); 145.16 (C-phenyl). EI-MS (70 eV): 278 (26.62), 155 (27.96, $[CH_3-C_6H_4-S(O)_2]^+$), 139 (100, $[CH_3-C_6H_4-S(O)]^+$), 123 (40.04, $[CH_3-C_6H_4-S]^+$), 91 (51.19, tropylium from $C_6H_4-CH_3$). Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.43; H, 5.03; S, 23.02. Found: C, 60.40; H, 5.39; S, 21.07.

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