Supporting information

Depolymerization of P4HB and PBS Waste and Synthesis of the Anticancer Drug Busulfan from Plastic Waste

Daniel L. Lourenço and Ana C. Fernandes *

Centro de Química Estrutural, Institute of Molecular Sciences, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal; daniellourenco98@hotmail.com

* Correspondence: anacristinafernandes@tecnico.ulisboa.pt; Tel.: +351-218419220

1. General information

Sodium molybdate, $PhSiH_3$, TMDS, PMHS, $(OEt_3)_2MeSiH$, HBpin, MsCl were obtained from commercial suppliers and were used without further purification. P4HB surgical suture (model monomax) was generously donated by B. Braun Medical Portugal. The ether solution of $MoO_2Cl_2(H_2O)_2$ was prepared according to the method reported by Arnáiz and coworkers.[1] ^1H NMR spectra were measured on a Bruker Avance II+ 400 MHz and 300 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from an internal standard.

A busulfan sample (1×10^{-4} M) prepared in methanol was analysed on an UHPLC Elute interfaced with a QqTOF Impact II mass spectrometer equipped with an ESI source (Bruker Daltonics, Bremen). Chromatographic separation was carried out on a Kinetex C18 column (150 mm x 2.1 mm, 2.6 μm particle size; Phenomenex), at a column temperature of 45ºC. An isocratic mobile phase of 10 mM ammonium acetate/acetonitrile (20:80, v/v) containing 0.1% of formic acid was used at a flow rate of 600 μL min^{-1}. High resolution mass spectrum was acquired in the ESI positive mode; the internal calibration of the mass analyser was performed with a solution of sodium formate 10 mM introduced to the ion source *via* a 20 μL loop, at the beginning of each analysis using a six-port valve. Acquisition was performed in the full scan mode in the *m/z* 100-1000 range. Data acquisition and processing were performed using the Data Analysis 5.1 software. (Bruker Daltoniks).

2. Reductive depolymerization of P4HB plastic waste

2.1. Reductive depolymerization of P4HB with the system $MoO_2Cl_2(H_2O)_2$/TMDS

A mixture of P4HB (0,043 g, 0.5 mmol), obtained from a surgical suture cut in small pieces, ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (0,265 mL, 1.5 mmol) in toluene (2 mL) was heated at reflux for 24 h. After cooling the reaction mixture at room temperature, a solution of HCl 1M (1 mL) was added and the mixture was stirred overnight at room temperature. The reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separated. The aqueous layer was re-extracted with dichloromethane (2 x 20 mL) and the combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo, giving 1,4-butanediol. The product was purified by column chromatography.

^1H NMR (300 MHz, $CDCl_3$): 3.86 (t, J = 5.46 Hz, 5.59 Hz, $2CH_2$), 2.07 (brs, 2H, 2OH), 1.68 (t, J = 5.67 Hz, 5.64 Hz, 4H, $2CH_2$) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): 62.6, 29.8 ppm.

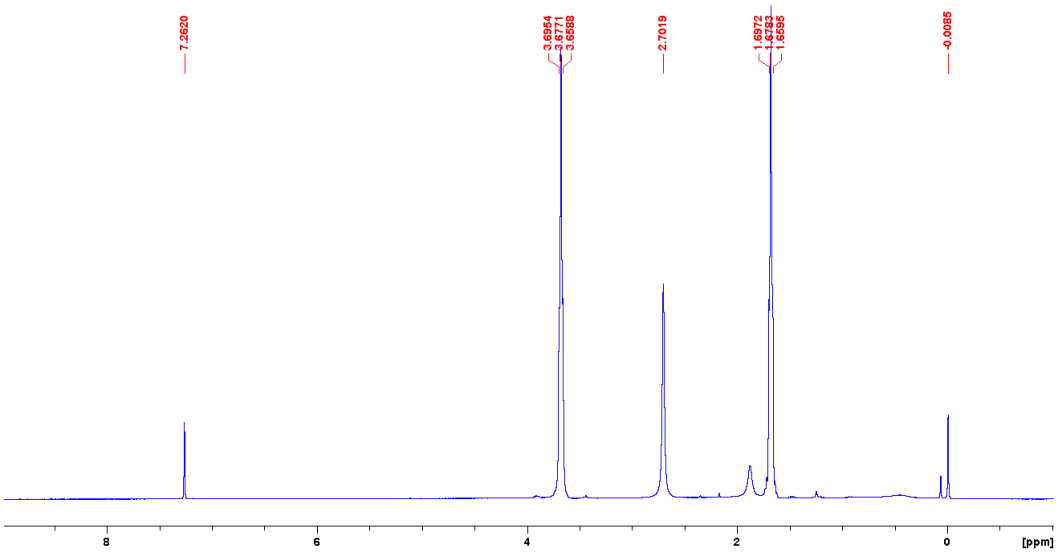


Figure S1. – ^1H NMR spectrum of 1,4-butanediol in $CDCl_3$.

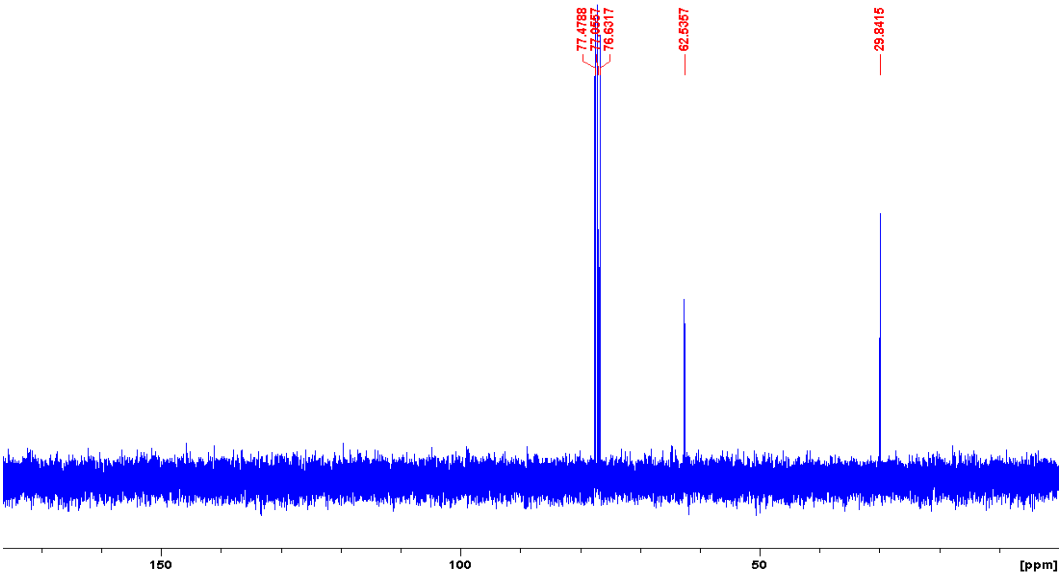


Figure S2. – ^{13}C NMR spectrum of 1,4-butanediol in $CDCl_3$.

2.2. Use of catalyst $MoO_2Cl_2(H_2O)_2$ in several cycles

To a solution of a surgical suture of P4HB (0.043 g, 0.5 mmol), cut into small pieces, in toluene (3 mL) was added the ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (0.265 mL, 1.5 mmol). The reaction mixture was stirred at reflux temperature for 24 h. After cooling, the yield of 1,4-butanediol was determined by ^1H NMR spectroscopy using mesitylene (0.070 mL, 0.5 mmol) as an internal standard. Without separating the catalyst, in the following catalytic cycles, P4HB (0.043 g, 0.5 mmol), TMDS (0.265 mL, 1.5 mmol) and mesitylene (0.070 mL, 0.5 mmol) were added and the reaction mixture was stirred at reflux temperature for another 24 h. The reaction mixture was cooled and the yields were determined by ^1H NMR spectroscopy.

2.3. Reductive depolymerization of P4HB with the $PhSiH_3$/HBpin system

To a solution of P4HB, obtained from a commercial surgical suture (0.043 g, 0.5 mmol) cut into small pieces, in toluene (3 mL) were added ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and HBpin (0,218 mL, 1.5 mmol) and the mixture reaction was stirred at reflux temperature for 24 h. The yield of pinBO$(CH_2)_4$OBpin (71%) was determined by ^1H NMR spectroscopy using mesitylene as an internal.

^1H NMR (300 MHz, $CDCl_3$): δ 3.83 (m, 4H, $2CH_2$), 1.61 (m, 4H, $2CH_2$), 1.11 (s, 24H, CH_3) ppm.

2.4. Reductive depolymerization of P4HB with the $PhSiH_3$/KOH system

To a solution of P4HB, obtained from a surgical suture (0.043 g, 0.5 mmol) cut into small pieces, in toluene (3 mL) were added KOH (11 mg, 0.2 mmol) and $PhSiH_3$ (0.185 mL, 1.5 mmol) and the mixture reaction was stirred at reflux temperature for 24 h. The yield of 1,4-butanediol (95%) was determined by ^1H NMR spectroscopy using mesitylene as an internal standard

3. Reductive depolymerization of PBS plastic waste

3.1. Reductive depolymerization of PBS with the catalytic system $MoO_2Cl_2(H_2O)_2$/TMDS

A mixture containing PBS (0.043 g, 0.25 mmol), obtained from a Delta Q eQo coffee capsule cut into small pieces, ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (0.265 mL, 1.5 mmol) in toluene (3 mL) was heated to reflux for 24 h. After cooling, a solution of HCl 1M (1 mL) was added and the reaction mixture was stirred overnight at room temperature. Then, the reaction mixture was partitioned between dichloromethane (20

mL) and H_2O (15 mL) and separated. The aqueous phase was extracted with dichloromethane (2 x 20 mL) and then the organic phase was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo to give 1,4-butanediol. The product was purified by column chromatography.

3.2. Reductive depolymerization of PBS with the $PhSiH_3$/HBpin system

To the PBS solution (0.043 g, 0.25 mmol), obtained from a Delta Q eQo coffee capsule, in toluene (3 mL) was added ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and HBpin (0.218 mL, 1.5 mmol) and the mixture was stirred at reflux temperature for 24 h. The yield of $pinBO(CH_2)_4OBpin$ (73%) was determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

3.3. Reductive depolymerization of PBS with the $PhSiH_3$/KOH system

To the PBS solution (0.043 g, 0.25 mmol), obtained from a Delta Q eQo coffee capsule, in toluene (3 mL) was added KOH (11 mg, 0.2 mmol) and $PhSiH_3$ (0.185 mL, 1.5 mmol) and the mixture was stirred at reflux temperature for 48 h. The yield of 1,4-butanediol (61%) was determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

4. Synthesis of busulfan from P4HB plastic waste

A mixture containing a P4HB surgical suture (0.172 g, 2 mmol), cut into small pieces, ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (1.06 mL, 6.0 mmol) in toluene (6 mL) was heated at reflux temperature for 24 h. After cooling, a solution of HCl 1M (3 mL) was added and the reaction mixture was stirred for 16 h at room temperature. Then, the reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separate. The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the organic phase was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo, giving 1,4-butanediol, which was used in the synthesis of busulfan. After dissolving 1,4-butanediol in dry dichloromethane (5 mL), Et_3N (0.31 mL, 2.2 mmol) was added and the reaction mixture was stirred at room temperature for 10 minutes under nitrogen atmosphere. Then, MsCl (0.17 mL, 2.2 mmol) was added and the mixture was stirred at room temperature overnight under nitrogen atmosphere. After evaporation, the residue was dissolved in dichloromethane (20 mL) and extracted with H_2O (15 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). Finally, the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuum. The product was purified by column chromatography.

^1H NMR (300 MHz, $CDCl_3$): 4.32-4.25 (m, 4H, $2CH_2$), 3.03 (s, 6H, 2OMs), 1.97-1.86 (m, 4H, 2 CH_2) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): 68.8, 37.5, 25.5 ppm.

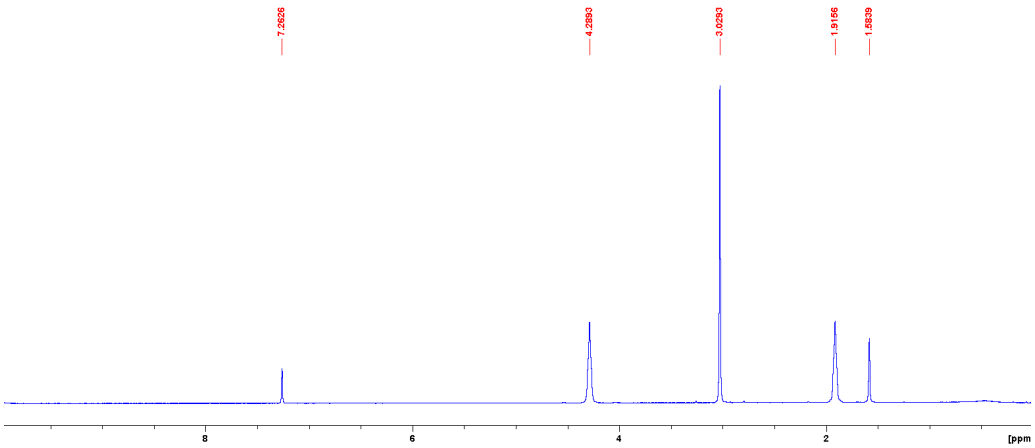


Figure S3. – ^1H NMR spectrum of busulfan in $CDCl_3$.

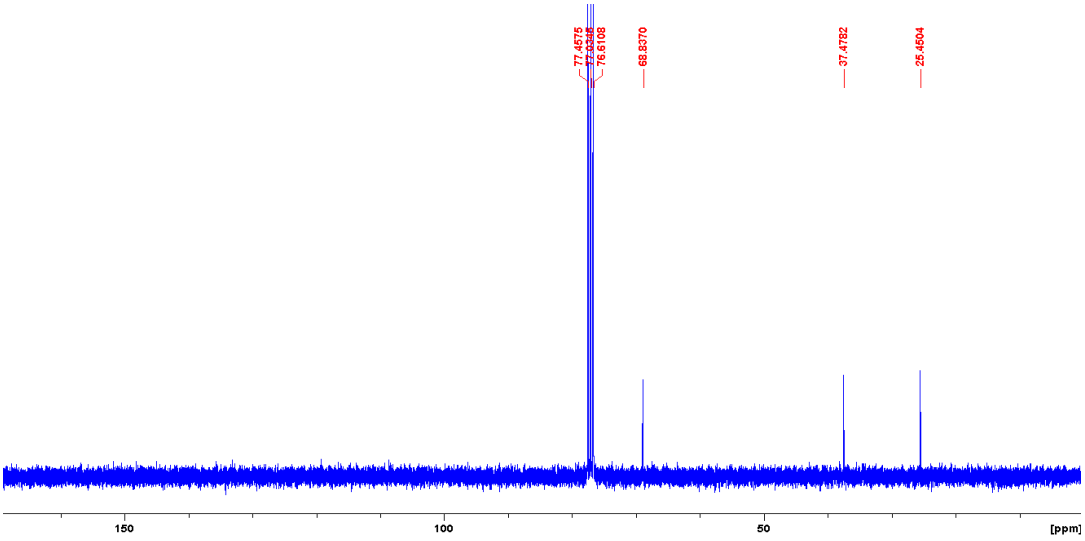
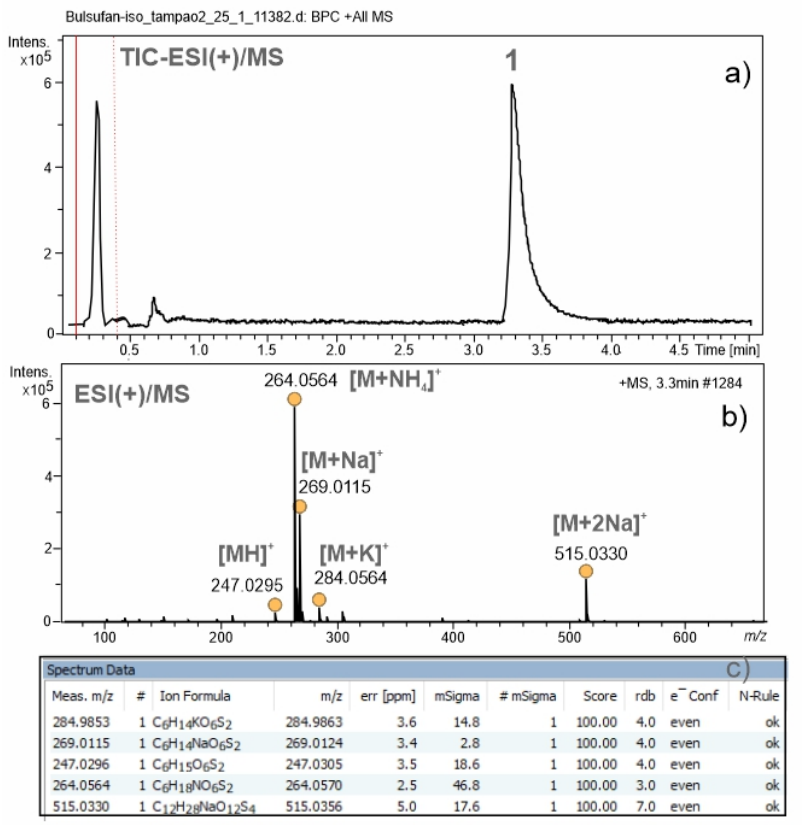


Figure S4. – ^{13}C NMR spectrum of busulfan in $CDCl_3$.

5. Synthesis of busulfan from PBS plastic waste

A mixture containing PBS (0.344 g, 2 mmol), obtained from a Delta Q eQo coffee capsule, ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol%) and TMDS (2.12 mL, 12 mmol) in toluene (10 mL) was heated at reflux temperature for 48 h. After cooling, a solution of 1M HCl (3 mL) and the reaction mixture was stirred for 16 h at room temperature. Then, the reaction mixture was partitioned between dichloromethane (20 mL) and H_2O (15 mL) and separate. The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the organic phase was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuo, yielding 1,4-butanediol, which was used in the synthesis of busulfan, without further purification. After dissolving 1,4-butanediol in dry dichloromethane (5 mL), Et_3N (0.61 mL, 4.4 mmol) was added and the mixture was stirred at room temperature for 10 minutes under nitrogen atmosphere. Then, MsCl (0.34 mL, 4.4 mmol) was added and the mixture was stirred at room temperature overnight under nitrogen atmosphere. After evaporation, the residue was dissolved in dichloromethane (20 mL) and extracted with H_2O (15 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). Finally, the organic phase was dried with anhydrous $MgSO_4$, filtered and evaporated in vacuum. The product was purified by column chromatography.



Spectrum Data

Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
284.9853	1	$C_6H_{14}KO_6S_2$	284.9863	3.6	14.8	1	100.00	4.0	even	ok
269.0115	1	$C_6H_{14}NaO_6S_2$	269.0124	3.4	2.8	1	100.00	4.0	even	ok
247.0296	1	$C_6H_{15}O_6S_2$	247.0305	3.5	18.6	1	100.00	4.0	even	ok
264.0564	1	$C_6H_{18}NO_6S_2$	264.0570	2.5	46.8	1	100.00	3.0	even	ok
515.0330	1	$C_{12}H_{28}NaO_{12}S_4$	515.0356	5.0	17.6	1	100.00	7.0	even	ok

Figure S5. - HPLC-HRMS analysis of a sample of Busulfan in methanol: a) total ion chromatogram obtained in the ESI positive mode; b) mass spectrum obtained at the top of peak **1** (t_R 3.3 mim) showing a peak with *m/z* 247.0296 assigned to the protonated molecule of busulfan, and respective gas phase adduct ions; c) table displaying the accurate mass measurements, proposed ionic formulas, and exact mass for each ion together with the mass deviation (err, ppm), and several calculated parameters that´s support the identification and of the busulfan molecule.

Reference

1. Arnáiz, F.J.; Aguado, R.; Pedrosa, M.R.; De Cian, A. Addition compounds of dichlorodioxomolybdenum(VI) with sulfoxides. Molecular structure of $[MoO_2Cl_2(Me_2SO)_2]$. *Inorg. Chim. Acta* **2003**, 347, 33.