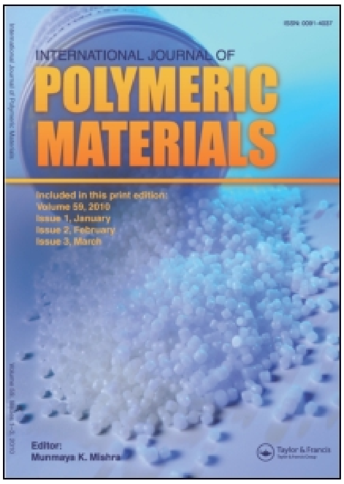

International Journal of Polymeric Materials
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

Synthesis of pva and dextran derivatives 2,4-d adducts. Influence of the presence of a spacer group on the bioactive controlled release behavior

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To cite this Article Bermello, J. Coro , Nápoles, M. N. Lores and Allonso, F. Arranz(2002) 'Synthesis of pva and dextran derivatives 2,4-d adducts. Influence of the presence of a spacer group on the bioactive controlled release behavior', International Journal of Polymeric Materials, 51: 8, 675 — 683

To link to this Article: DOI: 10.1080/714975828

URL: http://dx.doi.org/10.1080/714975828

International Journal of Polymeric Materials, 51:675–683, 2002

0091-4037/02 $12.00 + .00
DOI: 10.1080/00914030290046228

SYNTHESIS OF PVA AND DEXTRAN DERIVATIVES 2,4-D ADDUCTS. INFLUENCE OF THE PRESENCE OF A SPACER GROUP ON THE BIOACTIVE CONTROLLED RELEASE BEHAVIOR

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Polymeric systems for controlled release of 2,4-D acid were prepared using a biodegradable substance. Chloroacetylated dextran can be derivatized with 2,4-dichlorophenoxyacetic acid (2,4-D) by direct reaction with the potassium salt of 2,4-D. The release of 2,4-D linked to both supports is dependent on the temperature, pH value as well as on the hydrophilic/hydrophobic balance of the polymer. The presence of a spacer group in the molecule is also important and it is closely related to the hydrophobity of the system.

Keywords: 2,4-D acid, poly(vinyl alcohol), dextran, controlled release pesticides

INTRODUCTION

Controlled release polymeric systems in which bioactive agrochemical agents are bound to a polymeric backbone *via* covalent bonds of limited stability have emerged recently to overcome the serious environmental problems, which accompany the use of these agents by conventional methods [1–3]. PVA have been used in several cases as macromolecular bioactive agent carrier, mainly for pharmaceutical purposes [4–9].

Dextran is one of the most useful polysaccharides as supports for bioactive controlled release systems [10–13]. In some cases this support has been previously transformed into a suitable reactive derivative in order to achieve the attachment of agrochemical compounds [14, 15].

Received 27 December 2000; in final form 31 December 2000.

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In this paper, the release behavior of compounds with and without a spacer group is discuss. The synthetic route of 2,4-D chloride PVA and dextran adducts has been reported before [16, 17] and the synthesis of the compounds with a spacer group is new for 2,4-D acid and these supports.

A gradual release of the bioactive agent can be achieved by hydrolytic or enzymatic cleavage of the linking bond. The influence in the release rate of pH of the medium, the temperature, the degree of substitution (DS) of the adducts and the presence of a spacer group, are studied. The Equilibrium Water Content (EWC) of all compounds is also determinated for comparing their hydrophobic character.

EXPERIMENTAL

Materials

As reactants were used commercial products, they were duly purified. The PVA was a commercial product (Gohsenol NL-05) thoroughly hydrolyzed. Its molecular weight, as measured by osmometry, was 22 000 g/mol, and purification was performed by a conventional reprecipitation method using a water/methanol mixture as solvent/precipitant system.

Dextran used was a commercial product (T-70 from Pharmacia Fine Chemicals) with a lineal structure (as revealed by ^{13}C-NMR) and average molecular weight Mw (from light scattering) of 70 000 g/mol. Both polymers were dried *in vacuo* for a few days at 80°C in the presence of phosphorous pentoxide to constant weight.

The potassium salt of 2,4-dichlorophenoxyacetic acid was obtained by pouring an ethanolic solution of the acid in a 0,1 mol/L solution of KOH. The salt thus obtained was precipitated by pouring it into dry acetone. After filtration, the salt was dried *in vacuo* in the presence of phosphorous pentoxide.

Reaction of the Polymeric Supports with Chloroacetylchloride

Poly(vinyl alcohol) and dextran partially chloroacetylated were obtained as described earlier [4, 14]. Shortly, equimolar concentrations of chloroacetyl chloride and pyridine were reacted at 25°C with PVA (23 g/L) using N-methyl-2-pirrilidone as solvent; for dextran the reaction takes place at 30°C with 4 g (0.074 mol OH) of dextran using 200 mL of DMF containing 2 g of LiCl/100 mL as solvent. The modification extent was controlled by the amount of chloroacetyl chloride used. The modified polymers were isolated by precipitation using distilled water as non-solvent. All samples were purified by reprecipitation using tetrahydrofuran (THF) as solvent and distilled water as non-solvent, and then dried *in vacuo* in the presence of phosphorous pentoxide.

Reaction of Chloroacetylated Supports with the Potassium Salt of 2,4-D Acid

The chloroacetylated supports were dissolved in DMSO at room temperature for PVA and 45°C for dextran. The calculated amounts of potassium salt of 2,4-D acid were added while stirring. All the reactions were performed at constant temperature, and the polymer remained soluble throughout the process. All samples were purified by reprecipitation using THF as solvent and distilled water as non-solvent, and then dried *in vacuo* in the presence of phosphorous pentoxide.

Characterization of Supports-2,4-D Adducts

Synthesized compounds were characterized through the following spectroscopy techniques: IR (457 Perkin-Elmer Spectrometer on KBr disk); ^{1}H NMR (200 MHz Bruker AM 200 spectrometer in DMSO-d_6, 40°C) and ^{13}C NMR (Varian XL-300 spectrometer operating at 75.4 MHz in DMSO-d_6 at 40°C). The degree of substitution (mole of 2,4-D per mole monomeric unit) (DS) was measured by a total hydrolysis/ultraviolet technique [18]. The alkaline hydrolysis was carried out at 90°C using a standard solution of sodium hydroxide (0,1 mol/L). The resulting homogeneous solution contained the release 2,4-D which was quantitatively determined by UV spectroscopy (using water as solvent) at 282 nm, using a calibration curve of 2,4-D in the same solvent.

Release Experiments

The release experiments were made as described earlier [19]. In short, appropriate adduct amounts were intoduced into a small wire basket, which was placed in Pyrex stoppered test tubes, each containing 25 mL of the aqueous buffer solution. The tubes were then immersed at the corresponding temperature in a thermostatically controlled bath. Periodically, samples of 1 mL were withdrawn and replaced by 1 mL of the same solvent. The released bioactive compound was measured by UV spectroscopy at 282 nm using a calibration curve of 2,4-D in the same solvent.

Water Absorption

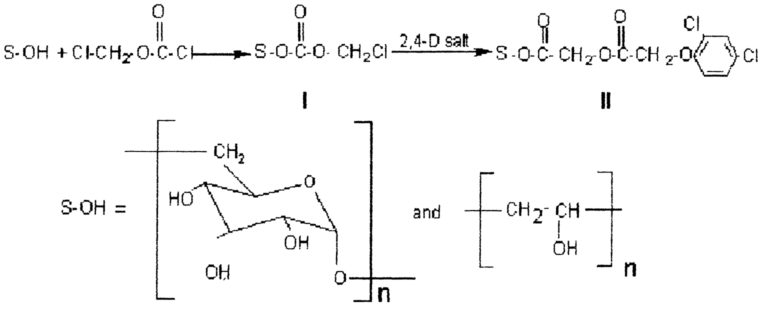
Films of the synthesized adducts were obtained by casting from THF solutions. Dynamic swelling experiments were performance by placing the disc in distilled water at 30°C. At various time the swollen disc were removed, surface dried with filter paper, weighted and replaced in the water. These films were treated with water at 30°C until equilibrium was reached. The equilibrium water content (EWC) is given by:

$$\mathrm{EWC} = 100\,\mathrm{h}\ (\mathrm{h} + \mathrm{m})$$

Where h is the amount of the water retained in the disc and m is the weight of the dry sample [19].

RESULTS AND DISCUSSION

Both polymers modified with chloroacetate groups with different modification extent were synthesized in a homogeneous medium. Using the potassium salt of 2,4-D acid according to the following scheme was carried out the covalent attachment of 2,4-D acid to chloroacetylated polymers through ester bonds by:



SCHEME 1.

In this way were obtained new adducts for 2,4-D acid with a spacer group between the polymer main chain and the bioactive group. The structures of the resulting polymers were confirmed by IR and NMR-^{1}H and NMR-^{13}C spectroscopy (Tab. 1).

Table 2 shows satisfactory coupling for the reaction between chloroacetylated polymers and potassium salt of 2,4-D.

In order to study the bioactive agrochemical release, three chloroacetylated supports-2,4-D adducts for each polymer with different composition were hydrolyzed in the heterogeneous phase at 30°C and several pH values.

Figure 1 shows typical profiles of the heterogeneous hydrolysis at 30°C of dextran-2,4-D salt (DS 0.55) and PVA-2,4-D salt (DS 0.26) in different pH values. As can be seen, the rate of hydrolysis was strongly affected by the pH of the medium. Under acidic conditions (pH = 4.7) the adducts show a slow rate of hydrolysis. Greatly enhance release rates are observed in basic conditions (pH = 9.0), increasing with the pH value. These results are in according with the influence of alkaline conditions on the rate of herbicide cleavage, as reported for other bioactive agrochemical containing polymers *via* an ester bond [4, 14, 15].

TABLE 1 Characteristic data of the IR, ^{1}H and ^{13}C-NMR spectra of compounds I and II

			δ(ppm)			
	IR (cm^{-1})		*^{1}H-NMR*		*^{13}C-NMR*	
Group	*PVA*	*Dextran*	*PVA*	*Dextran*	*PVA*	*Dextran*
			Compounds I			
$\underline{Cl}$—CH_2—COO—	1087, 692	1108, 745	–	–	–	–
Cl—$\underline{CH_2}$—COO—	2940	2935	4.38	4.40	64.3	41.1
Cl—CH_2—$\underline{CO}$O—	1735	1754	–	–	167.0	
			Compounds II			
$\underline{C}_6\underline{H}_3\underline{Cl}_2$	1481, 1430	1580, 1480, 1430	7.0 – 7.5	7.3 – 7.6	115.0 – 151.9	115.0 – 153.0
$C_6H_3Cl_2$—O—$\underline{CH_2}$—	2924	2937	4.9	5.1	65.5	66.4
$C_6H_3Cl_2$—O—CH_2—$\underline{CO}$—	1748	1757	–	–	169.6	169.6

TABLE 2 Degree of substitution obtained for reaction of chloroacetylated support with the potassium salt of 2,4-D at 45°C using DMSO as solvent

Reaction	*Compound I* (*DS*)	*Compound II* (*DS*)
1_{PVA}	0.28	0.26
2_{PVA}	0.40	0.31
3_{PVA}	0.52	0.42
1_{Dextran}	0.83	0.55
2_{Dextran}	1.06	0.77
3_{Dextran}	1.48	1.15

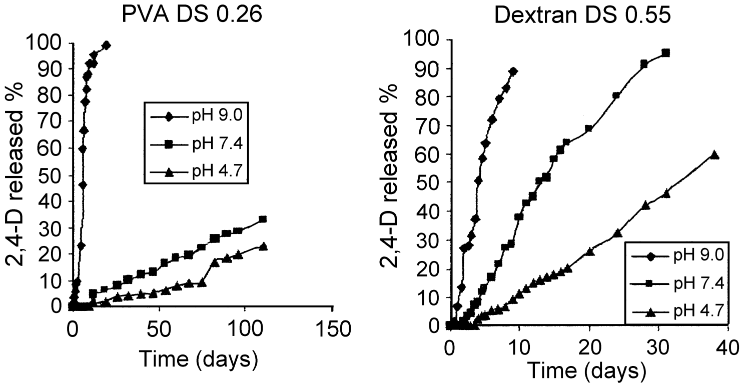


FIGURE 1 Heterogeneous hydrolysis at 30°C of supports 2,4-D salt at various pH values.

Figure 2 shows the release behavior at 30°C and pH 9.0 of six supports-2,4-D salt adducts (three for each polymer) with different compositions. The total release of the bioactive compound was reached more quickly in the case of the adducts with lower degree of modification. These results indicate that the hydrophilicity of the polymer determine the hydrolysis behavior. Decreasing the content of 2,4-D groups renders the polymer more hydrophilic and, therefore, facilitates the entry of hydrolytic species to the active sites, effectively increasing the relative hydrolysis rate.

For controlled release systems chemically bounded, the rate of release depends on the climate. For that reason, the study of the influence of the temperature in the release behavior of the agrochemicals is very important in order to predict what would happened when the adducts are applied in the soil. Figure 3 shows the changes in the speed of the heterogeneous hydrolysis of a dextran-2,4-D adduct (DS 0.77) and PVA-2,4-D adduct

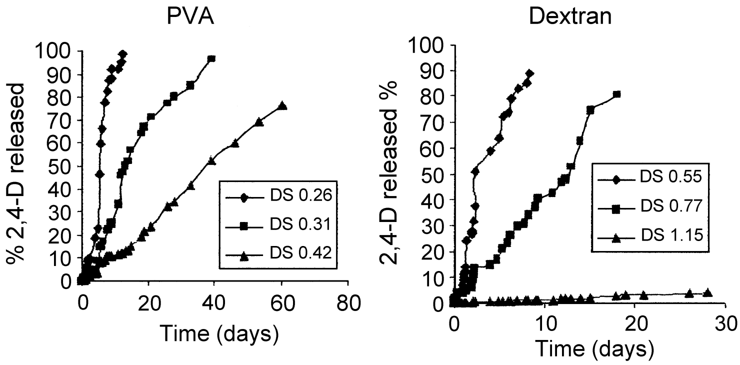


FIGURE 2 Heterogeneous hydrolysis at 30°C and pH 9.0 of supports-2,4-D adducts with different DS.

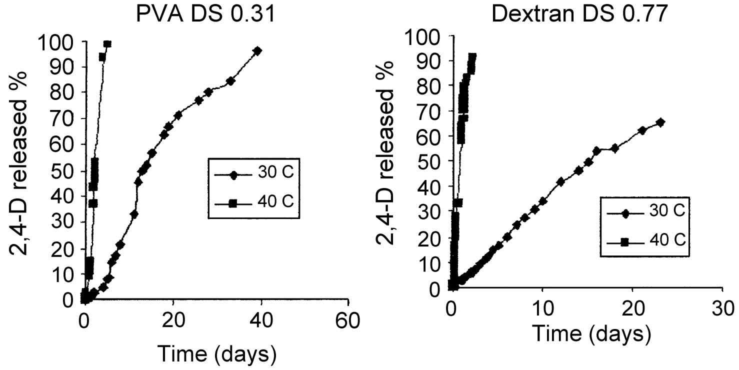


FIGURE 3 Heterogeneous hydrolysis for the adduct supports-2,4-D salt at pH 9.0 with different temperatures.

(0.31) at pH 9.0 for temperatures of 30°C and for 40°C. As it was expected, the release of agrochemical is higher as the temperature is higher.

In previous papers [16, 17] it was reported the synthesis and controlled release behavior of support-2,4-D adducts without a spacer group between the polymer main chain and the bioactive compound. As is shown in Figure 4 the release rate of the agrochemical is different when it is inserted in a polymer which has a spacer group in the molecule or not.

As can be seen in Figure 4, for these adducts, the presence of a spacer group diminish the hydrolysis rate of the bioactive compound. Akelah [2] has analyzed the influence of this factor and considers that when the bioactive compound is farther of the polymer main chain, covalent bound bioactive/polymer will be broken easier because there will be less bulky

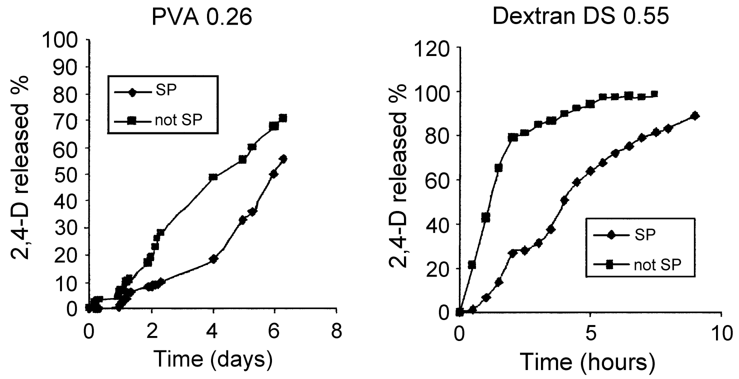


FIGURE 4 Influence of the presence of spacer groups at pH 9.0 and 30°C. SP = spacer group.

TABLE 3 Variation of the equilibrium water content (EWC) with the degree of substitution (DS)

	Compounds with a spacer group		*Compounds without a spacer group*	
Support	*DS*	*EWC (wt%)*	*DS*	*EWC (wt%)*
PVA	0.26	40.9	0.12	53.1
	0.31	30.4	0.26	45.0
	0.42	17.4	0.45	20.5
Dextran	0.55	50.2	0.55	68.8
	0.77	41.3	0.93	55.2
	1.15	12.0	1.97	42.8

impediments. This behavior is the opposite of the observed for us, but we consider it is necessary to take into account that the ester covalent bound is broken by the action of water molecules and the presence of a spacer group in the polymer make it very hydrophobic.

The degree of hydrophobity could be compared by means of the EWC values of the adducts and the values obtained are shown in Table 3.

REFERENCES

[1] Kenawy, E. R. (1998). *J. Macromol. Sci. Rev. Macromol. Chem. Phys.*, **C38**, 365.

[2] Akelah, A. (1996). *Mat. Sci. Eng.*, **C4**, 83.

[3] McCormick, C. L., Anderson, K. W. and Hutchinson, B. H. (1982). *J. Macromol. Sci. Rev. Macromol. Chem.*, **22**, 57.

[4] Arranz, F., Bejarano, E. M. and Sánchez-Chávez, M. (1994). *Macromol. Chem. Phys.*, **195**, 3789.

[5] Arranz, F., Sánchez-Chávez, M. and Baena, F. (1991). *Macromol. Chem.*, **192**, 1733.

[6] Batyrbekov, E. O., Isakov, R. and Zhubanov, B. A. (1998). *Macromol. Symp.*, **127**, 251.

[7] Desai, S. D. and Blanchard, J. (1998). *J. Pharm. Sci.*, **87**, 226.

[8] Mallapragada, S. K. and Chin, S. F. (1998). *ASC Symp. Ser.*, **709**, 176.

[9] Suzuki, Y., Tanihara, M., Nishimura, Y., Suzuki, K., Kakimaru, Y. and Shimizu, Y. (1998). *J. Biomed. Mater. Res.*, **42**, 112.

[10] Franssen, O., Vandervennet, V., Roders, P. and Henmink, W. E. (1999). *J. Control. Release*, **60**, 211.

[11] García, R., Fernández, M., Iraizoz, A. and Fernández, A. (1999). *Rev. Mex. Cienc. Farm.*, **30**, 27.

[12] Franssen, O., Stenekes, R. J. H. and Henmink, W. E. (1999). *J. Control. Release*, **59**, 219.

[13] Cortesi, R., Esposito, E., Osti, M., Squarzoni, G., Menegatti, E., Davis, S. S. and Nastruzzi, C. (1999). *Eur. J. Pharm. Biopharm.*, **47**, 153.

[14] Ramirez, J. C., Sánchez-Chávez, M. and Arranz, F. (1994). *Polymer*, **35**, 2651.

[15] Arranz, F. and Sánchez-Chávez, M. (1995). *Reactive Functional Polym.*, **28**, 69.

[16] Iglesias, M., Coro, J. and Lores, M. N. (2001). *Latin American Appl. Res.*, **31**, 27.

[17] Coro, J., Lores, M. N. and Rodriguez, E. (2000). *Revista ICIDCA* (in press).

[18] Rehab, A., Akelah, A., Issa, R. J., D'Antone, S., Solano, R. and Chiellini, E. (1991). *Bioact. Compat. Polym.*, **6**, 52.

[19] Ramirez, J. C., Sánchez-Chávez, M. and Arranz, F. (1994). *Polymer*, **35**, 4247.