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Some equilibrium and kinetic aspects of water sorption in poly(ortho ester)s

Tue Huu Nguyen[1], Kenneth J. Himmelstein[1,2,3] and Takeru Higuchi[1,3]

[1] Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66045, [2] Department of Chemical and Petroleum Engineering, The University of Kansas, Lawrence, KS 66045 and [3] Inter$_x$ Research Corp., Merck Sharp and Dohme Research Laboratories, Lawrence, KS 66044 (U.S.A.)

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Summary

Poly(ortho ester)s are a class of erodible polymers suitable for the construction of drug delivery systems. Since the release of bioactive substances from these polymers depends on the hydrolytic cleavage of the backbone, the isothermal sorption and transport of water in various poly(ortho ester)s have been investigated. At 25°C and relative vapor pressure equal to unity, the amount of water sorbed at saturation ranges from 0.3% to 0.75% w/w. Application of a modified Henry's law to the data yields reasonable correlation. The diffusion coefficient of water in poly(ortho ester)s appears to be independent of film thickness, molecular weight and water activity. At experimental temperatures above the glass transition temperature of the polymers, a marked increase in water diffusivity was observed. The activation energies of the transport process are within the range usually found for synthetic polymers. These equilibrium and kinetic studies suggest that membranes made of copolymers tend to have a more open structure than single diol poly(ortho ester)s.

Introduction

Poly(ortho ester)s have been extensively studied for their potential use in drug delivery (Heller et al., 1981; Nguyen et al., 1984; Shih et al., 1984; Sparer et al.,

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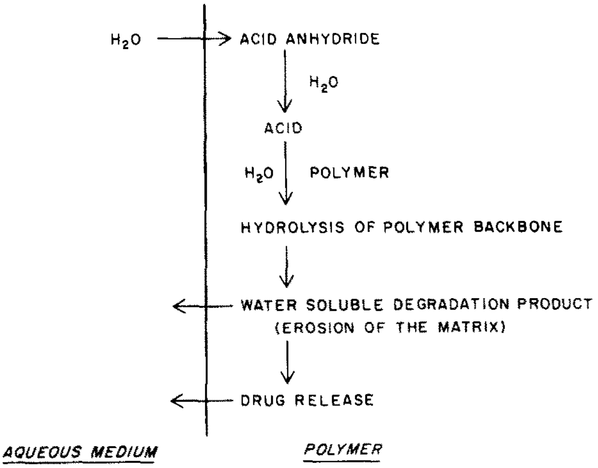
Correspondence: K.J. Himmelstein, INTER$_x$ Research Corp., Merck Sharp and Dohme Research Laboratories, 2201 West 21st Street, Lawrence, KS 66044, U.S.A.



Scheme 1.

1984; Thombre and Himmelstein, in press). As with most ortho esters, poly(ortho ester)s undergo acid catalyzed hydrolysis quite readily and are relatively stable in neutral or basic media (Ahmad et al., 1979; Bunton and De Wolfe, 1965; Cordes, 1969, Nguyen et al., 1984). Thus, when exposed to an aqueous environment, the erosion of a drug containing poly(ortho ester) matrix may be induced by the presence of an acidic catalyst resulting in the release of the active ingredient. Following this rationale, a delivery system has been proposed (Shih et al., 1984; Sparer et al., 1984) where an acid anhydride and the bioactive ingredient are incorporated in the polymeric matrix. The multistep mechanism of drug release may be described as follows: permeation of water into the matrix, hydrolysis of the anhydride to the corresponding acid, acid-catalyzed hydrolysis of the polymer backbone into small water-soluble molecules resulting in the erosion of the matrix and dissolution of the active ingredient into the medium (Scheme I). It is apparent, from the proposed mechanism, that the availability of water in the polymer matrix plays a crucial role in the performance of the device. This paper reports results obtained in the studies of some equilibrium and kinetic aspects of water sorption in poly(ortho ester)s.

Experimental

Materials

The polymers employed in this study were condensation copolymers of 3,9-bis(ethylidene)-2,4,8,10-tetraoxaspiro[5,5]-undecane (DETOSU) and diols such as 1,4-benzenedimethanol (BDM), trans-cyclohexanedimethanol (t-CDM), 1,6-hexanediol (HD) and ethylene glycol (EG). Copolymers derived from the con-

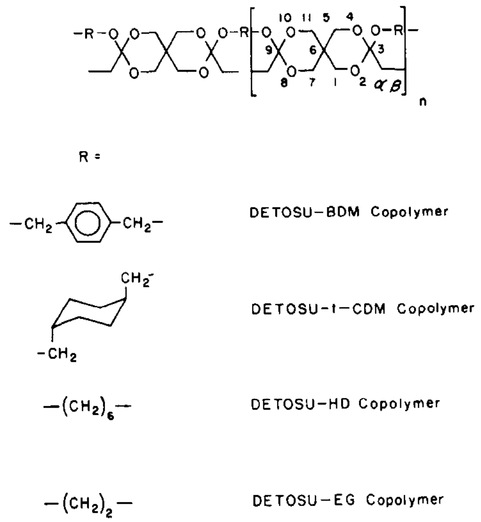


Fig. 1. General structure of poly(ortho ester)s.

densation of DETOSU and mixtures of HD:t-CDM at various ratios were also used. The general chemical formula of poly(ortho ester)s is shown in Fig. 1. All polymers were provided and characterized by Dr. J. Heller of SRI International, Menlo Park, CA (U.S.A.). The polymers are found to be amorphous as determined by X-ray diffraction. Water was distilled in an all-glass apparatus. Lithium chloride, sodium chloride, sodium bromide, potassium nitrate, potassium bromide, potassium carbonate (Fisher Scientific, Fair Lawn, NJ) were used as received.

Methods

For the equilibrium sorption studies, the polymers were injection molded (Mini Max Injection Molder CS-183, Customs Scientific Instruments, Whippany, N.J.) into rectangular slabs of 15 × 15 × 0.8 mm. The temperature of the injector was maintained at about 120°C while the mold temperature was kept 10°C lower than that of the injector. The polymer samples were placed in 50 ml beakers. The beakers were introduced into 400 ml jars containing 50 ml of saturated salt solution or distilled water. The jars were capped, sealed with parafilm then immersed in a water bath. Periodically, the samples were weighed on a microbalance with a sensitivity of 10 μg (Cahn 21 Automatic Electrobalance, Cahn Instruments, Cerritos, CA) until the weight gain was constant.

The diffusion coefficient of water in the various polymers studied was determined using lithium chloride discs encapsulated in poly(ortho ester)s as shown in Fig. 2. The injection molded polymer slabs were pressed into thin sheets by means of a carver press (Fred S. Carver, Menomonee Falls, WI) at a temperature approximately 20°C above the polymer glass transition temperature and the pressure was kept at 5000 lb./in.^{2}. Shims were employed to obtain desired thicknesses. The polymer sheet

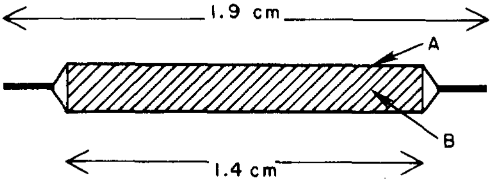


Fig. 2. Lithium chloride disc encapsulated in poly(ortho ester)s films. A: poly(ortho ester) film. B: LiCl disc.

was then cut into small discs of 19 mm in diameter. Lithium chloride was pressed into a disc 1 mm thick and 14 mm in diameter and sandwiched between two polymer films which were then heat-sealed. The encapsulated lithium chloride discs were immersed in 40 ml vials containing 10 ml of distilled water or a saturated salt solution. The vials were capped, sealed with parafilm and placed in a water bath maintained at constant temperature. At predetermined time intervals, the capsules were removed from the vials, quickly rinsed with distilled water, blotted dry, then weighed on the microbalance.

The total exposed surface area of the device was taken to be twice the surface of the lithium chloride disc, and found to be equal to 3.08 cm^2. The film thickness was measured with a micrometer (Starret Tools, Athol, MA). The relative water vapor pressures above lithium chloride, sodium chloride, sodium bromide, potassium nitrate, potassium bromide, potassium carbonate saturated solutions at various temperatures were taken from Rockland (Rockland, 1960).

The density of the polymer samples was determined using a pycnometer (Sargent Welch Scientific Laboratory Instruments, Skokie, IL) and computed from the following formula:

$$d = \frac{M}{V}$$

where M is the weight of the polymer sample and V its volume. Assuming the density of water is 1.0, the volume of the polymer sample was obtained from the weight of the water displaced from the pycnometer when the polymer sample was introduced.

$$V = A - (B - M)$$

where A is the weight of the pycnometer filled with water and B the weight of the pycnometer containing water and the polymer sample.

The solubility of water in benzene, cyclohexane and *n*-hexane was determined coulometrically by the Karl-Fisher method. 5 ml of the organic solvent were equilibrated with 5 ml of water at 25°C for 48 h. 50-μl samples were then carefully withdrawn from the organic phase and injected into a moisture analyzer (Metrohm Model 652, Brinkman Instruments, Westburg, NY).

Results and Discussion

Equilibrium water sorption

Figs. 3 and 4 are typical sorption isotherms obtained experimentally. The curves are constructed by plotting the amount of water absorbed expressed as grams of water per 100 grams of polymer versus relative water vapor pressure above saturated salt solutions and distilled water at 25°C. The sorption of water by poly(ortho ester)s is relatively small ranging from 0.3% to 0.75% at P/P_0 equal to unity. DETOSU-EG appears to have greatest affinity for water followed by DETOSU-BDM. The sorption isotherms appear to be linear, following Henry's law up to 70% relative water vapor pressure. At partial pressures above this point, the curves are slightly concave upward. Rowen and Simha (1949) and Starkweather (1959) have successfully treated similar data employing the modified Flory-Huggins equation (Flory, 1953).

$$\Delta F_{\text{mix}} = kT(n_1 \ln V_1 + X_1 n_1 V_2)$$

$$\frac{\partial \Delta F_{\text{mix}}}{\partial n_1} = kT\left(\ln V_1 + V_2 + X_1 V_2^2\right) = kT \ln P/P_0$$

Thus,

$$\ln P/P_0 = \ln V_1 + V_2 + X_1 V_2^2$$

Fig. 3.

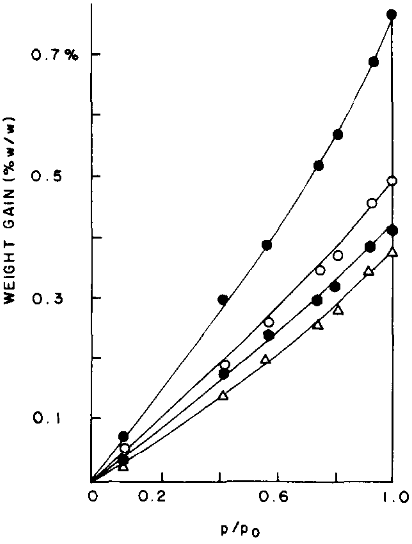


Fig. 4.

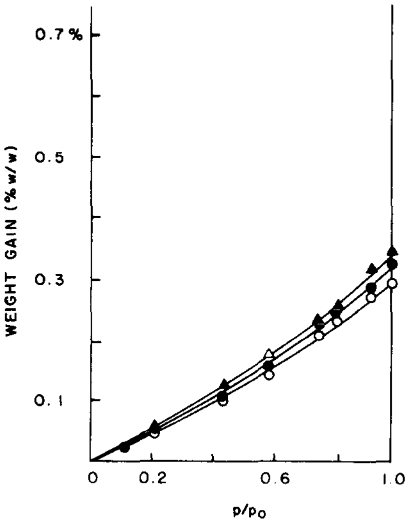


Fig. 3. Sorption isotherms at 25°C. ●, DETOSU : EG; ○, DETOSU : BDM; ●, DETOSU : HD; △, DETOSU-t-CDM.

Fig. 4. Sorption isotherms at 25°C. ▲, DETOSU-HD : DETOSU-t-CDM 30 : 70; ●, DETOSU-HD : DETOSU-t-CDM 83 : 17; ○, DETOSU-HD : DETOSU-t-CDM 50 : 50.

TABLE 1

EQUILIBRIUM WATER SORPTION IN POLY(ORTHO ESTER)S AT 25°C. TABLE OF THE FLORY HUGGIN'S INTERACTION PARAMETER AT VARIOUS RELATIVE VAPOR PRESSURES

Polymers	P/P_0						
	0.11	0.44	0.58	0.75	0.81	0.92	1.00
DETOSU-EG	3.88	3.95	3.94	3.91	3.90	3.87	3.84
DETOSU-BDM	4.32	4.38	4.36	4.32	4.30	4.27	4.25
DETOSU-HD	4.73	4.64	4.63	4.58	4.55	4.61	4.50
DETOSU-t-CDM	4.52	4.47	4.47	4.46	4.43	4.44	4.40
DETOSU-HD : DETOSU-t-CDM							
83 : 17	4.92	4.88	4.86	4.78	4.78	4.74	4.63
50 : 50	4.70	4.67	4.64	4.62	4.63	4.63	4.60
30 : 70	4.72	4.67	4.65	4.63	4.63	4.60	4.58

where ΔF_{mix} is the free energy of mixing; V_1, V_2 are the volume fraction of water and polymer; n_1, n_2 are the number of molecules of water and polymer; P/P_0 is the relative water vapor pressure at temperature T; and X_1 is the interaction parameter. The studies showed that the interaction parameter X_1 is inversely related to the amount of water absorbed at saturation. Thus X_1 is indicative of the hydrophobicity of the polymers. For example, collagen, cellulose and nylon 610 saturated with water have an X_1 of 0.77, 1.25 and 2.16, respectively (Starkweather, 1959). The interaction parameters obtained for the water-poly(ortho ester)s system at 25°C are listed in Table 1. The values range from approximately 3.9 to 4.9. Over all, poly(ortho ester)s appear to be highly hydrophobic. Again DETOSU-EG with a lower value of X_1 appears to be relatively more hydrophilic than other polymers studied. However, it is apparent that for many cases presented in Table 1, X_1 does not remain constant but tends to decrease as P/P_0 approaches 1.0. Since X_1 will be independent of the composition of a mixture only when the mixture is ideal from the viewpoint of the lattice theory, the data indicate that the water–poly(ortho ester)s interaction may in some cases depart from ideality. The greater hydrophilicity of DETOSU-EG appears to be related to the number of oxygen atoms per unit mass of polymer (Table 2) suggesting some type of specific interaction between the sorbed water molecules and the oxygen atoms in the polymer chain. Dole (1948) extended the BET (Brunauer et al., 1938) statistical approach to gases adsorption in solids to the cases of sorption of vapors by solids. The equation of the form:

$$\frac{N}{N_s} = \frac{kX}{1 - kX}$$

termed a modified Henry's law, was employed by Potts (1964) to successfully treat data similar to that obtained for the water–poly(ortho ester)s system. N and N_s are

TABLE 2

EQUILIBRIUM WATER SORPTION IN POLY(ORTHO ESTER)S AT 25°C. FIT OF THE EXPERIMENTAL DATA TO THE MODIFIED HENRY'S LAW EQUATION

Polymer	density	Average number of oxygen atoms per 100 g of polymer (mol)	k	N_s (mol/mol of monomeric unit)	r^2	N_{max} (% w/w)	Water sorption at $P/P_0 = 1$ (% w/w)
DETOSU-EG	1.13	2.20	0.16	0.61	0.99	0.76	0.75
DETOSU-BDM	1.15	1.71	0.17	0.47	0.99	0.48	0.50
DETOSU-HD	1.13	1.82	0.21	0.27	0.99	0.39	0.42
DETOSU-t-CDM	1.10	1.69	0.26	0.24	0.99	0.46	0.45
DETOSU-HD : DETOSU-t-CDM							
89 : 11	1.09	1.80	0.19	0.24	0.99	0.30	0.37
65 : 35	1.08	1.77	0.14	0.33	0.99	0.29	0.30
50 : 50	1.08	1.75	0.15	0.36	0.99	0.35	0.35
30 : 70	1.04	1.72	0.19	0.31	0.99	0.36	0.36

the total number of sorbed molecules and sorption sites, respectively; k is a constant and X is the relative water vapor pressure P/P_0. Upon rearrangement,

$$\frac{1}{X} = k + kN_s \cdot \frac{1}{N}$$

and at a relative humidity of 1,

$$N_{max} = \frac{kN_s}{1-k}, \qquad P/P_0 = 1$$

Thus when the inverse of the vapor pressure is plotted against the inverse of the number of sorbed molecules, the equation constant can be obtained from the intercept with the ordinate and the total number of sorption sites can be deduced from the slope of the line and the intercept. Table 2 lists the values derived from the experimental data. Even though the differences in the parameters are not large, a trend may be seen. DETOSU-EG, which has the highest average number of oxygen atoms per unit mass of polymer, has the largest value for N_s. The copolymers derived from the condensation polymerization of DETOSU and mixtures of t-CDM and HD appear to have higher number of sorption sites than DETOSU–t-CDM or DETOSU–HD. Since the number of sorption sites obtained experimentally depends not only on the total number of sorption sites on the polymer chains, but also on the accessibility to those sites, and, considering that the average number of oxygen atoms per unit mass of polymer for DETOSU–t-CDM: DETOSU–HD copolymers are not significantly greater than that of either DETOSU–t-CDM or DETOSU–HD, the experimental data seem to suggest that copolymerization of DETOSU and mixtures of t-CDM and HD results in polymers with more open structure. The density data appear to support the observation; DETOSU–HD and DETOSU–t-

CDM tend to have higher densitities than DETOSU–t-CDM: DETOSU-HD combinations. The relatively higher water sorption ability of DETOSU–BDM as compared to DETOSU–HD or DETOSU–t-CDM cannot be rationalized in terms of a specific interaction between sorbed water molecules and the oxygen atoms in the polymer chain alone. A contribution by the aromaticity of the benzene ring may offer a more plausible explanation. The solubility of water at room temperature in benzene, cyclohexane and *n*-hexane is 3.3×10^{-2} M, 2.8×10^{-3} M and 3.2×10^{-3} M, respectively.

Diffusion of water in poly(ortho ester)s

The diffusivity of water in poly(ortho ester)s was determined using the Fick's first law when the system is at steady-state.

$$J = \frac{dM}{dt} = -D(C)A \cdot \frac{\Delta C}{L}$$

and

$$D(C) = \frac{1}{C_1 - C_2} \int_{C_2}^{C_1} D \, dC$$

J is the steady-state flux of water across the film, A the total exposed surface area, L the film thickness, D(C) is the diffusion coefficient and ΔC is the water concentration gradient within the film. If D(C) is independent of the concentration of the diffusant, the expression is reduced to:

$$J = -DA \cdot \frac{\Delta C}{L}$$

Thus

$$D = \frac{-JL}{A\Delta C}$$

Experimentally, J is obtained from the slope of the plot of water uptake by the encapsulated lithium chloride disc vs time. The concentration gradient of water in the film is obtained from knowledge of the saturation water uptake of poly(ortho ester)s above lithium chloride and other salt saturated solutions or distilled water from the equilibrium sorption studies described above.

Table 3 shows the steady state flux of water across DETOSU–t-CDM : DETOSU-HD 50 : 50 films at 25°C in distilled water. The thickness L varies from 0.007 cm to 0.036 cm. The flux, as expected, is inversely related to L. The normalized water flux

$$J \times L = -DA \cdot \Delta C$$

appears to remain constant. Since A and ΔC were kept constant in this experiment,

TABLE 3

DIFFUSION OF WATER IN DETOSU-t-CDM:DETOSU-HD 50:50 AT 25°C. ACTIVITY OF WATER IN DONOR PHASE = 1.00. STEADY-STATE FLUX OF WATER THROUGH POLYMER MEMBRANES OF VARIOUS THICKNESSES

Membrane thickness (cm)	Steady-state flux ($mg \cdot h^{-1}$)	Flux × thickness ($J \times L$)
0.007	0.155	0.00108
0.01	0.108	0.00108
0.012	0.086	0.00103
0.017	0.061	0.00107
0.02	0.052	0.00104
0.036	0.028	0.00101

Average normalized flux: $0.00105 \pm 2.9\ 10^{-5}\ cm \cdot mg \cdot h^{-1}$

the data suggest that D is independent of the film thickness. In general, in non interacting systems, the dependence of the diffusion coefficient on film thickness results from stress developed by the formation of a swollen front on the water rich side of the membrane. This effect should be minimal in poly(ortho ester)s considering the very low moisture content at saturation. The diffusion coefficient of water across various poly(ortho ester) films at 25°C in distilled water is shown in Table 4. At experimental temperatures below the polymer glass transition temperature (T_g), no significant difference is found over a wide range of T_gs and molecular weights. The effect of polymer structure is also not obvious with the exception of DETOSU–HD. The diffusion coefficient ranges between $2.1 \times 10^{-8}\ cm^2 \cdot s^{-1}$ to $3.0 \times 10^{-8}\ cm^2 \cdot s^{-1}$. This is probably due to the small size of the water molecules and, as proposed by Kishimoto et al. (1960), local cooperative vibrations of only a few structural units are sufficient for the movement of water molecules; thus the

TABLE 4

DIFFUSION OF WATER IN POLY(ORTHO ESTER)S AT 25°C. ACTIVITY OF WATER IN DONOR PHASE = 1.00

Polymer	$(J \times L)/A$ ($g \cdot cm^{-1} \cdot s^{-1}$)	D ($cm^2 \cdot s^{-1}$)	MW (10^3)	T_g (°C)
DETOSU-BDM	1.42×10^{-10}	2.58×10^{-8}	56.2	55
DETOSU-t-CDM	0.96×10^{-10}	2.11×10^{-8}	40	122
DETOSU-HD	1.65×10^{-10}	4.07×10^{-8}	67.4	22
DETOSU-HD: DETOSU-t-CDM				
89:11	1.16×10^{-10}	2.77×10^{-8}	42.8	30
83:17	1.03×10^{-10}	2.95×10^{-8}	49.5	32
65:35	0.92×10^{-10}	2.82×10^{-8}	25.4	48
60:40	1.00×10^{-10}	2.96×10^{-8}	43	56
50:50	0.95×10^{-10}	2.66×10^{-8}	50	61
30:70	1.02×10^{-10}	2.74×10^{-8}	30.7	78

TABLE 5

DIFFUSION COEFFICIENT OF WATER IN POLY(ORTHO ESTER)S AT 25°C AS A FUNCTION OF WATER ACTIVITY

P/P_0	$(J \times 1)/A$ $(g \cdot cm^{-1} \cdot s^{-1})$		D $(cm^2 \cdot s^{-1})$	
	HD	50:50	HD	50:50
0.44	0.57×10^{-10}	0.34×10^{-10}	4.10×10^{-8}	2.43×10^{-8}
0.58	0.80×10^{-10}	0.51×10^{-10}	3.89×10^{-8}	2.62×10^{-8}
0.75	1.22×10^{-10}	0.68×10^{-10}	4.42×10^{-8}	2.72×10^{-8}
0.81	1.32×10^{-10}	0.74×10^{-10}	4.31×10^{-8}	2.59×10^{-8}
0.92	1.54×10^{-10}	0.89×10^{-10}	3.96×10^{-8}	2.72×10^{-8}
1.0	1.73×10^{-10}	0.95×10^{-10}	4.00×10^{-8}	2.82×10^{-8}
	Mean: $4.07 \times 10^{-8} \pm 5\%$		$2.65 \times 10^{-8} \pm 4.5\%$	

polymer free volume may not be a major contributing factor. However, a marked increase in the diffusion coefficient is observed when T_g of the polymer is lowered below the surrounding temperature as evident in the case of DETOSU-HD which

Fig. 5.

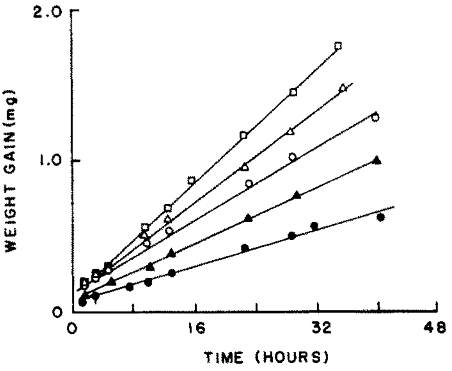


Fig. 6.

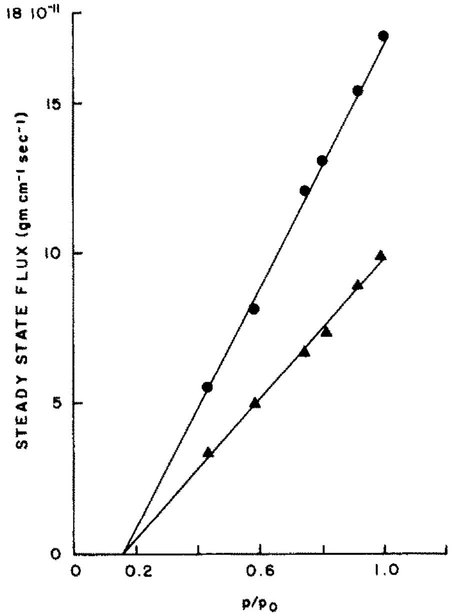


Fig. 5. Water transport across DETOSU-HD : DETOSU-t-CDM 50 : 50 film at 25°C. Film thickness = 0.02 cm. □, $P/P_0 = 0.92$; △, $P/P_0 = 0.80$; ○, $P/P_0 = 0.75$; ▲, $P/P_0 = 0.58$; ●, $P/P_0 = 0.44$.

Fig. 6. Water transport across poly(ortho ester) films at 25°C. Plot of normalized steady-state flux of water versus water activity of the donor phase. ●, DETOSU-HD; △, DETOSU-HD : DETOSU-t-CDM 50 : 50.

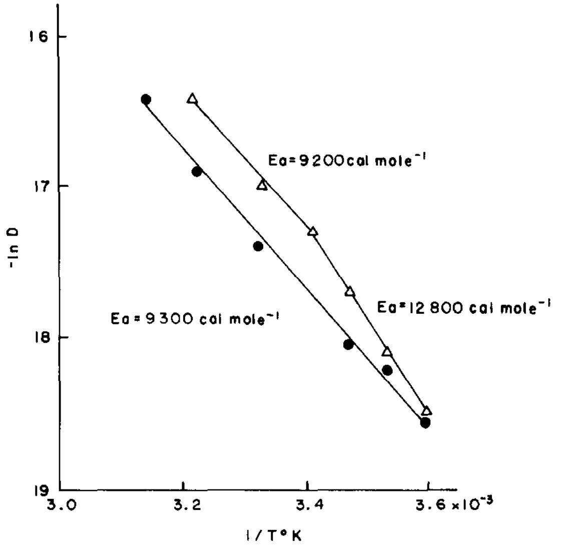


Fig. 7. Effect of temperature on the diffusion coefficient of water across poly(ortho ester) films. ●, DETOSU-HD : DETOSU-t-CDM 50 : 50; △, DETOSU-HD;

has a T_g of 22°C, the water diffusion coefficient is 4.07×10^{-8} $cm^{-2} \cdot s^{-1}$, about twice that found for other polymers studied.

The effect of water activity on the transport of water across poly(ortho ester)s was studied using DETOSU–HD and DETOSU–t-CDM : DETOSU-HD 50 : 50 copolymers at 25°C. The results are shown in Table 5 and Fig. 5. For both polymers, the diffusion coefficient of water appears to be independent of the relative vapor pressure in the donor phase. The non-zero intercept found in Fig. 5 can be attributed to the weight of water absorbed by the polymer membranes. In Fig. 6, the steady-state flux of water is plotted against the water activity. As expected, a straight line which intersects the abscissa at P/P_0 equal to the vapor pressure above lithium chloride saturated solution is obtained.

The activation energy E_a for the transport process is obtained from the plot in Fig. 7. An activation energy of approximately 9.3 kcal · mol^{-1} was obtained for DETOSU–t-CDM : DETOSU–HD 50 : 50 between 5°C and 45°C. A break is observed in the plot for DETOSU-HD. This corresponds to the glass transition temperature of the polymer at 22°C. Above the T_g, the activation energy is approximately 9.2 kcal · mol^{-1}, while below the T_g, E_a is equal to 12.8 kcal · mol^{-1}. These values are well within the range observed for synthetic polymers (Crank and Park, 1968). At temperature below their glass transition temperatures, the diffusion in DETOSU–HD appears to be more sensitive to temperature than in DETOSU–HD : DETOSU–t-CDM 50 : 50. As noted by Barrer (1941), this is generally an indication that the first polymer is more resistant to the transport of water. The data again suggest that membrane fabricated using DETOSU–HD : DETOSU–t-CDM copolymers have a more open structure than that of DETOSU–HD alone.

Conclusion

Some equilibrium and kinetic aspects of water sorption in poly(ortho ester)s were investigated. The experimental data suggest that the polymers are highly hydrophobic. The water content of the polymers equilibrated over distilled water at 25°C ranges from 0.3% to 0.75% w/w. The data are explained in terms of the number of sorption sites available and the hydrophobicity of the monomeric unit. The diffusion coefficient of water across poly(ortho ester) membrane appears to be independent of film thickness, water activity, polymer molecular weight and structure in the range studied. A significant increase in the diffusion coefficient of water was found as the glass transition temperature of the polymer is lowered below the experimental temperature. Both the equilibrium and kinetic studies suggest that polymer films obtained from DETOSU–HD : DETOSU–t-CDM tend to have a larger free volume than those made of pure DETOSU–HD or DETOSU–t-CDM.

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