for selective irreversible inhibition of heart LDH, but not skeletal muscle LDH, and vice versa, has been found, which is attributed to exploitable differences in the secondary-tertiary structure of these two substrate-identical enzymes. Differences in secondary-tertiary structure of these two substrate-identical enzymes have previously been shown by amino acid analysis (24) and by antisera cross reactions (14, 24). The LDH from skeletal muscle and heart in the same animal are distinctly different, but the skeletal muscle LDH from different species are more similar; also, heart LDH from different species are more similar. Even though the studies in this paper were carried out with the LDH's from two distinct tissues of two species, these experiments give a first approximation of the selective inhibition that may be obtained in tissues of the same animal.

If this irreversible specificity for substrate-identical enzymes, which is presumably due to exploitable differences in the secondary-tertiary structure of the enzymes, can be carried over to such critical areas for cell division as (*a*) purine (19) or pyrimidine biosynthesis of (*b*) the folic cofactor area, the potential utility in chemotherapy would be obvious. Such studies in area (*a*) (13) and area (*b*) (9) are continuing in these laboratories.

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Interaction of Weak Organic Acids with Insoluble Polyamides I

Sorption of Salicylic Acid by Nylon 66

By A. J. KAPADIA, W. L. GUESS, and J. AUTIAN

Insoluble polyamides have been shown to bind various chemical agents having acidic hydrogens. To explore in more detail the interaction of an acidic drug, salicylic acid, with a specific polyamide (nylon 66), a study was undertaken to ascertain the influence of concentration, temperature, pH, and solvent composition on the sorption phenomenon. From the sorption studies, a number of physical constants were evaluated: (*a*) saturation value, (*b*) standard affinities, (*c*) heat of sorption, (*d*) apparent diffusion coefficients, and (*e*) activation energy of diffusion.

EVEN THOUGH plastics have made a great impact in the various facets of pharmacy and medicine, some problems have occurred which should indicate that perhaps there should be a slower pace to the introduction of these items to the health professions. This laboratory in the past has reported on some of these problems (1, 2). To the industrial and hospital pharmacist an appreciation and understanding of drug-plastic interactions would help minimize costly errors and at the same time provide the many advantages to be gained by the use of plastics.

The insoluble polyamides (various types of nylon) have a number of applications as parts or component parts in various apparatus where strength and resistance to thermal changes are needed. In pharmaceutical and medical applications these nylon parts[1] may come in contact with drug or biological products for varying periods of time. Depending upon a number of factors, selective drugs and chemical

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[1] For example, component parts of heart lung machines, containers, tubings, syringes, valve parts for aerosol bottles, etc.

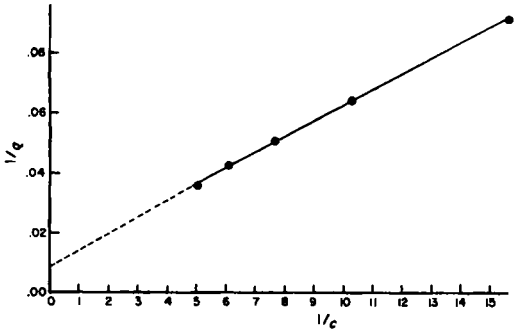


Fig. 1.—A Langmuir plot for the sorption of salicylic acid by nylon (41.5 C.°).

intervals aliquots of solution were withdrawn and the salicylic acid content remaining (in the solution) was determined by measuring the optical density of the sample at a wavelength of 296 mμ in a DU spectrophotometer, employing proper dilutions (using distilled water) and blanks. In all instances duplicate or triplicate tubes were run; the results reported in this paper are the average values of the two or three samples. The difference between the amount of salicylic acid remaining in the solution and the original concentration was then assumed to be the amount of the drug sorbed by the nylon.

Effect of Concentration on Equilibrium Sorption.—An experiment was conducted at a temperature of 41.5° to determine the equilibrium concentration of salicylic acid sorbed by nylon at different original concentrations. In all instances the strips of nylon were kept in contact with the solutions for sufficient periods of time to ensure that equilibrium had been reached.

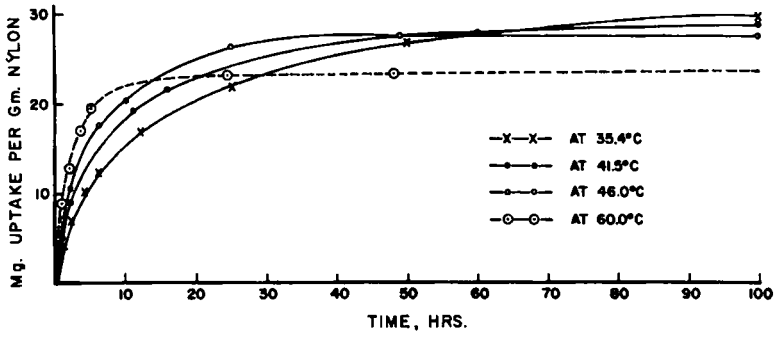


Fig. 2.—The effect of temperature on the sorption of salicylic acid.

agents might be sorbed by the nylon, reducing the concentration of the component in the solution.

Previous studies have revealed that nylon will sorb drugs and other agents having protonic groups (3, 4). This paper and others will present further information on drug-nylon interactions with the hope of relating structural configurations of solutes to their propensity to be sorbed by several types of nylon. This particular paper reviews the sorption of salicylic acid by nylon 66.

EXPERIMENTAL

General Procedures.—In all experiments reported in this paper, nylon 66 sheets[2] having a thickness of 0.012 in. were employed. The sheets were cut into strips measuring approximately 1 by 16 in., and soaked in a 50% alcohol-water solution for a period of 15 minutes, then repeatedly rinsed in distilled water to remove adhering contaminates. The strips were then dried to constant weight and placed into desiccators until ready for use. In any particular experiment, one or more strips were weighed accurately[3] and placed into a specially constructed glass tube. The particular solution (150 ml.) was then added and the tube closed by inserting a ground-glass stopper which was further secured to the tube by two metal springs. This tube and other tubes in the particular series were placed into a shaking device immersed in a constant temperature water bath. At various time

With Langmuir's equation in the following form

$$\frac{1}{q} = \frac{1}{KSC} + \frac{1}{S} \qquad \text{(Eq. 1)}$$

where q is the amount of salicylic acid sorbed at equilibrium in milligrams per gram of nylon, S is the saturation concentration when all sites in the nylon are occupied, C is the equilibrium concentration of the drug in solution (as grams per 150 ml.), and K a constant, a linear relationship was found when $1/q$ was plotted against $1/C$ for the range of concentrations employed in the experiment. From the intercept, the saturation value or S was calculated by the method of least squares and found to be equal to 117 mg./Gm. of nylon or 0.85 mole/Kg. (see Fig. 1).

Effect of Temperature on Sorption.—Nylon strips were kept in contact with 150 ml. of salicylic acid solution (0.15%), and at various time intervals the quantity of drug sorbed by the plastic was determined. This experiment was conducted at four different temperatures (35.4°, 41.5°, 46.0°, and 60.0°). A sorption isotherm is shown for each of these temperatures in Fig. 2, where milligrams of uptake per gram of nylon is plotted against time in hours.

Affinity and Heat of Sorption.—From equilibrium studies of sorption for salicylic acid by nylon, the standard affinity (5) was calculated using

$$-\Delta\mu^\circ = RT \ln C_s/C_l \qquad \text{(Eq. 2)}$$

where $-\Delta\mu^\circ$ is the difference in standard chemical potential between the solute in the liquid phase

[2] Polypenco Nylon 101, Polymer Corp. of Pennsylvania, Reading, Pa.
[3] Average weight of strips was 3.5 Gm.

(C_l) and the solute in the solid phase (C_s). The concentration terms for C_l and C_s are expressed for calculation purposes in moles per kilogram rather than in activities. For this specific nylon, standard affinities at several temperatures are shown in Table I.

From the relationship

$$-\frac{\Delta\mu^\circ}{T} = \frac{\Delta H^\circ}{T} + C \qquad \text{(Eq. 3)}$$

where $\Delta\mu^\circ$ is as previously defined, ΔH° is the standard heat of sorption, T is the absolute temperature, and C a constant, it is possible to evaluate ΔH° from the slope of the line when $-\Delta\mu^\circ/T$ is plotted against $1/T$. The heat of sorption was equal to -1.89 Kcal./mole in this case.

Diffusion of Salicylic Acid in Nylon.—To evaluate the apparent diffusion coefficient at one original concentration (0.15%) and at several temperatures, experiments were run as previously described where the uptake of a drug by the nylon was followed over a period of time at isothermal conditions. This type of experiment, where a limited volume of a solution is well agitated and in contact with a plane sheet, can be conveniently employed to accumulate data which can be treated by the method of Berthier (6, 7) using simple graphical procedures to evaluate the apparent diffusion coefficient.

The experimental data are plotted as M_t/M_∞ against the square root of time ($\sqrt{t}$) for each temperature as shown in Fig. 3. Correspondingly, for each temperature (each temperature has a different total uptake), a theoretical curve is plotted using the values of M_t/M_∞ (fractional uptake) *versus* $\sqrt{K}$ from Berthier's table (6). An example of this type of curve is shown in Fig. 4 for a total per cent uptake of 45.83 (at 35.5°). Clearly, it can be seen that at a particular M_t/M_∞ value from the experimental curve, a corresponding time (t) can be deduced and similarly at the same M_t/M_∞ value on the theoretical curve, a corresponding K can be found. Now since $K = Dt/l^2$ and since K, t, and l are known, it is a simple matter to calculate the diffusion coefficient D.

A second method which appears to give more accurate values for the apparent D is to determine the slopes of both the experimental and theoretical curves by the method of least squares. In this method the experimental curve may be expressed

$$M_t/M_\infty = S_e t^{1/2} \qquad \text{(Eq. 4)}$$

where M_t/M_∞ and t are the same as previously defined, and S_e is the slope of the line. Correspondingly, the theoretical curve may be expressed

$$M_t/M_\infty = S_t K^{1/2} \qquad \text{(Eq. 5)}$$

where S_t is the slope of the line and K is the same constant as defined before. When

TABLE I.—STANDARD AFFINITIES ($-\Delta\mu^\circ$) FOR SALICYLIC ACID AT SEVERAL TEMPERATURES[a]

Temp., °C.	$-\Delta\mu^\circ$ (Kcal./mole)
35.4	1.863
41.5	1.860
54.0	1.833
60.0	1.836

[a] Original concentration of solution: 225 mg. in 150 ml. Plastic sample: nylon 66.

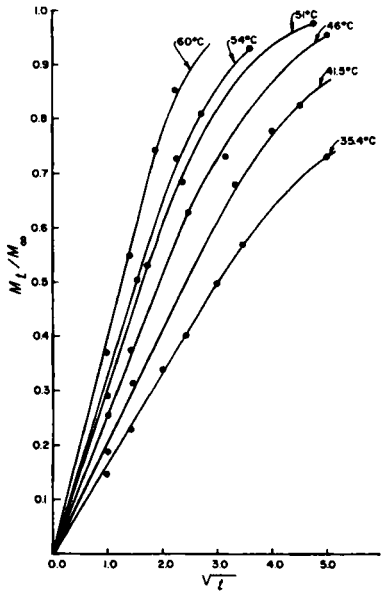


Fig. 3.—Fractional uptake of salicylic acid by nylon *vs.* square root of the time (in hours) at different temperatures.

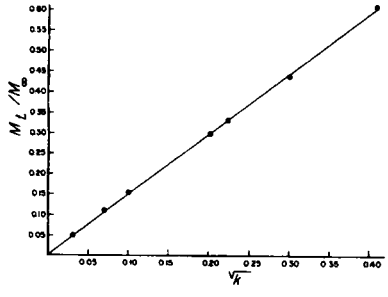


Fig. 4.—Theoretical plot of fractional uptake *vs.* K. From Berthier table (at total uptake of 45.83%).

$$M_t/M_\infty \text{ (experimental)} = M_t/M_\infty \text{ (theoretical)} \qquad \text{(Eq. 6)}$$

$$S_e t^{1/2} = S_t K^{1/2}$$

and since K is equal to Dt/l^2

$$S_e t^{1/2} = S_t (Dt/l^2)^{1/2} \qquad \text{(Eq. 7)}$$

or finally

$$D = \frac{S_e^2 l^2}{S_t^2} \qquad \text{(Eq. 8)}$$

Table II includes the data from the diffusion experiments with calculated apparent diffusion constants (by the slope method) for each temperature.

The influence of temperature may be noted by referring to Fig. 5. It follows a typical Arrhenius relationship which may be written

$$\log D = \log D_o + \Delta E/2.303\,RT \qquad \text{(Eq. 9)}$$

where D_o is a pre-exponential factor indicating the value of D at infinite temperature, ΔE the activation energy for diffusion, R the appropriate gas con-

TABLE II.—SORPTION DATA OF SALICYLIC ACID BY NYLON AS A FUNCTION OF TIME AND TEMPERATURE

Temp., °C.	t, Time in Hrs.	$\sqrt{t}$	M_t, mg./ Sample of Nylon	M_t/M_∞[c]	q, Mg. Sorbed per Gm. Nylon	S_e, Slope (Exptl.)	S_t, Slope (Theoret.)	D, Cm.²/Sec.
35.4	1	1.000	14.88	0.141	4.303	0.1701	1.443	...
	2	1.414	23.47	0.227	6.786	...	...	...
	4	2.000	35.21	0.341	10.178	...	...	...
	6	2.449	42.08	0.408	12.16	...	...	...
	9	3.000	50.95	0.494	14.79	...	...	8.97×10^{-10}
	12	3.464	58.68	0.569	16.96	...	...	...
	25	5.000	74.99	0.727	21.68	...	...	...
	50	7.071	92.02	0.892	26.60	...	...	...
	122.5	11.06	103.11[b]	...	29.58	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 45.83							
41.5	1	1.000	18.89	0.190	5.296	0.2024	0.0409	...
	2	1.414	31.48	0.316	9.049	...	...	...
	11	3.317	66.94	0.674	19.23	...	...	...
	16	4.000	75.53	0.760	21.71	...	...	1.26×10^{-9}
	20	4.472	81.87	0.823	23.58	...	...	...
	84	9.165	99.34[b]	...	27.99	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 44.17							
46.0	1	1.000	24.04	0.250	7.018	0.2575	0.0663	...
	2	1.414	36.07	0.376	10.42	...	...	...
	6	2.449	60.37	0.629	17.45	...	...	...
	10	3.162	64.56	0.725	20.10	...	...	2.08×10^{-9}
	25	5.000	91.31	0.952	27.57	...	...	...
	49	7.000	95.85[b]	...	...	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 42.60							...
51.0	1	1.000	25.60	0.289	7.26	0.2986	1.418	...
	3	1.732	46.77	0.529	13.26	...	...	...
	5.50	2.345	60.14	0.681	17.05	...	...	2.73×10^{-9}
	22.5	4.761	84.44	0.956	23.94	...	...	...
	41.5	6.442	88.31[b]	...	24.49	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 39.25							
54.0	2.5	1.581	45.67	0.500	12.47	0.3469	1.418	...
	5.0	2.236	66.51	0.728	18.17	...	...	...
	7.5	2.738	73.53	0.804	20.09	...	...	...
	13.0	3.605	84.78	0.928	23.16	...	...	3.86×10^{-9}
	25.0	5.000	88.08	0.964	24.06	...	...	...
	42.0	6.480	91.35[b]	...	24.36	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 40.60							...
60.0	1.0	1.000	30.08	0.370	8.578	0.4213	0.1775	...
	2.0	1.414	44.55	0.549	12.70	...	...	...
	3.5	1.870	60.12	0.741	17.14	...	...	...
	5.0	2.236	69.05	0.851	19.68	...	...	5.90×10^{-9}
	24.0	4.899	81.13[b]	...	23.38	...	...	...
	Total % Uptake (Amt. Removed from Soln. at Equilibrium) = 36.14							

[a] M_t/M_∞ = Fractional uptake. [b] M_∞ = Final uptake at each temperature.

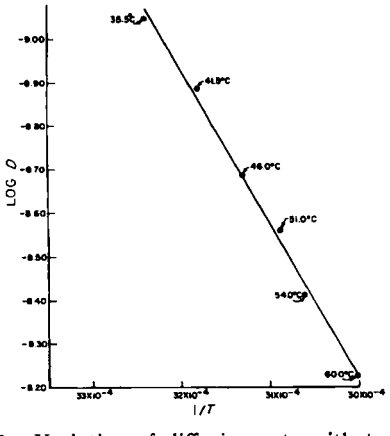


Fig. 5.—Variation of diffusion rate with temperature.

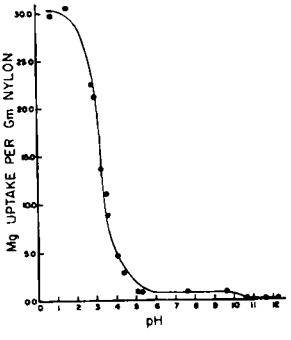


Fig. 6.—Effect of pH on the sorption of salicylic acid by nylon (41.5°C.).

stant, and T the absolute temperature. From the slope of the line ($\Delta E/2.303\ R$), ΔE may be calculated. In this case with the specific nylon samples

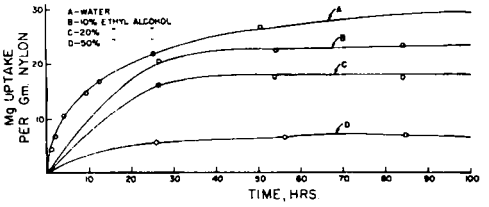


Fig. 7.—Effect of ethyl alcohol on the sorption of salicylic acid (0.15%) by nylon (41.5°C.).

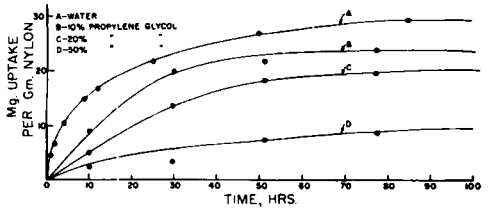


Fig. 8.—Effect of propylene glycol on the sorption of salicylic acid (0.15%) by nylon (41.5°C.).

used, the activation energy (ΔE) of diffusion was equal to 20.5 Kcal./mole.

Effect of pH on Sorption.—Salicylic acid solutions having an original concentration of 0.15% were adjusted to various hydrogen ion concentrations using hydrochloric acid at very low pH values and sodium hydroxide at the higher values. These were placed in contact with nylon strips as in the previous experiments. The tubes were placed in a constant temperature water bath having a temperature of 41.5° for a period of time to insure that equilibrium had been reached. The amount of salicylic acid which was sorbed by the nylon was then determined as well as the final pH of the solution. These data were plotted as milligrams uptake per gram of nylon against pH as shown in Fig. 6.

Effect of Solvents on Sorption.—Experiments were conducted to determine the effect several solvents might have on the uptake of salicylic acid. Several concentrations of alcohol–water, propylene glycol–water, glycerin–water, and polyethylene glycol 400–water were kept in contact with strips of nylon and the uptake of salicylic acid at various times observed. Sorption data of these results are shown in Figs. 7–10.

DISCUSSION

As has been demonstrated in the experiments reported in this paper, salicylic acid will be sorbed by nylon. The sorption of the drug may be thought of as an intermolecular reaction between binding sites in the polymer and the drug. An analysis of the chemical structure of nylon 66 reveals three polar sites which could attract solute particles. The structure of the plastic may be and shows a carboxylic group at one end and an amine group at the other end of the chain. In the chain proper, on every sixth carbon, an amide linkage is present. It may be seen clearly that the amide groups are far in excess of the terminal end groups. The binding of weak organic acids and phenols by both soluble and insoluble polyamides has been noted in the literature.

Much work has been performed on the dyeing of synthetic yarns with dyes which can be classified as organic acids. A nearly analogous situation may be drawn in the sorption of a drug by nylon as the dyeing of nylon yarn by a particular dye. Peters (8) has demonstrated both theoretically and experimentally that at pH values of 3 and above an ionic interaction takes place between the terminal amino group which in this pH range has a positive charge and the anion of the drug. The total amount of dye sorbed, however, is small and tends to be limiting. As the pH of the solution is decreased, a sudden surge of uptake or binding occurs; here the interaction is assumed to occur on the very weakly basic nitrogen in the amide which can take on a hydrogen atom (at very low pH

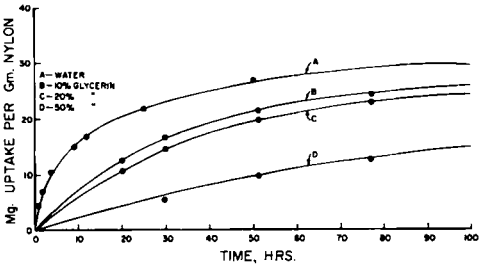


Fig. 9.—Effect of glycerin on the sorption of salicylic acid (0.15%) by nylon (41.5°C.).

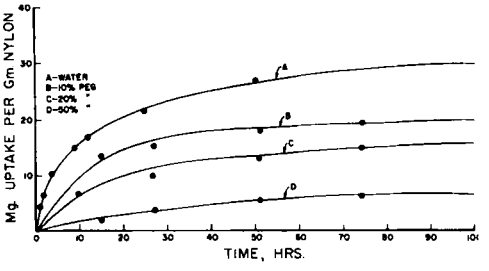
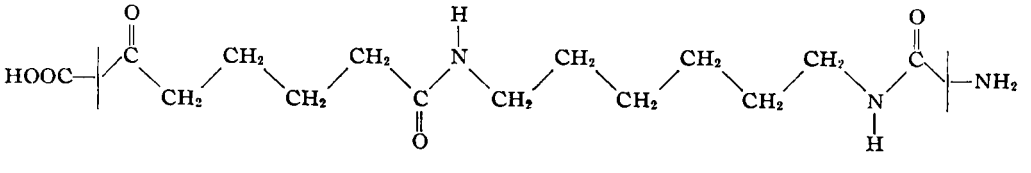


Fig. 10.—Effect of polyethylene glycol 400 on the sorption of salicylic acid (0.15%) by nylon (41.5°C.).

values). This positive site then attracts the negatively charged dye anion. In a later paper, O'Briain and Peters (9) indicated that high uptake at low pH may also be due to hydrolysis of the nylon permitting more binding sites than originally present.

In the case of salicylic acid the over-all pattern is the same, as may be noted by referring to Fig. 6. At high pH values little or no interaction is seen, but as the pH is decreased, the degree of binding



increases greatly. Here it may be assumed that in the pH range of 6 to 9, most of the binding is occurring at the amine end groups. The plateau effect indicates that all the available sites are filled and that the drug is bound as the salicylate ion. Below pH of 6.0 the large uptake of the drug may be ascribed to the binding of the drug in the unionized form through hydrogen bonding with the carbonyl group in the numerous amide linkages. Even at the lower pH values (below 3.0) this mechanism is probably still operating, and in this instance the mechanism differs from the case of the dye. At the very low pH values all of the drug is in the unionized form and it would seem difficult to vision an interaction of a solute having protonic characteristics to be attracted to a positive site (on the amide nitrogen). The organic dyes even at low pH values are dissociated to a significant degree and can thus appear as anions. In fact, Cannon (10) has excluded the possibility of phenolic compounds interacting with the amide nitrogen and postulates hydrogen bond formation with carbonyl groups. It is interesting to note that above a pH of 9.5 little sorption is detected, and this may be attributed to the loss of positive charges on the end terminal amines.

In the pH region of high uptake, one must consider that secondary valence forces are probably operating in stabilizing the interaction. This reasoning has already been demonstrated by other workers who have experimentally proved that the hydrophobic characteristics of the drug or agent can materially influence the degree of binding (11, 12).

What has been elucidated above is most likely an oversimplification of a highly complex mechanism. Obviously, other factors either recognized or completely obscured are surely influencing the uptake.

As might be expected (Table I) the standard affinity tends to decrease as the temperature is increased. This type of occurrence has been noted for other polymer-solute interactions and can be viewed as meaning that at the higher temperature the kinetic energy of the molecules of both the solute and the polymer is greater than at lower temperatures which in turn prevents proper orientation of the solute to the binding site and eventual loss of the solute from the particular site.

The heat of sorption (-1.89 Kcal./mole) found for salicylic acid (with the specific nylon 66 used in the experiment) indicates the low energy requirement for binding and supports the contention that dipole-dipole interactions (hydrogen bonds) with secondary valence forces are in operation.

The apparent diffusion values, as predicted by theory, increase as the temperature is increased (Table II). The diffusion values, as stated, are apparent values since a number of assumptions have been made (*i.e.*, diffusion in only one direction, constant D as diffusion takes place in the plastic, etc.).

From the apparent diffusion coefficient data at several temperatures it was possible to calculate the activation energy of diffusion which was found to be 20.5 Kcal./mole. The activation energy may be looked upon as the energy necessary for the solute to overcome the cohesive force existing between the polymers and other obstacles to migration.

The effect of concentration on sorption (equilibrium) which is shown as a Langmuir plot in Fig. 1 reveals a linear relationship. It should not be assumed that this linear relationship would continue had other concentrations been employed. Previous work in this laboratory has demonstrated that anomalous isothermal curves can result in different concentration zones. This point needs more attention both experimentally and theoretically.

The replacement of water with less polar solvents such as alcohol, glycerin, propylene glycol, and PEG 400 decreased the sorption of salicylic acid at the 20 and 50% levels. With hydrophilic plastics such as nylon, the water will have a great degree of attraction to the polymer and will in a sense help plasticize the nylon permitting greater ease of the solute to diffuse within the plastic.

SUMMARY

The sorption of salicylic acid by nylon 66 was studied at a number of conditions. Physical constants such as saturation value (S), standard affinity ($-\Delta\mu°$), standard heat of sorption ($\Delta H°$), apparent diffusion coefficients (D), and activation energy of diffusion (ΔE) were evaluated. Results of the various experiments indicate that the rate-determining step in the uptake of salicylic acid by nylon 66 is the diffusion of the solute within the polymeric structure of the plastic. The low energy requirement of sorption and the results from the pH experiments support the contention that the salicylic acid is most likely interacting in the undissociated state with basic groups in the nylon (amides) through hydrogen bonding. Secondary valence forces appear to stabilize the interaction. Finally, a decrease in the polarity of the solvent system decreases the extent of sorption.

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